Leitlinienprogramm
Onkologie

Evidenztabellen der erweiterten S3-Leitlinie Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung

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Evidenztabellen

DKG KREBSGESELLSCHAFT
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
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Inhaltsverzeichnis

1. Informationen zu den Evidenztabellen des Leitlinienreports

Aus Gründen der besseren Lesbarkeit wird auf die gleichzeitige Verwendung männlicher und weiblicher Sprachformen verzichtet. Sämtliche Personenbezeichnungen gelten gleichermaßen für beiderlei Geschlecht.

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1.2. Herausgeber

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF), Deutschen Krebsgesellschaft e.V. (DKG) und Deutschen Krebshilfe (DKH).

1.3. Federführende Fachgesellschaft der Leitlinie

DEUTSCHE GESELLSCHAFT FÜR PALLIATIVMEDIZIN

1.4. Finanzierung der Leitlinie

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

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1.6. Zitierweise des Leitlinienreports

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung, Evidenztabellen 2.0, 2019, AWMF-Registernummer: 128/001-OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/ (abgerufen am TT.MM.JJJJ)

1.7. Weitere Dokumente zur Leitlinie

Die Leitlinie liegt als Lang- und Kurzversion vor. Außerdem gibt es eine Patientenleitlinie (Laienversion der Leitlinie). Für die bessere Lesbarkeit dieses Reports sind die Evidenztabellen in einem gesonderten Dokument dargestellt.

Alle Dokumente zur Leitlinie sind über die folgenden Seiten zugänglich:

- AWMF (www.awmf.org/leitlinien/aktuelle-leitlinien.html)
- Leitlinienprogramm Onkologie (www.leitlinienprogramm-onkologie.de/OL/leitlinien.html)
- Guidelines International Network (www.g-i-n.net)
- Beteiligte Fachgesellschaften (z. B. www.dgpalliativmedizin.de)

1.8. Abkürzungsverzeichnis

Abkürzung	Erläuterung
ACT	Acceptance and Commitment Therapy
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
AML	Amytrophic Lateral Sclerosis
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
CALM	Managing Cancer and Living Meaningfully
CCRCT	Cochrane Central Register of Controlled Trials
CCT	Controlled Clinical Trial
CDSR	Cochrane Database of Systematic Reviews
CHMG	Cochrane Haematological Malignancies Group
CI	Confidence Interval
CIS-R	Revised Clinical Interview Schedule
CoI	Conflict of Interest
COPD	Chronic Obstructive Pulmonary Disease
COSMIN	COnsensus-based Standards for the selection of health status Measurement INstruments
CRQ	Chronic Respiratory Disease Questionnaire
CT	Computerized Tomography
DADDS	Death and Dying Distress Scale
DARE	Database of Abstracts of Reviews of Effects
DC	Decisional conflict
DDRS	Desire for Death Rating Scale
DLC	Dynamic Lung Compliance
ES	Effect Size
FEV1	Forced Expiratory Pressure in 1 Second
FRC	Functional Residual Capacity
GAD	Generalized Anxiety Disorder
GI	Gastrointestinal
GSFCH	Gold Standard Framework in Care Homes
GT	Gastrostomy tube
HADS	Hospital Anxiety and Depression Scale
HB	Hyoscine butylbromide
HPN	Home Parenteral Nutrition
HR	Hazard Ratio
HRQOL	Health-related Quality of Life

Abkürzung	Erläuterung
HIV	Human Immunodeficiency Virus
IBO	Inoperable Bowel Obstruction
ILD	Interstitial Lung Disease
ITT	Intention To Treat analysis
i. v.	intravenous
MA	Metaanalysis
MBO	Malignant Bowel Obstruction
MBSR	Mindfulness-Based Stress Reduction
MCP	Metoclopramide
MD	Mean Difference
MI	Myocardial infarction
MND	Motor Neurone Disease
MNXT	Methylnaltrexone
MS	Multiple Sclerosis
MSBO	Malignant Small Bowel Obstruction
NGT	Nasogastric Tube
NNT	Number Needed to Treat
NRS	Numeric Rating Scale
n.s.	non significant
OL	Leitlinienprogramm Onkologie
OR	Odd Ratio
OS	Observational study
PDT	Palliative Decompressive Treatment
PEF	Peak Expiratory Flow
PEG	Percutaneous Endoscopic Gastrostomy
PN	Parenteral Nutrition
p. o.	Per os
PAMORA	Peripherally acting μ-opioid antagonist
PRISMA	Preferred Reporting Items of Systematic reviews and Meta-Analyses
PROMs	Patient Reported Outcome Measures
QoL	Quality of Life
RCT	Randomized Controlled Trial
RFBM	Rescue-Free Bowel Movement
RR	Relative Risk
SAHD	Schedule of Attitudes toward Hastened Death
SBM	Spontaneous Bowel Movement

Abkürzung	Erläuterung
s. c.	subcutaneous
SCID	Structured Clinical Interview for Diagnostic Statistical Manual
SGRQ	St. George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
Sign.	significant
SMD	Standardized Mean Difference
SR	Systematic Reviews (SysRev)

Abkürzung	Erläuterung
SSD	Silver Sulfadiazine
TPN	Total Parenteral Nutrition
TXA	Tranexamic acid
US	Ultrasound
VAS	Visual Analogue Scale
WMD	Weighted Mean Difference
WTHD	Wish To Hasten Death

2. Hinweise zur Bewertung der Studien

2.1. Klassifikation des Studientyps

In der Abbildung 1 wird die Nomenklatur zur Beschreibung der verschiedenen Typen von Primärstudien dargestellt, die in den Evidenztabellen dieser Leitlinie vorkommen. Es handelt sich um Studien zur Wirksamkeit einer Intervention. Die Klassifikation der Studien basiert auf ein in Mc Gill University/Montreal sowie von NICE entwickeltes System (http://www.teachepi.org/documents/courses/Classification%20Design.pdf; http://www.sign.ac.uk/assets/study_design.pdf).

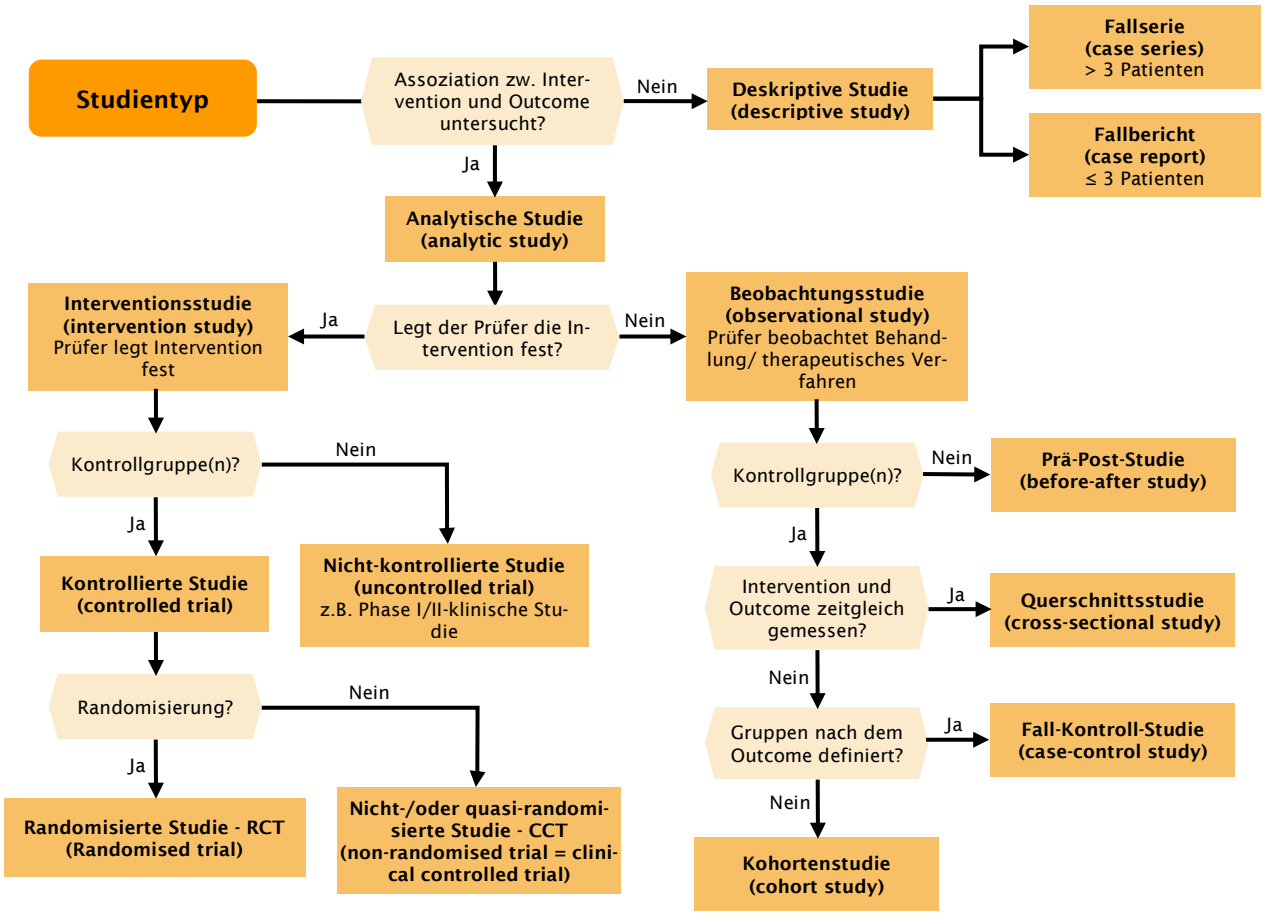


Abbildung 1: Nomenklatur und Klassifikation des Studientyps für die Zwecke dieser Leitlinie

2.2. Evidenzgraduierung

Zur Klassifikation des Verzerrungsrisikos der identifizierten Studien wurde in dieser Leitlinie das in **Tabelle 1** aufgeführte System des Scottish Intercollegiate Guidelines Network (SIGN) verwendet (siehe www.sign.ac.uk/pdf/sign50.pdf).

Unter dem in den Empfehlungen angegebenen Level of Evidence nach SIGN (siehe Langversion dieser Leitlinie) wird ein Body of Evidence verstanden, der die gesamte identifizierte Evidenz zusammenfasst. Deshalb ist auch der Level of Evidence einer Empfehlung,

deren Evidenzgrundlage auf einem Systematic Review basiert, der Body of Evidence der in diesem Review eingeschlossenen Primärstudien. Dieser Body of Evidence kann vom Level of Evidence des Systematic Reviews selbst (in den Evidenztabellen angegeben) abweichen. Die Qualität des Systematic Reviews kann nämlich hoch sein, während die Qualität der eingeschlossenen Studien, die sich im Body of Evidence widerspiegelt, niedrig ist.

Tabelle 1: Schema der Evidenzgraduierung nach SIGN

Grad	Beschreibung
1++	Qualitativ hochwertige Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2+	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z. B. Fallberichte, Fallserien
4	Expertenmeinung

3. Versorgungsstrukturen

3.1. Integration von Palliativversorgung

3.1.1. Zeitpunkt der Integration von Palliativversorgung: Aktualisierung 2019

3.1.1.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Adler, Anaesthesist 2017 [1]	SR To determine the current situation of palliative patients in ICU settings: what is the impact of palliative care interventions on the quality of care of ICU patients? To what extent is palliative care support at ICUs available and to what extent is it used? Which factors trigger palliative care	18 publications quantitative and qualitative studies and Review articles (2 Review articles, 2 retrospective cohort studies, 2 prospective cohort studies, 1 literature review, 1 RCT, 2 qualitative studies, 1 prospective case-control study, 1 prospective observational study,1 retrospective analysis, 1 qualitative interview study, 2 surveys (1 experts	Participants in the **intensive care unit (ICU)**, namely primarily intensive care Patients, their relatives and the intensive care team.	Palliative care Interventions and surveys	Benefit, needs and reasons for a palliative care Co-treatment and attitude the participants.	1 study (RCT, n=517): improvement of the communication between patients and doctors/ nurses and significantly increased patient satisfaction in one randomly offered palliative treatment on normal stations, fewer admissions to intensive care units and reduced treatment costs. 1 study (prospective/observational study, n=191): the length of stay in the intensive care unit significantly reduced from 16 to 9 days after the introduction of a palliative care Co-treatment.	▪ PICO-instrument (no control groups) ▪ not specified for patients with ▪ different sample sizes (from 17 interviews to 385.770 retrospective dates)	1- (Body of Evidence: 3)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	consultations?	study), 1 quantitative questionnaire, 1 mainly quantitative questionnaire						
Dalgaard, Palliat Support Care 2014 [2]	SR; To document the best evidence on **methods for early identification (EI)** of palliative trajectories in cancer, chronic heart failure (CHF), and chronic obstructive pulmonary disease (COPD) populations, and to identify preconditions for early integration of general PC in hospitals and outcomes for patients and relatives.	**44 articles** (10 methods for early identification of palliative trajectories in cancer, 10 methods for early identification of palliative trajectories in CHF, 4 methods for early identification of palliative trajectories in COPD, 9 General methods for early identification of palliative trajectories, 8 Preconditions for early integration of palliative trajectories in cancer, CHF, and COPD, 3 Outcome of early integration of palliative trajectories for	Patients with **cancer, CHF, and COPD**	Methods, preconditions, and outcomes for patients with cancer, CHF, and COPD	1.O: methods for EI of palliative trajectories in cancer, CHF, and COPD populations 2.O: preconditions for early integration of general PC in hospitals and outcomes for patients and relatives	1. trajectory approch 2. integrated tools 3. prognostic tool Common of all (1.-3.): Emphasis on prognostication based on assessment of functional status and needs. No methods can be recommended for routine clinical practice without further validation.	▪ The evidence about outcome is sparse and mostly relates to cancer populations receiving specialized PC ▪ There is an urgent need to develop and evaluate methods based on the holistic assessment of symptoms or needs. The barriers to early integration of PC are most extensive with regard to CHFand COPD. Professional training and education are recommended to facilitate early implementation of PC.	1- (Body of evidence: 3)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
		patients and relatives)						
Davis, Ann Palliat Med 2015 [3]	SR; to review and discuss randomized control trials examining the integration of palliative care earlier in the course of the disease trajectory for patients with serious illnesses as an outpatient and at home	Database: PubMed (no period mentioned); handsearch Study design: RCTs, SR	Patients with **serious illnesses**	**Early palliative care (PC)** (=early in the course of the disease) for outpatients and patients at home	Symptoms QoL Cargiver outcomes Length of stay, hospitalizations Costs	Study number: • 15 RCTs on outpatients • 13 RCTs on home PD • 7 SR Quality of included studies: high risk of bias Outcomes: incongruent results across studies: 10 RCTs showing some benefit: improvement in certain symptoms such as depression, improved patient QoL, reduced aggressive care at the end of life, increased advanced directives, reduced hospital length of stay and hospitalizations, improved caregiver burden and better maintenance of caregiver QoL and reduction in the medical cost of care as well as patient and family satisfaction 9 RCTs showing no benefit: symptoms and QoL, and resource utilization and costs not improved	Method: Literature search performed in 1 database only; Inclusion criteria not clearly defined Content: author's conclusions: Incongruent results may be attributed to: • Structures: interventions often did not involve full multidisciplinary PC team • Control (usual care) not standardized • Low quality of studies • Variable definition of "early PC": diagnosis of advanced cancer (or few months later), > 3 months before death, resistance to tumour therapy, prognostic signs and symptoms, etc. • Variable referral criteria for home PC: expected survival (varied between 2 years and 2 weeks), impairment of activities of daily living	1- (Body of evidence: 1-)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Gärtner, BMJ 2017 [4]	SR; MA To assess the effect of specialist palliative care on quality of life and additional outcomes relevant to patients with advanced illness.	3967 publications RCTs, cluster RCTs (specific palliative care compared with standard care (full text articles, abstract) 10 RCTs (12 articles; n=2454 patients; n=1766 [72%] patients with cancer) included in qualitative synthesis and quantitative synthesis (MA)	Patients with any **advanced illness**, inpatients and outpatients (hospital, hospice, or community settings) Age ≥18 years	Effect of specialist palliative care services on quality of life in adults with advanced incurable illness in hospital, hospice, orcommunity settings (specialist palliative care [SPC] vs. standard care (StC)	1.O: Quality of life (physical, psychological or social) 2.O: symptom burden (pain, fatigue, nausea, dyspnoea), psychosocial variables (distress, depression, anxiety, spiritual wellbeing, social wellbeing, satisfaction), survival time, place of death-cost of care, attrition (or completion rate)	The integration of specialised palliative care was associated with small effect for quality of life, pain and other secondary outcomes were inconclusive. **Quality of life**: 8 RCTs (80%) measured quality of life: 3 studies (38%) had a small significant effect (0.2-<0.5=small, 0.5-<0.8=moderate, ≥0.8=large) 7 RCTs (MA): Small significant effect in favour of specialist palliative care (SMD 0.16, 95% CI 0.01 to 0.31) The effect in favour of specialist palliative care was marginally higher for patients with cancer (SMD: 0.20, 95% CI 0.01 to 0.38; 5 RCTs (n=828) and highest for early care (0.33, 0.05 to 0.61) **Pain**: 7 RCTs (0.57, 95% CI -0.02 to 1.15); 3 RCTs included in the MA (-0.38, 95% CI -0.82 to 0.06)	▪ Body of evidence: Low (pain) and moderate (QoL) quality of evidence ▪ The true effect of the intervention might be substantially higher than reported due to a number of methodologic issues of the RCTs ▪ All RCTs provided specialist Palliative Care in addition to routine care to ALL patients (no focus or screening for those at need for a specialist intervention) ▪ Very strict inclusion criteria, especially concerning the mandatory multi-professional team.	1+
Haun, Cochrane 2017 [5]	SR, MA; To compare effects of early	Databases: Cochrane Central Register of Controlled	Adult patients whom had been given the **diagnosis of a malignant**	Professional **palliative care services that provided or co-ordinated comprehensive care for**	1.O: • HRQOL • Survival • Depression	Study number: 7 RCTs/cRCTs (n=1614) Models of care:	Well-conducted SR Although we found only small effect sizes,	1++ (Body of evidence: 1-)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	palliative care (PC) interventions versus treatment as usual/standard cancer care on health-related QoL (HRQOL), depression, symptom intensity, and survival among adults with a diagnosis of advanced cancer.	Trials (CENTRAL), MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, OpenGrey (grey literature), and three clinical trial registers to October 2016 Study design: RCTs, cluster-RCTs (cRCTs)	**tumour entity at an advanced stage** (as assessed by the oncologist and based on disease stage and tumour type) **and without curative treatment options** (i.e. owing to metastatic disease or inoperability, or both)	**adults at early advanced stages** of cancer vs. usual/standard cancer care	• Symptom intensity measured by means of a validated tool 2.O: • Caregiver burden • Healthcare utilization • Harms/adverse events (AE)	Specialised PC team: 4 RCTs Co-ordinated care: 3 RCTs Quality of studies: low/moderate risk of bias; evidence of low to very low certainty main outcomes Outcomes (Metaanalysis): • **HRQOL** (n=1028; low evidence): sign. small effect (SMD 0.27, 95% CI: 0.15 to 0.38) • **Survival** (n=800; very low evidence; I^2=81%): n.s. (death hazard ratio 0.85, 95% CI 0.56 to 1.28) • **Depressive symptoms** (n=762): n.s. (SMD -0.11, 95% CI -0.26 to 0.03) • **Symptom intensity** (n=1054): sign. small effect (SMD -0.23, 95% CI -0.35 to -0.10) The type of model used to provide early palliative care did not affect study results **AE** (1 RCT): higher percentage of participants with severe scores for pain and poor appetite	these may be clinically relevant at an advanced disease stage with limited prognosis, at which time further decline in quality of life is very common. ▪ We have to interpret current results with caution owing to very low to low certainty of current evidence and between-study differences regarding participant populations, interventions, and methods.	

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Hui, Oncologist 2015 [6]	SR; to identify articles addressing the clinical, educational, research, and administrative indicators of integration of palliative care and oncology	Databases: Ovid MEDLINE and Ovid EMBASE between 1948 and 2013 Study design: Original studies, reviews, systematic reviews, guidelines, editorials, commentaries, and letters	Oncology patients treated integratively by palliative care specialists and oncologists	(No intervention but collection of the following descriptive data): Clinical, educational, research, and administrative **indicators of integration of palliative care (PC) and oncology**	We used frequencies and percentages to summarize the data	Study number/design: 101 articles. A majority of these articles were review articles (n=59, 58%), published in oncology journals (n=60, 59%), and from North America (n= 64, 63%). Original articles: n=35 (34%); European origin: n=27 (27%) Clinical indicators: a) Structure: • Outpatient PC clinics (54%) • Community-based PC (32%) • PC units (24%) • Inpatient consultation teams (14%) b) Process (i.a.): • Interdisciplinary teams (71%) • Acceptance of patients on active cancer treatment (simultaneous care, 70%) • High degree of availability of PC clinics (10%) • Routine symptom screening (25%) • **Timing of PC referral** (18%): most articles gave the diagnosis of advanced/metastasized cancer or the weeks	Descriptive SysRev aiming at identifying indicators of integration from original publications (incl. RCTs), (systematic) reviews or discussion articles. Well conducted systematic review	3

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						after the diagnosis as timing of referral. c) Outcomes: Although many clinical outcomes were mentioned in the literature (e.g., survival, QoL), it could not be determined whether these outcomeswere related to the mere presence of a palliative care program, successful integration specifically, or other cointerventions (i.e., cancer treatments). Education indicators (i.a.): • Palliative skills for oncologists • Palliative skills for students Research/administrative indicators: discussion about needs for research and for policy on PC (i.a.)		
Hui, Oncologist 2016 [7]	SR; to identify criteria that are considered when an outpatient palliative cancer care referral is initiated.	Study design: Original studies, reviews, systematic reviews, guidelines, editorials, commentaries, and letters	**Cancer palliative patients** in outpatient setting	(No intervention but collection of the following descriptive data): Criteria that are considered when an **outpatient cancer palliative care referral** is initiated	We used frequencies and percentages to summarize the data If a referral criterion was described by at least 5 articles, it was considered as a major category.	Study number/design: 21 articles Major categories for referral criteria: • **physical symptoms** (n=13 [62%]): n=9 used a validated tool. From these, n=7 used ESAS (only n=2 set a cut-off: ≥6 or 5/10)	Descriptive SysRev aiming at identifying referral criteria for outpatient cancer PC from original articles (incl. RCTs), (systematic) reviews or discussion articles, as first step toward developing a standardized set of referral criteria.	3

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						• **cancer diagnosis/trajectory** (n=13[62%]): diagnosis of advanced cancer as most common criteria. Definition of advanced cancer varied between the 13 studies. • **prognosis** (n=7[33%]): wide variation • **performance status** (n=7 [33%]): n=5 used ECOG (cut-offs varied); n=2 used PPS (Palliative Performance Scale) • **psychosocial distress** (n=6 [29%]): n=2 used a tool (NCCN distress thermometer; cut-offs ≥4 or 6/10) **EoL care planning** (n=6 [29%]) as reason for referral	Well conducted SysRev	
Tassinari, Rev Recent Clin Trials 2016 [8]	SR; To assess the role of early palliative care in patients with advanced oncologic and non-oncologic chronic diseases	Databases: MEDLINE, EMBASE, CINAHL, CRISP and Cochrane Systematic Reviews Databases, from January 2000 to June 2015 Study design: RCTs phase III	patients with **advanced oncologic and non-oncologic** diseases	**early, simultaneous palliative care (PC) + standard care** vs. standard care alone	QoL symptoms control overall survival quality of care patients' and caregivers' satisfaction costs of the assistance	Study number: 9 RCTs + 2 prospective cohort trials (14 publications) Quality of studies: moderate to high risk of bias Outcomes: **QoL**: improved in 2/7 studies **Symptom control**: improved in 1/5 studies **Overall survival**: improved in 2/3 studies	Method: Clear focused question; Inclusion of non-randomized cohort studies despite clear RCT-inclusion criteria; Otherwise well-conducted Content: Heterogeneous results may be due to (author's conclusions):	1+ (Body of evidence: 1-)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						Quality of care: improved in 5/8 studies **Satisfaction**: improved in 3/4 Cost reduction: in 2/3 studies	• Lack of clear definition of "early" and "simultaneous" and of timing and setting for PC • Heterogeneity of PC service models included Moderate to high risk of bias	

3.2. Erfassen der Patientenbedürfnisse und Ermittlung der Komplexität: Aktualisierung 2019

Siehe dazu Evidenztabellen des Kapitels 3.1.1, Zeitpunkt der Integration von Palliativversorgung: Aktualisierung 2019

3.3. Interventionen für Angehörige

3.3.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Candy, Cochrane 2011 [9]	SR, MA	11 RCTs	Caregivers (CG)= Adults caring informally for a relative/friend with a disease in the terminal phase (n=1836) Most patients with cancer	Interventions providing support to the caregiver + usual care: Directly (9): support in the caring role (7), family life review (1), grief therapy (1) Indirectly via patients care (2)	1.O Psychological health (symptoms of depression/anxiety/ hopelessness, QoL, coping, …) Physical health Service delivery Adverse outcomes 2.O Acceptability to CG CG's knowledge of patient's disease Perceived impact of care by patient CG bereavement Cost	Interventions supporting directly the CG: Low quality evidence that they significantly reduce psychological **distress** in the short term (8 trials: standardised mean difference (SMD) -0.15; 95% confidence interval (CI) -0.28 to -0.02). Low quality evidence that they in the short term may marginally improve **coping** skills and **quality of life**, but neither results were statistically significant (7 trials: SMD -0.05; 95% CI -0.24 to 0.14; 6 trials: SMD 0.08; 95% CI -0.11 to 0.26, respectively) 1 trial assessed **physical** outcome: no difference Indirect interventions: May reduce psychological **distress**, but not sign. No study assessing health service use or adverse outcomes.	Risk of bias unclear, as all trials underreported methods	1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Harding, Pall Med 2003 [10]	SR (no MA due to heterogeneity)	22 studies (no design limit) Evaluation studies: 2 RCTs 2 prospective single-group 1 retrospective single-group 1 feed-back	CG = Adults providing informal care (including family members) for non-institutionalized cancer and palliative care patients.	Interventions for CG specifically for CG (6) home nursing care (4) respite services (3) social network and activity enhancements (2) problem solving and education (3) group work (10)	Description or evaluation of intervention	The current evidence contributes more to understanding feasibility and acceptability than to effectiveness.	Small sample size Lack of evaluation design Use of untested measures	1- (Englisch only, few databases, few RCTs)
Harding, Pall Med 2012 (update) [11]	SR (no MA due to heterogeneity)	33 studies (included are RCT, prospective, concurrent mixed-methods, qualitative, qualitative post-intervention data, before-after study): 10 (quasi-) experimental design	CG = Adults providing informal care (including family members) for non-institutionalized cancer and palliative care patients. (24 studies with CG of cancer patients)	Interventions for CG: specifically for CG (17) 1 to 1 psychological models (8) Psychological interventions for patient/carer dyads (4) Palliative care/hospice (6) Information and training (3) respite (1) group interventions (10) physical (1)	Description or evaluation intervention	Group interventions (2 RCTs, 2 quasi-experimental studies): 2/4 sign. benefit 1 to 1 psych. interventions (3 (quasi) experimental studies): 2/3 positive effect; sign. treatment effect with respect to positive rewards of caring Pt/carer dyads (3 RCTs: 3/3 sign. effect (improved QoL, reduced stress…). No sign. effect on coping, hopelessness and uncertainty. PC/hospice (1 RCT out of 6 studies): n.s. on carer outcomes post-death	(Quasi-)experimental studies: moderate to good quality	1+ (Englisch only, few databases)
Lorenz, Ann Int Med 2008 [12]	SR (no MA due to heterogeneity). Comprehensive review to EoL care, with one chapter analysing	8 SR 19 intervention studies (RCT, CCT)	EoL patients	Interventions for serving informal caregivers, including family, when patients are approaching EoL	CG outcomes (Burden relieve, Satisfaction)	Weak to moderate evidence suggests that caregiver interventions, especially when comprehensive and individually targeted, can relieve **burden**, although	Most literature related to dementia, less to cancer	1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	caregiver burden.					effect sizes are generally small. Moderate evidence suggests that palliative care interventions improve **satisfaction**. Because existing research focuses on dementia, evidence is moderate in dementia and weak in cancer. No evidence addressed caregivers in heart failure.		

3.3.2. Primärstudien

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Dropouts	Patients characteristics	Intervention/Control	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure	Results	Comment	Level of Evidence SIGN
Fegg, Psycho-Oncology 2013 [13]	RCT; parallel-group design (with equal randomisation 1:1)	n=160 (81 EBT; 79 control group) Dropouts=35	▪ 54.5+-13.2 years old; 69.9% were female ▪ Study participants were **informal caregivers (CG) of patients** receiving inpatient palliative care (**life expectancy≤6 months** according to the patient's	Intervention: EBT (**Existential behavioural** therapy) treatment to **support** informal CG of palliative patients: Six group sessions totalling 22 h ▪ First meeting: Becoming acquainted and introduction into mindfulness.	**1.O: mental stress and QOL** Severity of symptoms (Brief **Symptom Inventory** - BSI, sub-scales of; ▪ somatisation, ▪ depression ▪ anxiety Raw scores were transformed into gender-specific T-values (T≥60 is clinically striking). **QOL**	▪ no sign. differences between both groups at baseline ▪ The multivariate model was significant for the pre-/postcomparison (p = 0.005) and the pre-/12-month comparison (p = 0.05) but not for the pre-/3-month comparison. ▪ Medium to large effects on **anxiety** (regression	▪ Intention to treat analysis ▪ Powered study: 44 CG had to participate in the EBT to achieve a power of 0.8 at p = 0.05 ▪ Participants selected from different institutions, improving generalizability. ▪ A possible limitation is the heterogeneity of	1+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure	Results	Comment	Level of Evidence SIGN
			physician) and post-death; minimum 21 years of age ▪ Patients' diagnosis: Cancer (82,7%), neurological disease (12,8%), other (4,5%) ▪ Only one relativeper patient took part with the next of kin being selected. ▪ Exclusion criteria: severe mental illness	▪ Second meeting: Death, bereavement and mindfulness ▪ Third meeting: Activating resources and finding meaning. ▪ Fourth meeting: Self-care and stress management. ▪ Fifth meeting: Personal values for (re-)orientation. ▪ Sixth meeting: Saying goodbye and new steps. Control group did not receive any special comparative treatment. However, they were free to use the spectrum of available support at the institution or elsewhere	▪ Satisfaction with Life Scale (SWLS) assessing its cognitive aspects ▪ WHOQOL-BREF comprising QOL domains ▪ NRS on individual, overall QOL experience (QOL-NRS, range 0–10, 'How do you rate your quality of life at the moment?') (Data were collected at baseline, pre-treatment, post-treatment and follow-ups after 3 and 12 months.) **2.O:** ▪ changes in affect (Positive and Negative Affect Scale (PANAS) ▪ helpfulness ratings of specific intervention (0-4)	coefficient B (95% CI) =4,59 (1.34 to 7.85)) and **QOL** (SWLS: B (95% CI) =-0.39 (-0.69 to -0.10), WHOQOL-BREF: B (95% CI) =-3.68 (-6.34 to -1.02), QOL-NRS: B (95% CI) = -1.17 (-1.78 to -0.56)) were found at post-treatment; ▪ medium effects on **depression** (regression coefficient B (95% CI) =3.27 (0.15 to 6.39) and **QOL** (QOL-NRS: B (95% CI) =-1.18 (-1.90 to -0.45) emerged in the 12-month follow-up. ▪ **No adverse effects** of the intervention were observed. ▪ 2.O: EBT participants had significantly less **negative affect** (regression coefficient B (95% CI) =0.29 (0.10 to 0.49) and a tendency towards more positive affect in the pre-/post-comparison. At 3-month follow-up, differences in the same direction but not significant (p=0.05). At 12-month follow-up, significantly less negative (regression coefficient B (95% CI) = 0.33 (0.11 to	the sample. Participating informal CG had varying relationships to the patient, with partners being predominant. ▪ No reported calculation of overall effect of multivariate model ▪ No information about blinding	

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure	Results	Comment	Level of Evidence SIGN
						0.54) and by trend more positive affect in EBT compared with controls.		
Hudson, Psycho-Oncology 2013 [14]	Phase III randomised parallel group (three-arm RCT)	n=298 (control: n=148; Intervention 1: n=57; Intervention 2: n=93) Drop-outs: 21 at Time 1; 137 at Time 2 (46%): patient no longer met the inclusion criteria (n = 22); patient died before time 2 (n = 9); or the carer withdrew from the study (n = 17). In the majority of circumstances (n = 80), the reason(s) were not identified.	▪ primary **family caregivers** (CG) of patients with advanced **cancer** receiving home-based palliative care ▪ age > 18 years ▪ able to understand english ▪ exclusion criteria: confronted with significant emotional distress precluding them from completing questionnaires. CG of patients with a non-malignant diagnosis or a poor functional status (using a standardised measure) indicating likelihood of imminent death were excluded in order to reduce attrition.	Intervention: The psycho-educational focus included tailored **information** and **resources** (primary written resource was a family CG guidebook) given to family CG to promote psychological well-being by preparing them for their role. Each CG was allocated a Family CG Support Nurse (FCSN) who assisted the local palliative care service. The intervention was delivered over 4 weeks and comprised the following: ▪ Step 1: preparing CG for the intervention. ▪ Step 2: assessing caregiver needs and preparing a care plan. ▪ Step 3: re-assessing needs and evaluating the care plan ▪ Step 4: assisting the family caregiver to prepare for their relative's death and to prepare for bereavement. Arm 1: 1visit and 3 phone calls	**1.O**: ▪ psychological distress (General Health Questionnaire (GHQ) **2.O**: Caregiving experiences prior to the patient's death ▪ caregiver competence scale (CCS) (4 questions scored 0–3) ▪ preparedness for caregiving scale (8 questions scored 0–4, 'total' score is the mean of valid responses) ▪ family inventory of need—part/scale B (20 questions scored 0–4) ▪ rewards for caregiving scale (10 questions scored 0–4) Measurement at: ▪ baseline (T1) ▪ 1 week post-intervention (T2) ▪ 8 weeks post-patient death (T3)	▪ **Psychological well-being**: not sign. improved in intervention groups ▪ No significant reduction in **unmet needs** or improvements in positive aspects of caregiving amongst the intervention group were identified. ▪ significant improvement in **preparedness** and **competence** for Intervention 2: The difference in change between the two-visit group and the control group was significant (p = 0.035). The effect sizes for the one-visit group, the two-visit group and the two groups combined relative to the control group were 0.14, 0.29 and 0.22 indicating small effects. The change between Times 1 and 2 in the two intervention groups combined versus the control group was significant (p = 0.03), as was the change in the two-visit group versus	▪ Computer-gernerated randomization ▪ Research assistants blinded to group allocation to minimize response bias ▪ Selection bias: many relatives declines to participate ▪ Younger participants produced the higher scores (normally older people do) ▪ Attrition bias, with the biggest net loss between T1 and T2 ▪ no guarantee that implementation of the intervention was carried out routinely as intended (performance bias?)	1-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure	Results	Comment	Level of Evidence SIGN
				Arm 2: 2 visits and 2 phone calls Arm 3: control (standard care)		the control group (p = 0.04). The effect sizes of the changes in the one visit, two visits and both groups combined relative to the control group were 0.27, 0.33 and 0.30, respectively, indicating small effects.		
McLean, Psycho-Oncology 2011 [15]	Two-group RCT; couples randomly assigned to EFT or standard care (CTL) in a 1:1 ratio by statistician, no blinding of participants to their assignments. Study personal blinded to condition assignment	N= 42 couples 22 couples for intervention group and 20 for control group Dropout=2 couples (one patient died of cancer and one had progressive disease and was to ill to continue [both from CTL group])	▪ Participants were recruited from Princess Margaret Hospital (PMH), Canada's largest comprehensive cancer center ▪ Metastatic **cancer** ▪ English speaking ▪ >= 18 years old ▪ In a romantic partnership of >= 1 year, endorsing marital distress (Revised Dyadic Adjustment Scale (RDAS) <= 47) in minimally one partner ▪ Not currently in couple therapy ▪ Patient Karnofsky	Emotionally Focused Therapy (EFT), modified for the advanced cancer population versus standard care. Aim of the couple-based intervention: **support couples** facing death EFT: ▪ 8-session EFT intervention adapted for use with couples where one partner has advanced metastatic cancer. ▪ 1-hour weekly couple sessions (M = 7.7, SD = 0.94, median = 8, mode = 8) were delivered by one EFT-trained psychologist (LM) and occurred over a 2–3-month period. Sessions took place at PMH clinical offices or at alternative locations in four of the INT group couples, including home (n = 2)	**1.O:** ▪ marital functioning (Revied Dyadic Adjustment Scale = RDAS (standardized and validated 14-item self-report that is widely used to evaluate both individual and dyadic adjustments in distressed relationships.)) **2.O:** ▪ Psychological Symptoms (Beck Depression Inventory-II (BDI-II) and Beck Hopelessness Scale (BHS)) ▪ CG's Burden (two subscales [Demand/Difficulty] of the Caregiver Burden Scale were used to access objective and subjective caregiving burden (CG only) ▪ Patient's perspective of CG empathic behaviour (10-item Relationship-	▪ **Marital functioning**: At T1, sign. difference on the RDAS (p<0.0001), with the EFT having higher mean scores (better marital functioning) than the CTL group. Effect size for this difference: Cohen's d = 1.00, which is in the large range. In both groups, patients showed a marginally higher mean score for marital functioning compared with CG [EFT: M= 56.3, standard deviation (SD) = 4.6 vs M= 54.3, SD = 4.5; CTL group: M= 43.4, SD = 10.3 vs M= 42.4, SD = 6.8, respectively]. At T2, results were maintained. ▪ **Psychological Symptoms**: no difference in BHS between groups.	▪ Power analysis ▪ relatively small sample size. ▪ results limited to couples who were referred by their clinical team and met the RDAS cut-off for marital distress.	1+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure	Results	Comment	Level of Evidence SIGN
			Performance Status score of >= 60	and/or inpatient hospital room (n = 2), to accommodate needs and to maximize adherence. Control (CTL): ▪ standard care provided by the POPC department.	Focused Coping Scale [RFCS]) Measures at ▪ baseline (T0) (before random assignment), ▪ immediately post-intervention (T1), 3-month post-intervention follow-up (T2).	▪ **Caregiver Burden and Patient-perceived empathic behaviour:** sign. higher mean scores at T1 for EFT patients, indicating higher patient perceived caregiver empathic behaviour (p = 0.02). There was no sign. difference (p = 0.09) between groups in CG subjective difficulty in caregiving for their ill spouses.		
Northouse, Psycho-oncology 2013 [16]	RCT, blinded (three-arm RCT)	N= 484 dyads (completed baseline assessment) N= 343 dyads completed Time 2 assessments (70.9% retention); and N= 302 dyads completed Time 3 assessments (62.4% retention)	▪ advanced breast, colorectal, lung or prostate **cancer** (i.e., Stage III or IV), and were within a six-month window of having a new advanced cancer diagnosis, progression of their advanced cancer, or change of treatment for it. ▪ life expectancy ≥ 6 months, ▪ age 21 or older, ▪ living within 75 miles of participating cancer centers, and	Intervention: The original FOCUS Program was a home-based, dyadic intervention that provided **information and support** to cancer patients and CG together, as the **unit of care**. We revised the original five-session program into Brief and Extensive versions. ▪ Arm 1: Brief FOCUS: 3 contacts (two 90-minute home visits and one 30-minute phone session). ▪ Arm 2: Extensive FOCUS: 6 contacts (four 90-minute home visits and two 30-minute phone sessions). ▪ Control: All study participants received usual	**1.O:** Quality of Life: General Functional Assessment of Cancer Therapy (FACT-G), assessing 4 domains: social, emotional, functional, physical well-being **2.O:** Appraisals ▪ Appraisal of Illness and Caregiving (Appraisal of Illness Scale (patients) and Appraisal of Caregiving Scale (CG)) ▪ Uncertainty (brief version of the Mishel Uncertainty in Illness Scale) ▪ Hopelessness (Beck Hopelessness Scale) Resources: ▪ Coping: strategies (Brief Cope) and Healthy	▪ Significant Group by Time interactions showed there was improvement in dyads' ▪ **Coping** (F= 2.15, p = 0.013)**, self-efficacy** (F = 2.84, p = 0.024), and social QOL (F = 4.28, p = 0.002), and in CG' emotional **QOL** (p<.05). ▪ Effects varied by intervention dose. ▪ Most effects were found at 3 months only. ▪ Risk for distress accounted for very few moderation effects. > Both brief and extensive programs had positive outcomes for patient–caregiver	▪ stratified randomization process ▪ sample size calculation > powered study ▪ only patients' risk status (i.e., high versus low) were used as a stratification variable ▪ high drop out rate ▪ risk for distress measured instead of current distress	1-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure	Results	Comment	Level of Evidence SIGN
			▪ having a family caregiver willing to participate. ▪ CG were eligible if they were age 18 or older and identified by patients as their primary caregiver	care at their cancer center, consisting of the medical treatment of cancer and symptom management. Psychosocial support was provided occasionally, but was not delivered routinely to patients or CG.	behaviors (researcher-developed scale to assess activities that were encouraged in the intervention) ▪ Interpersonal relationship: Dyadic support (modified family support subscale of the Social Support Questionnaire) and Communication (Lewis Mutuality and Sensitivity Scale) ▪ Self-efficacy (Lewis Cancer Self-efficacy Scale) Measures at: ▪ Hopelessness (Beck Hopelessness Scale) ▪ baseline (T1), ▪ 3 months after baseline (T2) ▪ 6 months after baseline (T3)	dyads, but few sustained effects. Patient–caregiver dyads benefit when viewed as the 'unit of care'.		
Yun, J Clin Oncol 2011 [17]	RCT (two arms)	N=444	▪ primary family CG older than age 18 years ▪ patients of potentially eligible CG: were diagnosed with **terminal cancer,** older than age 18 years ▪ Korean speaking/reading	▪ DA (decision aid): professionally developed 20-minute take-home DVD and a companion 43-page workbook entitled *Patients Want to Know the Truth*. The material provided a protocol for informing patients about their terminal status and was aimed at **improving both communication**	**1.O**: ▪ CG decision to discuss a terminal prognosis with the patient **2.O:** ▪ Decision Conflict Scale (DCS): Total score, Support Score, Uncertainty score, Conflict Score, Informed Score, Value Clarity Score	▪ no difference in changes in the **decision to discuss terminal prognosis** between the two groups. ▪ **Conflict** (P=.003), **uncertainty** (P=.019), and **value clarity** (P=.007) subscale scores and total **DCS** score (P=.008) improved from baseline to 1 month significantly	▪ 80% power with min n=444 ▪ Descriptive statistics for estimation ▪ Analysis of covariances ▪ Analysis of baseline → no differences ▪ focus only on a family caregiver's prognostic disclosure to a terminally ill patient with cancer	1-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	• **Outcomes (1.O=primary outcome; 2.O= secondary outcome)** • **Outcome measure**	Results	Comment	Level of Evidence SIGN
				between patients and their families and **satisfaction with the decision-making process**. ▪ Control group received a Korean version of a US National Cancer Institute DVD of similar length on pain management entitled Controlling Cancer Pain: A Video for Patients and Families16 and 29-page educational book on pain control by the Korean Ministry of Health and Welfare entitled *Cancer Pain Can Be Controlled.*	▪ Hospital Anxiety and Depression Scale (HADS), ▪ Caregiver Quality of Life Index–Cancer (CQOL-C) Each completed by the caregiver at 0, 1, 3, and 6 months. ▪ Decision Regret Scale (DRS) at 1, 3, and 6 months (to measure decisional conflict and assessed conflict using personal perceptions of the level of uncertainty (uncertainty subscale), how well-informed patients felt about their choice (informed subscale), the clarity of personal values (values clarity subscale), and the support they had in the decision-making process (support subscale)	more in the DA than in the control arm. ▪ Over 6 months, the significant between-group differences continued for the **conflict** (P=.031), **uncertainty** (P=.014), and **value clarity** (P=.039) subscale scores and **total DCS** score (P .040).	▪ all study participants were Korean ▪ the outcomes we assessed were not typical end-of-life trial outcomes ▪ many CG were lost to follow-up	

3.4. Interventionen zur Trauerbegleitung

3.4.1. Systematic Reviews

Study (Author, journal, year)	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Gauthier, Clin Psychol-Sci Pr 2012 [18]	SR / no MA	8 studies (10 articles) : 2 RCTs 1 CBA (controlled before-after) 2 BA (before-after) 1 RCS (retrospective controlled study) 3 descriptive 1 quali	Bereaved spouses of patients with cancer. Most middle aged and women. (n=1366)	Bereavement interventions (4 studies, 6 articles): 3 BSG=bereave. support group (thereof: 1 RCT, 1 CBA) 1 relaxation training (BA) Prebereavement interventions (specialized EoL care) (4 studies, thereof 1 RCT)	Bereavement outcomes Prebereavement well-being (as factor for adjustement to bereavement)	Specialized EoL care: may impact favourably on bereavement **well-being** (1 RCT: distress sign. lower over 1 year, then no difference) Bereavement interventions (above all: BSG): little to no effect on psychological **well-being** (i.a. 1 RCT, 1 CBA) Studies did not include assessments of spouses' psychological well-being in the prebereavement period > effect of prebereavement well-being on spousal adjustement not measurable.	Body of evidence (1-): 2 RCTs without sample size calculation); 1 study fairly strong evidence; others weak evidence Few studies Because of no sample size calculation, it is difficult to determine whether the finding that bereavement interventions have little to no effect on psychological well-being is because of the effects of the interventions themselves or a result of insufficient power to detect an effect.	1++
Wittouck, Clin Psychol Rev 2011 [19]	SR / MA	14 RCTs: 9 RCTs: prevention of complicated grief (CG) 5 RCTs: treatment of (CG)	Adults who had lost a loved one through violent or non-violent death (n=1655; n=910 in the intervention group): 41 y mean age 70% female 4% of cancer survivors	Specific grief intervention to treat or prevent CG, initiated after the loss and non-psychopharmacological vs. control condition or an a-specific intervention (i.e. used for a variety of disorders)	(C)G: pre- and post- or follow-up-measurements, with a quantitative standardized questionnaire	Prevention: inconsistent support for the effectiveness of interventions. The meta-analysis of the interventions aiming at prevention of CG yielded a pooled standardized mean difference (SMD) of −0.03 (95% CI: −0.18−0.11; Z=0.47; p=0.64) at post-test and of 0.13 (95% CI:	Body of evidence: unclear quality often due to lack of reporting methodology > intermediate to high level of evidence (1+) At the moment CG is not recognized as an official (DSM-) diagnosis. Nevertheless, CG-symptoms have shown to be	1++ Only 2 data-bases searched Grey literature not searched, but MA

Study (Author, journal, year)	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				Number of sessions differed substantially among studies, with one to twelve sessions in preventive interventions and ten to sixteen sessions in treatment interventions.		−0.08−0.33; Z=1.21; p=0.23) at follow-up. With regard to the outcome variable, studies were homogeneous in the post-test analysis (p=0.12) and heterogeneous in the follow-up analysis (p=0.07). Treatment: efficacious in the short- and long-term. Contrary to preventive interventions, the positive effect of treatment interventions increases significantly over time. Positive results reported for interventions employing cognitive-behavioral techniques. The meta-analysis of the interventions aiming at treatment of CG yielded a pooled SMD of −0.53 (95% CI: −1.00−−0.07; Z=2.23; p=0.03) at post-test and of −1.38 (95% CI: −2.08 to −0.68; Z=3.87; p=0.0001) at follow-up. With respect to the outcome variable, studies were heterogeneous (p=0.009) in the post-test analysis and homogeneous (p=0.87) in the follow-up analysis. The difference among the pooled SMD's of preventive and treatment	different from other symptoms and disorders, such as normal grief reactions, mood disorders and anxiety disorders Only 4% cancer survivors. Wide range of death causes (violent and non-violent)	

Study (Author, journal, year)	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						interventions at post-test was significant in favor of treatment interventions (χ^2=3.71; df=1; p=0.05). Heterogeneity among the studies was found (p=0.0006)		

3.4.2. Primärstudie

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
Guldin, Family Practice 2012 [20]	RCT	N= 402 (drop-outs=107)	▪ >17 years ▪ registration with a Danish general practitioners (GP) and informed consent ▪ exclusion criteria: poor language (danish) skills or cognitive impairment	Information pamphlets were sent by mail after completion of the baseline questionnaire to GPs and patients. Pilot-tested pamphlets featured updated information on complicated grief (CG) symptoms, the dual-process model of adaptive coping and risk factors for the development of CG. GPs received information: results of the patient's baseline risk assessment based on the depression level 8 weeks post-loss; how to assess CG and simple	1.O: ▪ bereaved relatives' score on the Beck's Depression Inventory II (BDI-II) and the Inventory of Complicated Grief-Revised (ICG-R) ▪ GP's clinical assessment of the relative's grief reaction ▪ relative's number of contacts with general practice ▪ Clinical grief assessment by the GP	▪ Larger improvements in **ICG-R** scores were found in the intervention group than in the control group. ▪ The sensitivity of the GP's ▪ assessment in the intervention group was 42.9% (95% CI: 21.8–66.0) and the specificity 73.8% (95% CI: 61.5–84.0); the positive predictive value was 34.6% (95% CI: 17.2–55.7) and the negative predictive value 80% (95% CI: 67.7–89.2). In the control group, sensitivity	▪ Computerized Randomization ▪ Sample size calculation > power good, but could have been higher ▪ Risk of systematic bias because of the recruitment procedure ▪ Men were under-represented ▪ No Danish validation of ICG-R available	1-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
				suggestions; how to support the patient to ask about which reactions to grief the patient was experiencing and relate the reactions to the dual-process model of adaptive coping. Patients were encouraged to contact their GP if they showed signs of depression or CG or worried about their bereavement reaction. Questionnaires were mailed to the bereaved participants 2, 6 and 13 month post-loss. If the bereaved participant was still in the study 13 months after the loss, a clinical assessment questionnaire was sent to the GP. Assessment battery consisted of BDI-II and ICG-R and sociodemographic questions.		was 40% (95% CI: 19.1–63.9), specificity 83.7% (95% CI: 70.3–92.7), the positive predictive value 50% (95% CI: 24.7–75.3) and the negative predictive value 77.4% (95% CI: 63.8–87.7). ▪ In the intervention group, patients exhibiting **CG** symptoms were more likely to receive supportive care and to be referred to mental health practitioners, whereas GP's in the control group more often prescribed psychotropic drugs for patients with symptoms of CG. ▪ The GP's ability **to identify CG** at 13 months did not seem to be better in the intervention group than in the control group. ▪ **Contact frequencies** with GPs were generally higher in the control group both before and after the loss. Compared with the control group, IRs were lower among bereaved relatives in the intervention group after the loss [IR = 4.68 (95% CI = 3.90–		

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
						5.62)/5.08 (95% CI = 4.33–5.96); IRR = 0.92 (95% CI = 0.72–1.17); P = 0.50]. ▪ Changes in sum score between the two groups did not reach statistical significance.		

3.5. SPV-Interventionen

3.5.1. Systematic Reviews

3.5.1.1. Systematic Reviews, die verschiedene Strukturen einschließen („SPV allgemein“)

Study (Author, journal, year)	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
García-Pérez, Pall Med 2009 [21]	SR / no MA	6 SR 3 studies (4 publications) on effectiveness (1 RCT, 1 prospective cohort, 1 cross-sectional) 1 cost analysis	Terminally ill patients	Comparison of at least two different **specialised palliative care** programmes and/or their cost-effectiveness	• control of pain and other symptoms, • psychological symptoms, • health-related QoL, • well-being, • functional state, • satisfaction, • place • of death, • number of patients cared, • number of home visits, • number of days at hospital	All systematic reviews drew the conclusion that specialised palliative care is more effective than conventional care. The methodological limitations of the original studies and the heterogeneity of programmes did not allow to draw conclusions about whether a specific model of specialised palliative care is more or less effective or cost-effective than other.	SR of low quality studies RCT and cohort: good quality	1++
Higginson, Cancer J 2010 [22]	SR (meta-synthesis, but no MA)	8 RCTs, 32 observational or quasi-experimental studies	Patients with advanced cancer and their caregivers	**Specialist palliative care interventions** in the home, hospital or designated inpatient settings for patients with cancer	Pain, symptoms, QOL, use of hospital services, anxiety	Home, hospital, and inpatient specialist palliative care significantly improved patient outcomes in the domains of **pain** and **symptom control, anxiety**, and reduced hospital **admissions**. The results suggest that specialist palliative care should be part of care for cancer patients.	We were able to identify and include a wide range of robust literature, focusing more closely on specialist palliative care services and overcoming some of the weaknesses of earlier reviews that included specialist and nonspecialist services. Our review was still weakened by the wide range of outcomes measured.	1++

Study (Author, journal, year)	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Higginson, J Pain Symptom Manag 2003 [23]	SR / MA where possible	44 studies, mostly lower quality (retrospective, observational, cross-sectional studies). Anecdotal and case reports were excluded.	Patients with a progressive life threatening illness and their caregivers	Comparison of palliative care or hospice team (**PCHCT**) and conventional care. (Teams: home care (22), hospital-based (9), combined home/ hospital care (4), inpatient units (3), and integrated teams (6))	Pain and symptom control QOL and quality of death Patient and family satisfaction/ morbidity pre- and post-bereavement	Meta-regression (26 studies) found slight positive effect (0.1) of PCHCTs on **patient outcomes**, independent of team make-up, patient diagnosis, country, or study design. Meta-analysis (19 studies) demonstrated small benefit on patients' **pain** (odds ratio [OR]: 0.38, 95% confidence interval [CI]: 0.23–0.64), other **symptoms** (OR: 0.51, CI: 0.30–0.88), and a non-significant trend towards benefits for **satisfaction**, and therapeutic interventions. Data regarding **home deaths** were equivocal. Metasynthesis (all studies) found wide variations	First study to quantitatively demonstrate benefit from PCHCTs	1++
Thomas, Can J Aging 2006 [24]	SR / no MA	23 RCTs	Patients terminally ill, near death or dying	PC interventions	Effect of PC provided by community teams: QoL, manag. of symptoms Satisfaction with care Duration of care and place of death Effect of specific interventions (ACP, held records, etc…) Costs of PC compared to conventional care	Effect of PC provided by community teams: **QoL** and manag. of **symptoms**: Some improvement in 6 studies, no improvement in 3 studies **Satisfaction** with care: higher satisfaction of patient (1 study) and caregivers (2); no increase in 2 studies **Duration** of care and **place of death**: 4 studies schowed no increase of death at home. 1 RCT	RCTs mostly published in the late 1990s or early 2000s and mostly single-site studies with small sample sizes. 10 included a power computation.	1+ (poor description of inclusion criteria, and interventions)

Study (Author, journal, year)	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						found it, as well as shorter survival		
Zimmermann, JAMA 2008 [25]	SR (no MA due to the heterogeneity of the studies	22 RCTs	Patients receiving specialized PC (the majority were cancer patients) USA, UK, Canada, Norway	**Specialized palliative care** (11 in a home setting, 5 at outpatient clinics, 1 in a nursing home, 1 in a combined inpatient and home setting, 4 assessed patients)	QOL Satisfaction with care Economic cost	The existing evidence does not conclusively support specialised palliative care programmes. **QoL** (13 RCTs): 9 RCTs showed no significant difference between specialist palliative care and control treatments, one favoured the control and three favoured the intervention. **Symptoms** (14 RCTs): 1 RCT demonstrated significant benefits for the palliative care group for any measured single symptom, while three found a benefit of palliative care for reduction of symptom distress but not symptom severity. Patient **satisfaction** with care (10 RCTs): 1 RCT showed a significant difference between groups in favour of the intervention at 30 days but not at 60 days.	Most of the studies were small and likely to be underpowered.	1++

3.5.1.2. Palliativstation und Konsildienst

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Evans, Cochrane Review (Protocole)	SR (MA if possible)	RCTs, CCTs, CBA (controlled before and after studies), ITS (interrupted time series analyses with min 3 data collection points before and 3 after the intervention)	Adults patients with advanced malignant or non-malignant disease and their caregivers, receiving support from SPCT	Effectiveness of SPCTs (specialist palliative care teams) in **in-patients** settings Control: general hospital/oncology services or usual care	1.O: pain control 2.O: symptom control, depression, satisfaction with care, time spent in hospital, caregiver burden/strain/distress, professionals' adherence to guidelines, prescribing rationale			

3.5.1.3. Home-care Programme

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Candy, Int J Nurs Stud 2011 [26]	SR (MA not possible because of heterogeneity)	18 comparative studies (thereof 2 RCT) 4 qualitative studies	Patients and their family in the final phases of a terminal disease	Specialist hospice care provided at **home**, in **nursing home** or in **hospice** Control (quantitative studies): usual generalist healthcare	▪ symptom management ▪ pain assessment and other aspects of patient care ▪ satisfaction with services family carer well-being such as care burden and bereavement/grief ▪ health service use ▪ costs ▪ place of death	Hospice care at home reduced general health care use and increased family and patient satisfaction with care	Mostly limited quality of quantitative evidence Low concordance of identified studies in comparison with other SysRev (e.g. Gomes 2013), what raises the question of the accuracy of the search strategy and selection process	1-

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Gomes, Cochrane Review 2013 [27]	SR and MA	16 RCTs (6 high quality), 4 CCTs, 2 CBA (controlled before and after studies), 1 ITS (interrupted time series analyses)	Adults patients and/or caregivers in receipt of a home palliative care service (n=37.561, 4.042 caregivers; majority cancer)	**Home** specialist palliative care service Control: usual care Reinforced home specialist PC Control: home specialist PC	1.O: death at home 2.O: time spent at home, satisfaction with care, pain/ other symptoms control, physical function, QOL, caregiver outcomes, costs and cost-effectiveness measures	Sign. increase of **death at home** (Meta-analysis for dying at home (7 trials, 3 of high quality): odds ratio (OR) 2.21, 95% CI 1.31 to 3.71; P value = 0.003) Small but sign. reduction of **symptom burden** for patients No effect on caregiver grief **Cost-effectiveness**: inconclusive results		1++
Hall, Cochrane Review 2011 [28]	SR (MA not possible because of heterogeneity)	2 RCTs and 1 controlled before-and-after study included	Residents of care homes for older people (care home = institutional settings where care is provided 24 hours a day, 7 days a week)	Palliative care service delivery interventions for **residents of care homes for older people** (referrals to external palliative care services and/or palliative care training for care home staff)	We extracted all measures reported as outcomes for individual residents, including process of care (e.g. completion of advance care plans and place of death)	One study reported higher **satisfaction** with care and the other found lower observed **discomfort** in residents with end-stage dementia (mean [SD] 218.10 [142.10] and 368.88 [168.30] respectively, t = 3.80, difference in means = 150.78, 95% CI for difference = 77.38 to 230.18. Two studies reported group differences on some **process measures**. Both reported higher referral to hospice services in their intervention group (,enrolment to hospice within 30 days of the intervention (21/107 [20%] compared with 1/98 [1%]) and (24/346 [6.8%] compared with	Few studies identified, and all were in the USA	1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						2/113 [2%]), one found fewer hospital admissions and days in hospital in the intervention group , (0.28 [range 0-4] compared with 0.49 [range 0.4] and 1.2 [range 0-18] compared with 3.0 [range 0-29] respectively) the other found an increase in do-not-resuscitate orders and documented advance care plan discussions . (225/346 [65%] compared with 50/113 [44%], chi-square = 15.32, absolute risk reduction = 20.78%, 95% CI = 10.34% to 31.23%, NNT = 5, 95% CI for NNT = 3.2 to 9.7)		
Shepperd, Cochrane Review 2011 [29]	SR and MA Aim: To determine if providing home-based end of life care reduces the likelihood of dying in hospital and what effect this has on patients' symptoms, QoL, health service costs and	4 RCT (thereof 1 cluster-RCT)	Adults at the end of life and requiring terminal care	End of life care at home Control: inpatient hospital or hospice care	▪ Place of death ▪ Patients' preferred place of death ▪ Control of symptoms (pain, breathlessness, nausea and vomiting, constipation, terminal agitation) ▪ Delay in care (medical, nursing or domiciliary care) from ▪ point of referral to intervention (end of life home care/hospice at home or inpatient care) ▪ Family or care giver stress ▪ Family or care giver	**Place of death**: patients receiving home-care sign. more likely to die at home (RR 1.33, 95% CI 1.14 to 1.55, P=0.0002 – 2 trials, n=652) No sign. differences for **functional status**, **psychological well-being**, **cognitive status** **Hospital admission**: high variation between studies, no conclusion possible Some evidence of increased **satisfaction** with	Moderate quality of included studies, due to lack of power by high mortality, unblinded trials and difficulty in measuring symptoms in a way that permits comparability.	1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	caregivers compared with inpatient hospital or hospice care.				unable to continue caring ▪ Patient anxiety ▪ Family/care giver anxiety ▪ Unplanned/precipitous admission or discharge	home-based end of life care Little evidence of the impact of home-care on **caregivers**		

3.5.1.4. Tageskliniken

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Davies, Support Care Cancer 2005 [30]	SR /no MA	12 studies in 15 publications (any design, only English) : 1 CBA (prospective) 6 observational (no comparision) 5 qualitative	Adults receiving care from specialist palliative day-care services	Specialist day-care services with reported information on service structure, care processes or outcomes	Service structure: • Funding, organization and management of services • Staff skill mix and interventions offered to patients and relatives Care processes: • Referral, allocation of places to patients and discharge • Uptake of interventions by patients and relatives Patient outcomes: • symptom control, • health related quality of life • social and psychological support	**Service structure**: Most services are nurse-led, but varied in the facilities, staff mix, care models, activities and places they offered. **Process**: Patients attending seemed a selected group of those already receiving palliative care who were mostly white, aged over 60 years and retired, with needs for emotional and social support and pain control. **Patient outcomes**: insufficient studies to provide conclusive evidence of improved symptom	Low grade of evidence of most studies	2++ (no RCTs, CCTs)

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
					• patient or relative satisfaction with care	control or health related quality of life, but all qualitative studies found evidence for high satisfaction in the social, psychological and spiritual domain		
Stevens, Pall Med 2011 [31]	SR /no MA	35 studies in 36 publications (any design, only English): 4 reviews 2 controlled cohort studies Others observational not controlled or qualitative	Population attending PDS (no more description)	PDS (palliative care day services)	Outcomes of PDS utilizing the perceptions of attendees/other stakeholders Outcomes of PDS using validated measures	some quantitative evidence showing that PDS had an impact on attendees' **quality of life** or wellbeing	• less than half of the studies could be fully analysed for quality • Fewer studies utilized validated outcome measures to determine the effect of PDS on attendees' wellbeing • Small sample sizes combined with high attrition rates influenced the significance of some the results.	2- (unclear question and results)

3.5.2. Primärstudien

Im Folgenden werden Interventionsstudien dargestellt, die aus Systematic Reviews zu SPV identifiziert wurden (zur Methodik, siehe Leitlinienreport). Ergänzend zu den eingeschlossenen Primärstudien sind Begleitstudien (weitere Publikation derselben Studie) in hell-grau dargestellt. Obwohl diese Begleitstudien die Einschlusskriterien nicht erfüllen, wurden sie extrahiert mit dem Ziel, ergänzende Informationen zu den Interventionsstudien darzustellen.

Study characteristics								Patients' characteristics at baseline						
Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Coun-try	Level of Evidence =LoE (SIGN) / Justification	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Perform-ance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)
ZEITPUNKT INTEGRATION PALLIATIVVERSORGUNG/PATIENTENBEDÜRFNISSE														
Bakitas, J Clin Oncol, 2015 [32]	Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial	RCT	to investigate the effect of early versus delayed PC on quality of Life (QOL), symptom impact, mood, 1-year survival, and ressource use.	Age ≥ 18 years, advanced-stage solid tumor or hematologic malignancy, oncologist-determined prognosis of 6 to 24 months, and able to complete the baseline questionnaires	National Cancer Institute cancer center, a Veterans Affairs medical Center, and community outreach clinics	USA	1+	n=207 (104 early group (intervention), 103 delayed group (control))/ n=109 drop out through death	intervention/control: male n=56/53	64 years (Interv.: 64.03, 10.28 ; control: 64.6, 9.59)	100%	1. (intervention/control): Lung (n=46/42), GI tract (n=26/24), Breast (n=10/13), Other solid tumor (n=10/10), Genitourinary tract (n=7/9), Hematologic malignancy (n=5/5) 2. disease status (interv./control): new diagnosis (n=48/46), recurrence (n=29/20), progression (n=27/36), do not know (n=0/1), brain metastasis (n=17/18)	Karnofsky Performance Status: early group: 10.82; delayed goup: 9.74	
Maltoni, Eur J Ca	Systematic versus on-demand early palliative care: results from a multicentre, randomised clincal trial	RCT, multicentre	to define the optimal way for activating EPC.	Age ≥ 18 years, diagnosis of inoperable locally advanced and/or metastatic pancreatic cancer for a maximum of 8 weeks, ECOG PS: 0-2, life expancy >2 months, candidate for antitumour treatment (chemotherapy or target therapy)	multicentre	Italy (21 centres)	1-	n=186 (interv.: n=97, control: n=89)/ n=57 droup out (to ill or died)	male (interv./control): 59/47; female (interv./control): 37/42	Median age (interv./control): 67/66 years	100%	1. Locally advanced and/or metastatic pancreatic cancer for a maximum of 8 weeks, life expancy >2 months 2. unresectable phase 3. candidate for antitumor treatment (Chemotherapy- or target therapy)	[illegible]	[illegible]
Rugno, Gynecologic Oncology, 2014 [34]	Early integration of palliative care facilitates the discontinuation of anticancer treatment in women with advanced breast or gynecologic cancers	prospective study	to evaluate some health indicators in women with advanced breast or gynecological cancers (ABGCs) after discontinuation of active cancer treatment in function of the model of care received.	Woman, ≥ 18 years, advanced breast or gynecologic (endometrium, ovary, uterine cervix, vulva or vagina) cancers, not receive anticancer treatment from the moment on and would insteast receive only follow-up care with the PC (palliative care) team	Barretos Cancer Hospital (BCH)	Brazil	1-	n=87	Female n=87, Interv./control: n=37/50	Median Age: 56 years (IQR: 19.0), interv./control: 53 (19.5)/45.75 (10.5)	100%	1. Primary tumor site (interv./control): Breast (n=25/25), Cervix (n=9/10), Ovarian (n=3/11), Vulva (n=0/2), Endometrium (n=0/2); 2. Last treatment (interv./control): palliative chemotherapy (n=29/39), palliative hormone therapy (n=3/4), palliative radiotherapy (n=1/1), no palliative treatment (n=4/6)	[illegible]	[illegible]
Temel, J Clin Oncol, 2017 [35]	Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial	nonblinded RCT	to evaluate the impact of early integrated palliative care (PC) in patients with newly diagnosed lung and GI cancer to compare with usual oncology care.	≥18 years, 8 weeks of diagnosis of incurable lung (NSCLC, smale-cell, or mesothelioma) or noncolorectal GI (pancreatic, esophageal, gastric, or hepatobiliary) cancer, ECOG PS: 0 to 2	Massachussets General Hospital (MGH)	USA	1+	n=250 (175 intervention, 175 control)	intervention: 9/91, control: 2/98	mean age 64,84 years intervention: 65.64; control: 64.03	100%	intervention/control: Lung (54,3%/54,9%): Non-small-cell (n=80/74), Small-cell (n=13/17), Neuroendocrine (n=1/3), Mesothelioma (n=1/2), EGFR mutation (n=19/10), ALK translocation (n=4/4); GI (45,7%/45,1%): Pancreatic (n=44/43), Esophageal/GE junction (n=15/17), Gastric (n=3/4), Hepatobiliary (n=18/15)	[illegible]	[illegible]
SEKTORENÜBERGREIFENDE SPV-STUDIEN (Hiermit werden Studien verstanden, die SPV-Interventionen untersuchen, deren Setting strukturenübergreifend ist. Das sind Interventionen, die mindestens zwei SPV-[illegible])														
Dunt, Palliative Medicine, 1989 [36]	The cost-effectiveness of the citymission Hospice Porgramme Melbourne	quasiexperimental	to examine costeffectiveness, according to costs and clinical benefit, of hospice care in comparison to standard care.	known histologically confirmed diagnosis of cancer and terminal phase (less than six months)	single center	Australia	2-	n = 120 (65 intervention, 55 control) creating 271 patient and 195 caregiver interviews	intervention: 33/32, control: 26/29	less than 60 interv. 21 and control 16 ; age not otherwise specified	100%	intervention: 1. Lung (n=14), Breast (n=8), colorectum (n=11), Other (n=32); control lung (n=7), Breast (n=9), colorectum (n=6), others (n=33)	[illegible]	[illegible]
Kane, The Lancet, 1984 (part 1) [37]	A randomised controlled trial of hospice care	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-92	100%	1. Cancer mentionend primary sites: intev.: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. temrinal phase according to clinical judgement	not specified	not specified
Kane, JAMA 1985 (part 2) [38]	Hospice Effectiveness in controlling pain	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care on pain	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-93	100%	2. Cancer mentionend primary sites: intev.: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. terminal phase according to clinical judgement	not specified	not specified

Study characteristics								Patients' characteristics at baseline								Informal caregivers' (CG) characteristics at baseline				
Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others	Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others
Kane, J Chron Dis, 1986 [39]	The role of hospice in reducing the impact of bereavement	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-92	100%	1. Cancer mentionend primary sites: intev.: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. temrinal phase according to clinical judgement	not specified	not specified	none	n = 152 (83 inv = hospice, 69 controls = regular care)	72 female in intervention / 56 in control	58 (SD 12) years in interv, 56 (14) in control	anxiety, depression bereavement	20 chronic health problems (list)
Wales, J, Medical Care, 1983 [40]	UCLA Hospive Evaluation Study	RCT	to establish robust methodology		single center	USA	1-													
Zimmermann, Lancet, 2014 [41]	Early palliative care for patients with advanced cancer:a cluster-randomised controlled trial	Cluster-Randomised Controlled Trial	To evaluate if, compared with standard cancer care, early intervention (clinical prognosis of 6–24 months) by a palliative care team would be associated with improved patient quality of life, symptom control, and satisfaction with care, and less difficulty with clinician–patient interactions.	Age > 18 years, stage IV cancer breast or prostate cancer refractory to hormonal therapy: patients with stage III cancer and poor clinical prognosis were included at the discretion of the oncologist); an estimated survival of 6–24 months (assessed by their main oncologist); and ECOG-performance status of 0, 1, or 2 (assessed by their main oncologist).	24 clinics randomized, stratified by clinic size and tumour site (4 lung, 8 gastrointestinal, 4 genitourinary, 6 breast, 2 gyn.). 8 oncologists had clinics in 2 tumour sites (randomised to 2 clusters); 5 oncologists had their 2 clinics randomised within same trial group, 3 to diff. groups.	Canada	1++	24 Clusters (clinics) randomised: 12 clinics allocated to control group and 12 clinics allocated to intervention group n=233(control) NO=24 NO=17 n=228 (intervention) NO=12; NO=15	Intervention: 136/92, control: 125/108	Intervention: 61,2 (SD 12,0) Control: 60,2 (SD 11,3)	100%	Cancer: 1. stage IV 2. stage III cancer and poor clinical prognosis were included at the discretion of the oncologist 3. estimated survival 6-24 month	ECOG= 0, 1 or 2 (assessed by the patients main oncologist) Intervention ECOG=0 61 (26,8%) ECOG=1 149 (65,4%) ECOG=2 18 (7,9%) Control: ECOG=0 76 (32,6%) ECOG=1 143 (61,4%) ECOG= 2 14 (6,0%)	Intervention: FACIT-Sp (n=443) 101 (SD 20,3) QUAL-E (n=436) 73 (SD 11,1) ESAS (n=461) 28 (15,5) FAMCARE-P16 (n=449) 64 (9,7) CARES-MIS (n=448) 4·7 (5,6) Control: FACIT-Sp (n=443) 105 (18,8) QUAL-E (n=436) 74 (11,5) ESAS (n=461) 23 (15,7) FAMCARE-P16 (n=449) 68 (9,7) CARES-MIS (n=448) 3·9 (5,4)						As an exploratory substudy, we also collected data from caregivers; these data will be reported separately
PALLIATIVSTATION																				
Greer, J Chron Dis 1986 [42]	An alternative in terminal care: Results of the national hospice study	quasi experimental study	1. What is the difference between hospice and conventional care? 2. What is the differential impact of hospice and conventional care on the quality of life of patients and their families? 3. What is the impact of hospice on the health care costs incurred by terminal cancer patients?	cancer patients served in HC or HB hospices or in CC settings; cancer; remote metastasis (except for lung, brain, and pancreatic cancer); presence of a primary care person (PCP), generally a family member in the household (this excluded all nursing home patients); age 21 or older; CC patients only: Karnofsky Performance Status (KPS) of 50 or less	multicentric (40 hospices and 14 conventional oncological care settings; 26 hospices received special Medicare demonstration waivers allowing payment for normally non-covered services))	USA	2+ (some risk of bias because only patients with cancer and with a primary care person were inlcuded, i.a. patients living alone excluded)	n=1754 (833 HC, 624 HB, 297 CC) / drop out: 4.4% with no differences across settings / n.d.*	% female (HC vs. HB vs. CC): 51.3 vs. 51.8 vs. 52.7	means n.d.; HC vs. HB vs. CC in %: 21-54 years 10.3 vs. 9.3 vs. 26.6, 55-64y: 21.5 vs. 14.3 vs. 30.6, 65-74y: 42.4 vs. 44.8 vs 28.3, ≥75y: 25.8 vs. 31.6 vs. 14.5	100%	1. lung, breast, prostate, colorectal cancer; 2. metastatic at diagnosis: HC 49.6 vs. HB 50.4 vs. CC 47.6%; 3. "terminally ill"/"terminal cancer"	HC vs. HB vs. CC: least functional (10-30): 45.8 vs. 49.8 vs. 67.7 % most functional (40 and over): 54.2 vs. 50.2 vs. 32.3%	Patient awareness at initial interview comparable (full mental capacity HC vs. HB vs. CC): 48.9 vs. 49.9 vs. 54.3%;	non-white (% HC vs. HB vs. CC): 1.5 vs. 4.7 vs. 8.1; *Only patients who died during the study period were included in the final analytic samples since outcomes were assessed in relation to proximity to death;	same as patients (study describes sample of patients with a primary caregiver (=PCP)	n.d.			PCP was the patient's spouse or child in 4 out of 5 cases; In HC hospices the PCPs were significantly less likely to be employed at the time of hospice entry. At the onset of the disease, a higher percentage (46%) of all PCPs were employed; those with patients entering hospice were only slightly less likely to be employed at this juncture (42 vs 48% and 51% for HB and CC, respectively).
Greer, J Chron Dis 1983 [43]	National hospice study analysis plan	Analysis Plan	(1) What is the differential impact of hospice on the QoL of terminal patients and their families, as compared to "conventional" care? (2) What are the differential costs of caring for comparable terminally ill patients? (3) What are the differences in the services? (4) What is the likely impact of Medicare reimbursement on the organizational structure? (5) What are the likely national cost implications of reimbursed hospice care?"			USA														
Morris JN, J Chron Dis, 1986b [44]	The effect of treatment setting and patient characteristics on pain in terminal cancer patients: a report from the National Hospice Study	subanalysis	Relationship between measures of pain. Comparison of prevalence and severity of pain among TCPs served in different settings. Description of shifts in the prevalence and severity of pain as patients approach death	idem	idem	idem		idem	idem	idem	idem	idem plus additional information: **HC vs. HB vs. CC:** Primary breast cancer: 13.4 vs. 11.1 vs. 3.0 %, Primary lung cancer: 25.7 vs. 22.6 vs. 25.3%, brain metastases: 18.6 vs. 14.8 vs. 18.5%, bone metastases: 35.5 vs. 34.1 vs. 36.0%	idem	at study entry, 12.1% of patients reported "horrible" or "excruciating" pain (PCP reported "frequent" or "persistent" pain in 82% of the cases); 31% of patients reported that pain was "not present" (8.8% of patients were "free of pain" according to the PCP)		idem	n.a.	n.a.	n.a.	
Morris JN, J Chron Dis, 1986a [45]	Last days: a study of the quality of life of terminally ill cancer patients	secondary analysis	Behavior of a number of Quality of Life measures gathered from two samples of terminal cancer patients over the last weeks of their lives are reported.	idem plus additional study (only results or NHS study participants reported in the following)	idem	USA and Canada (only results or NHS study participants reported in the following)														
Birnbaum HG, AJPH 1984 [46]	What Does Hospice Cost?	subanalysis (cost analyis)	To address the question: What is the cost of hospice? (…) a second question: Does hospice care provided to Medicare beneficiaries cost less than conventional methods of caring for terminally ill cancer patients?	idem	idem	idem														

Author, Journal, Year	Needs assessment: Who assesses	When	How (tool)	Needs complexity: Categories	Process of categorisation (needs > complexity)	Intervention characteristics (structure and process quality criteria): Overall description – Intervention	Overall description – Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/housing)	Funding – Who (source)	Funding – How much	Organisation / Management related to structures – Who	Organisation / Management – How	Referral criteria / allocation of place	Description of intervention – Schedule/Frequency	Description of intervention – Content (clinical/non-clinical)	Description of bereavement intervention – Schedule/Frequency	Description of bereavement intervention – Content	Description of control intervention	Coodination of intervention – Who	Coodination of intervention – How	Discharge criteria	Integration of oncological and palliative structures – Who	Integration – How	Others	Outcomes: Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs	Results for each outcome	Results for outcomes related to informal CG	Comments
Kane, J Chron Dis, 1986 [39]	not specified	additional interviews 6weeks, 6, 12 an 18 months after death	anxiety measure: Rand Health Insurance Study; depression: CES-D Scale, sequelae of bereavement: participation in social activities and social contacts, smoking habits and alcohol consumption, use of medication, bed disability days, work loss days, restricted activity days, hospitilisation, physician visits, self assessment of health scale	not specified	not specified	hospice care	conventional care	inpatients, hospice home care	not specified	11 beds	not specified	VA Medical Center	not specified	not specified	not specified	clinical judgement of terminal prognosis	hospice care due to hospice program assessment and its own treatment plan	not specified	none	none	conventional care	hospice team	by routine practice	none	none	none	none	differences in anxiety scale, CES-D Depression Scale, health scale score and items of the sequelae bereavement list	no	no sign effects between the two groups	no sign effects	intervention not clearly defined; exactly the same study gender bias, methodology remains vague
Wales, J, Medical Care, 1983 [40]																																[illegible]
Zimmermann, Lancet, 2014 [41]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
PALLIATIVSTATION																																
Greer, J Chron Dis 1986 [42]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Greer, J Chron Dis 1983 [43]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Morris JN, J Chron Dis, 1986b [44]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Morris JN, J Chron Dis, 1986a [45]	idem	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Birnbaum HG, AJPH 1984 [46]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Study characteristics: Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification	Patients' characteristics at baseline: Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others	Informal caregivers' (CG) characteristics at baseline: Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others	Needs assessment: Who assesses	When	How (tool)	Needs complexity: Categories	Process of categorisation (needs > complexity)	Intervention characteristics (structure and process quality criteria): Overall description – Intervention	Overall description – Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/housing)	Funding – Who (source)	Funding – How much	Organisation / Management related to structures – Who	Organisation / Management related to structures – How	Referral criteria / allocation of place	Description of intervention – Schedule/Frequency	Content (clinical/non-clinical)	Description of bereavement intervention – Schedule/Frequency	Content	Description of control intervention	Coodination of intervention – Who	Coodination of intervention – How	Discharge criteria	Integration of oncological and palliative structures – Who	Integration of oncological and palliative structures – How	Others	Outcomes: Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs	Results for each outcome	Results for outcomes related to informal CG	Comments
Mor 1990 [47]	A comparison of hospice vs conventional care in the terminally ill cancer patient	review/narrative report	n.d.	idem	idem	idem																																As much a philisophy of care as an istitutional entity, hospices stresses: palliative rather than curative care; the patient and family as the unit of care; the administration of care by an interdisciplinary team whose members are geared toward meeting the unique needs of terminally ill patients and their families												Hospice patients are less likely to receive aggressive interventions in the two weeks prior to death (p<0.001 for surgery, chemo- or hormone therapy, radiation therapy; n.s. for thoracentesis)		#WERT!
Powers JS, Public Health Reports 1988 [48]	Terminal Care Preferences: Hospice Placement and Severity of Disease	secondary analysis	National Hospice Study data for 1981-82 were used to predict the location of care for terminal cancer patients.	idem	idem	idem		idem	idem	64.1 years; HB=65.4 HC=64.0 vs. CC= 61.7	idem	idem	idem					total=57.5 (SD n.d.); HB=57.9 HC=48.5 vs. CC=53.9																																location of care was best explained by the patient's functional capacity; location of care was found to be poorly explained by extent of organ involvement or specific symptoms; only some examples extracted here: • Patients receiving conventional care were more disabled than other patients according to the modified [illegible]	PCP of patients under hospice home care experienced more stress but reacted no differently when compared with PCP at other care sites	Home hospice care is not a panacea for treatment of the elderly with chronic or terminal disease. We need both good home services and good institutional care alternatives for humane and effective care. Deciding how to use these alternative [illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				[illegible]																																												[illegible]
PALLIATIVSTATION (Fortsetzung)																																																				
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]		[illegible]	[illegible]																																					[illegible]		[illegible]		
[illegible]	[illegible]	[illegible]	[illegible] … the impact of hospice care.	[illegible] … bereavement interview between 90 and 120 days after the death of the patient.	[illegible]									[illegible]							[illegible]	[illegible] … from PCP rated QOD data for last three days of life of patient	[illegible] … The weights were derived from the interviews of all patients when they were admitted into the study. A single open-ended question, "What would you like your last 3 days of life to be like?"; more: see outcomes																									[illegible] … • Participatein normala ctivities like any other day • Able to stay at home as long as he/she wanted • Feel at peace with God • Die in sleep, without awareness • Stay mentally alert etc. • Complete tasks he/she wished to do • Able to accept death • Know ahead of time that death is imminent • Live until a key event occurred	[illegible]	[illegible]		[illegible]
Kane, The Lancet, 1984 (part 1) [37]	A randomised controlled trial of hospice care	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-92	100%	1. Cancer mentionend primary sites: intev.: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. temrinal phase according to clinical judgement	not specified	not specified	none	73% of partiens had FCG; 95% gave consent; 6% withdrew consent	not specified	not specified	not specified	not specified	not specified	regular interviews (7 cohorts = 18 weeks) Methodology outlined separetly in Wales J, Kane RL, Robbins S, Bernstein L, Krasnow R. The UCLA hospice evaluation study: Methodology and instrumentation. Med Care 1983; 27: 734-44.	tools: Pain scores according to Melzak; Symptom Scale adapted from the California Pain Assessment Profile; depression scale adapted from the National Institute of Mental Health's Center for Epidemiologic Studies' scale; anxiety derived from a section of the General Well-Being Measure; satisfaction measures included the interpersonal care scale adapted from the Ware scale, physical environment scale and involvement-in-care questions adapted from the National Cancer Institute's Hospice Study; functional status assessed by the Katz ADLS	not specified	not specified	hospice care	conventional care	inpatients, hospice home care	2 physicians, 19 nurses, a social worker, a chaplain, and about 30 volunteers for 11 beds; a homecare programme serving about 25 patients at any given time; a consultation service for patients awaiting admission	11 beds, about 25 home care patients	not specified	VA Medical Center	not specified	not specified	not specified	clinical judgement of terminal prognosis	hospice care due to hospice program assessment and its own treatment plan	not specified	none	none	conventional care	hospice team	by routine practice	none	none	none	none	differences in pain, symptoms, activities of daily living and affects satisfaction (patients) satisfaction (carers) utilisation of services costs	yes	differences in….: no sign. effects Satisfaction (pts): sign better (for interpersonal care in 5 cohorts (3): p<0,02; (4):p< 0,001, (5):p< 0,003; (6): p< 0,002; (7): p<0,004 for involvement in care (4):p<0,02; (5):p<0,05; (6):p< 0,003; (7):p<0,003 utiltisation of services: no sign difference **Costs:** no sign difference	satisfaction equally improved	presumably bias due to gender, intervention not clearly defined
Kane, JAMA 1985 (part 2) [38]	Hospice Effectiveness in controlling pain	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care on pain	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-93	100%	2. Cancer mentionend primary sites: intev.: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. temrinal phase according to clinical judgement	not specified	not specified	none	none	not specified	not specified	not specified	not specified	not specified	referal to methodology being published elswhere:Wales J, Kane RL, Robbins S, Bernstein L, Krasnow R. The UCLA hospice evaluation study: Methodology and instrumentation. Med Care 1983; 27: 734-44.	tools Pain scores according to Melzak	not specified	not specified	hospice care	conventional care	inpatients, hospice home care	not specified	11 beds, 30 home care patients	not specified	VA Medical Center	not specified	not specified	not specified	clinical judgement of terminal prognosis	hospice care due to hospice program assessment and its own treatment plan	not specified	none	none	conventional care	hospice team	by routine practice	none	none	none	none	differences in pain scores, correlation with other symptoms use of analgeics	no	no sign effects	none	intervention not clearly defined; exactly the same study and the same results reportes as in Lancet 1984
Kane, J Chron Dis, 1986 [39]	The role of hospice in reducing the impact of bereavement	RCT, parallel, nonblinded	to compare the effect of hospice care with conventional care	diagnosis of cancer and clinical judgement of terminal progonsis (2 weeks - 6 months)	single center	USA	1-	n=263 (eligibile) n= 237 participants n= 10 drop outs after enrolment	231/6	interv. (mean) 63,3 (no SD), control (mean) 64,0 (no SD), range: 34-92	100%	1. Cancer mentionend primary sites: lung (36,5), prostate (11,0), ENT (9,5), brain (7,3), others (35,6); control : lung (35,5), prostate (10,0), ENT (10,9), brain (7,3), others (36,4) 2. not specified 3. temrinal phase according to clinical judgement	not specified	not specified	none	n = 152 (83 inv = hospice, 69 controls = regular care)	72 female in intervention / 56 in control	58 (SD 12) years in interv, 56 (14) in control	anxiety, depression bereavement	20 chronic health problems (list)	not specified	additional interviews 6weeks, 6, 12 an 18 months after death	anxiety measure: Rand Health Insurance Study; depression: CES-D Scale, sequelae of bereavement: participation in social activities and social contacts, smoking habits and alcohol consumption, use of medication, bed disability days, work loss days, restricted activity days, hospitilisation, physician visits, self assessment of health scale	not specified	not specified	hospice care	conventional care	inpatients, hospice home care	not specified	11 beds	not specified	VA Medical Center	not specified	not specified	not specified	clinical judgement of terminal prognosis	hospice care due to hospice program assessment and its own treatment plan	not specified	none	none	conventional care	hospice team	by routine practice	none	none	none	none	differences in anxiety scale, CES-D Depression Scale, health scale score and items of the sequelae bereavement list	no	no sign effects between the two groups	no sign effects	intervention not clearly defined; exactly the same study gender bias, methodology remains vague
Wales, J, Medical Care, 1983 [40]	UCLA Hospive Evaluation Study	RCT	to establih robust methodology		single center	USA	1-																																													[illegible]

Study characteristics								Patients' characteristics at baseline								Informal caregivers' (CG) characteristics at baseline				
Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others	Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others
SPEZIALISIERTE AMBULANTE PALLIATIVVERSORGUNG																				
Ahlner-Elmqvist, PallMed 2004 [52]	Place of death: hospital-based advanced home care versus conventional care	CCT, non randomized	to evaluate HRQL of patients, with cancer in palliative stage, receiving either hospital-based advanced home care (AHC)	above 18 years of age, had a histological verified malignant disease, were informed about their diagnoses and were in a palliative care situation (life expectancy 2-12months)	single center	Sweden	1- (CCT)	n= 722 (targets), recruited 297, intervention 119, control 178	56/61 (interv.) and 88/75 (control)	Interv (mean): 67 Control: 68yrs, SD not mentioned, range intervention (38-88), control (28-85)	100%	primary cancer (interventional group/control): lung (16/38) (p=0.007)!, prostate (10/5), gastrointestinal (43/73), breast (9/18), urogenitalia (16/11), others (23/18)	KPS > 70 interventional group 55%, control group 71% (p=0,007)	nor assessed		not assessed	not assessed	not assessed	not assesed	
Ahlner-Elmqvist, J Pain Sympt Manage, 2008 [53]	Characteristics and Quality of Life of Patients Who Choose Home Care at the End of Life	prospective, non randomized	to evaluate HRQL, sociodemographic data and medical data of patients, with cancer in palliative stage, receiving either hospital-based advanced home care (AHC)	above 18 years of age, had a histological verified malignant disease, were informed about their diagnoses and were in a palliative care situation (life expectancy 2-12months)	single center	Sweden		n= 722 (targets), recruited 297, intervention 119, control 179	56/61 (interv.) and 88/75 (control)	Interv (mean): 67 Control: 68yrs, SD not mentioned, range intervention (38-88), control (28-85)	100%	primary cancer (interventional group/control): lung (16/38) (p=0.007)!, prostate (10/5), gastrointestinal (43/73), breast (9/18), urogenitalia (16/11), others (23/18)	KPS > 70 interventional group 55%, control group 71% (p=0,007)	measured in both groups		not assessed	not assessed	not assessed	not assesed	
Ringdal, Pall Med, 2004 [54]	Health-related quality of life (HRQOL) in family members of cancer victims: results from a longitudinal intervention study in Norway and Sweden	longitudinal intervention study (In the Norwegian site a cluster randomized experimental design was adopted, whereas a nonrandomized controlled design was applied in the Swedish site.)	to compare the health-related quality of life (HRQOL) of family members of patients who participated in a program of palliative care with those in conventional care (control family members); based on two hypothesis:H1: The respondents' HRQOL scale scores will decrease from the inclusion in the study and reach a low point a few months after the death of the cancer victim, and thereafter show an increase. H2: The trajectories of the HRQOL scale scores for the intervention and the control groups will show an increasing difference over time in quality of life in favor of the intervention group.	incurable malignant disease,over 18 years, predicted survival time of two to nine months.	two centres	Norway and Sweden		n= 183/130 (interv/control) in Norway und n= 102/102 in Sweden (n= not patients but enrolled caregiver!)			100%	Almost half of the patients suffered from gastrointestinal cancer. Other common cancer diagnoses in the sample were lung, breast/female genitalia, prostate and urological cancer				183/130 N and 102/102 in Sweden at baseline	128/55 in interv. N, 87/41control N and 72/30 interv. S and 59/43 control in S	median age was 67/69 years	by SF36	
Axelsson, Palliat Med, 1998 [55]	Evaluation of a hospital-based palliative support service with particular regard to financiel outcome measures	CCT	financial assessment of a hospital-based palliative support service	incurable cancer patients, treated at the Department of General Surgery (DGS)	single canter	Swedish	1-	41 / 2 drop-out(1 because death one day after including in the study, 1 because of lack of care-giver, no wish to live at home)	48/34	median 72 (58-87)	100%	5 criteria: 1. symptomatic, incurable cancer disease; 2. a cancer disease within the realm of general surgery; 3. living within 40 km of the Country hospital; 4. wish to stay at home; 5. having a primary care giver	60 (10-90)		median survival time from diagnosis to death 23 month					
Bakitas, JAMA, 2009 [56]	Effects of a Palliative Care Intervention on Clinical Outcomes in Patients With Advanced Cancer The Project ENABLE II Randomized Controlled Trial	RCT	To determine the effect of a nursing-led intervention on quality of life, symptom intensity, mood, and resource use in patients with advanced cancer	prognosis of approximately 1 year and within 8 to 12 weeks of a new diagnosis of incurable cancer of gastrointestinal tract (unresectable stage III or IV), lung (stage IIIB or IV non–small cell or extensive small cell), genitourinary tract (stage IV), or breast (stage IV and visceral crisis, lung or liver metastasis, estrogen receptor negative [ER−], human epidermal growth factor receptor 2 positive [Her 2 neu]) cancer. Patients were asked to select a caregiver to participate in the study.	single center, rural area	USA	1++	n=322 (randmoized), screened 1222	Male sex intervention 96 (59.6) control 91 (56.5)	Age, mean (SD), y intervention 64.7 (10.8) control 65.4 (11.6)	100%	Primary disease site (intervention / Control) Gastrointestinal tract 66/67 Lung 59/58 Genitourinary tract 19/19 Breast 17/16 Anticancer treatment at enrollment Chemotherapy 137/134 Radiation therapy 20/21	Karnofsky Performance Status, mean (SD) intervention 77.9 (11.1) control 76.6 (13.1)	ESAS	not assessed	not assessed	not assessed	not assessed	not assesed	n
Bakitas, Palliat Support Care, 2009 [57]	The project ENABLE II randomized controlled trial to improve palliative care for rural patients wiht advanced cancer: baseline findings, methodological challenges and solutions			prognosis of approximately 1 year and within 8 to 12 weeks of a new diagnosis of incurable cancer of gastrointestinal tract (unresectable stage III or IV), lung (stage IIIB or IV non–small cell or extensive small cell), genitourinary tract (stage IV), or breast (stage IV and visceral crisis, lung or liver metastasis, estrogen receptor negative [ER−], human epidermal growth factor receptor 2 positive [Her 2 neu]) cancer. Patients were asked to select a caregiver to participate in the study.	single center, rural area	USA	2	n=322 (randmoized), screened 1222	Male sex intervention 96 (59.6) control 91 (56.5)	Age, mean (SD), y intervention 64.7 (10.8) control 65.4 (11.6)	200%	Primary disease site (intervention / Control) Gastrointestinal tract 66/67 Lung 59/58 Genitourinary tract 19/19 Breast 17/16 Anticancer treatment at enrollment Chemotherapy 137/134 Radiation therapy 20/22	Karnofsky Performance Status, mean (SD) intervention 77.9 (11.1) control 76.6 (13.1)	ESAS	not assessed					
O'Hara , Palliat Support Care 2010 [58]	Impact on caregiver burden of a patient-focused palliative care intervention for patients with advanced cancer	RCT	to determine the effect of a nursing-led intervention on quality of life and burden of caregivers	prognosis of approximately 1 year and within 8 to 12 weeks of a new diagnosis of incurable cancer of gastrointestinal tract (unresectable stage III or IV), lung (stage IIIB or IV non–small cell or extensive small cell), genitourinary tract (stage IV), or breast (stage IV and visceral crisis, lung or liver metastasis, estrogen receptor negative [ER−], human epidermal growth factor receptor 2 positive [Her 2 neu]) cancer. Patients were asked to select a caregiver to participate in the study.	single center, rural area	USA		n=322 (randmoized), screened 1222	Male sex intervention 96 (59.6) control 91 (56.5)	Age, mean (SD), y intervention 64.7 (10.8) control 65.4 (11.6)	300%	Primary disease site (intervention / Control) Gastrointestinal tract 66/67 Lung 59/58 Genitourinary tract 19/19 Breast 17/16 Anticancer treatment at enrollment Chemotherapy 137/134 Radiation therapy 20/23	Karnofsky Performance Status, mean (SD) intervention 77.9 (11.1) control 76.6 (13.1)	ESAS	not assessed	n= 220 (interv 106, control 116)	not specified	not specified	not specified	
Brumley, JAGS 2007 [59]	Increased Satisfaction with Care and Lower Costs: Results of a Randomized Trial of In-Home Palliative Care	RCT, parallel,	to test an in-home palliative care model at two sites using a randomized, controlled design; Standard care compared with standard care plus an in-home palliative care program to determine the program's ability to improve patient outcomes and reduce the costs of medical care at the end of life; hypothesized that the program would increase patient satisfaction, reduce costs of medical care, and increase the proportion of terminally ill patients dying at home.	primary diagnosis of CHF, COPD, or cancer; life expectancy ≤12 months*; ≥1 visit of emergency department or hospital within previous year; ≤70% on the Palliative Performance cale; * primary care physician was asked "Would you be surprised if this patient died in the next year?"	multicentric (2 sites)	USA (Colorado, California, Hawaii)	1+ (not blinded, endpoints not clearly defined, some risk of bias)	n=310 randomized (n=155 IG / CG) / drop out: n=13 / n=8 died before intervention	146/151	IG: 73.9 (11.1), CG: 73.7 (13.0), total: 73.8 (12.1)	IG: 44%, CG 49%, total: 47%	CHF, cancer, COPD; "terminally ill" (≤12months)	Palliative Performance Scale score mean (SD): IG=57.8(13.1), CG= 58.5(12.0), total=58.2(12.5)	Reid-Gundlach Satisfaction with Services instrument - mean(SD): 40.1(5.7); Palliative Performance Scale (mesuring severity of illness) - mean (SD): 58.2(12.5)	37% ethnic minority: 18% Asian/Pacific Islanders, 13% Hawaiian, 4% Latino, 2% other					

Author, Journal, Year	Needs assessment: Who assesses	Needs assessment: When	Needs assessment: How (tool)	Needs complexity: Categories	Needs complexity: Process of categorisation (needs > complexity)	Overall description: Intervention	Overall description: Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/ housing)	Funding: Who (source)	Funding: How much	Organisation / Management related to structures: Who	Organisation / Management related to structures: How	Referral criteria / allocation of place	Description of intervention: Schedule/Frequency	Description of intervention: Content (clinical/non-clinical)	Description of bereavement intervention: Schedule/Frequency	Description of bereavement intervention: Content	Description of control intervention	Coodination of intervention: Who	Coodination of intervention: How	Discharge criteria	Integration of oncological and palliative structures: Who	Integration of oncological and palliative structures: How	Others
Ahlner-Elmqvist, PallMed 2004 [52]						AHC Programme (regional palliative care programme, 24/7 on call, complementary to conventional care)	conventional care	AHC: 25 housebound patients at a time (3 backup beds)	The staff included a team of nine experienced nurses, an oncologist, a physiotherapist, a social worker and a secretary. A priest was associated on a consultation basis. All the professionals had long experience from advanced cancer care, but had no formal palliative care education or training.	25 outpatients (3 backup beds)	not specified	The hospital-based AHC service was affiliated to the Department of Oncology at Malmo¨ University Hospital.	not specidfied	hospital based home care team		clinical judgement--> proposal for refferral, patient preference	AHC 24/7 care	not specified	none	none							
Ahlner-Elmqvist, J Pain Sympt Manage, 2008 [53]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Ringdal, Pall Med, 2004 [54]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Axelsson, Palliat Med, 1998 [55]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Bakitas, JAMA, 2009 [56]	questionnaire	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Bakitas, Palliat Support Care, 2009 [57]	questionnaire	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
O'Hara , Palliat Support Care 2010 [58]	questionnaire	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Brumley, JAGS 2007 [59]	Undergraduate- and graduate-level research assistants, blinded to group assignments, were recruited and trained to conduct telephone interviews with the patient or, if the patient was unable to participate, the primary caregiver	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Author, Journal, Year	Outcomes: Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Outcomes: Costs	Results for each outcome	Results for outcomes related to informal CG	Comments
Ahlner-Elmqvist, PallMed 2004 [52]	1. place of death 2. days spent in hospital 3. differences in sociodemographic prerequisites	no	1. place of death: more home deaths in the AHC (interventional) group: 53/17 (p<0.001) 2. time spent in hospital: AHC 18% of time; Control 31% of time (p<0.005) 3. sociodemographic data associated with place of death: Living situation (living with someone) p=0.0014, OR 2.4 in both groups	none	no defined intervention, bias due to preferred care, bias in baseline data!
Ahlner-Elmqvist, J Pain Sympt Manage, 2008 [53]	HRQL (symptom presence and severitiy: EORTC QLQ-C30, psychological distress: IES, social: five questions of Mc Adam´s questionnaire, general well being: Norwegian Health Survey)	no	**HRQL:** **EORTC QLQ-C30 significantly poorer in AHC group for (ONLY SIGN RESULTS FEATURED)** Physical (AHC/CC) 29/51 p<0.001 Role (AHC/CC) 17/37 p<0.001 Emotional (AHC/CC 50/63 p<0.001 Cognitive (AHC/CC) 58/73 p<0.001 Social (AHC/CC) 45/58 p=0.001 Global health (AHC/CC) 35/44 p=0.003 **Symptom Scales** Fatigue 77/56 <0.001 Pain 53/41 0.002 **Single items** Dyspnea 56/40 <0.001 Appetite loss 53741 0.009 **IES mean** Intrusion 16/13 0.008 **Mc Adam´s Questionnaire** Worried about families future 54/34 0.001 Share feelings with others 77/71 0.009 **General wellbeing (comparison with normative data)** AHC (being "Tired and worn out" or "Very tired and worn out") (69%) CC patients (48%) (P < 0.001) Overall, both groups of patients reported reduced physical and psychological well-being compared with data from a Norwegian population study	none	results are more related too different phases of disease than to specific interventional features; possibly more a study for needs than SAPV
Ringdal, Pall Med, 2004 [54]	HRQOL measured by the short-form (SF-36) health survey questionnaire, including eight subscales	no	sign differences found for subscales at different time points (very complex statistical construction) the scale scores varies across time according to H1; The group by time interaction is, however, only statistical significant at the 0.05 level for the role limitation, emotional scale and the mental health scale.	highly complex methodological approach - almost too complex to follow. Bias due to different ways of recruitment and gender imbalnace very likely. Intervention not clearly explained. Whether the detected statistical differences are related to clinically relevant effects remians very dubious	
Axelsson, Palliat Med, 1998 [55]	duration of terminal hospitalization, ratio of days at home / to toal inclusion days; days at home during the last two month of life, economic advantages	palliative support team defrayed ist own costs and saved another SK17.000 / patient (=US$2.500)	intervention group significant less duration of terminal hospitalization (p=.005); ratio days at home / inclusion days higher (p=.001); more days at home (p=.001)		
Bakitas, JAMA, 2009 [56]	PO patientreported quality of life, symptom intensity and resource use. (assessed with the Functional Assessment of Chronic Illness Therapy for Palliative Care), symptom intensity (assessed with the ESAS), and resource use by chart review SO mood (assessed with CES-D)	no	Longitudinal intention to-treat analyses for the total sample revealed higher quality of life (mean [SE],4.6 [2]; P=.02) (Functional Assessment of Chronic Illness Therapy for Palliative Care scores and CES-D mood score p=0.02 no further sign results	robust methodology, straight forward.Simply a well done and important study.	
Bakitas, Palliat Support Care, 2009 [57]				does not add any information regarding evidence for interventional effects	
O'Hara , Palliat Support Care 2010 [58]	Montgomery Borgotta Caregiver Burden Scale; After Death Bereaved Familiy Memeber Interview (ADI), no caregiver centered intervention, simply monitoring effects of patient centered intervention on caregivers	no effects shown			
Brumley, JAGS 2007 [59]	1.O: medical care costs; 2.O: • satisfaction with care (Reid-Gundlach Satisfaction with Services instrument); • sevice use • proportion of terminally ill patients dying at home	Service costs= actual costs for contracted medical services (services provided by non-HMO contracted facilities) + proxy cost estimates for all services provided within the HMO; costs for: emergency + physician office visits + home health and palliative care visits + cost for each discipline's reimbursement rate; **total cost variable** constructed by aggregating costs for physician visits, emergency department visits, hospital days, skilled nursing facility days, and home health or palliative days accumulated from the enrollment until the end of the study or death.	• **cost of care:** sign.lower in IG vs CG: overall costs IG 33% less (P=.03; 95% CI= $12,411 to $780; R2=0.16), mean costs per patient $12,670 ±$12,523 vs. $20,222 ±$30,026 (p<.001), average per day $95.30 vs. $212.80 (p=.02); • **satisfaction with care:** no sig. difference at 60days after enrollment (OR=1.79; 95% CI=0.65–4.96; P=.26); signif.increased in IG at 30 days (OR=3.37, 95% CI=1.42–8.10; P=.006) and 90 days (OR=3.37, 95% CI=0.65–4.96; P=.03) after enrollment; 93% vs. 81% patients very satisfied with care at 90 days after enrollment; •**service use:** 20% vs. 33% went to emergency departement (P=.01), 36% vs. 59% hospitalized (P<.001); •**site of death:** 71% vs. 51% died at home (p<.001), IG 2.2 times as likely to die at home OR=2.20 (CI= 1.3-3.7; R2=0.27, p<.001)		* primary vs. Secondary endpoints not clearly defined; power calculation based on medical care costs; • satisfaction with care: potential of bias since analysis is based on comparison of percentages satisfied at each time-point - instead of analysing "change" (satisfaction with services was different at study entry, thus likely to stay better over all timepoints???) • conducted within closed-system managed care settings; as a result, it may be less generalizable to all healthcare settings, and the relative cost savings may not be realized across other settings • use of proxycosts of care calculated from aggregated patient records limits the ability to generalize findings across settings • Relying on death at home as a measurement of patient preferences for site of death

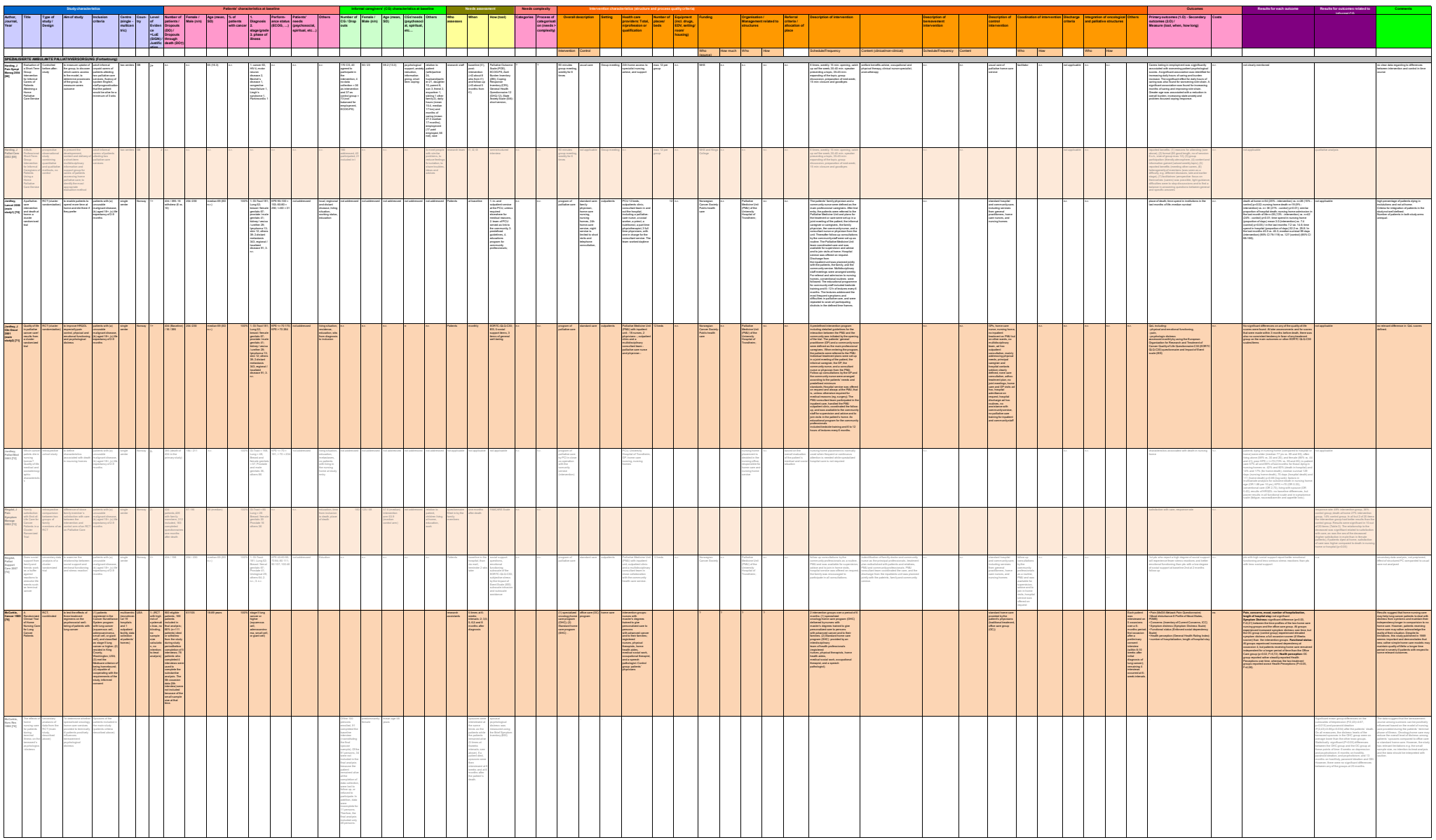
Study characteristics: Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification	Patients' characteristics at baseline: Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, ...)	Patients' needs (psychosocial, spiritual, etc...)	Others
SPEZIALISIERTE AMBULANTE PALLIATIVVERSORGUNG (Fortsetzung)															
Brumley, J Pall Med 2003 [60]	Effectiveness of a Home-Based Palliative Care Program for End-of-Life	CCT (nonequivalent comparison group)	1) to provide documentation of the effectiveness of a home-based palliative care model through the following research hypothesis: total medical service use during the last months of life will be less under the palliative care model than under the traditional model of care; 2) to determine if patients enrolled in the palliative care program were more satisfied with their care compared to those receiving traditional care.	IG: life-threatening disease (primary COPD, CHF, or cancer) and a prognosis of approximately 1 year or less to live; CG: diagnosis of COPD, CHF, or cancer, two or more emergency department visits or hospitalizations in the last year, and a prognosis of less than 24 months to live	multicentric but one site (three Kaiser permanente medical centres)	USA (southern California)	1- (no randomization, nonequivalent samples, high risk of bias)	IG n=210, CG n=348 enrolled; analyzed: subgroup of patients who died: IG n=161, CG n= 139; / drop out: n=73 (13%) refused to participate in the interview	female IG=50.9%, CG=55.4%	IG: 70 (n.d.), CG: 74 (n.d.)	IG: 60.9%, CG 39.1%	CHF, COPD cancer; life expectancy of ≤12 vs. 24months	PPS mean (SD n.d.): IG 46.94, CG 52.5	mean days on service: IG 102, CG 159; PPS mean: IG 46.94, CG 52.5 (SD n.d.); Reid-Gundlach Satisfaction with Services instrument mean(SD): n.d., Text info: high for both groups (mean >40)	Ethnicity (% IG vs. CG): White 65.6vs. 52.5, Latino 17.4 vs. 16.5, African American 9.4 vs. 18.7, Asian 6.3 vs. 10.1
Buckingham, Death Educ 1978 [61]	A Guide to Evaluation Research in Terminal Care Programs	CCT	to find evidence for or against the thesis, that a hospice home care program provides effective care to ist terminal patients	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Casarett, JAMA 2005 [62]	Improving the Use of Hospice Services in Nursing Homes	RCT, nonblinded	To examine whether promoting communicatin about hospice care can increase hospice enrollment and improve quality of care for nursing home residents	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cummings, Arch intern Med 1990 [63]	Cost-effectiveness of Veterans Administration Hospital-Based Home Care (VA HBHC)	RCT	to determine whether VA HBHC is more cost-effective than customary follow-up care alternatives	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hughes, Health Serv Res 1991 (Begleitstudie) [64]	A Randomized Trial of the Cost Effectiveness of VA Hospital-Bases Home Care for the Terminally Ill	RCT?		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, BMJ 1999 [65]	Does hospital at home for palliative care facilitate death at home? Randomised controlled trial	RCT, parallel, nonblinded	To deteminde whether hospital at home enabled more patients to remain at home until death	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, J Pall Care 2004 (Begleitstudie 1) [66]	Caregiver Bereavement Outcome: relationship with hospice at home, satisfaction with care, and home death	RCT, parallel, nonblinded	to investigate the impact of hospice at home on caregiver bereavement outcome	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, Palliat Med 2000 (Begleitstudie 2) [67]	A randomized controlled trial of a hospital at home service for the terminally ill	RCT, parallel, nonblinded	to test whether Hospital at Home differs from standard care in terms of perceived symptom control, adequacy of care and patients' ability to remain at home during their final 2 weeks	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Greer, J Chron Dis 1986 [42]	An alternative in terminal care: Results of the national hospice study	quasi experimental study	1. What is the difference between hospice and conventional care? 2. What is the differential impact of hospice and conventional care on the quality of life of patients and their families? 3. What is the impact of hospice on the health care costs incurred by terminal cancer patients?	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[Begleitstudien von Greer: s. unter Palliativstation]															

Author, Journal, Year	Informal caregivers' (CG) characteristics at baseline: Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc...	Others	Needs assessment: Who assesses	When	How (tool)	Needs complexity: Categories	Process of categorisation (needs > complexity)
Brumley, J Pall Med 2003 [60]	-					data from telefone interviews: undergraduate and graduate-level research assistants with either the patient or the primary caregiver if the patient was unable to participate; [illegible]	Interviews were conducted via telephone at 7 days after enrollment in either palliative care or the comparison group and every 60 days thereafter; Pain is assessed at each visit.	Palliative Performance Scale (PPS) (11 categories that are measured in 10% decrements ranging from fully ambulatory to death); tool for pain assessment n.a.	-	
Buckingham, Death Educ 1978 [61]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Casarett, JAMA 2005 [62]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cummings, Arch intern Med 1990 [63]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hughes, Health Serv Res 1991 (Begleitstudie) [64]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, BMJ 1999 [65]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, J Pall Care 2004 (Begleitstudie 1) [66]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, Palliat Med 2000 (Begleitstudie 2) [67]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Greer, J Chron Dis 1986 [42]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Author, Journal, Year	Intervention characteristics: Overall description – Intervention	Overall description – Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/ housing)	Funding – Who (source)	Funding – How much	Organisation / Management related to structures – Who	Organisation – How	Referral criteria / allocation of place
Brumley, J Pall Med 2003 [60]	Palliative Care Program (interdisciplinary, home-based)	usual care	interdisciplinary home-based system of health care	n: n.d.; professions: home visits from the palliative care physician; nurse, and social worker with expertise in symptom management and biopsychosocial intervention	n.d.; total member enrollment of 675,000 (=patients)	TriCentral Service Area is comprised of three KP medical centers and provides home health care and hospice services for all medical centers through a central Continuing Care Department. (...) Telephone [illegible]	Kaiser Permanente Garfield Memorial Fund	-	care team	coordinating and managing care across all settings and providing assessment, evaluation, planning, care delivery, follow-up, monitoring and continuous reassessment of care. The team also [illegible]	IG: various sources including physicians, discharge planners, home health nurses, and social workers, liason nurses; CG: identified on enrollment in home health services and received standard KP health care in [illegible]
Buckingham, Death Educ 1978 [61]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Casarett, JAMA 2005 [62]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cummings, Arch intern Med 1990 [63]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hughes, Health Serv Res 1991 (Begleitstudie) [64]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, BMJ 1999 [65]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, J Pall Care 2004 (Begleitstudie 1) [66]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, Palliat Med 2000 (Begleitstudie 2) [67]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Greer, J Chron Dis 1986 [42]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Author, Journal, Year	Description of intervention – Schedule/Frequency	Description of intervention – Content (clinical/non-clinical)	Description of bereavement intervention – Schedule/Frequency	Bereavement – Content	Description of control intervention	Coodination of intervention – Who	Coodination – How	Discharge criteria	Integration of oncological and palliative structures – Who	Integration – How	Others
Brumley, J Pall Med 2003 [60]	program structure is similar to the Hospice Medicare benefit with modifications to provide care over longer periods of time; purpose= to provide an improved model of care combining care modalities and cost savings from the Hospice Model with curative care; (...) By including restorative therapy (...) "hospice philosophy" may be introduced without the negative connotation of "giving up" that is often associated with hospice (...) care team is responsible for coordinating and managing care [illegible]	• alleviating the physical, emotional, social, and spiritual discomforts of an individual with a terminal illness who is in the last phases of life; • patients may elect to continue restorative treatment (=ameliorative, referring to treatment that will not cure their disease, but will maintain and sustain a reasonable quality of life). • symptom control, patient education (self-management and crisis intervention in the home), and psychosocial services • training staff, patients, and families on use of medications • patient and family education and support	-		standard Kaiser Permanente TriCentral Service Area care and follows Medicare guidelines for home health care criteria.	central care team (patient and family, physician, nurse, and social worker with expertise in symptom management and biopsychosocial intervention)	responsible for coordinating and managing care across all settings and providing assessment, evaluation, planning, care delivery, follow-up, monitoring and continuous reassessment of care		-		
Buckingham, Death Educ 1978 [61]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Casarett, JAMA 2005 [62]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cummings, Arch intern Med 1990 [63]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hughes, Health Serv Res 1991 (Begleitstudie) [64]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, BMJ 1999 [65]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, J Pall Care 2004 (Begleitstudie 1) [66]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, Palliat Med 2000 (Begleitstudie 2) [67]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Greer, J Chron Dis 1986 [42]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Author, Journal, Year	Outcomes: Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs	Results for each outcome	Results for outcomes related to informal CG	Comments
Brumley, J Pall Med 2003 [60]	outcomes not clearly defined; as apparent from context: 1.O: sevice use (utilization data from KP mainframe database: number of emergency department visits, physician office visits, hospital days, skilled nursing facility days, home health and palliative visits, and days on hospice) and costs of care 2.O: • patient satisfaction with care (Reid-Gundlach Satisfaction with Services instrument); • severity of illness (Palliative Performance Scale (PPS)) • proportion of patients dying at home	calculated based on the 1999 cost of staff time associated with the care. Medication, facility, and administrative costs were not included in the calculations. As a result, the estimates of the costs of care are very conservative. Application of these costs to a nonmanaged care [illegible]	• **cost of care:** average IG= $7,990, CG=$14,570 (programm reduced medical costs of care by 45%, p<0.001); • **service use (IG vs. CG; mean(SD), p):** Physician visits 5.335 (13.97) vs. 11.089 (13.81), p=0.001, Hospital visits 2.359 (10.96) vs. 9.352 (10.82) p<0.001, Emergency department visits 0.930 (2.51) vs. 2.297 (0.92) p<0.001, Skilled nursing care visits 0.851 (11.0) vs. 4.575 (10.87), p=0.005, Total home health visits 35.048 (31.83) vs. 13.247 (31.44) p<0.001; • **satisfaction with care:** at 60 days following enrollment: IG: "significantly higher satisfaction than at baseline (t=-2.57, p<0.01)", IG: satisfaction remained the same for comparison group members (t=-0.5, p=0.6) (mean(SD) [illegible]	-	• The reduction in use of emergency care, hospital, skilled nursing facility, and physician office visits for the palliative care group while concomitantly increased home health service use demonstrates the palliative care program's ability to effectively transfer end of life care from high-cost acute care services to a lower cost home based arena that allows patients to die in the comfort of their homes. • significant increase in level of satisfaction with services of palliative care patients from baseline to 60 days after study enrollment supports the transfer of care [illegible]
Buckingham, Death Educ 1978 [61]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Casarett, JAMA 2005 [62]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Cummings, Arch intern Med 1990 [63]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hughes, Health Serv Res 1991 (Begleitstudie) [64]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, BMJ 1999 [65]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, J Pall Care 2004 (Begleitstudie 1) [66]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Grande, Palliat Med 2000 (Begleitstudie 2) [67]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Greer, J Chron Dis 1986 [42]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]



Study characteristics								Patients' characteristics at baseline								Informal caregivers' (CG) characteristics at baseline					Needs assessment			Needs complexity		Intervention characteristics (structure and process quality criteria)																						Outcomes		Results for each outcome	Results for outcomes related to informal CG	Comments
Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others	Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others	Who assesses	When	How (tool)	Categories	Process of categorisation (needs > complexity)	Overall description		Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/ housing)	Funding		Organisation / Management related to structures		Referral criteria / allocation of place	Description of intervention		Description of bereavement intervention		Description of control intervention	Coodination of intervention		Discharge criteria	Integration of oncological and palliative structures		Others	Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs			
																										Intervention	Control					Who (source)	How much	Who	How		Schedule/Frequency	Content (clinical/non-clinical)	Schedule/Frequency	Content		Who	How		Who	How						
SPEZIALISIERTE AMBULANTE PALLIATIVVERSORGUNG (Fortsetzung)																																																				
McKegney, Gen Hosp Psychiatry 1981 [77]	Prediction and Management of Pain in Patients with Advanced Cancer	CCT	The major hypothesis of the study was that visits in the home by trained oncology nurse practitioners would result in improved quality of life for an experimental group of patients, compared with a carefully matched control group of patients who did not receive such home visits but whose care was otherwise the same as that of the experimental group. Multiple psychosocial and biological variables were also studied, as they might identify those patients with predictably greater difficulties in pain management over their last months of life.	terminal cancer; mental competente; a minimum age of 16 years; a signed informed consent; and an expected survival of greater than three months but less than one year as judged by an experienced oncologist	multicetric? (multiple health providers, home patients, but one site coordinated study/intervention)	USA, Vermont	1- (no randomization, high risk of bias)	n=199 patients (intervention group n=98, control group n=101) included, thereof n=139 had died during the study and thereof 38 intensive and 45 non-intensive patients had a sufficient number of pain ratings (=were analyzed)*	IG: n=21/19, CG: 27/16	IG mean (SD): 58.7 (1.7); CG: 56.1 (2.2)	100%	1. types of cancer n patients included: IG: lung=20, breast=6, GI=8, other=6; CG: lung=14, breast=6, GI=9, other=14; 2. n.d., "varying stages of their illness"; 3. terminal cancer patients (expected survival of greater than three months but less than one year as judged by an experienced oncologist)	s. Yates et al. 1977	• pain: not reported for initial assessment; • CMI: 23/55 patients had initially a mild to severe emotional disturbance ("high CMI" group). • Rotter Lotus of Control (I-E) Scale: 34/55 initially gave 4 or more "external" responses on the 8-item I-E scale ("high I-E" group), and 21 patients gave 0-3 external responses ("low I-E" group)	* no data on drop out but improtant hint: Of the 139 patients who died during the study, 38 intensive and 45 non-intensive patients had a sufficient number of pain ratings (three or more) to compare the effectiveness of pain management over time in the two groups.	-					trained independent raters (non medical observers); nurse in pain assessment?	same frequency as the nurses' visits (beweekly in patients with an expected survival of less than three months and monthly in those expected to live longer)	structured interviews in the patients' homes, done at the same frequency as the nurses' visits: • "Pain Estimate" score by Sternbach (0-100 self-report of pain) • modified Rotter Lotus of Control (1-E) scale (internal-external expectation of control) • Cornell Medical Index (CMI) M-R scales (psychological symptoms) • initial research data base (IRDB) (medical, nutritional, physical, psychosocial, and religious status) • Karnofsky Performance Status (KPS)	• Cornell Medical Index (CMI): "High CMI" = 6 or more "yes" responses on the M-R section of the CMI, indicating a mild to severe emotional disturbance vs. "low CMI"= 0-5 yes responses • Rotter Locus of Control (I-E) Scale: "high I-E"= ≥4 'external' responses on the 8-item I-E scale; "low I-E"= 0-3 'external' responses on the 8-item I-E scale	• CMI: "cut score" of 6, slightly above the customary 4 or 5, was chosen in order to increase the accuracy of positive prediction; • Rotter Lotus of Control (1-E) scale: n.d.	standardized home visits by a nurse practitioner acting as an extension of a multidisciplinary team; multidisciplinary care at the MCHV and/or from their private physicians	multidisciplinary care at the MCHV and/or from their private physicians without home visits	home care, rural setting	nurse was chosen as the interface between the multidisciplinary team and patients receiving palliative therapy, since normal activities for nurses encompass many of the skills carried out by individual team members. Nurse practitioners with extensive experience in care of the patients with advance cancer; Regular participants in the multidisciplinary team consisted of medical and radiation oncologists, psychiatists, social workers, physical therapists, nutritionists, occupational therapists, enterostomal therapists, and clergymen.			NIMH Training Grant MH08057-17 and NCI grant 17868	-	Vermont Regional Cancer Center (VRCC) at the University of Vermont; major medical center, the Medical Center Hospital of Vermont (MCHV), responsible for most of the region's cancer surgery, radiation therapy, and chemotherapy.		All new patients seen by radiation therapy and medical oncology were eligible for accession to the study.	the visit rarely exceeded 30-45 minutes; Patients with an expected survival of less than three months were visited by nurses biweekly and those expected to live longer were visited monthly.	The home visit by the nurses was primarily focused on attending to the needs of the patient, and interactions with family members were incidental to that task. In addition to providing physical care, much of the nurse's time was spent in talking with the patient about their illness and its implications. The nurse frequently mobilized family and other social resources to meet the patient's needs and also coordinated with the patient's local physician. These nurses thus served in the well-known public health, or visiting nurse, role, with the differente that the project nurse had the benefit of a multidisciplinary health care team back-up resource.	-		patients received only multidisciplinary care at the MCHV and/or from their private physicians, without home visits by the nurse	Nurse practitioners with extensive experience in care of the patients with advance cancer; multidisciplinary health care team back-up resource	A "Protocol for Management of Pain" was developed by the team and used by the nurses as part of their wide range of physical treatments and psychosocial interventions. This protocol was based upon sound pharmacological principles, many of which are often ignored (i.e. oral methadone is an effective and longer lasting analgesic than other narcotics, and was used extensively in this program);		Medical Center Hospital of Vermont (MCHV), multidisciplinary team, local physicians	Medical Center Hospita1 of Vermont (MCHV), responsible for most of the region's cancer surgery, radiation therapy, and chemotherapy; nurse was chosen as the interface between the multidisciplinary team and patients receiving palliative therapy.		1.O: pain as a reflection of quality of life ("Pain Estimate" score described by Sternbach, a 0-100 self-report of pain at the present time) 2.O: • expectation of control (modified Rotter Lotus of Control (1-E) scale) • psychological symptoms (Cornell Medical Index (CMI) M-R scales, a 51-item self-report measure) • overall health status (Karnofsky Performance Status (KPS) scale) • patient's medical, nutritional, physical, psychosocial, and religious status	-	*means not reported for the single time-points; means are only presented in figure and the following information available in the text:* • **pain control:** with nearing death, mean pain scores in intervention ("Intensive") group were significantly lower than in the control ("Non-intensive") group in the last period (0-30days before death); in the last 90 days before death mean pain scores in the non-intensive group of patients continued to rise until death, whereas the mean pain scores in the intensive group of patients plateaued; the two groups had essentially the same mean pain scores until the last 90 days before death; • **CMI:** "High CMI" group (n=34) had higher mean pain scores than the "Low CMI" group (n=21) in the last 120 days before death; this differente being statistically different in the last 60 days before death (P < 0.05) • **Rotter Locus of Control (I-E) Scale:** High 1-E group had significantly higher mean pain scores than did the Low 1-E group in the 180-120-day and 120-60-day periods before death (P < 0.05). This differente persisted in the last 60 days before death but was no longer statistically significant at the 0.05 level. Mean pain scores in the High and Low 1-E groups not different in the 240-180-day period.	-	• **potential bias: 1. incomplete data:** problems in gathering complete initial data bases: the observer-scored IRDB, and the patient-completed Cornell Medical Index, Pain Estimate and Lotus of Control scales because of a) patient factors: serious physical illness and the presence of mild mental confusion, b) observer factors: discomfort with asking upsetting questions about patients' disabilities and unhappiness, and a reluctance to impose yet another burden on patients with progressive illness; **2. observer effect:** Early in the study, it became apparent that home observers could not restrain themselves from offering help to patients and families when their needs became apparent in the process of data gathering. Although personnel changes were made later in the study, the human contact between the research observers and the patients in the home may have reduced differences in quality of life outcomes between the intensive and non-intensive groups (...) supported by the fact that the major difference between the two groups was in pain management, the one problem which the nurses could address, but which the nonmedical observers could not. • **first study examining the impact of standardized home intervention for pain problems** in patients with cancer; demonstrated benefit by home intervention strongly supports the current "Hospice" home care nursing movement, at least in terms of pain management • multidisciplinary team developed a **Pain Management Protocol**, available from the authors, with clear guidelines for appropriate and effective interventions in
Kassakian, Nurse Pract 1979 [78]	The Cost and Quality of Dying: A Comparision of Home and Hospital	retrospective chart review (preliminary subanalysis of main CCT study)	assessing the financial aspects of health care in the last month of life for 71 patients (who participated in the CCRRS(="Cancer Care and rehabilitation in a Rural Setting" study) team project - this paper does not evaluate costs/benefits/risks of the intervention described by McKegney et al. but does compare four groups of patients who died and were included in this study; the aim of this subanalysis was to evaluate costs depending on the place of death of these patients, not for the intervention (home visiting nurses)!	over 16 years, histologically proven cancer and prognosis of less than one year	see above	USA, Vermont	3 (retrospective subanalysis of patients included in the CCT study repoted by McKengney et al.)	n=71 (subsample of patients who died with information of their place of death)	28/43	*	100%	*	n.a.	place of death: "home"/"home-hospital" n=23, nursing home n=11, hospital n=37	aim of this subanalysis was to evaluate costs depending on the place of death of these patients, not for the intervention (home visiting nurses)! description of subsample of patients who died with information of their place of death, only; characteristics (age) are presented for time of death; all patients included were expected to die and were no longer receiving chemotherapy or raqdtiation therapy								• activity and disease status (Karnofsky Performance status scale); • psychosocial impact of dying assessed by questions which measure areas of concern on a five point scale (instruments not reported): "social activities"(0=none to 4=full), "hobbies and crafts"(0=none to 4=full), "difficulty walking"(0=dependent to 4=independent), bathroom activity (0=dependent to 4= independent), pain with activity (0=incapacitated to 4=functional), "future planning" (0=very realistic to 4= very unrealistic)	• classifications made according to the place of death • social acitivies / hobbies and crafts: "none" = 0, "some"=1-4 • difficulty walking / bathroom activities: "dependent"=0, "independent"= 1-4 • pain with acitivity: "incapaciated= 0, "some to none"=1-4 • future planning: "unrealistic"=0-1, "realistic"=2-4		idem	diem	idem	cancer rehabilitation team and oncology nurse practitioner		for evaluation of these activities, statistical and data manegement personnel are also inlcuded in the team sessions; written protocols prepared by oncology nurse practitioners and the medical oncologists provide structured laitude for the nurse p. in the management of pain, nauseas and vomiting, and the administration of intravenous chemotherapy in the home			Vermont regional cancer center;	team sessions, including statistical and data manegement personnel;		no further information		-		no further information	multidisciplinary team (see above)	weekly team conference; team nurse practitioners keep the local physicians well informed of the patients' status and collaborate with local physicians when confronted with complex medical problems; written protocols prepared by oncology nurse practitioners and the medical oncologists provide structured laitude for the nurse p. in the management of pain, nauseas and vomiting, and the administration of intravenous chemotherapy in the home		members of the "Cancer Care and rehabilitation in a Rural Setting (CCRRS)" study	weekly team conference; team nurse practitioners keep the local physicians well informed of the patients' status and collaborate with local physicians when confronted with complex medical problems; written protocols prepared by oncology nurse practitioners and the medical oncologists provide structured laitude for the nurse p. in the management of pain, nauseas and vomiting, and the administration of intravenous chemotherapy in the home	this paper does not evaluate costs/benefits/risks of the intervention described by McKegney et al. but does compare four groups of patients who died and were included in this study; the aim of this subanalysis was to evaluate costs depending on the place of death of these patients, not for the intervention (home visiting nurses)!	• 1.O **fincancial impact of dying** (average cost per patient in each "place of dying" group for the last month of life) • 2.O **psychosocial impact of dying:** assessed by questions which measure areas of concern on a five point scale (instruments not reported): "social activities"(0=none to 4=full), "hobbies and crafts"(0=none to 4=full), "difficulty walking"(0=dependent to 4=independent), bathroom activity (0=dependent to 4= independent), pain with activity (0=incapacitated to 4=functional), "future planning" (0=very realistic to 4= very unrealistic)	cost factors examined were: visiting nurse visits (oncology nurse practicioner visits included in the category), home health aide visits, hospital days, home visits made by physicians, physicians office visits, hospital visits made by physicians and nursing home costs	this paper does not evaluate costs/benefits/risks of the intervention described by McKegney et al. but does compare four groups of patients who died and were included in this study; the aim of this subanalysis was to evaluate costs depending on the place of death of these patients, not for the intervention (home visiting nurses)! In addition, presentation of results (numbers/means) is in figure / tables, only. As results do not relate to the intervention but another research question, only some relevant inforamtion (cost data, description of psychosocial impact of dying) data are extracted here: • 1.O **fincancial impact of dying** (relative cost per patient in each "place of dying" group for the last month of life): home (n=15) $45013; hospital-home (n=7) $56100, "hospice (projected)" $104297, "nursing home" (n=11) $149636, "hospital" $189631 • 2.O: **psychological impact of dying (% in the home / nursing home/ hospital group): social activities** comparable between groups; **hobbies/crafts** pursued more by those at home than among institutionalized patients (% of patients answersing 1-4 respresenting "some"= 38/10/25; **difficulty walking** - % "independent" (answers 1-4): 65/45/46; **bathroom activity** - % "independent" (answers 1-4): 65/45/46; **pain with activity** - % "some to none" (answers 1-4). 73/100/100; **future planning** - % realistic (ansers 0-1): 60/14/45, % unrealistic (2-4) 40/38/36, unable to evaluate: 0/48/18.		[illegible] costs/benefits/risks of the intervention described by McKegney et al. but does compare four groups of patients who died and were included in this study; the aim of this subanalysis was to evaluate costs depending on the place of death of these patients, not for the intervention (home visiting nurses)! • intransparent presentation of methods and especially data used for this subanalysis; also intransparent and sparse presentation of results (numbers/means in figure / tables, only) and especially of costs; • due to sprase information given on data collection, risks of bias unclear / intransparent
Mulligan, University of Wales 1989 [79]	An evaluation of a specialist home care service	CBA (doctor thesis)	The central aim of the present study is the evaluation of a specialist home care team for the terminally ill. The service aims to provide good terminal care in the manner described above as effective.	patients referred to St. Patricks Foundation (see referral criteria); Those living in two boroughs of Gwent were included. Among these patients, some were excluded from the study for a number of reasons: a) if they were first seen by a Foundation nurse while they were in hospital; b) if they were seriously confused and had no key relative; c) if the patient was very near to death at the time of the referral; d) if for any other reason it was considered inappropriate to ask families to complete questionnaires at the first visit.	single center	UK (Wales, Gwent)	2+	119 (63 patients in group A, 42 in group B, and 14 in group C)	55/64	median(range) = 65 (25-87)	98%	1. cancer sites: ca. 30% respiratory system cancer (lung/bronchus), ca. 16% Upper Digestive System, ca. 14% Male & Female Reproductive System, ca. 13% breast cancer, ca. 10% Lower Digestive System, ca. 5% Lympho-reticular disorders ….; non-cancer: n=1 terminal respiratory disease, n= 1other from longstanding poliomyelitis and diabetes; 2. n.d.; 3. "terminally ill"	n.d.								5 nurses, 1 researcher	study entry, 2-4 weeks later, and then at approximately 2 month intervals where possible	• **pain:** Site of pain ; intensity (10cm VAS) • **symptoms** (13 item checklist of principal symptoms) • **psychological distress patients** (Scale B (Anxiety and Insomnia), C (Social Dysfunction) and item D5 from the GHQ-28; VAS for Depression) • **psychological distress relatives** (Scale A (Somatic Symptoms), B (Anxiety and Insomnia), C (Social Dysfunction) and item D5 from the GHQ-28; VAS for Depression) • **Distress in Bereavement:** General distress ; Resolution of grief (Expanded Texas Inventory of Grief (TIG));			**Home Care service** Foundation Group A: Patients in this group are those referred to the Foundation from one borough in the catchment area which has received a service from the Foundation for some years. Foundation Group B: Patients in this group are those referred to the Foundation from a borough in the catchment area where the Foundation had only been offering a service for a few months at the onset of the study.	no specialist service for the terminally ill operating	home care, St. David's Foundation, registered charity, South Wales industrial valleys (Newport, Gwent)	nine nurses operated throughout the county of Gwent; no medical practitioner of its own, close conjunction with General Practitioners and District Nurses			funding from a variety of sources, including a substantial amount from local fundraising activity		team of nine nurses operated throughout the county of Gwent; a day centre was open for two days a week in Newport;	operates in close conjunction with General Practitioners and District Nurses	The referral criterion for people with cancer is that the presence of metastases must have been diagnosed. This criterion is waived in the case of people having primary tumours with particularly poor prognostic implications, for instance some lung and brain tumours. Referral criteria for other conditions are the loss of the swallowing reflex for neurological conditions, and the point when inevitable disease progression changes from chronic to acute for other conditions.	twenty four hour call service, so that a patient or relative can speak to a nurse at any time of day or night, and receive a visit if necessary; limited night nursing service is also available to give relatives involved in fulltime caring the possibility of a full night's sleep at least every few days;	• Home Care Nurses provide advice with regard to pain and symptom control, and counselling and emotional support patients and their families; provides a service to people with a variety of potentially terminal conditions, although the vast majority are cancers; • volunteers who will sit with patients for relatives to go out, or who will take patients to the Foundation's day centre or to hospital appointments; • one of its aims: to enable more people to die at home rather than in hospital; • •	All relatives are visited at least once after the death, and some many times. All are invited to attend coffee mornings a few months after bereavement	support to families after bereavement, although this is often limited in practice due to pressure of work; All are invited to attend coffee mornings a few months after bereavement at which most of the nursing team as well as several volunteers are present, and many attend these. When people appear to have persisting difficulty in coping they are referred to Cruse, which has several counsellors in Gwent. However a problem commonly expressed by the home care nurses is that their workload is such that there is less time than they would like for bereavement support.	This group is drawn from a nearby area (in Mid Glamorgan) where there was no specialist service for the terminally ill operating. The General Practitioners involved in the project were asked to refer patients to the study who would meet the referral criteria for St. David's Foundation.							**1.O: pain:** Site of pain; intensity (10cm VAS), type (McGill Pain Questionnaire) **2.O symptoms** (13 item checklist of principal symptoms commonly experienced by people with terminal illness; dichotomous response) • **psychological distress patients** (Scale B (Anxiety and Insomnia), C (Social Dysfunction) and item D5 from the GHQ-28; VAS for Depression) • **psychological distress relatives** (Scale A (Somatic Symptoms), B (Anxiety and Insomnia), C (Social Dysfunction) and item D5 from the GHQ-28; VAS for Depression) • **Distress in Bereavement:** General distress (s.psychological distress relatives); Resolution of grief (Expanded Texas Inventory of Grief (TIG));		Pain: sign. more pain if patients referred 2 weeks or less before dying		
Ventafridda, Tumori 1985 [80]	The importance of a Home Care program for patients with advanced cancer	CCT	To show the effect of a multimodal Home Care Service for patients in Milan and their families	Patients with far advanced cancer, who could no longer be treated in an out-patient cancer clinic and received assistance at home	single center	Italy	1-	30 pts with Home Care Service, 17 pts without , 2 dropouts because of +	no demographic data	no demographic data	100%	no data	no data	LASA Scale		Home Care Service Team										Family Support and Home Care Team in Milan(32 pts)	Family Support	outpatients (ambulant)	no description	not relevant	not described	no statement		Volunteer Group Coordinator ?			Schedule/Frequency				Home Care Sevice in Milan - no clear descriptioin				Home Care Service, Outpatient Clinic, Palliative Care Unit, Pain Ambulance	regular or on needs		• • Pain (Integrated Pain Score) • Performance Status (Karnofsky) • Quality of life (QLI Spitzer) • Weakness, mood anxiety, side-effects (Linear Analogue Scale Assessment = LASA) At week 0, 2 and 6	no results	Integrated **Pain** Score decreased for both groups during the period running with statistically significant difference in favor of the Home Care group. No difference in the **Performance** (Karnovsky Index) during the 6-weeks investigation period. **Quality of life** (Spitzer Index) remained unchanged in the Home Care group and deteriorated progressively in the Control group monitored by their families with statistically significant difference (p<0.02) at the 6th week. Feelings of **weakness, anxiety, mood and magnitude of side effects** (evaluated by Linear Analogue Scale Assessment LASA) showed signs of improvement in the Home Care group with statistically significant differences in week 2 and 6. Anxiety and Mood in family members measured LASA showed better results in the Home Care groupresults for family. Partially significant better results for the parameters pain, QoL, feelings of anxiety, weakness and side-effects measured over a 6-weeks period of 32 patients treatd by a Home Care Service compared to 16 patients treated by the family without Home Care Pain week 6: 12 vs 24 (p< 0.05); anxiety week 6: LASA: 5,7 vs 2,5 (p <0.01), weakness week 6: LASA 3,9 vs 1,4 (p<0.01), relatives anxiety (a) and mood (b) week 6: LASA a: 3,5 vs 1,3 (p<0.05), LASA b: 3,8 vs 1,3 (p<0.02)		A nice early study to show the importance of a Home Care setting but with limited generalization as the two groups and the kind of family caring was not examined
Ventafridda, Tumori 1989 [81]	Comparison of Home and Hospital Care of advanced incurable Cancer Patients with	CCT	To show the difference in the care of patients cared by multimodal Home Care Service compared to a sample of patients hospitalised with Palliative Care	Patients with incurable cancer and painful symptoms who needed palliative care assistance at home or in hospital			1-	30 pts in Home Care Service, 30 pts hospitalised supported by the Pain and Palliative Care Service	48 males, 22 females	59 yrs in both samples	100%	incurable cancer, no radio- or chemotherapy,	Karnofsky 30 - 70	Integrated Pain Score, Spitzer Quality of Life Index		Home Care Service Team vs. Pain & Palliative Care Service in hospital										weekly assessment of 30 pts in hospital palliative care vs 30 pts in outdoor Home Care		inpatients vs. Outpatiens	Outpatients: Home Care Service Team (9 physicians,9 nurses, 1 social worker, 1 psychologist, 43 voluteers Inpatients: hospitalised in various wards cared by Pain Therapy and Palliative Care Service of the hospital (Palliative Consultation Team?)	not relevant	not described	Floriani Foundation		not described		Any type of painful advanced neoplastic disease, both sexes between 20 & 70 yrs., no more anticancer treatment, patients treatable according WHO Guideline adapted to individual needs.	Daily recording of clinical and behavioural data on pain, hrs of sleep, side effects and therapies using integrated pain score and Spitzer Index											• Pain (Integrated Pain Score: integrates intensity and duration of pain in a single score) • Hours of sleep, hours standing, sitting and lying • Performance Status (Karnofsky) • Side effects • QoL (Spitzer QoL index and social care records) • Costs	yes	Only week 1 and week 2 could be compared. Afterwards no comparison possible because of dropouts (discharges and deaths) . No sign. difference in the two samples except for education (higher in the home care group), no significant difference in survival time. Home care group showed better **performance status** at T14 (Anova H 7.062, p=0.01, otherwise no significant difference in **pain** intensity or **sleep** Significant difference in **QoL** (better at T14 in the Home Care group: F=11.473, p=0.001) None of the hospitalised pts fully aware of illness, while 26.7% at home were fully aware p< 0.05. Mean daily **costs** of care calculated for hospitalised pts: 261,4 $, for the Home Care pt: 37,4 $ The results showed that Home Care produced signifcant better results for psychological and social parameters (Spitzer Score at T14) patients satisfactiion und costs, while clinical parameter (survival, pain,activity showed no difference to the hospitalised group		A nice study to show the importance of a Home Care setting especially for psychosocial well-being and lower costs without increasing suffering compared to inpatient treatment. The dropout rate of the two samples was quite high because of discharges and deaths in both groups, so only the first two weeks (of intended 6) were compared. Description of Home Care Team
Ward, Community Med 1987 [82]	Home Care Services - an alternative to hospices?	prospective cohort study (PCS)/CBA randomised pts with interviews	to show differences in outcome and places of deaths in pts treated by Home Care Services attached or not attaches to Inpatient hospices in GB	957 pts with advanced cancer newly reffered to 8 Home Care Services followed up till death or one year after 1st enrollment	eight services (4 attached to inpatient hospice, 4 not attached to inpatient hospice)	GB	2+	n=957	29% widowed no demographic data	no data	no data on diagnosis but mostly cancer pts. (MacMillan Nurses)	no data	no data	no data		McMillan Nurses					Nurses completed forms, reearch workers collected data, more detailed interviews with a sample of 40 pts selected from a sample of 83					Nr of visits/pts of home care nurses		outpatients (ambulant)																				O1: In the four centres attached to an in-patient hospice 29% of pts died at home compared to 65% treated by the four services not so linked, O2 Compared to the periods before the inception of Home Care Services the proportion of home deaths decreased slightly in regions with hospice based services and increased slightly in districts served by home care only services				A study with an interesting well founded result, that the implementation of an inpatient hospice based home Care service decreases home deaths while services not based to an hospice increase the proportion of patients dying at home, but probably this result is difficult to generalize for Germany becaus of the different health system.

Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)
PALLIATIVDIENST IM KRANKENHAUS (KONSIL)													
Gade, J Pall Med 2008 [83]	Impact of an Inpatient Palliative Care Team:	RCT	to measure the impact of an interdisc. palliative care service (IPCS) on patient satisfaction,clinical outcomes, and cost of care	18 or more years of age, hospitalized, and whose attending physician indicated they would not be surprised if the patient died within 1 year	multicenter	USA	1+	N=517; 5 drop-outs (withdrew their consent)	283/329	IPCS: 73,6/ Usual Care: 73,1	27.3% bzw. 34.4%	1. cancer, CHF, MI, other heart disease, COPD, other pulmonary disease; ESRD; organ failure; stroke, dementia	ECOG Score:IPCS: 2; usual care: 2; Quality of Life (Physical area scale; Emotional/relationship area scale; self reproted quality of life. All measured on a 11-point scale). No differneces in both groups.
Hanks, Br J Cancer (2002) [84]	The imPaCT study: a randomised controlled trial to evaluate a hospital palliative care team	blinded RCT	asses the effectiveness of a hospital palliative care team on physical symptoms and health related quality of life(HRQoL): compare outcomes symptom control, health-related quality of life, duration of hospital admission, rate of re-admission)	initially only patients with cancer, later on all diagnostic groups (since they represent ~10% of the total)	single center	Bristol, UK	1 ++	684 / 261 left for randomisation	119/142 (= study patients)	68,4	93% / 88%	cancer or non-cancer	-
Jack, Eur J Cancer Care 2006 [85]	Improving cancer patients' pain: the impact of the hospital specialist palliative care team	non-equivalent control group design /CBA	measuring symptom control and effectiveness of a hospital palliative care team	confirmed diagnosis of cancer	single center	UK	**2-**; the non-equivalent control group design clearly impairs comparability, and intervention was not described	n=100, control group n=50/ n=5/ n=0 intervention n=50 /n=19/ n=16	42/58 total control: 13/37 intervention: 29/21	-	100	Confirmed diagnosis of cancer, intervention group with referral to PCT, control group without PCT; primary sites: 27% colon/rectum CA 24% lung	PACA tool
Norton, Crit Care Med 2007 [86]	Proactive palliative care in the medical intensive care unit: Effects on length of stay for selected high-risk patients	prospective pre/post nonequivalent control group design, performance improvement study /CBA	examine the effect of proactive palliative care consultation on length of stay for high-risk patients in the medical intensive care unit	MICU patients at high risk of dying werde screened within 72h of admission: a) intensive care admission following a current hospital stay of >/= 10days; b) age >80yrs in presence of >/= 2 life-threatening comorbidities; c)diagnosis of an active stage IV malignancy; d)status post cardiac arrest; e) diagnosis of an intracerebral hemorrhage requiring mechanical ventilation	singlecenter	USA	**2+** (sequential, non-randomized observational design)	Usual care: n=65/ - / n=36 (55,4%) death in hospital; intervention: n=126/ -/ n=75 (59,5%) death in hospital;	Usual Care: (32/33) intervention: (69/57)	Usual Care: 68,75 intervention: 66,31	Usual Care: 7 (10,8%) intervention: 26 (20,6%)	see "inclusion criteria"	mainly two outcome measures: days in MICU; total days in hospital
SUPPORT, JAMA 1995 [87]	A Controlled Trial to Improve Care for Seriously Ill Hospitalized Patients	prospective observational cohort study (phase I) plus RCT (phase II)	improving end-of-life decision making, reduce frequency of mechanically support painful, prolonged process of dying	adults, hospitalized with ≥1 of nine life-threatening diagnoses; an 47% overall death mortality rate	multicenter (five Hospitals)	USA	1 -	n=9105 [phase I: n=4301; phase II: n=4804 in two groups: n(intervention)= 2652 and n(control)=2152	I = 1849/2452 II = 2128/2676	I = 65 II = 65	I = 16.9% II = 14.4%	acute organ system failure (I/II= 42,9%/49,6%) (acute respiratory failure, multiple organ system failure with sepsis, multiple organ system failure with malignancy), chronic disease(I/II= 34,4%/28,8%)	ADL (I/II=1,6/1,5) APS of Apache (I/II= 33/32)

Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification	Number of patients / Dropouts (DO) / Dropouts through death (DO‡)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Performance status (ECOG, …)
SPEZIALISIERTE PALLIATIVAMBULANZ													
Rabow, Arch Intern Med 2004 [88]	The Comprehensive Care Team. A Controlled Trial of Outpatient Palliative Medicine Consultation	CCT (randomisation of primary care physicians (not patients))	We compared physical, psychological, social, and spiritual outcomes between an intervention group of patients receiving a multifaceted, outpatient, palliative medicine consultation intervention plus usual primary care and a control group receiving only usual primary care.	adult patients with diagnoses of cancer, advanced COPD, or advanced CHF, whom they believed had a life expectancy of 1 to 5 years and who were not yet ready for hospice care. We excluded patients with nonmelanoma skin cancers, dementia, or psychosis; those enrolled in hospice care; and those unable to complete a written survey in English or Spanish.	single center	USA	1-	intervention group/comparison group: N=50/40 enrolled / drop outs: 15/9 / deaths:10/5	37/13 and 21/19	The mean age of study participants (N = 90) was 68.6 years (no diff between groups)	26%/42%	CHF 34%/35%; COPD 40%/20%. Mean baseline forced expiratory volume in 1 second for patients with COPD was 1.29 (SD, 0.32), and the mean baseline ejection fraction for those with CHF was 46.9% (SD, 13.0), with no significant difference between groups (*P* = .85 and *P* = .40, respectively).	There was no significant group difference (*P* = .15) in baseline mean functional status on the Rapid Disability Rating Scale (27.5 [SD, 6.2] for the intervention group; 25.1 [SD, 7.8] for the control group).
Rabow, J Palliat Med 2003 [89]	The Comprehensive Care Team: A Description of a Controlled Trial of Care at the Beginning of the End of Life	Survey (quantitative descriptive/observational). The paper does summarize feedbacks, experiences and observations during the study without being a formal survey.	This paper presents a basic description of the CCT project and research program. In addition, it outlines the major challenges, successes, and lessons learned in the course of developing and implementing this outpatient palliative care intervention.	see above	see above	see above	3	see above	see above	see above	see above	see above	see above
Temel, NEJM 2010 [90]	Early palliative care for patients with metastatic NSCL cancer	RCT, parallel, nonblinded	to examine the effect of early PC integrated with standard oncologic care	pathologically confirmed metastatic NSCL within previous 8 weeks; ECOG 0-2, not receiving PC	single center	USA	**1++** (no blinding but otherwise high quality)	n=151 / drop outs n=43 († 27)	78/73	Interv (mean): 64.98±9.73 Control: 64.87±9.41	100%	Newly diagnosed metastatic NSCL cancer (26-31% brain metastases)	ECOG 1 (n=81) ECOG 2 (n=14)
Yoong, JAMA Intern Med 2013 [91]	Early Palliative Care in Advanced Lung Cancer	Qualitative (content analysis on health records)	to (1) identify key elements of early PC clinic visits, (2) explore the timing of key elements, and (3) compare the content of PC and oncologic visit notes at time points of clinical deterioration / radiographic disease progression.	idem	idem	idem		n=20 from PC intervention group (5 patients from 4 survival groups: < 3 months, 3-6 mth, 6-12 mth, 12-24 mth)	12. Aug	Mean: 68 (47-84)	idem	Survival: < 3 months (n=5), 3-6 mth (n=5), 6-12 mth (n=5), 12-24 mth (n=5)	-

Study characteristics / Patients' characteristics at baseline

Author, Journal, Year	Title	Type of study / Design	Aim of study	Inclusion criteria	Centre (single - multicentric)	Country	Level of Evidence =LoE (SIGN) / Justification	Number of patients / Dropouts (DO) / Dropouts through death (DO†)	Female / Male (n/n)	Age (mean, SD)	% of patients with cancer	1. Diagnosis 2. stage/grade 3. phase of illness	Perform-ance status (ECOG, …)	Patients' needs (psychosocial, spiritual, etc…)	Others
TAGESKLINIK															
Goodwin, J Pain Symptom Manage 2003 [92]	Effectiveness of Palliative Day Care in Improving Pain, Symptom Control, and Quality of Life	Prospective comparative study (cohort study)	This analysis aims to evaluate the effectiveness of palliative day care in improving pain, symptom control, and QoL.	The day care patients were consecutive new referrals to the five centers. Eligibility criteria for both groups of patients were: over 18 years of age, well enough to be interviewed (for approximately 35–45 minutes), and no obvious confusion /not severely cognitively impaired.	5 day care centers in the UK.	UK	2-	intervention group/comparison group: N=120/53: first interview 102/47 / drop outs: 88/29 / deaths ?	first interview 50/52 (interv) 23/24 (comparison)	interv (mean): 64.39±13.17 Control: 69.98±10.62 (p=0.009)	99%	Lung cancer 24 (23.5%)/14 (31.8%); Gastrointestinal 20 (19.6%)/8 (18.2%); Breast 18 (17.5%)/3 (6.8%); Genitourinary/Prostate 20 (19.6%)/12 (27.2%); Gynae 16 (15.5%)/5 (11.4%); Other cancer 4 (3.9%)/2 (4.5%)	nn	There was a marginally significant baseline difference for the POS item 'pain control' (*P* 0.053), where the comparison group had more severe/overwhelming scores.	
Higginson, Support Care Cancer 2010 [93]	Does a social model of hospice day care affect advanced cancer patients' use of other health and social services? A prospective quasi-experimental trial	CBA (quasi-experimental trial)	to evaluate the effect of a new HDC (Hospice Day Care) on the use of health and social services	• >18 y • advanced cancer • receiving palliative care (included in hospice programm)	single center	GB	2- (high drop out rate)	163 (HDC:37, Standard: 50, before: 76) 104 drop-outs (death or too ill)	Male: HDC: 62% Standard: 52% Before: 40% Female: HDC:38% Standard:48% Before: 60%	70,5-75,7	100%	1. Cancer 3. Advance		**POS** (Palliative Outcome Scale): mean 7.9-8.4, similar in all groups **HHI** (Hope): lower in HDC group at baseline	**General health status** (EQ-5D VAS 1-100): 60.2-64.7; similar in all groups
Sviden, Palliat Med 2009 [94]	Palliative day care – a study of well-being and health-related quality of life	controlled cohort study (matched controls 2:1 re age, gender and functional status) - only after-measurements	to study the outcomes of palliative day care, in terms of health-related quality of life and the emotional well-being of cancer patients participating in a palliative day-care programme for a period of 5 weeks, compared with a group of patients in palliative care but not participating in day care.	cancer; no confusion - recruitment between 2003 and 2005	two day care centers	Sweden	2-	Included: 31/17; completed: 23/12	female: 25/14	Majority between 50-69 y	100%	not reported	between 50-70 Karnofsky	not reported	
STATIONÄRES HOSPIZ (keine Studien identifiziert)															

Informal caregivers' (CG) characteristics at baseline / Needs assessment / Needs complexity

Author, Journal, Year	Number of CG / Drop outs	Female / Male (n/n)	Age (mean, SD)	CGs'needs (psychosocial, spiritual, etc…	Others	Who assesses	When	How (tool)	Categories	Process of categorisation (needs > complexity)
Goodwin, J Pain Symptom Manage 2003 [92]						Researcher	1. baseline; 2. 6-8 weeks; 3. 12-15 weeks	POS	siehe POS	siehe POS
Higginson, Support Care Cancer 2010 [93]						trained interviewers				
Sviden, Palliat Med 2009 [94]										

Intervention characteristics (structure and process quality criteria)

Author, Journal, Year	Overall description: Intervention	Overall description: Control	Setting	Health care providers: Total, n/profession or qualification	Number of places/ beds	Equipment (incl. drugs, EDV, setting/ room/housing)	Funding: Who (source)	Funding: How much	Organisation / Management related to structures: Who	Organisation / Management related to structures: How	Referral criteria / allocation of place
Goodwin, J Pain Symptom Manage 2003 [92]	day care (palliative/hospice): For the purpose of this study, palliative day care was defined as day care in a hospice setting; it did not include attendance at day care for outpatient appointments.	without day care: All patients received the usual palliative care services (home care, in-patient sevices, and outpatient services), but the comparison group did not attend day care.	day care at day care centers: Five palliative day care centers in the UK provided facilities for medical and nursing assessment of all patients. At each center, there was a variety of social, recreational, and therapeutic activities. The centers often employed specialists, such as art therapists and aromatherapists.	At each center, there was a variety of social, recreational, and therapeutic activities. The centers often employed specialists, such as art therapists and aromatherapists.							The reasons for referral to day care given by the health care professionals included: social support (49%), time out of home (20%), symptom management (14%), therapeutic intervention (12%), psychological support (2%), respite for caregiver (4%).
Higginson, Support Care Cancer 2010 [93]	Hospice Day Care (HDC) in addition to standard palliative care	1. Before group (historical group, recruited before HDC unit was built) 2. Standard palliative care group	Hospice programm in South East England (HDC, in-patients, home care)		HDC: 10-15 places/day, opened 3 days/week						<u>Reasons</u> for referral to HDC included: • social support (37%) • respite for carer (22%) • social and • psychological support (19%) • social and medical support (15%) • time out of home (7%)
Sviden, Palliat Med 2009 [94]	palliative day care settings in Sweden could be described as applying a social model of care placed within a medical context, providing an environment for social and therapeutic activity.	no day care (but could have had home palliative care)	hospital-based outpatient service	Occupational therapists and nurses managed the programmes, and a multiprofessional team comprising of a physiotherapist, a physician, a social worker and a chaplain was available for the participants if required.	8 to 10	not reported	not reported	not reported	occupational therapists and nurses		not reported

Intervention characteristics (continued) / Outcomes / Results / Comments

Author, Journal, Year	Description of **intervention**: Schedule/Frequency	Description of **intervention**: Content (clinical/non-clinical)	Description of **bereavement intervention**: Schedule/Frequency	Description of **bereavement intervention**: Content	Description of **control** intervention	Coodination of intervention: Who	Coodination of intervention: How	Discharge criteria	Integration of oncological and palliative structures: Who	Integration of oncological and palliative structures: How	Others	Primary outcomes (1.O) - Secondary outcomes (2.O) / Measure (tool, when, how long)	Costs	Results for each outcome	Results for outcomes related to informal CG	Comments
Goodwin, J Pain Symptom Manage 2003 [92]												1. QoL (McGill Quality of Life Questionnaire); 2. POS (single items (symptom control) + overall (QoL)) at each interview time point		The comparison group had marginally more severe pain at baseline (p= 0.053) and more severe **symptoms** at second assessment (p= 0.025). Both patient groups maintained overall **health-related quality of life** during the three months of the study (p= 0.065). Palliative day care was not found to improve overall health-related quality of life. (effect sizes not mentioned)		Limitations related to difference at baseline (characteristics/pain, number of pts) and the lack of randomisation.
Higginson, Support Care Cancer 2010 [93]	usually 1 day a week, 10am-3pm	Mainly social content: • lunch, tea, coffee, social activities, including discussion and art and craft, supported by volunteers • aromatherapy, massage, or reflexology, offered individually • If required, patients could see a physiotherapist or a nurse • Volunteer transport was available to take patients to and from the day unit			1. **Before group**: Patients who were receiving hospice services (home care or in-patients) and lived in the catchment region of the planned day hospice were recruited. As soon as the day unit opened, recruitment to this group ceased. 2. **Standard palliative care group:** Home care palliative nursing teams of the hospice. They were not receiving day care usually because of choice or convenience (travel distance).							Patient outcomes: • Overall health status (EQ-5D, VAS 1-100) • Self-assessment of patients' hope (Herth Hope Index, HHI, Likert 1-4) • Palliative needs (POS, Palliative Outcome Scale, Likert 0-4) Difference in use of following services: • Community (GP, district nurse, …) • Hospice (PC doctor or nurse) • Social care support (social worker, home help, melas, priest) • Hospital (cancer specialist, other doctor or nurse) • Therapist (occupational, dietician, physiotherapist, chiropodist) <u>Time of measures:</u> • Baseline • 6-8 weeks • 12-15 weeks		Patient outcomes: • **Overall health status**: n.s. • **HHI:** sign. improvement compared to Before group at 1st follow-up (mean change, 2.2 versus −1.0; p=0.050, F= 4.19) • **POS:** n.s Difference in **use of services**: • <u>At baseline</u>: patients in the HDC group used almost all services, except for hospital services, more than the standard care (P=0.004, Wilk's λ=0.74, F5,57=4.00) and before groups, although the difference with the latter (P=0.07, Wilk's λ=0.87, F5,81=2.18) was not significant. • <u>Baseline -> 1st follow-up</u>: sign. change of therapist service use between HDC and standard group (adjusted P=0.003). The change was in the opposite direction, with a reduction in the HDC group and an increase in the standard care group (mean change±SD, 0.1±0.5; 95%CI, −0.1 to 0.3). • None of the other baseline or service change differences reached significance level.		<u>Limitations:</u> • Sample size calculation but high rate of dropouts (total: 63%; HDC: 70%; Standard: 60%; Before: 63%) -> limited power. • the before group was slightly different from the HDC and standard care groups—in particular comprising more patients with breast cancer. Breast cancer has a longer survival than many other cancers and it may be that the before group comprised longer surviving patients who had been 'waiting' for HDC to start. This may explain some of the differences in baseline service use. <u>Findings:</u> • The lack of particular trends towards differences suggests that if HDC does have an effect, it is small. Indeed it is usual that non-randomized studies find a greater effect than randomized studies. Our findings support the proposal of Hopkins and Tookman of a move away from the social model of HDC to a more therapy-based model. • Our data appear to suggest that HDC supplements existing services.
Sviden, Palliat Med 2009 [94]	The participants visited the day care setting one to three times a week, depending on their situation, needs and desires. There were about 8–10 participants attending each day, spending between 2 and 5 h in the setting.	The programme aimed to enhance well-being and quality of life. The main focus of the programme was to offer opportunities to participate in creative and social activities. Included in the programme were different activities, like arts and crafts, gardening, physical exercise, outings and gathering around for coffee and lunch. Activities were organised both on a group and on an individual basis. The goal and the content of the two different facilities were the same.	-		no day care service; usual care (including home palliative care services)	occupational therapists and nurses		not explicit stated	not explicit stated			weekly during 5 weeks. Quality of life/symptoms (EORTC QLQ-30) + emotional weel-being (Mood Adjective List (MACL))	-	Higher levels of emotional well-being for the day-care-group (but not statistical sign). Same levels for QoL/symptoms	-	Limitations: only after-measurements; lack of information about pts characteristics (e.g. cancer diagnosis etc.); no sample size calculation

4. Kommunikation

4.1. Vorausschauende Versorgungsplanung

4.1.1. Primärstudien

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evi-dence SIGN
Bakitas, JAMA 2009 [56]	RCT	n=322 (279 included in primary outcome analysis, 322 included in survival outcome analyses)	▪ Patients with cancer of the gastrointestinal tract, lung, genitourinary tract and breast ▪ Patients with impaired cognition mini-mental state, an axis I psychiatric disorder or active substance use were excluded.	▪ Multicomponent, psychoeducational intervention conducted by advanced practice nurses consisting of 4 weekly educational sessions and monthly follow-up telephone sessions until death or study completion (n=161). The education manual contained 4 modules of problem solving, communication and social support, symptom management, advance care planning and unfinished business, and an appendix listing supportive care resources ▪ Usual care (n=161).	**1.0:** Higher scores for quality of life (p=0.02) in the intervention group as compared to the control group, no improvements in symptom intensity scores or reduced days in hospital or ICU or emergency department. **2.0:** Higher scores in mood (p=0.02 for all participants, p=0.03 for patients who died during the study)) in the intervention group as compared to the control group Post hoc, exploratory analyses demonstrated no statistically significant differences in survival between the intervention and the control group **Quality of life**: assessed with the Functional	Estimated treatment effects (intervention minus usual care) for all subjects were 4.6 (P = 0.02) for QOL, −27.8 (P = 0.06) for symptom intensity, and −1.8 (P = 0.02) for depressed mood. Estimated average treatment effects in the sample of participants who died during the study were 8.6 (P = 0.02) for QOL, −24.2 (P = 0.24) for symptom intensity, and −2.7 (P = 0.03) for depressed mood. Compared with participants receiving usual oncology care, those receiving a nurse-led, palliative care–focused intervention addressing physical, psychosocial, and care coordination provided concurrently with oncology care	▪ ACP as part of a multicomponent, psychoeducational intervention	1+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evi-dence SIGN
					Assessment of Chronic Illness Therapy for Palliative Care **Mood**: assessed with the CES-D 2 sets of longitudinal, intention-to-treat analyses for all participants with baseline and 1 or more follow-up assessments using repeated measures analysis of covariance to examine the effect of the intervention on (1) the total sample in the year after enrollment and (2) the sample of participants who died.	had higher scores for quality of life and mood, but did not have improvements in symptom intensity scores or reduced days in the hospital or ICU or emergency department visits.		
Clayton, Clin Oncol 2007 [95]	RCT / coder blinded / Parallel	174/4	Advanced **cancer** patients and their caregivers who were referred for palliative care. Inclusion criteria: 1) diagnosis of an advanced progressive life limiting illness, (2) English speaking, (3) older than 18 years of age, and (4) able and well enough to read QPL and complete questionnaires.	Provision of a question prompt list (QPL) with structured questions to patients before consultation /usual care consultation	**1.0** number of patient questions during consultation and topics of topics relevant to end-of-life care during consultations with a palliative care (PC) physician **2.0** total numbers of items discussed, patient concerns and caregiver questions/concerns, number of items discussed and patient/caregiver questions/concerns about nine individual topics covered by the QPL, achievement of patient information preferences, patient satisfaction with the consultation, patient anxiety, physician	Compared with controls, QPL patients and caregivers asked **twice as many questions** (for patients, ratio, 2.3; 95% CI, 1.7 to 3.2; P _ .0001), and patients discussed 23% more issues covered by the QPL (95% CI, 11% to 37%; P _ .0001). QPL patients asked **more prognostic questions** (ratio, 2.3; 95% CI, 1.3 to 4.0; P _ .004) and discussed more prognostic (ratio, 1.43; 95% CI, 1.1 to 1.8, P _ .003) and end-of-life issues (30% v 10%; P _ .001). Fewer QPL patients	Well done study, intelligent design Intervention is a tool to facilitate ACP / encourage asking important q.s Prim. Outcome is difference of ACP consultation quality: contents: #, duration and content of questions No harm done in terms of anxiety etc., but also no clinical criteria Not about the clinical impact of ACP, but how to best realise ACP	1+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
					satisfaction with communication during the consultation, and consultation duration	had unmet information needs about the future (_2 1 _ 4.14; P _ .04), which was the area of greatest unmet information need. QPL consultations (average, 38 minutes) were longer (P _ .002) than controls (average, 31 minutes). No differences between groups were observed in **anxiety** or **patient/physician satisfaction**	Ilicited questions re. caregiver that otherwise were not asked Setting: SAPV-Äquivalent	
Dyar, J Pall Med 2012 [96]	Initially designed as a randomized phase 2 Trial with a goal of accruing 100 patients with-metastatic cancer (50 patients per arm). Patients were randomized to either a control arm or an intervention arm.	Final questionnaire data could not be analyzed for eight patients, two in the intervention group and six in the control group. Two patients, both in the control group, were too ill to complete the baseline and follow-up questionnaires. Two participants withdrew because of lack of compliance	See summary in table 1, keine signifikanten Unterschiede zwischen beiden Gruppen	The control group completed baseline and one month later (or at the time of hospice referral if that occurred earlier) hospice knowledge questionnaires (HKQ) and QoL tools, including the Functional Assessment of Cancer Therapy-General [FACT-G] and the Linear Analogue Self Assessment scale (LASA), but did not receive any mandatory palliative care intervention. These patients had access to palliative care consultations and hospice referrals as	Relevant endpoints included **change from baseline QoL and improvement in hospice knowledge.** Although an original primary endpoint of the study was to assess time to hospice referral in the two groups, the frequently prolonged period to hospice referral, relatively short study follow-up, and small sample size made it difficult to assess this outcome. By the same token, sense of abandonment upon hospice referral, which was a secondary endpoint of the study, could not be properly evaluated from the data collected. We set out	This study closed after the first 26 patients were entered in view of the finding of the positive effects of a nurse intervention in terminal cancers as reported by Bakitas and colleagues, and in view of the preliminary data analysis of the patients offered participation in this study that showed that many patients refused study participation as a result of the control arm and their desire to receive the ARNP intervention. There was a statistically significant improvement in the **FACT-G emotional domain** in the	Outcomes not clear defined; Early break of the study; Few patients; ACP is only part of the intervention	1-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
		with the required visits and consultations. One of them had expressed interest in the intervention arm and was not interested in participating in the control portion of the study after randomization. Four patients died prior to completing the followup survey (one in intervention group, three in control group).		deemed indicated by their oncology team. Patients on the intervention arm, in addition to completing the questionnaires and QoL tools at baseline (pre-intervention) and one month later (post-intervention), had an initial and a one-month followup consultation with an oncology ARNP who taught them about hospice, helped fill out the Five Wishes and living will forms, and assessed their psychological, physical, intellectual/ cognitive, social, and spiritual needs	to demonstrate that QoL outcomes can be improved with ARNP-directed education and follow-up. **Outcome measures:** Hospice knowledge questionnaires (HKQ) QoL tools, including the Functional Assessment of Cancer Therapy-General [FACT-G] Linear Analogue Self Assessment scale (LASA)	intervention group [Mean 1.2 (SD 2.94) vs. Mean – 4.5 (SD 4.54) in non-interventional group] . None of the additional FACT-G domains had statistically significant differences between groups. **LASA scale**: The change from baseline mental QoL was statistically improved. p = 0.0219		
Loberiza, Leukemia & Lymphoma 2011 [97]	prospective observational study	770 were found to be eligible, participation rate of 47% (364/770). The current analyses are focused on 293 (80%) participants who completed a	Lymphoma, Leukaemia or MDS, detailed characteristics see table 1, p.2344	In this study, we defined ACP in two ways. First, as used in our previous study [4], we ascertained the presence of written plans of ACP as those who responded " yes " to having both a living will and health care proxy, while patients with only one or neither	Keine Klare Zielkriterienbestimmung: Stepwise covariate selection was performed to identify psychosocial domains and patient characteristics (as listed in Table I) associated with having ACP. Physician estimate of life expectancy was also tested as a	Nur für „verbal ACP": As for factors associated with discussions about life support with family/friends and/or health providers (verbal plans), Table III also shows that lower physical component score of the SF-36 (OR 0.98, 95% CI 0.96 – 0.99, p _		2-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
		preconsultation self-administered survey, a pre-consultation interview and a post-consultation (after 3 months) interview, and had their consultation successfully audiotaped.		were considered to have no ACP. Second, we also defined verbal ACP based on whether or not patients reported having discussions about life support with their family/friends and medical care team, based on clinical practice, which largely defers to orally communicated wishes over written documents Anmerkung: nur "verbal ACP" relevant für SR, wobei hier auch Situationen dabei gewesen sein könnten, in denen Patienten nur mit Angehörigen gesprochen haben:	covariate in the all-model building. A separate logistic model was also constructed to evaluate whether the above factors were associated with discussing life support with family and/or physician (verbal plan). Covariates with an α of less than or equal to 0.05 were retained in the model.	0.03); lower score on general health (OR 0.98, 95% CI 0.97 – 0.99, p _ 0.007); and lower physician estimate of life expectancy (OR 0.82, 95% CI 0.67 – 0.99, p _ 0.04) were the only factors associated with having discussed life support with family/friends and/or health providers.		
Loggers, JCO 2009 [98]	multisite, prospective, interview-based cohort study	Black (n _ 68) and white (n _ 234) patients. Of the 944 patients who were initially approached and confirmed to be eligible, 274 (29.0%)	Patients with **stage IV cancer** and caregivers participated, September 2002 to August 2008. (Coping with Cancer study)	The following questions (with response options of "yes" or "no") were asked to assess having an EOL discussion, and having a DNR order, respectively: "Have you and your doctor discussed any particular wishes you have about the care you would want	**1.O.:** intensive EOL care defined as CPR and/or ventilation within the last week of life followed by death in an intensive care unit (ICU). Selection of this end point targets those receiving the most aggressive EOL care and eliminates consideration of individuals who, for example, received a brief trial of ventilation and then	White patients who reported an EOL discussion or DNR order did not receive intensive EOL care; similar reports were not protective for black patients (aOR 0.53, P .460; and aOR 0.65, P .618, respectively)	Generalisability of ACP intervention that does only work with white patients?	2-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
		declined participation. Given the outcomes of interest, the sample was further limited to patients who had died (n_371) with complete information on location of death (n_370), self-reported black or white race (n _ 303, those excluded reported other racial or ethnic backgrounds, the majority being self-identified as Hispanic), and complete information on at least four of the five predictors of interest, resulting in a total of 302 patients		to receive if you were dying?";	elected to die athomeor in hospice.			
Mack, JCO 2012 [99]	Cancer Care Outcomes Research and Surveillance	1231	patients with **stage IV lung or colorectal cancer** in the Cancer Care	EOL discussions were identified if the patient or surrogate reported a discussion with the	**Keine klare Benennung von primären/sekundären Zielkriterien:**	Patients who had EOL discussions with their physicians before the last 30 days of life were less	"End of life discussion" ist auch erfüllt, wenn über Wiederbelebung mit dem Arzt	2-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
	Consortium, a population- and health system–based prospective cohort study, who died during		Outcomes Research and Surveillance Consortium, who died during the 15-month study period but survived at least 1 month	physician about resuscitation from patient and surrogate interviews for living patients) or hospice care (eg, "After your cancer was diagnosed, did any doctor or other health care provider discuss hospice care with you?" from all interview types, or "Was hospice recommended by any doctor or other health care provider?" from follow-up interviews.) EOL discussions were identified in medical records if there was documentation of a discussion about advance care planning (do-not resuscitate order, hospice, palliative care, or not otherwise specified) or venue for dying (hospice, home, hospital, nursing home, or not otherwise Specified	After characterizing attributes of EOL care, bivariate logistic regression was used to investigate the association between attributes of EOL discussions (for the full sample, presence and source of EOL discussion; for MRA documented discussions, days between first EOL discussion and death, presence of medical oncologist, and inpatient discussion) and aggressiveness of EOLcare received. Multivariable logistic regression models were fitted for each marker of aggressive EOL care and hospice. The attributes of EOL discussions were included in multivariable models regardless of significance. Patient characteristics were sequentially removed from models using backward selection until remaining characteristics had a significance level_.10.	likely to receive aggressive measures at EOL, including chemotherapy (P = 0.003), acute care (P = 0.001), or any aggressive care (P = 0.001). Such patients were also more likely to receive hospice care (P = 0.001) and to have hospice initiated earlier (P = 0.001).	gesprochen wurde, oder wenn es in der Akte einen Hinweis auf eine Diskussion über Hospice oder palliative care gibt.	
Mack, 2010 [100]	longitudinal multi-institutional cohort study	325	Patients recruited as part of the Coping with Cancer Study. Patients with **advanced cancer**.	Patients were asked in "yes/no" format whether they and their physician had discussed any wishes about the care	**1.O.:** Measures Treatment preferences, EOL treatment received, Receipt of care consistent with preferences.	Patients who reported having discussed their wishes for **EOL care** with a physician (39%, 125 of 322 patients) were more likely to receive care that		2-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			This report describes 325 patients recruited between October 2002 and September 2007 whose self-reported treatment preferences were available and who died during the course of the study	they would want to receive if they were dying.	**2. O.:** Measures Quality of life and distress. Survival.	was consistent with their preferences, both in the full sample (odds ratio [OR] _ 2.26; P = 0.0001) and among patients who were aware they were terminally ill (OR = 3.94; P = 0.0005). Among patients who received no life-extending measures, physical distress was lower (mean score, 3.1 v 4.1; P = 0.03) among patients for whom such care was consistent with preferences.		
Stein, A J Clin Oncol 2013 [101]	RCT/	120/16 (primary outcome)/58 (secondary outcome)	diagnosis of **metastatic cancer**, no further curative treatment, estimated life expectancy of 3 to 12 months, awareness of prognosis, and English literacy.	Pamphlet and Discussion pamphlet and discussion with a psychologist (R.A.S.). The pamphlet was called “Living with Advanced Cancer” and contained five sections: “Communicating with the health care team,” “Anticancer treatments,” “Symptom management,” “Psychological care,” and “Planning for the future.” The pamphlet was developed according to the CREDIBLE	**1.0.**The primary outcomes were the place of death (in hospital or not), whether a patient had a DNR order, and the number of days between the earliest DNR order documentation and death. **2.0.** Depression and anxiety. The Hospital Anxiety and Depression Scale (HADS)21 assesses anxiety and depression. There is good evidence for its reliability and validity in oncology.22 Cronbach _ in this sample was 0.77 for anxiety and 0.80 for depression.	intention-to-treat analyses, neither remained significant (P = 0.06).In per-protocol analyses, DNR orders were placed earlier for patients who received the intervention (median, 27 v 12.5 days; 95% CI, 1.1 to 5.9; P = 0.03) and they were more likely to avoid a hospital death (19% v 50% (95% CI, 11% to 50%; P = 0.004). Differences between the groups over time were evident for estimates of cardiopulmonary		1+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
				(Competently, Recently Updated, Evidence, Devoid of Conflicts of Interest, Balanced Presentation of Options, Efficacious) criteria19 for patient decision aids. During the development phase, it was reviewed by patients, oncologists, and allied health professionals. The discussion was based on a shared decision-making model. The aim was to encourage patients to consider their preferences and values toward the end of life. The discussion was semistructured with four themes: (1) communicating with the doctor and family; (2) symptoms and their adverse effects; (3) psychological and palliative care; and (4) end-of life decision making and planning. Questions about end-of-life decision making included: "Have you been able to talk to people in your life and settle	Caregiver burden. The Caregivers Reaction Assessment (CRA)23 provides a measure of caregiver burden. It has five subscales: caregiver's selfesteem, family support, finances, disruption to schedule, and health. There is good evidence that the CRA has good validity and reliability in patients with metastatic cancer.23 The Cronbach _ in this sample was 0.82. Process measures: knowledge. The knowledge questionnaire was adapted from Kerridge et al.24 Patients indicate which, from a list of 10 procedures, are involved during CPR and estimate the success rates of CPR in different situations.	rehabilitation (CPR) success rates (P _ .01) but not knowledge of CPR (P _ .2). There was no evidence that the intervention resulted in more anxious or depressive symptoms. Caregivers experienced less burden in terms of disruption to schedule if the patient received the intervention (P _ .05)		

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
				unfinished business?" "Have you thought about how you would like to say goodbye?" "Have you been able to talk about your wishes in the event that you become more unwell?" "Have you thought about decisions like whether you would choose to be resuscitated				
Wright, JAMA 2008 [102]	prospective, longitudinal cohort study	n=332	▪ Patients with diagnosis of **advanced cancer** from 7 different outpatient sites in the USA ▪ age at least 20 years ▪ presence of an informal caregiver ▪ clinic staff and interviewer assessment that patient had adequate stamina to complete interview Of the 917 eligible patients, 638 patients (69.6%) consented and enrolled in the larger	In the baseline interview, patients were asked: "Have you and your doctor discussed any particular wishes you have about the care you would want to receive if you were dying?" Responses were coded as 1 for yes and 2 for no.	**1.O:** Aggressive medical care (eg, ventilation, resuscitation) and hospice in the final week of life. **2.O:** patients' mental health and caregivers' bereavement adjustment Mental health measures included the Structured Clinical Interview for DSM-IV , the Endicott Scale, and McGill Quality of Life psychological subscale. Patients' functional status and comorbid medical conditions were measured with the Karnofsky score and the Charlson Comorbidity Index, respectively. Quality of life was assessed with the McGill Quality of Life Index's physical health,	One hundred twenty-three of 332 (37.0%) patients reported having end-of-life discussions before baseline. Such discussions were not associated with higher rates of major depressive disorder (8.3% vs 5.8%; adjusted odds ratio [OR], 1.33; 95% confidence interval [CI], 0.54-3.32), or more worry (mean McGill score, 6.5 vs 7.0; P=.19). After propensity-score weighted adjustment, **end-of-life discussions** were associated with lower rates of **ventilation** (1.6% vs 11.0%; adjusted OR, 0.26; 95% CI, 0.08-0.83), **resuscitation** (0.8% vs 6.7%; adjusted OR, 0.16; 95% CI, 0.03-	The findings are constrained by the limited information available on the end-of-life discussions. There is no information who initiated the conversation, when it happened, or what was said. the study does not include interviews with physicians or audiotaped conversations. Since there is no independent validation, the accuracy of patients' reported rates of discussions remains unknown. In addition, the study sample had disproportionately high rates of ethnic minority patients who	2-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			study. Of the 279 patients who refused participation, 120 were not interested, 69 cited other reasons, and 37 patients' caregivers refused participation. For the analysis, the sample was restricted to the 332 patients who died to examine the medical care that patients received in the final week of life. The deceased cohort did not differ significantly by cancer type, psychological distress, or rates of psychiatric disorders.		symptom, and social support subscales.	0.80), ICU admission (4.1% vs 12.4%; adjusted OR, 0.35; 95% CI, 0.14-0.90), and earlier **hospice enrolment** (65.6% vs 44.5%; adjusted OR, 1.65; 95% CI, 1.04-2.63). In adjusted analyses, more **aggressive medical care** was associated with worse patient quality of life (6.4 vs 4.6; F=3.61, P=.01) and higher risk of major depressive disorder in bereaved caregivers (adjusted OR, 3.37; 95% CI, 1.12-10.13), whereas longer hospice stays were associated with better patient quality of life (mean score, 5.6 vs 6.9; F=3.70, P=.01). Better patient quality of life was associated with better **caregiver quality** of life at follow-up (=.20; P=.001).	were highly symptomatic and had poor performance statuses.	
Zhang, Arch Intern Med 2009 [103]	prospective, longitudinal cohort study	n=603	▪ Patients with diagnosis of **advanced cancer** from 7 different outpa-tient sites in the USA ▪ age at least 20 years ▪ presence of an	In the baseline interview, patients were asked: "Have you and your doctor discussed any particular wishes you have about the care you would want to receive if you were dying?"	**1.O:** Aggressive medical care (eg, ventilation, resuscitation) and hospice in the final week of life. **2.O** Secondary outcomes included patients' mental health and caregivers' bereavement adjustment	Patients with advanced cancer who reported having **EOL conversations** with physicians had significantly lower health care costs in their final week of life. Higher costs were associated with worse quality of death in	The findings are constrained by the limited information available on the end-of-life discussions. There is no information who initiated the conversation, when it happened, or what was said. the	2-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			informal caregiver ▪ clinic staff and interviewer assessment that patient had adequate stamina to complete interview Of 875 patients approached for inclusion in the study and confirmed to be eligible, 627 patients (71.6%) were enrolled. The most common reasons for nonparticipation among 248 patients (28.3%) included "not interested" (n=118) and "caregiver refuses" (n=37). Compared with participants, nonparticipants were less likely to be of Hispanic race/ethnicity (5.5% vs 13.5%, P=.001). Otherwise, nonparticipants did not differ significantly from participants	Responses were coded as 1 for yes and 2 for no.	Mental health measures included the Structured Clinical Interview for DSM-IV , the Endicott Scale, and McGill Quality of Life psychological subscale. Patients' functional status and comorbid medical conditions were measured with the Karnofsky score and the Charlson Comorbidity Index, respectively. Quality of life was assessed with the McGill Quality of Life Index's physical health, symptom, and social support subscales.	the final week of life (Pearson production moment correlation partial =−0.17, P=.006).	study does not include interviews with physicians or audiotaped conversations. Since there is no independent validation, the accuracy of patients' reported rates of discussions remains unknown. In addition, the study sample had disproportionately high rates of ethnic minority patients who were highly symptomatic and had poor performance statuses.	

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			in age, sex, education status, or white, black, or Asian race/ethnicity. Of 627 patients enrolled, 603 (96.2%) responded to the question regarding prior EOL discussions that forms the basis for this study. Nonrespondents to the question did not differ significantly from respondents in cancer type, health status, recruitment site, or sociodemographic characteristics.					

5. Therapiezielfindung und Kriterien der Entscheidungsfindung

5.1. Entscheidungshilfen

Zwei Systematic Reviews bilden die Evidenzgrundlage zu Entscheidungshilfen [104, 105]. Da beide Reviews nicht auf Patienten mit einer Krebserkrankung fokussieren, sondern eine breitere Population einschließen, wurden im Folgenden die Primärstudien aus beiden Reviews neu extrahiert, die speziell Patienten mit einer Krebserkrankung untersuchen. Studien, die Entscheidungshilfen nur zum Screening einer Krebserkrankung einsetzten, wurden ausgeschlossen.

5.1.1. Primärstudien

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
STACEY ET AL. 2017 [105]								
Auvinen, BJU Int 2004 [106]	RCT; To determine whether different approaches in the choice of treatment affect the treatment chosen by the patient for prostate cancer.	n=103 + 100	Men newly diagnosed with **prostate cancer** in Finland	I: DA (Decision aid): pamphlet patient decision aid created for study on options' outcomes, outcome probability, guidance C: usual care by clinical guideline	- Uptake of options* - Participation in decision making	Patients not eligible for radical prostatectomy: chose orchidectomy less frequently and favoured nonsurgical endocrine treatment than in the treatment protocol arm Patients eligible for radical prostatectomy: Radical prostatectomy was the most commonly chosen treatment option in both arms The way treatment options were presented affected the treatment chosen for prostate cancer	Patients with prostate cancer are willing and able to take an active role in making decisions Method: - No blinding - not powered	1-
Berry, Urol	RCT; to compare usual	n=266 + 228	Men with newly **diagnosed localized prostate cancer**	I: DA: interactive web based video on options' outcomes,	- Decisional conflict (DC)*	**DC**: - **Total DC score**: n.s. (but trend to reduction:	the first intervention to significantly reduce decisional	1-

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Oncol 2013 [107]	patient education plus the Internet-based Personal Patient Profile-Prostate, vs. usual education alone, on conflict associated with decision making		considering treatment in the USA	clinical problem, outcome probabilities others' opinion, guidance (list of questions to ask doctor and automated summary) C: usual care	- preferred/actual treatment choice (pre and post DA) - Proportion undecided	estimate: -1.75; CI: -3.61,0.11; p=0,04) - **Uncertainty subscale**: sign. reduced (estimate: -3.61; CI: -7.01, 0.22) - Lack of values clarity subscale: sign. reduced (estimate: -3.57;CI: -5.85, -1.30; p=0.002) **Time-to-treatment**: n.s. **Undecided** men in the intervention group chose brachytherapy more often than in the control group	conflict in a multicenter trial of American men with newly diagnosed localized prostate cancer Method: - simple randomization - no blinding - not powered - ITT unclear	
Chabrera, Cancer Nurs 2015 [108]	RCT	n=73 + 74	Men recently diagnosed with **localized prostate cancer** considering treatment options	I: DA: 2-part decision support booklet with clinical problem, options' outcomes, outcome probabilities, patient stories, explicit values clarification, and guidance C: usual care	1.O: knowledge, decisional conflict (DC), satisfaction with decision-making process 2.O: coping Outcomes assessed at 3 months post-intervention	**DC**: sign. improved (p <.001): mean scores: - DA: Pre: 53.0 ±16.9; Post: 31.2 ± 10.2 - C: Pre: 49.1 ±13.7; Post: 51.7 ±13.3 **Knowledge**: sign. improved (p<.001): mean scores - DA: Pre: 38.6 ±16.5; Post: 75.7 ±19.0 - I: Pre: 42.0 ±17.6; Post: 49.9 ±16.0 **Satisfaction With Decision**: sign. improved (p<.001): mean scores	Method: - Allocation concealment unclear - Blinding unclear - not powered - no ITT	1-

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
						- DA: Pre: 81.1 ±8.92; Post: 95.7 ±6.89 - I: Pre: 82.5 ±12.0; Post: 79.3 ±10.3		
Davison, Cancer Nurs 1997 [109]	RCT; To explore the hypothesis that assisting men with prostate cancer to obtain information would enable them to assume a more active role in treatment decision making	n=30 + 30	Men with **prostate cancer** considering treatment in Canada	I: DA: written + audiotape consultation of options' outcomes, clinical problem, outcome probability, others' opinion C: usual care (general information pamphlets on clinical problem)	- Role in decision making* - Anxiety - Depression	**Role in decision making**: sign. better with DA **Anxiety**: sign. reduced with DA **Depression**: n.s.	Method: - block-randomized - no blinding - not powered	1-
Heller, Plast Reconstr Surg 2008 [110]	RCT; To assess effectiveness of interactive digital education aid for breast reconstruction patients	n=66 + 67	**Breast cancer** patients eligible for breast reconstruction in the USA	I: DA: interactive software programme on options' outcomes, others' opinions C: standard patient education	- Knowledge - Anxiety - Satisfaction with treatment choice - Satisfaction with decision-making ability	**Anxiety, knowledge, satisfaction with dec-making ability**: n.s. (trend to improvement in both groups) **Satisfaction with the method of receiving information**: sign. better	Method: - no blinding - not powered - no validated test tools	1-

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Jibaja-Weiss, Patient Educ Couns 2011 [111]	RCT; To evaluate an entertainment-based patient decision aid for early stage breast cancer surgery in low health literacy patients	n=51 + 49	Women diagnosed with **breast cancer** considering surgical treatment in the USA	I: DA: computer program on options' outcomes, clinical problem, outcome probabilities, explicit values clarification, others' opinion and guidance (step by step process for making the decision) C: usual care + breast cancer treatment educational materials normally provided to patients	- Surgical treatment preference (post DA) - breast cancer knowledge (pre, post DA, post DA and consult) - satisfaction with surgical decision (post DA) - satisfaction with decision making process (post DA) - decisional conflict (pre, post DA, Post DA and consult) - proportional undecided	**Surgical preference**: sign. more choice of mastectomy rather than breast-conserving surgery **Knowledge**: sign. better **Satisfaction** with surgical decision and with dec. making: n.s.	Method: - block-randomized - no blinding - not powered	1-
Lam, J Clin Oncol 2013 [112]	RCT; To evaluate a decision aid administered after consultation for Chinese women deciding on breast cancer surgery	n=138 + 138	Women considering breast cancer surgery for **early-stage breast cancer** in Hong Kong	I: DA: take-home booklet on clinical problem, options' outcomes, outcome probabilities, guidance, explicit values clarification C: standard information booklet	1.O: treatment decision making difficulties and decisional conflict scale at 1 week post consultation knowledge at 1-week postconsultation decision regret at 1 month after surgery 2.O: - postoperative psychological distress (anxiety and depression) at 1, 4, and 10 months after surgery	**Decision conflict**: sign. reduced at 1-week postconsultation (p=0.016) **Decision regret**: sign. reduced at 4 (p=0.026) and 10 months (P =0.014) after surgery **Depression**: sign. reduced at 10 months after surgery (P =0.001).	Method: - no blinding - powered - block-randomized	1+

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
					- decision regret at 4 and 10 months after surgery - treatment decision			
Leighl, J Clin Oncol 2011 [113]	RCT	n=107 + 100	Patients diagnosed with **metastatic CRC** considering advanced chemotherapy in Australia and Canada	I: DA: booklet and audiotape on option' outcomes, clinical problem, outcome probabilities, explicit values clarification and guidance (steps in decision making + worksheet) C: usual care	- anxiety (pre and post DA), knowledge* (post DA) - satisfaction with consultation (post DA) - choice leaning (postDA) - decisional conflict (postDA) - achievement of their information preference (post DA) - participation in decision making (post DA) - acceptability (post DA) - satisfaction with decision* (post DA) - QoL (post DA)	**Knowledge/Understanding**: sign. increased (p<0.001) **Decisional conflict, treatment decisions, achievement of involvement preferences**: n.s. **Anxiety**: n.s. (decreased in both group) **Decision** during the first consultation: 74% chose chemotherapy, 7% supportive care alone, and 10% observation	Method: - no blinding - powered - 31% dropout rate, but similar losses across all groups	1+
Sawka, J Clin Oncol 2012 [114]	RCT	n=37 + 37	Individuals with **early-stage papillary thyroid cancer**	I: DA: web-based decision aid with clinical problem, options' outcomes, outcome probabilities, guidance, printout summary C: usual care (consultation with a	1.O: medical knowledge (baseline and immediately post intervention) 2.O: decisional conflict (DC), undecided, treatment decision (baseline, immediately post	**Medical knowledge**: sign. greater (p <0.001) **DC**: sign. reduced (p <0.001) **Treatment decision** (use of adjuvant radioactive iodine): n.s.	Method: - no blinding - powered - rel. small sample size	1+

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
				specialized head and neck surgeon, and with 1 or more medical specialist)	intervention, 6 to12 months), individual primarily responsible for the treatment decision (6 to 12 months)			
Vodermaier, Br J Cancer 2009 [115]	RCT	n=74 + 78	Women with **breast cancer** considering treatment options in Germany	I: DA: Decision board and booklet on options' outcomes, clinical problem, outcome probability C: booklet on clinical problem	1.O:decisional conflict* (DC) 2.O: choice, length of consultation, satisfaction with decision making, participation in decision making	**DC total**: n.s. **DC, "uninformed" subscale**: sign. improved (effect size: η^2_p =0.06; t-test: -2.01; p=0.048) **Uptake rates** of treatment options, **length** of consultation, **time point** of treatment decision making, **perceived involvement** in decision making, decision related nor general **satisfaction**: n.s.	Method: - no blinding - not powered	1-
Whelan, J Natl Cancer Inst 2003 [116]	RCT; To determine whether adding a Decision Board to the medical consultation improved patient knowledg e and	n=82 + 93	Women with **node negative breast cancer** considering adjuvant chemotherapy in Canada	I: DA: Decision board and booklet on options' outcomes, clinical problem, outcome probability, guidance/coaching C: booklet on clinical problem	satisfaction of patient*, preferred option, knowledge*, anxiety, accurate risk perceptions, participation in decision making	**Knowledge** about cancer and adjuvant chemotherapy: sign. better mean score DA: 80.2 [scale 0-100], 95% CI =77.1-83.3 mean score C : 71.7, 95% CI =69.0-74.4; P<.001 **Satisfaction** with decision making: sign. higher in DA group (p=0.032) **Preferred option**: n.s. difference in the number choosing adj. chemotherapy	Method: - no blinding - not powered - unclear reporting	1-

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
	satisfaction compared with the medical consultation alone.							
Whelan, JAMA 2004 [117]	Cluster RCT; To evaluate the impact of a decision aid regarding the different surgical treatment options on patient decision making.	n=94 + 107 (Cluster RCT with 27 surgeons randomised)	Women with **Stage 1 or 2 breast** cancer considering surgery in Canada	I: DA: decision board on options' outcomes, outcome probability, guidance/coaching C: usual care	- knowledge* - decisional conflict (DC)* - satisfaction with the decision making* - preferred option* accurate risk perceptions - anxiety	**Knowledge** about treatment options: sign. higher (66.9 vs 58.7; P<.001) **DC**: sign. reduced (1.40 vs 1.62, P=.02) **Satisfaction** with decision making: sign. higher (4.50 vs 4.32, P=.05) **Preferred option**: DA-group sign. more likely to choose breast conservation therapy (94% vs 76%, P=.03).	Method: - no blinding - not powered	1-
BUTLER ET AL. 2015 [104]								
Green, Health Expect 2009 [118]	Uncontrolled pilot pre-post observational study	n=34 (cancer)	**Cancer**	Self-directed computer program	- Satisfaction / Perceived Benefits of Tool - Care Intensity Consistent with Patient Preferences - Levels of hopefulness, hopelessness, anxiety:	- **Satisfaction / Perceived Benefits of Tool**: positive effect (mean = 8.5, where 1 = not at all satisfied and 10 = extremely satisfied) - **Care Intensity Consistent with Patient Preferences**: positive effect (pre: mean accuracy = 5.5 (1 = not at all accurate, 7 = very accurate); post: 6.5 post-editing; P < 0.001)		3

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
						- **levels of hopefulness, hopelessness, or anxiety**: no effect		
Smith, Support Oncol, 2011 [119]	Uncontrolled pilot pre-post observational study	n=27	**Advanced cancer**		- Satisfaction / Perceived Benefits of Tool - Advance directive or Disease Knowledge - Patient Hope - Patient Stress or Anxiety	Before-after comparison: - **Satisfaction / Perceived Benefits of Tool**: positive effect - **Advance directive or Disease Knowledge**: positive effect - **Patient Hope**: no effect - **Patient Stress or Anxiety**: no effect		3
Vogel, Gynecol Oncol, 2013 [120]	Pilot RCT	n=53 Drop outs: 18	Women with **ovarian cancer**	I: Self-directed computer program C: control Web site with usual care information	- Satisfaction / Perceived Benefits of Tool - Reduce Decisional Conflict - Advance directive Documentation / Palliative Consult	- **Satisfaction / Perceived Benefits of Tool**: no effect - **Reduce Decisional Conflict**: no effect - **Advance directive Documentation / Palliative Consult**: no effect	Method: - Pilot study - no blinding - not powered - no data on randomization	1-
Volandes, Cancer 2012 [121]	Uncontrolled prospective pre-post observational study	n=80	**Advanced cancer**	ACP Advanced Cancer Video	- Satisfaction / Perceived Benefits of Tool - Care Intensity Consistent with Patient Preferences - Advance directive or Disease Knowledge	Before-after comparison: - **Satisfaction / Perceived Benefits of Tool**: positive effect - **Care Intensity Consistent with Patient Preferences**: no effect - **Advance directive or Disease Knowledge**: positive effect		3

6. Atemnot

6.1. Nicht-medikamentöse Therapie

Aktualisierung 2019: Es liegt inzwischen ein Update des Cochrane Reviews von Bausewein et al. (2008) vor, welches die überwiegende Mehrheit aller nicht-medikamentöser Therapien zur Linderung von Atemnot umfasst. Das ursprüngliche Cochrane Review wurde für das Update in vier Cochrane Reviews aufgeteilt. Es liegt inzwischen vor (Erst- bzw. Letztautorin des ursprünglichen bzw. der vier neuen Reviews ist Koordinatorin dieser Leitlinie), ist aber bei Cochrane noch nicht publiziert.

6.1.1. Therapien ohne „körperliche Übungen (*exercise*)“

6.1.1.1. Systematic Reviews

Study, journal, year	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Bausewein, Cochrane Review 2008 [122]	SR (MA not possible)	47 RCTs and CCTs (n=2532)	Patients with breathlessness due to: • Advanced cancer • COPD • ILD • Chronic heart failure • Motor neurone disease Most studies have been conducted in COPD patients.	• Interventions: Non-pharmacological and non-invasive (walking aids (n = 7), distractive auditory stimuli (music) (n = 6), chest wall vibration (CWV, n = 5), acupuncture/acupressure (n = 5), relaxation (n = 4), neuroelectricalmuscle stimulation (NMES, n = 3) and fan (n = 2)) • Control: placebo or usual therapy (Intervention excluded as already topic of other Cochrane Reviews:	1.O: • Subjective measures of breathlessness on VAS, NRS, categorical scales, modified Borg scales. • If subj. measures were not present, breathlessness specific scales or disease specific scales were defined as a 1.O. 2.O: • Domain specific measures for depression and anxiety. • Quality of life. • Participants satisfaction. • Adverse-effects. • Participants withdrawal from the studies.	**Breathlessness (no MA)**: • High strength of evidence that NMES and CWV could relieve breathlessness • Moderate strength for the use of walking aids and breathing training. • Low strength of evidence that acupuncture/acupressure is helpful • No evidence for the use of music. • Not enough data to judge the evidence for relaxation, fan, counselling and support, counselling and support with breathing-relaxation	• Breathlessness was mostly a secondary outcome • Metaanalysis not possible due to heterogeneity	1++

Study, journal, year	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				Pulmonary rehabilitation, non-invasive ventilation, nutritional supplementation, oxygen, self-management, exercise)		training, case management and psychotherapy.		
Effing, Cochrane Review 2007 [123]	SR (MA where possible)	14 RCTs and CCTs	**COPD**	COPD **education** defined as a programme which transfers information about COPD and treatment of COPD Form: written, verbal, visual or audio. Content: smoking cessation, improving exercise, nutrition, self-treatment of exacerbations, inhalation technique or coping with activities of daily living or a combination of these	• health-related quality of life scores, • symptom scores, • number and severity of exacerbations, • courses of oral steroids or antibiotics, • use of rescue medication, • hospital admissions, • emergency room visits, • use of other health care facilities, • days lost from work, • lung function, • exercise capacity.	• A small but significant reduction was detected in **dyspnoea** measured with the BORG-scale (WMD -0.53; 95% CI (-0.96 to -0.10)) • On the disease specific **SGRQ**, differences reached statistical significance at the 5% level on the total score (WMD -2.58; 95% CI (-5.14 to -0.02)) and impact domain (WMD -2.83; 95% CI (-5.65 to -0.02)), but these difference did not reach the clinically relevant improvement of 4 points. • No significant effects found in **exercise capacity**	Because of heterogeneity in interventions, study populations, follow-up time, and outcome measures, data are still insufficient to formulate clear recommendations regarding the form and contents of self-management education programmes	1++
Ferreira, Cochrane Review 2005 [124] **Update 2012**	SR, MA	14 RCTs (n=487) Update: 3 RCTs (n=145)	Stable COPD	• Interventions: oral, enteral or parenteral **nutritional support** • Control: placebo or usual patient's diet or other treatment regimens such as anabolic substances	1.O: • Anthropometric (body weight, lean body mass, body mass index) and functional exercise (timed walk test, submaximal or graded exercise) 2.O: • Included pulmonary mechanics (lung volumes,	Too few studies reported **dyspnea** or quality of life to generate combined effect estimates. Three studies (n=123) reported data to the CRQ subdomain "dyspnea" and showed no sign. benefit of supplemental nutrition.	Data of dyspnea only in three RCT	1+

Study, journal, year	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
					respiratory muscle function), • peripheral muscle function • health related quality of life incl. CRQ "Dyspnea" subdomain score			

6.1.1.2. Primärstudien

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
FAN								
Bausewein, BMC Pall Care 2010 [125]	RCT embedded in longitudinal cohort study	n=70 (dropouts=34)	• **primary and secondary lung cancer** • **COPD III/IV**	▪ Hand held fan (HHF) ▪ wristband	1.O: ▪ use of the HHF and the wristband after 2 months measured on the modified Borg scale 2.O: ▪ recruitment into the trial and change of breathlessness severity after 2 months on modified Borg scale	Post intervention, about half of the patients used the HHF but only 20% the wristband without a statistical difference (Fisher's exact test p = 0.2). 9/16 patients judged the HHF as helpful and 4/5 patients the wristband. No difference in mean breathlessness change scores between the HHF (Borg change score: mean 0.6 (SD 2.10)) and the wristband (mean 0.8 (SD 2.67)) after two months (p = 0.90). No significant difference but high drop out		1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Galbraith, J Pain Symptom Manag 2010 [126]	RCT crossover	n= 50 (drop-outs=1)	refractory breathlessness from any **nonmalignant or malignant** cause and **Dyspnea Exertion Scale (DES)** Level 2 or above	Hand held fan directed on face region innervated by the second and third branches of the trigeminal nerve or leg mid-calf 5 min with washout period of 10min.	1.O: ▪ Decrease in breathlessness of 1cm or more assessed by a 10cm vertical visual analog scale (VAS) ▪ Monitoring of SaO2, VAS and pulse rate ▪ Measurement timing: baseline, after each use of fan and end of washout period	1.O: significant (P= 0.003) improvement of breathlessness with an effect size of 7.0 mm (95% confidence interval [CI]: 2.5-11.7 mm) but potentially carry over effect in washout period ▪ no detectable effect on participants' SaO2 or PR after use of the fan		1+
SELF-MANAGEMENT PROGRAM								
Garcia, Resp Med 2007 [127]	RCT, parallel	n=113 (51 drop-outs = 43%: death, lost, …)	**COPD** patients after hospital discharge following episode of exacerbation. 86% male, >70y, FEV1 1.2 (0.5)l	• 1st arm: Integrated care - IC (n=44) with: (1) comprehensive assessment of the patient at discharge by a spec. nurse (2) educational session at discharge by spec. nurse (3) individually tailored care plan. Joint visit of the spec. nurse and the primary care team within 72h. Weekly phone calls during the first month; one phone call at months 3 and 9. (4) access to the specialized nurse at the hospital was guaranteed through a web-based call centre • 2nd arm: Usual care (n=69)	• Dyspnea (MRC) • HRQL (SGRQ, EQ-5D) • Self-management, lifestyle, BMI • Treatment adherence • Identification of exacerbation • Skills for administration fo drugs • Drug treatments • Pulmonary function tests Measures at baseline, 6 and 12 months	There were no differences in the evolution of **dyspnea** (UC: 0.15 (1.44) – IC: -0.52 (1.12)) or **quality of life** scores.	• Adequate randomisation and concealment • 43% drop-outs > ITT analysis not possible • No details to baseline data	1+

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Nguyen, J Med Internet Res 2008 [128]	Pilot RCT	n=50 (11 drop-outs)	Moderate to severe **COPD**, FEV1 < 80% predicted. Current Internet users.	A 6-month Dyspnea self-management programm (DSMP), delivered in 2 modalities: • 1st arm (n=24): internet-based (eDSMP) • 2nd arm (n=26): face-to-face (fDSMP)	1.O: Dyspnea with activities of daily living (ADL) (by means of CRQ) 2.O: • Exercise behaviour in 1 week • Exercise performance (6 min walking test) • HRQL (CRQ and SF-36) • COPD exacerbations • Mediators such as self-efficacy and social support Measured at baseline, 3 and 6 months	The fDSMP and eDSMP showed similar clinically meaningful changes in **dyspnea** with ADL from baseline to 3 months (fDSMP: + 3.3 points; eDSMP: + 3.5 points) and sustained these improvements at 6 months (fDSMP: + 4.0 points; eDSMP: + 2.5 points; time effects **P** < .001; group by time **P** = .51). Distance covered during the **6-min. walk test** declined in the fDSMP and increased in the eDSMP over time with a marginal group by time difference (P = .05). Total scores on the CRQ, reflecting disease-specific **HRQL**, improved over time for participants in both the eDSMP and fDSMP (**P** < .001). There were also positive changes in the SF-36 physical composite scores over time for both groups (**P** = .04).	• Compares 2 modalities of self-management. No "placebo". • Stopped early due to technical challenges (eDSMP), but follow-up for 6 months • ITT analysis for the 39 pts who completed the study • Adequate randomisation and concealement • Small sample size > underpowered	1-
Wakabayashi, Geriatr Gerontol Int 2011 [129]	RCT, parallel-group	n=102 (Drop-outs: 17)	**COPD**, older patients > 65 years. No specific grade of disease.	• 1st arm I (n=52): Integrated care: individually tailored education program according to the patients' needs (measured with LINQ) + booklet. Intensive	• Information needs of patients with COPD (LINQ = Lung Information Needs Questionnaire) • Pulmonary function tests • Dyspnea severity (MMRC)	No significant differences between the baseline and the 6-month follow up in either group for **6MWT distance**, **MMRC**. A significant improvement was noted in **MMRC** at 12	• Adequate randomization and concealment • Proposed sample size not achieved • No mention of ITT	1+

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				education monthly for 6 months, then usual care for 6 months. • 2nd arm U (n=50): usual care: general education based on the domains of LINQ but without knowing the individual LINQ scores obtained by the patients; no booklet	• Exercise capacity (6-min walk test) • BMI • Activities of daily living • BODE index (=BMI+airflow obstruction+dyspnea + exercise capacity) • Health status (SGRQ) • Comorbidities (Charlson index) At baseline, 6 and 12 months	months compared to the baseline in group I (P < 0.01), whereas group U showed a significant worsening in MMRC at 12 months (P < 0.03). No sign. Between group difference for **MMRC** and **6MWT distance** (p=0.88, p=0.363 resp.). There were no significant changes in the total **SGRQ**.		
OTHERS								
Neuromuscular stimuli								
Lau, Australian J Physiotherapy 2008 [130]	Randomised, placebo-controlled trial	N=46 (no drop-outs reported)	Patients>60years; had to have stable **COPD** GOLD I or II	Intervention: ▪ 45 Minutes of Acu-Trans-cutaneous-nerve-stimulation (ACU-TENS) at a single time. Control: • Sham Procedure without electrical output	▪ Pulmonary Function (FEV1, FVC) • Dyspnoea (100mm VAS-Scale)	• Increase of FEV1 by 0.12 litres more in the intervention group compared to control (p<0.001). • Increase of FVC by 0.05 litres more in the intervention group compared to control (p=0.09). • Dyspnoea decreased by 11mm more in the intervention group, p not provided but confidence interval suggests significance).	▪ COPD GOLD I and II patients do not suffer from dyspnoea at rest or light exertion normally. ▪ A difference of 120ml in FEV1 is of questionable relevance. • The sham procedure is not really a placebo procedure because in opposite to the TENS-Procedure, patients do not experience the flow of current.	1-
Chestwall vibration								
Mahajan,	multi-center, double-	n=52 active (n = 25)	**COPD, Asthma**	▪ High frequency chest wall oscillation active	1.O:	1.O:	•	1+

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Resp Res 2011 [131]	masked phase II RCT	or sham (n = 27) treatment		or sham treatment for 15 minutes three times a day for four treatments. • Medical management was standardized across groups.	▪ Patient adherence to therapy after four treatments (minutes used/60 minutes prescribed) and satisfaction. 2.O: ▪ change in Borg dyspnea score (≥ 1 unit indicates a significant change) ▪ spontaneously expectorated sputum volume • forced expired volume in 1 second.	▪ Adherence similarly high in both groups (91% vs. 93%; p = 0.70). Patient satisfaction was also similarly high in both groups. 2.O: After four treatments, patients in the active treatment group had a clinically significant improvement in **dyspnea** ((70.8% vs. 42.3%, p = 0.04).		
Breathing training								
Barton, Lung Cancer 2010 [132]	Feasibility RCT	n=22 (drop-outs =14)	**Malignant lung/ intrathoracic disease** with refractory breathlessness. Inclusion criteria: • Expected prognosis of > 3 months • Karnofsky > 40% • Therapy refractory breathlessness Exclusion criteria: • Intercurrent illness • Severe co-morbidity • Rapidly worsening breathlessness	• Intervention: 3 three breathlessness management training sessions of 1h once a week, provided by a specialist physiotherapist (AE) or a lung cancer nurse specialists trained by AE. Sessions include: diaphragmatic breathing, pacing, anxiety management and relaxation). Patients received written and DVD/video reinforcement material and a telephone call from their therapist aweek after the last training session. • Control: 1 session of 1h, otherwise same as intervention	As this was a feasibility study there were no designated primary or secondary outcome measures Outcome measures: • *Questionnaire*: - Severity of breathlessness - Distress caused by breathlessness - Ability to cope with breathlessness (10=Fähigkeit, Luftnot zu bewältigen (10=have coped very well) - satisfaction with management of breathlessness (respectively NRS 0-10) • *QoL:* EQ-VAS, EQ-5D • *Depression/anxiety:* HADS	Study appears to indicate that three sessions of training may be more effective for **breathlessness** management than a single session	Study design was shown to be inadequate. Strategy for patients' recruitment, inclusion and exclusion criteria, Method of randomization will be changed for follow-on study.	1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			• Radical radiotherapy in the las 6 months • Palliative radiotherapy within 4 weeks • Chemo/anti-cancer hormone treatment in the last 2 weeks Prior experience of breathlessness training		• *Coping response:* BriefCOPEQuestionnaire Follow up: Measures at baseline, 1, 2, 3, 4 and 8 weeks			
Battaglia, Arch Phys Med Rehabil 2009 [133]	RCT Double blind	n=32	Patients with **COPD** GOLD I-IV without significant improvement after bronchodilation test. Mean age 68y All ex-smokers All with inhaled steroids	• Intervention: breathing training with inspiratory device Respivol ® in combination with expiratory Respilift®, 15 min twice daily over 12 months. • Control: sham training	1.O • Maximal inspiratory pressure (MIP), max. expiratory pressure (MEP) • Dyspnea perception	Patients benefit from training with the combined insp. and exp. devices: Sign. improvement of MIP (81±4 at 12 months vs 57±7 as basal values expressed in cm H20; p<0.5) and MEP and of **dyspnea** grade on Borg Scala (97±2 at 12 months vs 62±4 as basal values; p<0.5) Patients with COPD GOLD III + IV sign. less than GOLD I + II.	4 patients of the intervention group and 2 patients of the control group had an exacerbation during the study. No sample size calculation > underpowered, no mention of ITT	1-
Bosnac-Guclu, Resp Med 2011 [134]	Prospective RCT Double blind	n=36, drop-out = 6 Intervention: n=16 control: n=14	Pat. with **heart failure** Inclusion criteria: • Clinically stable • LVEF<40% • NYHA II-III	A one-week familiarization period and instruction about IMT= Inspiratory Muscle Training (20-30% of MIP) or sham IMT Intervention:	Pulmonary function tests, dyspnea, quality of life Outcome measure: • Pulmonary function tests (spirometry with FEV1, FVC, PEF)	Sign. improvement with IMT for: • **Functional capacity** (418.59±123.32 to 478.56±131.58 m, p < 0.001) and functional balance	Patients without resp. muscle weakness improved too. Sample size calculation: n=15/group No mention of ITT	1+

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			• No change in medication over 3 monthskeine Änderung in der Medikation in den letzten 3 Monaten • Patients with pacemaker if 6 weeks after implementation Exclusion criteria: • Acute myocardial infarction • Cognitive disorders • Complex arrythmias • Uncontrolled hypertension • Angina pectoris • viral infection in the last 6 months • orthopedic problems rheumatologic disease	• Pat. received IMT at 40% of MIP *(pressure threshold device – POWERbreathe®),* 30 min per day for 6 weeks. Control: ▪ Pat. received sham IMT 30 min per day for 6 weeks. • In total, 8 sessions were supervised, 2 calls a week, diary.	• Respiratory muscle strength (Max. inspiratory pressure (MIP) and max. expiratory pressure (MEP) with MicroRPM). Quadriceps femoris isometric strength (JTECH Power Track Commander II) • Functional capacity (6MWT in combination with dyspnea (Borg)) • Balance (Berg Balance Scale) • Fatigue (Turkish version of Fatigue Severity Scale with 9 Items) • Depression (Turkish version of Montgomery Asberg Depression Rating Scale) • Dyspnea severity (Medical Research Council dyspnoe scale, 0-4) • Quality of life (SF-36) Follow up • Before and after interventions	• Respiratory (MIP=62.00±33.57 to 97.13±32.63 cmH2O, p < 0.001) and periphery muscle strength (240.91±106.08 to 301.82±111.86 N, p < 0.001) ▪ **Dyspnea** (2.27±0.88 to 1.07±0.79, p < 0.001 • Depression (11.47±7.50 to 3.20±4.09, p < 0.001), No sign. Improvement with IMT for: • **QoL** Fatigue	Adequate randomization, no mention of concealment	
Ekman, Eur J Heart Fail 2011 [135]	RCT	n= 72 (m=52, w=20), drop-out=7 Intervention: n=35, drop-out=5 Control:	Patients with stable chronic heart failure (NYHA II-IV) with persistent symptoms of breathlessness despite optimal pharmacological treatment.	• Intervention: a 20 min, twice-daily session of DGB=Device Guided Breathing (with RESPeRATE®) for 4 weeks. Goal of the respiratory modulation (RM) was to progressively slow the	Dyspnea, changes in NYHA class, Fatigue Outcome measure: • NT-proBNP • Blood pressure • Self-rated sleep quality • Dysnea (5 point Likert-scale)	No sign. Improvement of dyspnea and of NYHA-class by DGB. Some patients (responder, n=14) seem to respond to DGB. They show a symptom improvement and a	No ITT, no sample size calculation No description of randomization	1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
		n=37, drop-out=2	Inclusion of patients with Dyspnea ≥2/5 on Likert-scale Exclusion criteria: • if performing Device-guided breathing (DGB) not possible (psychiatric illness, chemical dependency, unstable angina pectoris, or COPD) • expected survival shorter than study • poor communication skills or compliance	respiration rate to 10 breaths per min and to increase the exhalation time (Tex) • Control : a 20 min, twice-daily session with music using a CD player über einen CD-Player for 4 weeks	• Fatigue (5 point Likert-scale) *In addition fort he DGB-group:* Respiratory rate, inspiration time (Tin), exhalation time (Tex), Tex/Tin ratio Follow-up: Before start of the study and at the end *In the intervention group:* • Before and after every session	significant change of NYHA-class (20.64+0.20, P , 0.01). The criteria of a responder are not further defined. With DGP, the responders raise their Tex/Tin ratio.		
Faager, Clin Rehabil 2008 [136]	RCT Open-label cross-over	n=32	Moderate to severe **COPD** Inclusion criteria: - clinically stability - physical performance limited by dyspnoea - oxygen desaturation to less than 95% at the end of the incremental shuttle walking test (ISWT) Exclusion criteria	• Pre-test: ISWT • Intervention: endurance shuttle walking test-ESWT: Walking speed 85% of max. ISWT performance. Patients used spontaneously pursed lips breathing and became a nose clip. • Control: patients received a mouthpiece during ESWT, to prevent them using	Endurance by walking, O2 saturation and dyspnea Outcome measure: • Heart rate • O2 saturation • Perceived dyspnea (Borg scale CR-10) • Leg fatigue (Borg scale CR-10) • Peak expiratory flow (Mini-peak Flow Meter) Follow up	Pursed lips breathing sign. increases **endurance** (patients walked for 37 seconds (16%) longer ($p<0.01$) and reduces O2 desaturation. No sign. change of **dyspnea** with pursed lips breathing (nor of leg fatigue, heart rate or Peak expiratory flow).	During the test, 25 were responders and 7 non-responders (walking distance, O2 saturation) Bei dem Test galten 25 als „Responder“ und 7 als „Non-Responder“ (Gehstrecke, Sauerstoffsättigung). Discussion: Breathing through mouthpiece is uncomfortable and wearing.	1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			- cardiac comorbidity - neurological or orthopaedic mobility impairments	pursed lips breathing, and a nose clip	Before, directly after, 5 and 10 min later		Non-responder had usually a lower FEV1, worse O2-saturation and a lower endurance. One patient had a FEV1 > 80%. Normal mouth or nose breathing through nose clip/mouthpiece not possible. No sample size calculation > underpowered; no ITT No details to randomisation or concealment	
Kunik, Psychol Med 2008 [137]	RCT	n=238	**COPD**	Intervention: Treatment consisted of eight 1-h sessions of CBT: ▪ education and awareness training ▪ relaxation training ▪ increasing pleasurable activity and decreasing anxiety-related avoidance ▪ cognitive therapy ▪ problem-solving techniques ▪ sleep management skills	1.O: ▪ COPD-specific QoL (Chronic Respiratory Questionnaire) ▪ generic QoL (SF-36) 2.O: ▪ depressive and anxiety symptoms ▪ 6-minute walking distance (6MWD) ▪ use of health services	▪ Both treatments significantly improved QoL, anxiety and depression ($p<0.005$) over 8 weeks; the rate of change did not differ between groups. ▪ Improvements were maintained with no significant change during follow-up.		1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				▪ skills review and planning for maintenance of gains ▪ additional home practice were assigned Control: ▪ Eight 1-hour sessions of COPD education				
Lidell, Physiotherapy 2010 [138]	RCT	n=30	**COPD**	Intervention I (n=15): • once-weekly group received one supervised rehabilitation session per week Intervention II (n=15): • Twice-weekly group received two sessions per week • Both for 8 weeks • Together with a home exercise plan	1.O: ▪ Incremental Shuttle Walking Test (ISWT) ▪ Endurance Shuttle Walking Test (ESWT) ▪ St George's Respiratory Questionnaire (SGRQ) ▪ Assessed at baseline and at completion of the supervised programme. 2.O: ▪ home-exercise activity ▪ attendance levels ▪ patient satisfaction with the programme	groups showed similar improvements in ▪ exercise tolerance (median values: ISWT once-weekly 60 metres, twice-weekly 50 metres; ESWT once-weekly 226 seconds, twice-weekly 109 seconds) ▪ Patient satisfaction with both formats was high and almost identical between the groups. Intervention I: ▪ No improvement in QoL (SGRQ 0) Intervention II: ▪ Improvement in QoL (SGRQ 3.7).		1-
Magadle, Resp Med 2007 [139]	Cross-sectional RCT Double blind, placebo controlled	n=34 (m=26,w=8) Drop-out Phase1=3 Drop-out Phase2=4	<u>Significant **COPD**</u> FEV1 <50%, FEV1/FVC <70% All were on regular long-acting bronchodilators and inhaled corticosteroid therapy.	*Phase1:* All patients participated in a general exercise reconditioning (GER) for 12 weeks, then randomization. *Phase2:*	Spirometry, insp. muscle strength, dyspnea, quality of life <u>Outcome measure:</u> • Spirometry (FVC and FEV1)	Pat. benefit from IMT. *Phase1:* a small but non-significant decrease in the POD (from 22.870.6 to 20.670.5 total Borg score),	No details to randomization or concealment No sample size calculation > underpowered; no ITT	1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			All new to a pulmonary rehabilitation program Exclusion: • Cardiac disease • Bad compliance • Patients with long-term supplemental O2	• Intervention: inspiratory muscle training (pressure threshold device – POWERbreathe®) (IMT) three times a week for 12 weeks. • Control: sham IMR three times a week for 12 weeks.	• 6 min walking test (6 MWT) • Insp. Muscle strength (PImax) • Perception of dyspnea by breathing against resistance (BORG CR-10 Skala (POD) • Quality of life by means of St George Respiratory Questionaire Score (SGRQ) Follow up Before, 3, 6 and 9 months after intervention	SGRQ score (from 60.1±2.1 to 56.3±2.5 total SGRQ score) significant increase in the 6MWT (from mean±SEM 254can to 322±42 m, 26%, p<0.01), *Phase2:* Significant decrease in the POD in the training group (from 20.2±0.4 to 14.9±0.3 total Borg score, p<0.001), but not in the control group. The difference between the two groups was statistically significant. No change of **6 MWT**		
Masanga, Respirology 2011 [140]	RCT	n=21 (11 IMT, 9 control)	moderate to severe **COPD**	Intervention (n=11): ▪ Education ▪ dietary instruction ▪ occupational therapy ▪ ± daily High-intensity Inspiratory Muscle Training (IMT) Control (n=9): ▪ Education ▪ Dietary instructions ▪ Occupational therapy Duration 4 weeks	▪ FEV1 ▪ PiMax ▪ 6MWT ▪ Dyspnea and QoL (CRDQ) ▪ Measured at baseline and end of the study IMT – reached intensity level 40 -90cmHg (baseline 10 cmHg)	▪ sub-analyses: improvement after pulmonary rehabilitation - 6MWT (p<0.0001), CRDQ (p= 0.022), EV1(p=0.9573) ▪ among the IMT group significant improvement PiMax p=0.0001- but no additional improvement in exercise capacity, CRDQ and FEV1 ▪ Adverse effects were at all minimal and self-limited.	▪ Small number of patients ▪ short duration of intervention ▪ No details about division between moderate and severe COPD	1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Mota, Respir Med 2005 [141]	RCT, placebo-controlled	n=18 (drop outs=2)	severe **COPD**	Intervention: ▪ expiratory muscle training Control: ▪ sham training group both completing: ▪ 4-weeks run-in ▪ 5-week program ▪ 3xweekly 30min breathing through an expiratory threshold valve -50% max. exspirat.pressure vs. placebo	▪ lung function ▪ exercise tolerance (bic.ergomet. and walking test) ▪ clinical outcomes (dyspnea and QoL>SGRQ) ▪ Measurement timing at baseline and following training period	▪ Lung function unchanged ▪ Sign. improvement in exercise capacity, symptoms and **quality of life** (r=0.634, P<0.05).	▪ Small number of patients	1+
Mularski, J Altern Complem Med 2009 [142]	RCT	n=86 (drop outs=36)	advanced and symptomatic **COPD** GOLD stage ≥ II (64% severe, pre6MWTdistance 278m) Nonreversible airflow limitation Average age 67 years	Mindfulness-based breathing therapy (MBBT)- once-weekly-group meetings and daily self-administered MBBT practice (defin.strategy mindfulness-based stress reduction program with supplemental relaxation response training) improving dyspnoea and HRQoL • compared to support groups	▪ 6MWT ▪ modified BORG dyspnoea scale other outcome measures: ▪ HRQoL(SGRQ) ▪ 6MWTdistance ▪ symptom scores ▪ exacerbation rates ▪ measures of stress and mindfulness 8-week program and evaluation	▪ No measurable improvement in **dyspnoea** or/and any other outcome measures	▪ No details about division between moderate and severe COPD ▪ High risk of bias ▪ High dropout rate	1-
Nield, J Cardiopulm Reha 2007 [143]	RCT	n=40 (drop outs=2(w4) and 12(w12))	Stable **COPD** 65±9y	Intervention I: ▪ Pursed-Lips Breathing Intervention II: ▪ Expiratory Muscle Training Control ▪ Daily practice sessions	Focus: voluntary prolongation of experatory time SF-36 physical function score –greatest improvement in the PSBgroup ▪ Dyspnea: modified Borg after 6MWD and	▪ No significant Group x Time difference was present for PEmax (P = 0.93). ▪ Significant reductions for the modified Borg scale after 6MWD (P = 0.05) and physical	▪ Small groups of intervention ▪ short time	1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				▪ Logs to record practice times and potential adverse events ▪ 4 weekly visits research laboratory Intervention: Patients education handouts and audiovisual aids Control: education pamphlet and the same monitoring	Shortness of Breath Questionnaire ▪ Functional performance: Human Activity Profile and physical fuction scale of Short Form 36-item Health Survey	function (P = 0.02) from baseline to 12 weeks were only present for pursed-lips breathing. ▪ Positive effects on **self-care management** and self-efficacy.		
Padula, Appl Nurs Res 2009 [144]	RCT	n=32	Chronic stable **HF** 74,7(32-94)y 47% male NYHA II 51,8 % NYHA III 48,3 %	Intervention: ▪ 3month nurse-coached IMT program and education control: • education alone with standard educational protocol	▪ PImax ▪ Borg scores ▪ Blood pressure ▪ Heart rate ▪ Respiratory rate a. o. ▪ Health-related QOL	▪ No statistically differences ▪ Borg scores from baseline to Week 12 were significantly different as evaluated by repeated-measures analysis of variance (ANOVA), Wilk's k = 0.626, F(2,30)=17.36, p b .0001. ▪ Home-based IMT can be effective in improving **dyspnoea** and IM Strength ▪ Questionable improvement in **QoL** and self-efficacy for breathing	▪ Sample size relatively small	1+
Pinto, Respir Man 2012 [145]	RCT, delayed start study design	n=19 (drop outs=4)	**ALS**,13 men 57,7±8,8y mean disease duration 13,2± 7,7mo ALS-FRS 25-38	randomized in two groups: G1- efficient load group G2-non-efficient load group (after 4 month (first 4 month work-out with lowest possible	Evaluation 3 times- at entry and every 4 month: ▪ Functional amyothrophic lateral sclerosis rating scoreALSFRS ▪ FCV ▪ MIP	▪ ALSFRS (Mean difference 0.846 (SD 1.455)) and MVV higher decrease in G2 (first four month) ▪ VAS for dyspnea: Mean difference -0.231 (SD 0.715)	▪ Small number of patients	1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				load, after 4 month exercise with efficient load	▪ MVV ▪ SNIP ▪ VAS for fatigue and dyspnoea ▪ Subj. respire.control feeling ▪ FSS ▪ Epworth`s scale ▪ FIM ▪ Euro-QoL 5D ▪ Hamilton`s scale	▪ No other differences ▪ All patients described a better voluntary control over respiratory dynamics		
Acupressure/acupuncture								
Suzuki, J Altern Complem Med 2008 [146]	prospective trial with matched-pair parallel groups of patients	n=30	**COPD**	▪ Intervention: Acupuncture 1per week for 10 weeks and medication ▪ Control: medication only	1.O: Breathlessness before and immediately after the 6-minute walk test (6MWT), using a modified 10-point Borg category scale. 2..O: ▪ SpO2, lung function, vent. Musclestrength /endurance, Fletcher Hugh-Jones categories	1.O: Improvement in ▪ Borg scale (p=0.000) ▪ 6MWT (p =0.0002) 2.O: Improvement in ▪ SpO2 (p= 0.0001) minimum and mean ▪ Fletcher Hugh-Jones categories significantly higher in intervention group	Japanese study: ▪ Cultural influences? ▪ Transferability and generalization might be questionable?	2++
Whale, Acupuncture in Medicine 2009 [147]	double blinded RCT	N=11 (drop outs=2)	**COPD** with acute exacerbation	▪ Intervention: real acupuncture device (n=4) ▪ Control: sham needle device (n=5) ▪ over three consecutive days	▪ Credibility of acupuncture (Borkovec and Nau Credibility Questionnaire) ▪ Dyspnea and anxiety (Modified borg scale)	▪ Credibility of acupuncture was acknowledged ▪ Mean dyspnea and anxiety scores improved, no difference between intervention and control group		1-
Wu, J Altern Complem Med 2007 [148]	randomized, block experimental design	n=44	**COPD**	▪ Intervention: true acupressure group received an acupressure program that used the acupoints of Great Hammer, Celestial	1.O: ▪ Geriatric Depression Scale (GDS) ▪ Dyspnea Visual Analogue Scale (DVAS)	▪ GDS scores (decreased in sham acupuncture group by 0.14 points), **DVAS scores (p<0.01)**, oxygen saturation, and physiological indicators	Taiwanese study: ▪ Cultural influences? ▪ Transferability and generalization might be questionable?	2++

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				Chimney, Lung Transport, Kidney Transport, Fish Border ▪ Control: sham acupoints used were Shang Hill, Supreme White and Large Pile ▪ Both treatments extended over 4 weeks and consisted of 16-minute sessions given five times a week.	▪ on baseline and post intervention 2.O: ▪ SpO2, blood pressure, respiratory rate and pulse pre/post session	significantly improved p=0.00		
Music								
Singh, Chron resp Disease 2009 [149]	RCT	N=72 (drop-outs=8)	Patients who just recovered after an acute COPD exacerbation and are stable for at least seven days since then. COPD defined as FEV1/FVC <70% und FEV1<80% of predicted. "Self reported Shortness of breath (SOB)"	Arm A: ▪ music (self selected, indian instrumental music with 60-80 beats per minute) for 2x30 Minutes in the morning and afternoon. Arm B: ▪ Progressive muscle relaxation (PMR): Patient listened to instructions and performed the relaxation of 16 muscle groups.	▪ Dyspnoea: 100mm VADS ▪ Anxiety now: Speilbergers state anxiety inventory (SSAI) ▪ General Anxiety: Speilberger´s trait anxiety inventory (STAI) ▪ Physiologic paramters: Blood pressure (BP), pulse (HR), and respiratory rate (RR)	▪ SSAI 8.4 Points better after second session of music compared to baseline, ▪ SSAI 4.8 points better after PMR compared to baseline. ▪ STAI change was significant for interaction but not clinically significant. ▪ **Dyspnoea** reduction was 23,1 mm on 100mm VAS in the music group and 12.9 mm in the PMR group. ▪ BP, RR and HR decreased after both interventions significantly. ▪ Music: Systolic BP pre: 136.88 to 127.8 post; diastolic BP 87 to 85; HR 89 to 81; RR 27 to 19.	▪ Statistic is hard to understand. ▪ No information about cancer patients.	1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
						▪ PMR: SPB 134 to 130; DBP 84 to 83; HR: 87 to 81 and RR 22 to 17.		
Relaxation								
Chan, Complement Ther Med 2011 [150]	RCT single blind	n=206	**COPD**	Intervention: ▪ 3 months Tai Chi Qigong with two 60-min sessions each week, 1 hour daily self-practice 1st control: ▪ exercise group with pursed-lip breathing, diaphragmatic breathing and self-paced walking, 1 hour daily self-practice 2nd control: ▪ usual care	▪ Lung functions ▪ Borg scale before and after 6-min walk test ▪ COPD exacerbation rate ▪ Timing of measurement: baseline, 6 weeks, 3 months	Significant interaction effects between time and group in : ▪ forced vital capacity (p = .002) ▪ forced expiratory volume in 1 s (p < .001) ▪ walking distance (p < .001) ▪ Exacerbation rate (p = .006) at 3 months. ▪ Improvements were noted in the TCQ group. ▪ No changes were observed in the exercise group, while a decline in lung functions was noticed in the control group. ▪ No significant differences in Borg scale		1+
Donesky-Cuenco, J Altern Complem Med 2009 [151]	Open label RCT	N=41 (no drop-outs)	Pts > 40 Years/ old ADL limited by dyspnoea Stable COPD Pts were recruited by advertising	Intervention: ▪ 12-week Yoga training program (twice weekly) with posture and breathing elements. Control: ▪ "Usual care", interventions and no. of visits not specified	▪ Dyspnoea intensitiy (DI) and Dyspnoea related distress (DD) measured with a modified Borg scale after a 6MWD and every minute within an ergometer test:Two Questions: "How short of breath are you right now?" for DI and "How bothersome or	▪ DI did not improve after intervention ▪ DD improved significantly in the intervention arm measured by 6MWD but not on ergometer. ▪ The 6MWD improved significantly after the intervention but not in the	▪ The population was not representative (recruitment via advertising) with more females than males. ▪ Primary endpoint was not precisely defined (DI or DD?) so levels of significance are questionable.	1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
					worrisome is your shortness of breath to you right now?" for DD. ▪ A 5-item dyspnoea subscale of the CRQ was used to measure dyspnoea during five patient-chosen ADL´s, ▪ Secondary: Pulmonary Function, HRQL, physical performance on Ccke and 6MWD	control arm. (+71.7 ± 21.8 feet versus -27.6 ± 36.2 feet; ES = 0.78, p = 0.04) ▪ No difference in the other secondary endpoints.		
Oh, Am J Chin Med 2008 [152]	RCT	N=30 (dropouts=12)	**Cancer** diagnosis any state, ECOG 0-3, expected survival length > 12 months	Intervention: ▪ in addition to usual medical care a MQ group intervention once or twice a week for eight weeks, daily self-practice one hour ▪ end of the program: all patients completed the follow-up QOL measure and blood test. Control: ▪ continued usual care	1.O: ▪ QoL and symptoms (EORTC QLQ-C30) 2.O: ▪ Inflammation (CRP)	▪ Individually reported better **QoL** and lower symptoms, lower inflammation ▪ Results were not statistically significant between treatment and the control groups.		1-
Yeh, Resp Care 2010 [153]	RCT	N=10	Pts with **COPD** FEV1<65% predicted FEV1/FVC<0,7 Age 45 or older	Intervention: ▪ 12 Weeks of tai chi classes biweekly plus usual COPD care Control: ▪ Usual COPD Care alone ▪ (Defined as pharmacologic therapy + exercise advice per ACCP-Guidelines)	▪ "Exercise Capacity and functional status" (Ergometry and 6 MWD at baseline and 12 Weeks as well as "timed-up-and-go" assessment) ▪ HRQL (CRQ), ▪ Dyspnoea (UCLA San Diego Shortness of Breath Questionaire and Modified Medical Research Council	▪ Although there was a nonsiginifcant relief of Dyspnoea in both arms, the baseline value was significantly worse in the control group. (1.4 ± 1.1) vs. (-0.1 ± 0.4) (P = 0.03). ▪ Significant improvements were seen in the	▪ Nearly more endpoints than patients.	1-

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
					Dyspnoea Scale and many more…) ▪ Pulmonary function (spirometry) ▪ Physical Activity ("Community Healthy Activities Model Program for Seniors (CHAMPS)")	CRQ total score and CRQ emotion domain.		
Counseling, support and breathing								
Moullec, Clin Rehabil 2010 [154]	Prospective controlled trial	N=40	moderate to severe **COPD**	Intervention: (n =11) maintenance integrated health care programme for 12 months Control: (n =16) usual care for 12 months	1.O: ▪ change in functional and emotional dimensions of quality of life (SGRQ), (Brief-WHOQOL) and six specific questions (VAS) 2.O: ▪ change in exercise tolerance measured by six-minute walking test and cycle exercise.	1.O: ▪ improvements in functional and emotional dimensions scores of **quality of life** and exercise tolerance in intervention group. ANCOVA revealed a significant interaction effect (time x group) for symptom ($F(3,75)=5.11$, $P< 0.01$; $\beta=0.80$; n"P=0.18) and activity ($F(3,75)=8.24$, $P<0.001$; $b=0.95$; n"P=0.26) ▪ In control group maintenance of functional dimension scores of **quality of life**, clinically relevant decline in emotional scores of quality of life and in six-minute walking distance.	▪	2+
Singing class								
Bonhila, Int J COPD 2009 [155]	RCT	N=43 (drop-outs=30)	**COPD**	Intervention:	▪ Baseline Dyspnoea Index (BDI) ▪ Borg scale	▪ singing group: directly after singing small but		1+

Study, journal, year	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				▪ Singing group (weekly classes for 1 hour, 24 weeks) Control: ▪ Handcraft work (weekly classes for 1 hour, 24 weeks)		significant increase in **dyspnoea** ▪ after 24 session no significant difference between groups		
Nutrition								
Laviolette, J Med Food 2010 [156]	Double-blind, randomized controlled pilot study	N=22 (no drop-outs)	**COPD**	Intervention: ▪ Active pressurized whey Control: ▪ Placebo (casein) dietary supplementation ▪ Duration: 16 weeks ▪ Patients continued their usual activities for the first 8 weeks ▪ In the remaining 8 weeks they were subjected to an exercise training program	▪ cycle endurance test (CET) ▪ CRQ Measurement timing: ▪ 8 weeks ▪ 16 weeks	week 8: ▪ no increase in both groups week 16: ▪ statistically significant increase in CET time in the whey only group (277.2±108.8 vs. 226.6±77.1 seconds for whey and casein, respectively; P=0.23) ▪ clinically significant improvement in the **Dyspnea scale** of the CRQ in both groups		1+
Laughing								
Lebowitz, Heart Lung 2011 [157]	RCT	N=46 (drop-outs=22)	**COPD**	Intervention: ▪ 30 min humoreous video presentation Control: ▪ 30 min instructional videos on practical topics ▪ Timing of measurement: before and during video presentation (after 15 min)	▪ Dyspnoea NRS	▪ No effect on dyspnea		1+

6.1.2. Intervention „körperliche Übungen (*exercise*)“

Die systematische Literatursuche ergab keine Systematic Reviews oder Primärstudien zu Interventionen mit körperlichen Übungen bei Patienten mit einer Krebserkrankung für die Linderung von Atemnot.

6.2. Opioide

6.2.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Jennings, Cochrane Review 2001 [158]	SR (18 RCTs) MA (12 trials)	18 RCTs, double-blind, cross-over, placebo-controlled	Patients with dyspnea n=293 COPD(178) cancer (92) CHF (13) IPD (10)	Any opioid to alleviate breathlessness: ▪ oral or parenteral opioids (dihydrocodeine in the range of 15-60mg 3x/d, diamorphine in the range of 2.5- 5 mg 4x/d, oral morphine 30mg and morphine sc. average 34 mg) ▪ nine nebulised opioids (1mg- 50mg)	1.O: subjective measures of breathlessness: ▪ Borg und modifizierte Borg-Tests ▪ Verbal categorical scales of breathlessness ▪ VAS of breathlessness 2.O: ▪ Exercise tolerance ▪ Arterial blood gases ▪ Pulse oximetry ▪ Adverse effects of opioid drugs ▪ Quality of life	This review shows a strong effect of treatment for breathlessness (12 studies: SMD = -0.31; 95 % confidence interval -0.50 to - 0.13, P = 0.0008). For the breathlessness results, meta-regression comparing the non-nebulised and nebulised studies showed a significantly stronger effect for the non-nebulised studies (P = 0.02). A small but statistically significant positive effect of opioids was seen on breathlessness in the analysis of studies using non-nebulised opioids. There was no statistically significant positive effect seen for exercise tolerance in either group of studies or for breathlessness in the studies using nebulised opioids. For the exercise tolerance, an effect of treatment is indicated, although statistical significance is not achieved (12 studies: SMD=0.20; 95 % confidence interval -0.03 to 0.42, p = 0.09.)	Small sample sizes	1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
King Palliative Med 2011 b [159] *[Although this paper refers to the symptom pain, it was included regarding evidence for the use of opioids in renal impairment which is unrelated to the indication, e.g. pain, breathlessness]*	SR / no MA to identify and assess the quality of evidence for the safe and effective use of opioids for the relief of cancer pain in patients with renal impairment and to produce guidelines.	15 trials (no RCTs) • 8 prospective • 7 retrospective	N=1179	Assessment of ▪ pharmacokinetics and neuropsychological effects of morphine ▪ morphine and metabolite levels ▪ relationship between morphine concentrations and opioid side-effects ▪ relationship between plasma concentrations of morphine and its metabolites and pain scores ▪ whether routine monitoring for morphine and morpine metabolite concentrations ▪ biochemical and haematological factors ▪ the use of alfentanil, fentanyl, sufentanil, hydrmorphone ▪ factors associated with pethidine toxicity ▪ the effect of rotation from oral morphine to oxycodone ▪ the occurrence of toxicity	Different clinical outcomes that are relevant to the use of selected opioids in cancer-related pain and renal impairment.	• Risk of opioid use in renal impairment is stratified according to the activity of opioid metabolites, potential for accumulation and reports of successful or harmful use. • Fentanyl (1st line), alfentanil (2nd line) and tramadol/hydromorphone (use with care) are identified, with caveats, as the least likely to cause harm when used appropriately. • Morphine may be associated with toxicity in patients with renal impairment. ▪ Unwanted side effects with morphine may be satisfactorily dealt with by either increasing the dosing interval or reducing the 24 hour dose or by switching to an alternative opioid. ▪ No results for diamorphine, codeine, dihydrocoedeine, buprenorphine, tramadol, dextropropoxyphene, methadone, remifentanil	▪ Recommendations regarding opioid use in renal impairment and cancer pain are made on the basis of pharmacokinetic data, extrapolation from non-cancer pain studies and from clinical experience. • All included studies have a significant risk of bias inherent in the study methodology and there is additional significant risk of publication bias • Overall evidence is of very low quality • Direct clinical evidence in cancer-related pain and renal impairment is insufficient to allow formulation of guidelines but is suggestive of significant differences in risk between opioids.	2++

6.2.2. Systematic Reviews der Aktualisierung 2019

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Barnes, Cochrane 2016 [160] *(update of Jennings, Cochrane 2001; see above)*	SR, MA; To determine the effectiveness of opioid drugs in relieving the symptom of breathlessness in people with advanced disease due to malignancy, respiratory or cardiovascular disease, or receiving palliative care for any other disease;	Searches on CENTRAL, MEDLINE, EBASE, CINAHL, and-Web of Science up to 19 October 2015. Handsearch of review articles, clinical trial registries, and reference lists of retrieved articles; Included studies: double-blind RCTs	Adults with any type of **advanced progressive illness** with persistent **breathlessness** despite optimal or appropriate treatment of reversible factors	Any **opioid** drug, given by any route in any dose, for the treatment of breathlessness compared to placebo, or any other pharmacological or non-pharmacological interventions	1.O: Subjective measurement of breathlessness intensity or severity, including but not limited to Borg and the modified Borg scale, verbal categorical scales of breathlessness, and visual analogue scales (VAS) of breathlessness 2.O: ▪ QoL ▪ Any physiological and functional assessments of breathlessness including but not limited to six-minute walk tests (6MWT), shuttle tests, and actigraphy ▪ Performance status ▪ Pulse oximetry ▪ Arterial blood analysis ▪ Adverse events (AE) ▪ Mortality	Studies included: 26 RCTs in qualitative synthesis (526 patients); 18 RCTs in meta-analysis Participants: COPD (10 RCTs); cancer (4 RCTs); CHF (2); interstitial lung disease (1) **Subjective breathlessness** (MA): ▪ Mean change from baseline (7 RCTs, n=117, very low quality of evidence): -0.09 points reduction of breathlessness in opoid group vs. placebo (95% CI: -0.36 to 0.19) ▪ Mean post-treatment dyspnea (11 RCTs, n=159; low quality of evidence): -0.28 points reduction in oipioid group vs. placebo (95% CI: -0.5 to 0.05) **6MWT**: results conflicting. The total distance in 6MWT was 28 metres (m) better in the opioids group compared to placebo (range: 113 m to 58 m) (1 RCT, n=11, very low quality evidence). However, the change in baseline was 48 m worse in the	▪ There is some low quality evidence that shows benefit for the use of oral or parenteral opioids to palliate breathlessness, although the number of included participants was small. We found no evidence to support the use of nebulised opioids. ▪ Well conducted systematic review ▪ Risk of bias: size bias included in assessment ▪ Crossover studies analysed as parallel RCTs	1+ *(body of evidence: 1-)*

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						opioids group (range: 36 m to 60 m) (2 RCTs, n=26, very low quality evidence) **AE**: participants were 4.73 times more likely to experience nausea and vomiting compared to placebo, 3 times more likely to experience constipation, and 2.86 times more likely to experience drowsiness (9 studies, n=162, very low quality evidence). **QoL** (4 RCTs): n.s. change		
Ekström, Ann Am Thorac Soc 2015 [161]	SR, MA; To estimate the efficacy and safety of opioids on refractory breathlessness, exercise capacity, and HRQL in COPD	Search in Cochrane Central Register of Controlled Trials, MEDLINE, and Embase up to 8 September, 2014; hand search Included studies: RCTs, double-blind	**COPD** patients (at least 1 per study)	Any **opioid** as intervention; placebo as control	1.O: effect on breathlessness of systemic (nonnebulized) opioids at steady state in the nonlaboratory (outpatient) setting 2.O: exercise capacity, distance on 6-min.-walk, duration on cycle test	Studies included: 16 RCTs (15 crossover), n=271 (95% severe COPD) **Breathlessness**: reduced by opioids: SMD, 20.35 (95% CI, 20.53 to 20.17; I2, 48.9%), by systemic opioids (8 studies, n=118): SMD, 20.34 (95% CI, 20.58 to 20.10; I2, 0%), and less consistently by nebulized opioids (4 studies, n=82): SMD, 20.39 (95% CI, 20.71 to 20.07; I2, 78.9%). **Exercise capacity**: no improvement **HRQL**: not analysable	▪ Opioids improved breathlessness but not exercise tolerance in severe COPD. ▪ Moderate quality of evidence for systemic opioids; low for nebulized opioids ▪ Well conducted systematic review1	1++
Ekström, Thorax	MA To determine the reasons for the different conclusions	Included studies: RCTs, double-blind,	Patients with **chronic breathlessness** (COPD, chronic heart	Oral or parenteral **opioid**; placebo or any other pharmacological	effect of **opioid treatment on chronic breathlessness**	**Breathlessness:** 17 RCTs (n=220) decrease in breathlessness. There 9 RCTs (n=118) in a primary	Unclear or low risk of bias (MA of Jennings and Ekström) to high risk of bias (MA of	1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
2018 [162]	and to re-evaluate the efficacy of systematic opioids for chronic breathlessness. *(MA of Jennigs Cochrane, 2001; Ekström Ann Am Thorac Soc, 2015; Barnes Cochrane, 2016)*	placebo, 28 crossover, 1 parallel	failure, cancer and other)	or non-pharmacological interventions as control		analysis systematic opioids improve breathlessness in COPD outpatients measured at steady state (5 studies, n=91), SMD -0.33 (95% CI -0.52 to -0.14). Point estimates from SMD -0.27 (oral opioid, post-treatment scores) to mean difference 0.20 (subcutaneous opioid, change scores). 12 RCTs (n=198): opioids decrease breathlessness, SMD -0.32 (95% CI -0.47 to -018; p<0.001) compared with placebo (constistent to Jennings, 2001 and Ekström, 2015)	Barnes) due to sample size size definied as <50 participations in each treatment arm. Level of evidence is from moderate (Ekström, 2015) to low or very low (Barnes, 2016) Low-dose morphine is the first-line paharmacological treatment for the relief of chronic breathlessness in severe illness	
Verberkt Eur Respir J 2017 [163]	SR, MA To report respiratory adverse effects of opioids in patients with advanced disease and chronic breathlessness.	Search in PubMed, Embase on Ovid, Cochrane Central Register of Controlled Trials, CINAHL on EBSCO (inception date to March 31, 2016), ClinicalTrials.gov (May 29, 2017) and the reference lists	Patients with **advanced disease** and **chronic breathlessness**	**Opioid** as intervention	1.O: effect of **opioid treatment on breathlessness** 2.O: effects on: ▪ arterial carbon dioxide tension ($PaCO_2$) ▪ end-tidal carbon dioxide tension ($PETCO_2$) ▪ arterial oxygen tension ($Pa0_2$) ▪ arterial oxygen saturation ($Sa0_2$) ▪ respiratory rate (*RR*) and occurance respiratory depressions (*RD*)	63 articles; 67 studies, 35 RCTs, 17 nonrandomised trials (NRTs), 4 prospective observational studies (POSs), 5 retrospective observational studies (ROSs), 6 case reports, 6 ongoing studies (4 RCTs, 2 NRTs) ***PaCO***$_2$: (5 RCTs), increase (MD 0.27, 95% CI 0.08 - 0.45; I^2 0%) ***PETCO***$_2$: (5 RCTs), nonsignificant increase (MD 0.13, 95% CI -0.02-0.27); I^2 0%.)	▪ No evidence for clinical ly relevant respiratory AE of opioids for chronic breathlessness. ▪ Low to moderate quality of evidence for the different outcomes ▪ Limitations in the design and implementation ▪ The risk of bias is low or unclear in the RCTs, in the other sources high risk in 43% of the studies ▪ A small number of RCTs included	1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
		of relevant systematic reviews Two idenpendent researchers screened predefined inclusion criteria and extracted data				***Pa0₂:*** (4 RCTs), nonsignificant decrease (MD -0,26, 95% CI -0.68-0.15; I^2 0% ***Sa0₂***: (14 RCTs), decrease (MD -0.41, 95% CI -0.73—0.08: I^2 0%) ***RR***: (13 RCTs), significantly decrease (MD -1.10, 95% CI -1.49—0.71; I^2 0%) ***RD***: (5 RCTs, 11 NRTs, 2 POSs, 3 ROSs, 4 case reports) 11 defined respiratory depression: increase in *Pa*C0₂ of >0.5 kPa or to >6.0 kPa, a decrease in respiratory rate of >10% or to <10 breaths·min^{-1} and a decrease in *Sa*O^2 of >5% kPa or to <90%	assessment of PaCO2 and PaO2	

6.2.3. Primärstudien

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Abernethy, BMJ 2003 [164]	RCT, double-blind, crossover	n=48 10 drop outs	▪ Opioid naive outpatient adults with dyspnea at rest in spite of receiving optimal	▪ 4 days of 20mg oral morphine with sustained release followed by ▪ 4 days placebo, or vice versa.	1.O: **Dyspnea intensity** in the evening (VAS, 0-100 mm), 2.O: ▪ Dyspnea in the morning (VAS, 0-100 mm),	▪ morphine superior to placebo in evening **dyspnea** (improvement of 9.5 mm (95% confidence interval 3.0 mm to 16.1 mm))	▪ Only very weak strategy to control compliance with medication intake ▪ no washout period	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			treatment of reversible factors. ▪ 88% **COPD** ▪ 6% **cancer** ▪ 2% **motor neuron disease** ▪ 4% **restrictive lung disease** ▪ 73% male ▪ 71% received supplemental oxygen ▪ Overall poor functional status	Laxatives provided as needed	▪ exercise tolerance (self-report) ▪ respiratory rate, blood pressure, heart rate, oxygen saturation ▪ self-report of sleep disturbance by breathlessness, nausea, vomiting, constipation, confusion, somnolence, appetite, and overall wellbeing as measured at the mend of the four days treatment period. Outcomes analysed at 4th day of respective treatment and compared to 4th day of other treatment (but not to baseline values)	▪ morphine superior to placebo in morning dyspnea (improvement of 6.6 mm (95% confidence interval 1.6 mm to 11.6 mm)) ▪ less sleep disturbances by breathlessness with morphine compared to placebo (P = 0.039) ▪ no effects on exercise tolerance, overall wellbeing, sedation and respiratory rate ▪ morphine caused more distressing constipation than placebo ▪ dropouts due to (potential) side effects of morphine	▪ baseline values were not taken into account ▪ no details on measurement procedures of respiratory rate, blood pressure, heart rate, oxygen saturation provided ▪ for some secondary measures, no data is provided, but only statements such as “no difference” between treatments occurred”	
Allard, J Pain Symptom Manage 1999 [165]	randomized continuous sequential clinical trial, double-blind	n=33 (for some measures only 30 patients available)	Terminally ill **cancer** patients (median days of survival: 14,5-19) who were already receiving opioids regularly for pain relief and had persistent dyspnea after rest and treatment with oxygen of ≥ 2 on 10cm VAS	Patients received in addition to regular opioid regimen once either: ▪ Arm 1: 25% or ▪ Arm 2: 50% of their regular 4-hourly opioid dose Route of administration was same as the regular opioid regimen (oral and subcutaneous)	1.O: **Intensity of dyspnea** as measured 5x during 4 hours after drug administration on 10cm VAS 2.O: Respiratory frequency	▪ significant reduction of **dyspnea** relative to baseline after both treatments, but no difference between 25% or 50% supplementary dose; The overall mean difference between pre- and post-randomization respiratory frequencies was 1.56 (SD =2.28 paired t-test: P = 0.0004). ▪ dyspnea reduction lastet up to 4 hours	▪ no details on measurement procedures of respiratory frequency ▪ Impact of regularly scheduled or “as-needed” medications for breakthrough pain or dyspnea on outcomes cannot be estimated ▪ small sample size ▪ treatment duration too short with only 1 treatment	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
						▪ sign. reduction of respiratory frequency relative to baseline after both treatments, but no difference between 25% or 50% supplementary dose ▪ reduction of respiratory frequency lastet up to 4 hours ▪ dyspnea reduction was relatively greater in patients with low /moderate dyspnea at baseline (33.1; (95% CI:1.0–65.4)) compared to those with high dyspnea intensity at baseline (11.1 (95% CI: 3.0–19.2))		
Bruera, J Pain Symptom Manage 2005 [166]	RCT, double blind, crossover	n=12 (1 drop out)	▪ Patients with advanced **cancer** and resting dyspnea intensity ≥3 on 0–10 scale who received regular oral or parenteral opioids ▪ Patients had predominant restrictive ventilation	▪ 1 day with subcutaneous morphine plus nebulized placebo followed by ▪ 1 day with nebulized morphine plus subcutaneous placebo, or vice versa (in addition to patients' regularly scheduled opioid dose)	1.O: **Intensity of dyspnea** as measured 1 hour after drug administration on 0-10 scale 2.O: ▪ global assessment of benefit, nausea, sweat, wheezing, and sedation on 0-10 scale ▪ dyspnea ratings ▪ over time	▪ significant reduction of **dyspnea** after both treatments, but no difference between subcutaneous and nebulized morphine ▪ no significant differences in nausea, sweat, wheezing, sedation between treatments ▪ dyspnea reduction lastet up to 4.5 hours for both treatments ▪ preference of patients and investigators greater for nebulized morphine, but not statistically tested	▪ no washout period ▪ very small sample → power problem ▪ treatment duration too short with only 1 day	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Charles, J Pain Symptom Manage 2008 [167]	Pilot-RCT, double blind, crossover	n=25 (5 drop outs)	**Cancer** patients experiencing incident dyspnea who were using a stable regular dose of an opioid.	On 3 occasions of breathlessness patients received either ▪ nebulized hydromorphone or ▪ a systemic breakthrough dose of hydromorphone ▪ or nebulized saline together with a blinding agent	1.O: **Intensity of dyspnea** as measured 10 min post-treatment (nebulizer) and 18-19min post-treatment (oral or subcutaneous) on 10cm vertical VAS 2.O: ▪ Intensity of dyspnea as measured 20, 30, and 60 minutes post-treatment on 10cm VAS ▪ patients subjective reports which treatment was most effective ▪ pulse rate, peripheral oxygen saturation, respiratory rate	▪ significant reduction of **dyspnea** relative to baseline after all 3 treatments, but no sign. difference between treatments ▪ dyspnea reduction continued up to 60min post-treatment with no sign. difference between treatments ▪ no difference in patients subjective reports on which treatment was most effective ▪ significant reduction in respiratory rate 10min post-treatment lasting until 60min post-treatment F(1,19)=10.04, P=0.005, but no differences between treatments ▪ no consistent effects for pulse rate and peripheral oxygen saturation	▪ small sample size ▪ treatment duration too short with only 1 use of each treatment ▪ nebulized saline (as control treatment) as effective as medical treatments → placebo effects or psychological effects (i.e., anxiety)? ▪ occasions of acute breathlessness were based on patients wish to receive treatment→ could be influenced by psychological factors	1+
Grimbert, Rev Mal Respir 2004 [168]	RCT, placebo-controlled, double-blind, cross-over	n=12 (2 Drop-outs (not intervention-related)	Adults receiving palliative care with dyspnea due to primary or secondary **lung neoplasia**, despite conventional treatment	▪ Arm 1: Morphine aerosols 20 mg, every 4 hrs during the day and on demand in the night (max 6 times in 24hrs) ▪ Arm 2: Placebo = normal saline	1.O: dyspnea score by means of VAS before and within 15 min after nebulisation; evaluation by 7 categories of persons independently of each other (patient, physiotherapist, nurse, enrolled	▪ Significant improvement in the **dyspnea score** after inhalation of morphine and placebo (p =0.00001; effect size not mentioned) ▪ No significant difference in the **dyspnea score** between morphine and	▪ Small sample size ▪ Inclusion of 5 patients receiving oral or transdermal morphine for pain ▪ 11 men and 1 woman recruited > general applicability?	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				(Wash-out period of 24 hrs)	nurse, physician, resident, medical student) 2.O: respiratory rate and oxygen saturation before and after nebulisation	placebo (p > 0.05). It.suggests that humidification or placebo effect leads to an subjective improvement ▪ No change in respiratory rate or oxygen saturation ▪ Significant differences between the **dyspnea score** according to the evaluator: the scores of the physicians, residents and medical students were similar to those of the patients; scores of the nurses, enrolled nurses and physiotherapists underestimated the subjective sensation of the patients. ▪ Upward trend of **dyspnea score** by higher dosis of morphine ▪ No side effects in the morphine group	▪ No details to baseline data	
Jensen, J Pain Symptom Manage 2011 [169]	RCT, placebo-controlled, double-blinded	n=12	patients with stable **COPD**, ≥ 40 years, ≥ 20 py nicotine abuse	• 50 µg fentanyl inhalatation vs. • placebo 10 min. later measurement of pulmonary function and exercise tests within 1 h,	▪ pulmonary function testing ▪ exercise endurance time ▪ dyspnoea intensity during exercise (Borg scale)	Fentanyl inhalation significantly increases exercise endurance time (p=0.01) and inspiratoy capacity at peak exercise (p≤0.03); increase in **dyspnoea intensity** less with fentanyl (p=0.03)	Fentanyl inhalation significantly increases exercise endurance time and improves inspiratory lung capacity at peak exercise. Small study but sample size calculation. No wash-out	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				cross over for each patient on two separate days				
Johnson, Eur J Heart Fail 2002 [170]	RCT, placebo-controlled, double-blinded (pilot study)	n=10	Patients. with **chronic heart failure**, NYHA III/IV (EF ≤ 35%), clinically stable with-out changed NYHA status for 1 month and unchanged medication for 2 weeks, male gender, age 45-85, median 67 years	▪ 5 mg morphine p.o. 4x per day for 4 days vs. ▪ placebo cross over for each patient on day 2	**dyspnoea intensity** by VRS (0-100)	morphine relieves breathlessness (p=0.022), when given orally by day 2; side effects with sedation from day 3 (p=0.013) and constipation (p=0.026) under morphine treatment	• Orally taken morphine can reduce breathlessness due to chronic heart failure, • small underpowered study • All men > general applicability?	1-
Mazzocato, Ann Oncol 1999 [171]	RCT, placebo-controlled, double-blinded	n=9; (opioid-naiv: n=7; opioid pretreated: n=2)	Elderly patients. (66-83, median 73 y.) with **advanced cancer** disease	▪ 5 mg morphine s.c. in opiate naïve patients (or +3.75 mg morphine additionally to preexisting oral morphine dosage), versus ▪ placebo, cross over for each patient on day 2	1.O: dyspnoea intensity by VAS (0-100) and Borg scale 2.O: • pain, somnolence, anxiety • respiratory effort • respiratory rate • O2 saturation before and 45 min after injection of Mo or placebo. VAS every 15 min for 2 hrs, then every hour up to 4 hours after injection	morphine significantly better than placebo for **dyspnoea** relief (VAS p<0.01; Borg: p= 0.03)	morphine s.c. appears effective for cancer dyspnoea, but very small study with n=9 patients without achieving recruitment aim of 20 patients. No description of randomisation, concealment and blinding.	1-
Navigante, J Pain Symptom Manage 2006 [172]	RCT , single-blinded	n=101; morphine treated group (Mo; n=35), midazolam treated group (Mi; n=33),	Terminal **advanced cancer** disease, life expectancy < 1 week, ≥ 18 years, ECOG 4, severe dyspnoea	▪ Mo group: 2.5 mg morphine s.c. every 4 h for opioid naive patients, in case of opioid baseline therapy 25% increase above baseline dosage, in case of breakthrough	1.O: ▪ dyspnoea intensity (Borg scale), ▪ dyspnoea relief after 24 / 48 h (yes/no)	Dyspnoea relief after 24 h significantly better in MM group with p=0 0004 vs. Mi and with p=0.03 vs. MO group, at 48 h percentage of pt. without dyspnoe relief with 4% in MM group (p=0.04 vs. Mi)	Addition of midazolam to morphine therapy is beneficial in controlling dyspnoea for dying cancer patients. Single blinding questionable: Patients who received mo. were	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
		morphine + midazolam treated group (MM; n=33) Drop-outs: n=31 (death)		dyspnoea midazolam 5 mg ▪ Mi group: 5 mg midazolam s.c. every 4 h, in case of breakthrough dyspnoea morphine 2.5 mg s.c. ▪ MM group: combination of both baseline drugs, in case of break-through dyspnoe ▪ a morphine 2.5 mg s.c.		**Dyspnea intensity:** The median values of dyspnea intensity (considering all the patients) were 3 (IR 2--5.5), 4 (IR 2--6.2), and 3 (IR 2--5) for Mo, Mi, and MM, respectively (P=NS for intergroup comparison).	systematically premedicated with laxatives. No mention of ITT-analysis. Drop-out ca. 33% (due to death by terminal advanced disease). No sample size calculation	
Navigante, J Pain Symptom Manage 2010 [173]	RCT, single-blinded	n=63; morphine treated group (Mo; n=31), midazolam treated group (Mi; n=32). Drop out: n=2	ambulatory patients. with **advanced cancer** disease, ≥ 18 years, ECOG ≤ 3, moderate and severe dyspnoea	▪ Mo group: 3 mg morphine p.o. with incremental steps of 25% every 30 min. until dyspnoea intensity is reduced at least 50%, then every 4h (except for sleeping time) ▪ Mi group: 2 mg midazolam p.o. with incremental steps every 30 min. until dyspnoea intensity is reduced at least 50%, then every 4 h (except for sleeping time)	▪ dyspnoea intensity by NRS (0-10 scale) for follow-up phase (FUP) ▪ dyspnea relief for fast titration phase ▪ side effects	Dyspnea relief in both groups, after 2d significantly better in midazolam vs. morphine group, p<0.001. **Dyspnea intensity:** significantly lower dyspnea intensity level in midazolam group in comparison with the morphine group, during the four days of follow-up.(midazolam 6 (MAD = 1) and morphine 4.5 (MAD = 1.5) (P < 0.001, to baseline) No serious **AEs** that required drug discontinuation. Most common AE: somnolence.	midazolam p.o. appears to be a better option than morphine p.o. for controlling dyspnoea in ambulatory cancer patients Single blinding questionable: Patients who received morphine were systematically premedicated with laxatives. Sample size calculation > powered study.	1+
Oxberry, Eur J Heart Fail	RCT, placebo-controlled,	n=39 (drop out: n=4)	patients with **chronic heart failure**, NYHA III/IV (EF	▪ 5 mg morphine p.o. 4x per day for 4 days vs.	1.O: mean change in dyspnoea intensity by NRS (0-100) over the past 24h.	**Mean change in dyspnoea intensity**: no statistically significant effect for	no benefit shown for the relief of breathlessness with low-dose	1++

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
2011 [174]	double-blinded		< 45%), clinically stable with-out changed NYHA status for 1 month and unchanged medication for 2 weeks, age 41-89, mean 70.2 years	▪ 2.5 mg oxycodone p.o. 4x per day for 4 days vs. ▪ placebo Cross over for each patient after 3 days	2.O: • change in worst dyspnoea intensity by NRS (0-100) over the past 24h. • breathlessness now • breathlessness severity (Borg) • coping with breathlessness and satisfaction with treatment (NRS) • change in physical function (Karnofsky) • QoL (SF-12) • Adverse events	low-dose opioids (both morphine or oxycodone) in chronic heart failure detected [21.37 in NRS score for placebo group vs. 20.41 in morphine group (P ¼ 0.13) and 21.29 for oxycodone group (P ¼ 0.90)] **Adverse event**: opioids well tolerated. **QoL** unchanged.	oral opioids in chronic heart failure, follow-up study to Johnson, 2002, short treatment period for opioids to discover significant differences. Sample size calculation > powered study. ITT analysis.	

6.2.4. Primärstudien der Aktualisierung 2019

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Hui, J Pain Symptom Manage 2016 [175]	RCT, parallel, double-blind, placebo-controlled	24 patients enrolled with 96% completion	Patients with **cancer** and comorbidities, outpatients. Cancer most: n=5 breast, n=6 gastrointestinal) Comorbidities: COPD n=4 (FPNS n=2), Heart failure	First arm: same dose of **fentanyl** pectin nasal spray FPNS was given before the second and the third six-minutes walk tests (6MWT) using the following sliding scale. 100 mcg (one spray), 200 mcg (two sprays), 300 mcg (three sprays), and 400 mcg	1.O: Change in **dyspnea** 2.O: changes in physiologic variables, neurocognitive function (heart rate, respiratory rate, systolic and diastolic blood pressure, and oxygen saturation) 3. O: adverse effects	**Dyspnea** and **Walk Distance**: FPNS was associated with significant within-arm reduction in dyspnea NRS at rest (T2-T1: -0.9 [95% CI -1.7,-0.1]; T3-T1: -1.3 [95% CI -2.0-0.5] and at the end of a 6MWT (T2-T1: -2.0 [95% CI -3.5, -0.6]; T3-T1: -2.3 [95% CI -	Small sample size ▪ Multiple statistical tests for secondary outcomes as part of the pre-planned exploratory analysis ▪ The cancer patients where opioid tolerant and	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			n=1 (FPNS n=1), Asthma n=5 (FPNS n=5) Average age 52,4 years (47,5-57,4) 96% completed the three six-minutes walk tests (6MWTs), 4% (n=1) completed only 2 6MWTs	(four sprays) of FPNS for MEDD of 80-159 mg/day, 160-239 mg/day, 240-319 mg/day, and 320-540 mg/day, respectively Each dose designed to be equivalent to 15%-25% of MEDD, assuming 80% biovailability. Second arm: Placebo		4.0, -0.7]), and a longer walk distance T2-T1: +23.8 m [95% CI +1.3, +46.2 m]; T3-T1: +23.3 [95% CI -1.7, +48.2]) **Placebo**: no significant change in walk distance nor dyspnea NRS at rest, but significant reduction in dyspnea NRS at six minutes Tt2-T1: -1.7 [95% CI -3.3, -0.1]; T3-T1: -2.5 [95% CI -4.2, -0.9]) Vital sign, neurocognitive function, and adverse effects did not differ significantly	with a good performance status ▪ Imbalance of comorbidities between arms, which may potentially affect dyspnea response to FPNS	
Hui, J Pain Symptom Manage 2017 [176]	RCT, parallel, double-blind, placebo	22 patients enrolled with 91% completion	Patients with **cancer** (lung cancer n=8), COPD n=3 Female 60%, average age 55 (31-72 years) Induced episodic dyspnea (exercise) of at least 3 of 10 on Numeric Scale (NRS) , opioids tolerant at morphine equivalent daily dose (MEDD) of 60-130mg for at least one week,	First arm: single dose of **fentanyl** buccal tablet (FBT) equivalent to 20-50% of their total opioid dose over the past 24 hours) Second arm: Placebo	1. O: Prophylactic FBT to reduction external dyspnea 2. O: Compare between the first and second 6 MWT (effects on walk distance, fatigue, and physiological function)	**Dyspnea:** FBT was associated with a significant within-arm reduction in NRS between 0 and 6 minutes (mean change -2.4, 95% CI -3.5, -1.3). Placebo was associated with a nonstatistically significant decrease in dyspnea (mean change -1.1, 95% CI -2.5, 0.2. The patients had the **subject feeling**, that dyspnea was in the second MWT "somewhat better" then in the first 6 MWT (4 of 9 vs. 0 of 11, P=0.03)	▪ Multiple exploratory outcomes ▪ Patients from a single care cancer center ▪ MEDD was limited to 130mg/day ▪ Small sample size	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			ambulatory with or without walking aid, Karnofsky Performace Status ≥50%.			**Walk distance, fatigue and physological function:** FBT was associated with a significant reduction in respiratory rate between the first and the second 6 MWTs (mean change -2.6, 95% CI -4.7, -0.4). **Neurocognitive function**: FBT was associated with a significant improvement in one neurocognitive test (of four neurocognitive tests) between 6 MWTs (tapping mean change 4, 95% CI 0.5, 7.5).		
Pinna, AM J Hosp Palliat 2015 [177]	RCT, double-blinded cross-over	n=13 patients	·**Palliative patients** with **advanced cancer**, most lung cancer (76.9%) ·a moderate-effort **dyspnea** (eg, dyspnea caused by basic activities of daily living, similar in the 6MWT [6-minutes-walk test], ESAS [Dyspnea Edmonton Symptom Assessment System] Score in the last 24 hours with a intensity of at	First arm: Oral transmucosal fentanyl citrate (OTFC) in dyspnoe on exertion Second arm: Placebo The patients were classified in 3 categories according to the differences observed in the dyspnea between before and after the completion of the 6MWT: ▪ better response in the first period	1.O: Efficacy of OTFC 2.O: Treatment impact on the oxygen saturation baseline (Sa_{O_2}), distance walk change in ESAS symptom, any adverse events	**Intensity of dyspnea**: no differences between the groups - no change in oxygen saturation level before and after the 6 MWT, independent of the treatment sequence (P=0.7541). - Distance walked in the different sequences did not vary independently, regardless of whether the initial period corresponded with active medication or with the administration of placebo (P=0.6550)	• Sample size was small and insufficent to detect significant differences between the treatment groups and sequences. • ITT analyses.	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			least 3 (scale from 0=no dyspnea to 10= maximum severity), · Karnofsky index score must exceed 50, haemoglobin levels in the past month must have exceeded 10 mg/dL, and Sao2 >90% · male (84%) ·mean age 65.2 years	▪ same response to both the periods ▪ better response to the treatment in the second period.		- No proven differences in relation to the remainder of ESAS symptoms (P=0.1234) - adverse events in both groups (active treatment group: diarrhea [n=2], respiratory infections [n=1]; placebo: diarrhea [n=2], respiratory infections [n=2], but no causal correlation with the medication.		
Simon, J Pain Symptom Manage 2016 [178]	RCT, multicenter, open-label, crossover, Phase II	n=10 (drop out: n=4)	Patients with **incurable cancer** (life expectancy of at least one month, most lung cancer [n=4]) Episodic breathlessness (peak intensity ≥ on a numeric Rating Scale [0-10]) due to chronic breathlessness Opioid tolerant for at least one day (30mg oral morphine, 15mg oral oxycodone, 4mg oral hydromorphone 12µg/hour	First arm (intervention): Fentanyl buccal tablet (FBT) not more than 4x/day Second arm (comparator): IRM (Morphin Merck 2% solution, Merck), no restriction of application/day For both arms: Titration Phase (TPh) to determine the individual effective dose and adopted the procedures of fentanyl trials for breakthrough cancer pain as an model for episodic breathlessness Efficacy Phase (EPh): effective dose of each medication	1.O: Time to onset of meaningful breathlessness relief (measured by stop-watch) in minutes by the patients) 2.O: Efficacy breathlessness intensity difference at 10 and 30 minutes; sum of breathlessness intensity difference at 15 and 60 minutes), safety and feasibility	**Time to Onset:** mean time to onset of meaningful breathlessness relief was a mean difference of -10.9 minutes in favour for FBT (FBT-IRM) (95% CI = -24.5 to 2.7, P=0.094). Significant mean difference of -14.2 minutes (-27.1 to -1.4; P=0.036) when taking only episodes into account with at least four hours interval to the next treated episode (FBT 25/26 episodes, IRM 28/35) episodes) First efficacy phase time to onset was FBT 11.9 ± 5.5 minutes and IRM 17.0 ± 12.8 minutes (P=0.499) with a mean difference of -	• small sample size • Open-label design was subject to performance and detection bias as patients and clinicians were aware of which intervention is used. • no double-blind	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			trandermal fentanyl, or an analgesic equivalent of a different opioid or a different routes of application) Karnofsky score 67 ± 10.2 Male 6/10 Mean age 58 ± 11	Rescue medication allowed. EPh, FBT and IRM: 8 single doses of the individual effective dose identified by titration to treat of maximum of 8 breathlessness episodes during 2-day period. TPh and EPh were completed when FBT or IRM provided adequate breathlessness relief and minimizes undesirable effects within the first 30 min after administration of at least one breathless episode		8.4 minutes (-18.8 to 2.1, P=0.085) Karnofsky score 67 ± 10.2 at baseline to 42 ± 28.4 at final visit.		

6.3. Andere Medikamente (Benzodiazepine, Phenothiazine, Antidepressiva, Buspiron, Steroide)

6.3.1. Benzodiazepine

6.3.1.1. Systematic Reviews

Das Systematic Review von Simon et al. 2010, das zur Evidenzbasierung dieses Kapitels herangezogen wurde, wurde 2016 aktualisiert (s.u.).

6.3.1.2. Primärstudie

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Allcroft, J Pall Med 2013 [179]	Single-site open-label, uncontrolled phase II study (pilot)	N=11 drop-out=1	COPD patients (median age 78 years) 8 male 3 female	clonazepam 0.5 mg nocte orally plus 10 mg sustained release morphine sulphate orally mane together with docusate/sennosides	1.O: Breathlessness intensity on day 4 (VAS 0-100)	The median score for morning average dyspnea right now was 49.5 (6 to 87) with a median reduction of 9mm (23mm worsening to 80mm improvement) over baseline and in the evening a median of 45.4 (2 to 84) with a median improvement of 6.5mm (18mm worsening to 64mm improvement) over baseline.	• One person withdrew on day 4 because she was feeling unsteady on her feet. • Quality of sleep showed no change over baseline.	2-

6.3.1.3. Systematic Review der Aktualisierung 2019

Study	Type of study (SR=Systematic Review; MA=Meta-analysis))	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence
Simon, Cochrane Review 2016 [180] *Update of Simon, Cochrane 2010*	SR with MA	8 RCTs (2 RCTs single-blind, parallel 6 studies double-blind, cross-over, placebo-controlled) N=214 cancer (n=148), COPD (n=66)	Patients with cancer, COPD, Chronic Heart Failure (CHF), Motor Neurone Diease (MND), and Idopathic Pulmonary Fibrosis (IPF)	Alprazolam 0,75 and 1,0mg/day, diazepam 25mg/day with promethazine 125mg/day, midazolam 8 and 20mg/day, lorazepam 1mg/day, clorazepate 7,5 and 22,5mg/day, Temazepam 10mg/day oral; Control: placebo, morphine; treatment duration ranged between 48h and two weeks.	1.O: subjective measurement of breathlessness on validated and reliable scale: uni-dimensional scales (e.g. visual analogue scales (VAS), numeric rating scales (NRS), categorical scales, modified Borg scales) and multidimensional scales (e.g. St. George´s Respratory Questionnaire (CRQ) 2.O: measurement of anxiety, depression, adverse effects of benzodiazepines, functional exercise capacity (e.g. walking tests), quliaty of life and atrrition	There is no evidence that benzodiazepines relieve breathlessness in adults with advanced disease. No statistically significant effect of alprazolam, diazepam, or temazepam with a standardised mean difference (SMD) estimated as -0.12 (95% confidence interval (CI) -0.52 to 0.29).	• small sample sizes in the studies	1++

6.3.1.4. Primärstudie der Aktualisierung 2019

Study	Type of study Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Hardy, Support Care Center 2016 [181]	RCT, double-blind, intra-patient, crossover	n=75	**Palliative Patients with dyspnoe** with life-limiting disease In- and outpatients from a oncology/palliative care department in Australia (AUS) and three palliatice care services in New Zealand (NZ) Median age 70 years, males 48% Depression 33%, anxiety 31%, cancer 67%, hearth disease: 5%, respiratory disease 28%, Performance status (Median) 60 (30-80)	First arm: Midazolam hydrochloride injection 15mg/3ml, 2 ampoules (6 ml) in metered dose spray delivering 0.1 ml per spray (0.5 mg/spray) Second arm: Placebo One of the six SNS bottle on each day of breathless for 6 days within 2 weeks Dyspnea scores record before and at set time intervals following the first use of each SNS bottle Average dyspnea score of ≥3/10 on a dyspnoea screening scale (0=no breathlessness, 10=worst breathlessness · Performance status: Australian Karnofsky Performance Scale (AKPS) · Functional impair-ment: dyspnoea exertion scale (DES; 0-5) · Hospital Anxiety and Depression Scale (HADS)	1.O: effect of midazolam vs control 2.O: differences between the countries and study groups: Change of drowsiness and anxiety, general impression of benefit, adverse events	**COVI** (baseline)n=64, median 4 (range 3-14); · **DES (baseline)**: n=62, at baseline median 3 (range 1-5) · **CDS**: n=59, median 19 (range 5-46) Opioide: n=36, 20/75 (27%) were on supplemental oxygen **Comparison of the countries:** · **SNS episodes**: similar distribution (AUS, 56/111, 50.5%; NZ, 70/139, 50.4%; p=0.989) and results from 62 unique patients (AUS: n=30 (48%), NZ: n=32 (52%) **disease**: · Cancer: NZ: 80%, AUS n=55% · Respiratory disease: AUS 45%, NZ: n=9% (p=0.002) · Dyspnoea: no different in mean (SD) change from baseline and at all time points (5, 15, 30, 60 min) nor in the number of SNS bottles in which positive outcome was achieved (i.e.	• Some information are lacking or hard to find within the paper (e.g. number of total participants) • Study was orginially planned as a N=1 trial but because of difficulties in recruitment and funding the calculated sample size was not reached and re-analized. • There is a high risk of bias because of different reasons, e.g. no central monitoring, very limited ressources for recruitment and conducting the trial etc.	1-

Study	Type of study Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				·COVI anxiety scale Patients behaviour and somatic symp-toms of anxiety (3=does not appear anxious) to 15=very anxious) ·Cancer Dyspnoea Scale (CDS) (three domains=sense of effort, anxiety and discomfort, no dyspnoea=0 to 48 (very severe dyspnoea)		a reduction in dyspnoea score of ≥2) **Comparison of study groups:** No difference at any time point between arms Drowsiness and anxiety: Minimal change in mean drowsiness score Anxiety: minimal difference from baseline Significant association between gender and anxiety with female. General impression of benefit: 248 scores (125 midazolam; 123 placebo), median 2 ("good")		

6.3.2. Phenothiazine

6.3.2.1. Primärstudien

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= 117ignifdary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
O'Neill, Br J Clin Pharmac 1985 [182]	RCT, double-blind, cross-over	n=12	**Healthy subjects**: mean age 30 years (range=23-39 years, 10 non-smokers, 2 smokers)	n=12 ▪ Promethazine 25mg vs.placebo	1.O: dyspnea-intensity 2.O: lung function Measurement: ▪ VAS ▪ peak expiratory flow rate ▪ breath-holding time ▪ peak level of CO2 ▪ sedation	Promethazin: ▪ there were no significant difference between treatments in the relationship of **breathlessness** to ventilation during exercise. At the standardised level of ventilation the mean breathlessness score after placebo was 51.4% and after promethazine 50.2%.	▪ small sample size ▪ only healthy participants ▪ old study	1-
		n=6 out of n=12	n=6 Six of these subjects were selected on the basis of availability proceeded to the second part of the study	n=6 ▪ chlorpromazine 25mg vs.mebhydroline 50mg vs.placebo	Measurements started 75min after administration of the treatment.	Mebhydrolin: ▪ had no effect Chlorpromazine: ▪ reduced breathlessness without influencing ventilation and sedation		
Rice, Br J Dis Chest 1987 [183]	RCT, double-blind, cross-over trial	n=11 (4 drop out)	Clinically stable male patients, primary diagnosis **COPD** (FEV1<60%), aged between 50 and 70 years, long history of cigarette smoking. Exclusion criteria: PCO2>55mmHg, history of chemical	▪ Codeine 30mg 4xd vs. ▪ promethazine 25mg 4xd each for one month	1.O: intensity of dyspnea 2.O: lung function Measurements: ▪ VAS ▪ spirometer ▪ arterial blood gas analysis ▪ 12min walking test (all datas were collected daily, beginning one week	▪ No improvement in **breathlessness** or **exercise tolerance** with long-term administration of codeine (M=5.7; SEM= 0.6) or promethazine (M=6.0; SEM=0.4) ▪ Statistic significant increase of pCO2 while taking codeine (P<0.01	▪ 1 patient dropped out after developing acute urinary retention while taking codeine ▪ 2 patients exacerbate while taking codeine, 1 patient exacerbated while taking promethazine –	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= 117ignifdary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			dependence, significant liver or kidney disease		before taking drugs the first time except the 12min walking test: once a week, duration of study=2month)	at 24 hours; P>0.05 at 1 month)	all of them required hospitalisation. ▪ Drowsiness was reported often as a side effect. ▪ small sample size ▪ old study	
Stark, Clin Sci 1981 [184]	CCT, (double-blind), cross-over	n=6	**Healthy men**: 20-39 years old	Induction of dyspnea by exercise/ exposure to carbon dioxide to ▪ 10mg diazepam or ▪ 25mg promethazine or ▪ placebo	1.O: sensation of dyspnea, lung function; Measurement by ▪ VAS ▪ lung function parameter (before exercise or exposure to CO2, measure conducted 75 min after drug intake; during exercise or exposure to CO2, measure every 2-3 min)	No reduction of acute **dyspnea** during exercise or CO2 exposure by diazepam or promethazine (slight trend for promethazine for the improvement of dyspnea intensity during exercise without statistical significance)	▪ Placebos and drugs looked different and were applied by assistans ▪ Each patient received each drug and placebo during the study ▪ small sample size ▪ old study	1-
Woodcock, BMJ 1981 [185]	RCT, cross-over, double-blind, placebo-controlled	n=18 (3 dropout)	Men with **severe COPD**: without hyperkapnia with moderate or severe dyspnea (pink puffer), ex-smokers: packages per year (m=41,6; R=10-160) abstinent since (m=4,3 Jahre; R=0,5-20 Jahre)	▪ 25mg diazepam (5-5-5-2x5mg), ▪ 125mg promethazine (25-25-2x25 mg), ▪ placebo (1-1-1-2) in three consecutive two-week periods	1.O: exercise tolerance, dyspnea intensity ▪ dyspnea-measurement: VAS lungfunction measurement: expiratory flow rate, FEV1, FVC ▪ Walking distance/ bodily symptom scores /treadmill test/ progressive exercise test on bicycle ergometer 2.O: intensity of fear- and depression ▪ Psychological measurement with Morbid Anxiety Inventory/ Beck Depression Inventory	▪ Promethazine: Small but significant reduction of **breathlessness** and improvement of **exercise tolerance**, no effect on lung function (effect size not mentioned) ▪ Diazepam: Had no effect on breathlessness and noticeably reduced exercise tolerance, contraindicated in patients with obstructive airways disease, unless there is a serious unrest and a lower PaCO2	▪ 1 patient died during an exacerbation of breathlessness while taking diazepam ▪ 1 patient withdrawed because he suffered intolerable drowsiness (diazepam) ▪ Patients needed a reduction in dosage because of drowsiness (5 diazepam – 1 promethazine) ▪ It is unclear if they were provided between the two-week periods without	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= 117ignifdary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
					(measurement after five minutes exercise)		taking sedating medications ▪ small sample size ▪ old study	

6.3.3. Antidepressiva

6.3.3.1. Primärstudien

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Borson, Psycho-somatics 1992 [186]	RCT, double-blind, placebo-controlled	n =36	Patients with ▪ **COPD** (FEV1/FVC<60%) ▪ **coexisting depressive disorder**	▪ 1x0,25mg/kg per day Nortryptilin (n=13), increased weekly till 1mg/kg, then for 8 weeks administered (12 week duration) ▪ placebo (n=17)	**1.O**: ▪ „Mood“ (Clinical Global Improvement Scale, CGI) **2.O:** ▪ Dyspnea (Pulmonary Function Status Instrument, PFSI) and VAS. In addition, measurements with VAS before and after a 12min walking test. The most severe dyspnea and the median change were recorded before and after exercise. ▪ „Distressing physical symptoms“ (35-item „Patient Rated Anxiety Scale“)	**1.O**: ▪ Mood: 10 of 13 sustained improvement compared with placebo group and 2 of 17 in the placebo group showed improvement (Shi-Square=13.0, p=0.0003) **2.O:** ▪ **dyspnea**: no difference between the groups neither during rest nor during load. Only in ADL with mild exercise shows a positive effect of nortryptilins (p=0.04) ▪ „Distressing Physical Symptoms“: improvement with nortryptilin of somatic 120ymptoms (p=0.08) There is no significant effect about the relief of dyspnea. The authors ascertaining, there could be significancy with a bigger sample size at least for light exercise.	Although the study reached its primary endpoint, there is no significant effect on dyspnoea The authors speculate, that this could be due to the low patient number COPD Patients are not readily comparable with cancer patients. Fromm y point of view, nortryptiline cannot be recommended as a therapy for dyspnoea in cancer patients.	1-
Eiser, COPD 2005 [187]	randomized, placebo-controlled trial	N=28 (14 women, 14 men)	▪ **depressed COPD (**FEV1 ≤60%) **patients**	▪ Paroxetine 20mg daily or ▪ Matched placebo for six weeks.	**1.0:** ▪ QoL [St. Georges Respiratory Questionnaire (SGRQ)]	▪ After 6 weeks there were no clinically significant changes in 6MWD or SGRQ values, but all	The study was named as a „pilot study“ by the authors due to a protocol Amendement.	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				▪ Subsequently, all patients took un-blinded Paroxetine for 3 months.	▪ Depression [Montgomery Asberg Score (MADR)] ▪ 6 minute walking distance (6MWD) **2.0:** ▪ Lung function ▪ peak-flow ▪ dyspnea and effect of breathlessness on a quality of life on a 5-point scale (not mentioned in detail)	depression scores improved, particularly the MADR score. (baseline HAD(depression), BDI and MADRS scores of 12, 21 and 23 respectively fell significantly to 8, 12 and 9 ($p < 0.0001$) at the 12th week) ▪ After 3 month in the open label study, there is a significant improvement in 6MWD($r = -0.424$, $p < 0.01$), SGRQ and MADR (significantly correlated with improved symptom scores of the SGRQ ($r = 0.3372$, $p < 0.02$, and $r = 0.279$, $p < 0.05$, respectively)) compared to the baseline scores ▪ But no improvement in lung-function or **dyspnea-scores** ▪ The authors conclude, because of a number of problems in the conduct of the study, it should be regarded as a pilot study only. ▪ Besides 6 weeks of antidepressant treatment was insufficient to significantly ameliorate the depression.	They speculate, that the interval of six weeks might have been too short to see an effect. Due to the endpoint "dyspnoea", no valid conclusion is possible.	

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
						▪ The study does not allow any valid information regarding dyspnoea.		
Lacasse, Monaldi Arch Chest Dis 2004 [188]	Randomized, placebo-controlled	n=23	Patients with ▪ **COPD** ▪ **significant depressive symptoms**	▪ Paroxetine 5mg daily,(n=12) with weekly 5-mg increments up to a maximum of 20 mg ▪ placebo (n=11) ▪ 12 week-duration	**1.O:** ▪ „Emotional Function": change in score of this domain after 12 weeks, Chronic respiratory questionnaire (CRQ)	▪ The trial was stopped prematurely because of difficulties in patients' accrual. ▪ Significant improvement in the primary outcome, [emotional function (adjusted mean difference: 1.1; 95% confidence interval [CI]: 0.0- 2.2)] but its losing significancy in the ITT-analysis ▪ Improvement of **dyspnea** and fatigue without reaching statistical significance	The study is not feasible to answer the key question. Dyspnoea was not defined as an endpoint, the dropout rate was too high and no cancer patients were included.	1+
Perna, Depress Anxiety 2004 [189]	Case series	n=6	Patients with **severe COPD**	Citalopram 1x20mg/d for 4 weeks	**1.O:** ▪ FEV 1 ▪ paO2 ▪ paCO2 ▪ subjective measurement of dyspnea with the Borg-scale ▪ 6min. walking test	▪ Improvement in all parameters. **Dyspnea** measurement on the Borg-scale from 7.7 to 3.5. ▪ Extension of walking distance in average from 165m to 220m.	Placebo effect is not negligible, as long as there is no control group.	3
Smoller, Psycho-somatics 1998 [190]	Case series	n=7	Patients with ▪ **COPD (n=1)** ▪ **asthma (n=5)** ▪ **idiopathic emphysema (n=1)** ▪ **with and without mood or**	Sertraline 25-100mg/day for four weeks up to 16 months	▪ FEV1 ▪ FVC	▪ Report of **dyspnea** improvement in general without measurement ▪ SSRI may be particularly useful and well tolerated in anxious or depressed patients with COPD and	No data on dyspnea given only very unspecific description that dyspnoea improved. Only case series.	3

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			anxiety disorders			might diminish **dyspnea** in some pulmonary patients, even in the absence of a diagnosable psychiatric disorder ▪ No clinically significant changes in FEV1		
Ström, Eur Respir J 1995 [191]	Randomized, placebocontrolled, parallel-group, double-blind multicentric	n=26	Patients with ▪ **COPD** ▪ mild or moderate hypoxaemia (pAO2 :6,7- 8,7 kPa; FEV1/ FVC < 0,7) following a run-in period of 4 weeks, in order to assess the stability of hypoxaemia	▪ Protryptiline 10mg daily (n=14) ▪ placebo (n=12) ▪ 12 week-duration	▪ arterial blood gas tensions ▪ spirometry volumes ▪ QoL (Sickness Impact Profile; SIP; Mood Adjective Check List; MACL; und Hospital Anxiety and Depression Scale; HAD) ▪ dyspnoea score (graded on a six stepp scale, ranging from 0=no dyspnoea to 6=dyspnoea at the last effort))	▪ the mean PaO2 increased 0.2 kPa in both groups during the same time after exclusion of patients having an exacerbation of COPD ▪ **QoL** and **dyspnoea**: no differences ▪ High incidence of protriptyline-induced anticholinergic side-effects observed during the 12 week treatment period of our trial suggests that the tolerability of higher doses might be quite limited.	Placebo-group is significantly younger.	1-

6.3.4. Buspiron

6.3.4.1. Primärstudien

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Argyropolou, Respiration 1993 [192]	RCT, Double-blind, cross-over trial	n=16 (no dropouts)	**COPD** patients: FEV1 <1,5l PaCO2/ FVC ratio <65%	▪ 20mg Buspiron (5-5-10mg) daily ▪ placebo ▪ 2 consecutive15 days periods in a cross-over design	**1.O**: ▪ dyspnea on exertion and exercise tolerance (measurement: 6min walking test, incremental cycle ergometer test, incremental treadmill walking test ▪ self-assessment of dyspnea (Borg´s scale during exercise) **2.O**: ▪ respiratory drive (P 0,1) ▪ arterial blood gas ▪ Inspiration: expiration relation ▪ „Symptom Check List 90R“ (SCL-90)	**1.O:** ▪ significant improvement of **walking distance** while taking buspirone (placebo:377m, buspirone:387m) ▪ Perception of **dyspnea during exercise** improved as assessed by an increment in distance walked at dyspnea score 5 during buspirone treatment (placebo: 77m, buspirone: 86m). **2.O:** ▪ Arterial blood gases and respiratory drive do not differ significantly after the two different treatments. ▪ Significant improvement of SCL-90 Index in the dimensions general symptom index, depression, anxiety, hostility and phobic anxiety while taking buspirone.	In addition to the small sample size the cross-over design is not described in detail, neither about the wash-out period nor about the intra-individual differences.	1-
Singh, Chest 1993 [193]	RCT, Double-blind, placebo-controlled	Included in study n=15, included in analysis n=11 (due to 4 drop outs)	patients with stable **COPD**: FEV1 < 1,4 and FEV1/ FVC < 0,5,	▪ 3xd 10-20mg buspirone ▪ Placebo	**1.O:** ▪ reducing anxiety (State Trait Anxiety Inventory, STAI)	No significant differences in anxiety scores, workload, maximum oxygen consumption per minute, maximum expired volume	Imbalances between the arms. The patients cannot be described as anxious (STAI at screening >50, at	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			Score >50 on Spielberger State-Trait Anxiety Inventory Scale (STAI), aged 40-75 years	▪ for 6 weeks with the option to double the dosis after 3 weeks	▪ improving exercise tolerance: spirometry, 12min walk, Incremental exercise (ergometer) ▪ dyspnea: modified BORG	per minute, PETCO2, PETO2, 12 min **walking distance** or **dyspnea scores** after 6 weeks of buspirone or placeboe therapy. The mean Borg score at the end of the 12-min walk tended to be lower after the treatment with buspirone (4.6±3.8 vs 5.8±3.6 with placebo), but the difference did not achieve statistical significance and was due to one patient having a much higher Borg score while receiving placebo.	baseline <50). Sample size too small for valid results.	

6.3.5. Steroide (Glucocorticoide)

6.3.5.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Walters, Cochrane Review 2009 [194]	SR/MA	24 RCTs: ▪ 19 crossover ▪ 5 parallel	Stable **COPD** (moderate or severe in 15 studies)	Arm 1: Oral corticosteroids: ▪ Prednisolone (23) - Betamethasone (1) ▪ High dose (equivalent prednisolone 30-40mg/d) (21) ▪ Short term therapy (≤3 weeks) (19) ▪ Inhaled steroids excluded (16) Arm 2: Placebo	1.O: ▪ FEV1 (23) ▪ HRQL (3) 2.O: ▪ Proportion of responders ▪ Acute exacerbations (4) ▪ Symptom severity (13), of which breathlessness (3) ▪ Functional capacity (6) ▪ Adverse effects (6)	▪ Differences in **symptom scores** were not significant. ▪ The clinical importance of the differences found in **12min walk distance and shuttle walk distance** is uncertain and it probably depends on the severity of COPD ▪ All differences in health-related **quality of life** were less than the minimum clinically important difference. ▪ Increased risks of **adverse effects** on blood pressure, blood glucose, plasma cortisol and serum osteocalcin.	The absence of a washout period in many of the trials with a crossover design is of concern, particularly as the duration of improvement in outcomes detailed above is not clear. Fortunately, from the perspective of meta-analysis, this is likely to minimise rather than exaggerate the difference between active intervention and control.	1++
Yang, Cochrane Review 2007 [195]	SR/MA	47 RCTs (n=13.139), double-blind ▪ 12 crossover ▪ 35 parallel	**COPD** (according to international criteria or lung function and smoking history)	Arm 1: Inhaled (not nebulised) corticosteroids (ICS): ▪ Budesonide, beclomethasone, fluticasone, triamcinolone, mometasone ▪ Study duration: short term ≤2 months (16), medium term 2-6 months (15), long term ≥ 6 months (16)	1.O: ▪ Lung function 2.O: ▪ Mortality ▪ Exacerbations (4) ▪ QoL (SGRQ) and symptoms (CRQ) ▪ Use of rescue bronchodilators ▪ Exercise capacity ▪ Biomarkers ▪ Predictors of response ▪ Adverse effects	▪ Some medium term studies showed an improvement in **respiratory symptoms**, but not all studies were able to demonstrate this. ▪ **Exercise capacity** was only infrequently measured, and overall no significant difference was found with ICS. ▪ ICS slowed the rate of decline in **quality of**	There was wide variability in study characteristics, including dose and duration of ICS, severity of COPD, inclusion criteria and outcomes studied. Furthermore, results for outcomes were sometimes either missing or not able to be pooled.	1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				▪ Long-acting ß2-agonists as co-intervention excluded Arm 2: Placebo		**life**, as measured by the St George's Respiratory Questionnaire (WMD -1.22 units/year, 95% CI -1.83 to -0.60, 2507 participants) ▪ There was an increased **risk** of oropharyngeal candidiasis (OR 2.49, 95% CI 1.78 to 3.49, 4380 participants) and hoarseness. The few long term studies that measured bone effects generally showed no major effect on fractures and bone mineral density over 3 years.		

6.3.5.2. Systematic Review der Aktualisierung 2019

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Haywood, Cochrane 2019 [196]	SR, MA; To assess the effects of systemic corticosteroids for the management of cancer-related breathlessness (dyspnoea) in adults	Databases: CENTRAL, MEDLINE, Embase, CINAHL, Science Citation Index Web of Science, Latin America and Caribbean Health Sciences (LILACS) and clinical trial registries, from inception to 25 January 2018 Design: RCTs	Interventions: Systemic corticosteroids at any dose, administered for the relief of cancer-related dyspnoea or other cancer-related symptoms (where dyspnoea was also	Study number: 2 RCTs (n=157) Interventions: oral dexamethasone (8 to 16 mg/d) Outcomes: **Breathlessness intensity**: MA (n=114): n.s.: mean difference -0.85 (95% CI -1.73 to 0.03), very low QoL	Methods: Well conducted SR Content: We downgraded the quality of evidence due to very serious study limitations and imprecision. We	1++ (Body of evidence: 1-

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
		Population: Participants with cancer with cancer-related dyspnoea, aged 18 years and above.	measured), compared to placebo or any active comparator including supportive care or alternate non-pharmacological treatment. We excluded studies assessing inhaled corticosteroids. Outcomes: Primary outcomes: intensity, quality and burden/ impact of breathlessness Sec. outcomes: serious AE, satisfaction, participant withdrawal	**Breathlessness quality** (affective distress): results similar between groups, very low QoL **Breathlessness burden/ impact:** 1 RCT showed improvement for physical well-being scores, very low QoL **AE:** frequency similar between groups, corticoids well tolerated **Withdrawal:** 15% respect. 36% in 2 RCTs, due to lost to follow-up, participant or carer (or both) refusal, and death due to disease progression	judged the evidence to be of very low quality that neither supported nor refuted corticosteroid use in this population.	

6.3.5.3. Primärstudien

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Aaron, NEJM 2003 [197]	RCT, double-blind	n=147 (7 drop-outs)	Patients after emergency treatment for **COPD** exacerbations, asthma excluded, broad spectrum antibiotics 10d and inhalative broncholytics for all patients	• 1st arm: 40 mg Prednisone • 2nd arm: Placebo	• Unscheduled visit to a physician's office or a return to the emergency department because of worsening dyspnea within 30 days after randomization • FEV1, Dyspnoea, QoL within 10 days • Measures: FEV1 nach inhal. Bronchodilatation, Dyspnoe Index (-9/0/+9)	Significant improvement for **dyspnoea** and **QoL**. Transitional dyspnea index score on day 10: placebo 2.07±5.53, prednisone 3.95±4.62 (p 0.04); Chronic Respiratory Disease Index Questionnaire: mean change per question in dyspnea score from day 1 to day 10: placebo 0.97±1.83, prednisone 1.04±1.47 (p 0.02); Mean change per question in total score from day 1 to day 10: placebo 1.04±1.47, prednisone 1.42±1.43 (p 0.14)		1+
Choudhury, Resp Res 2007 [198]	RCT, double-blind, placebo –controlled 1 year follow-up	Fluticasone group: 128 Placebo group:132	**COPD** age 67 y; current smokers: ca. 40%; mean FEV: ca. 1.3 L Recruitment : primary care	Discontinue/ continue with inhalative corticosteroids (ICS) Fluticasone 500µg/d	1.O: Number of exacerbations 2.O: Time to first exacerbation Outcome measures: diary cards, medical records, symptoms: cough, wheeze, dyspnoea. HQL (SGRQ)	**Dyspnoea** OR 2.11 (1.25 to 3.57) sig. greater in placebo group after 3 months (similar for other symptoms). No sig. difference in **HRQL** and **adverse effects**.	Careful practical study in primary care. Indication of therapy with ICS not in conformity with guidelines. No data on symptoms about effect after 12 months.	1+
DuBois, Eur Respir J 1999 [199]	RCT, single-blind	n=43 (6 drop-outs)	Stable **chronic sarcoidosis** with limited lung function (<75% of predicted normal value), with stable corticoid	• 1st arm: Fluticasonpropionate (FP) 2000µg/d for 1-3 and 4-6 months • 2nd arm: Placebo	• Differences in standard lung function parameters (FEV1, PEF, FRC, DLCO), SF36 and ACE)	No statistical sign. difference for **breathlessness** between FP and placebo. Breathlessness: baseline FP 0.89 ±0.76, 3 months FP 0.72 ±0.57, 6 months	Groups different at baseline. Statistical data sometimes not provided. 1/5 authors Fa. Glaxo	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			medication or without corticoids.		• 4 points symptoms scala for cough, dyspnea, wheeze.	FP 0.73 ±0.59; baseline placebo 1.33 ±0.91, 3m placebo 1.14 ±0.85, 6m placebo 0.95 ±0.78 > all scores (incl. baseline) are lower in the FP group (statistically not sign.) No difference between groups and over time re SF36		
Guenette, Resp Med 2011 [200]	RCT double-blind, cross-over	n=17 (0 drop-outs)	Stable **COPD** (FEV1 <70% of predicted normal value)	• 1st arm: Fluticasonpropionate 1000 µg/d in addition to maintenance LABA and SABA therapy • 2nd arm: Placebo	1.O: • Dyspnea score measured during exercise (Borg) 2.O: • Cycle endurance performance • Spirometric parameters • Static and dynamic lung volumes	No **exercise dyspnoea** relief	Steroid only in combination with other drugs. 1/6 authors in relation with various industries.	1+
Melani, Monaldi Arch Chest Dis 1999 [201]	Randomized double-blind cross-over study	n = 20 (6 withdrawals)	Stable **COPD**: Exertional dyspnoea for ≥ 1 y without any significant symptom free survival; baseline FEV1 < 50%; history of previous tobacco smoking, difficulty in correct use of metered-dose (MDI) and dry powder inhalers (DPIs).PaO2 at rest > 7.3 kPa (55 mmHg);	▪ Intervention: Inhaled beclomethasone dipropionate 2 mg via nebulizer twice a day for 4-week period ▪ Control: placebo First treatment period followed by 1-3 month wash-out phase	1.O: ▪ dyspnoea level triggered by daily activities using the oxygen cost diagram 2.O: ▪ Spirometry ▪ exercise tests (12 MWD) on last 2 days of treatment period (greater distance recorded) ▪ VAS perceived intensity of dyspnoea after each 12 MWD (not at all breathless, the most breathlessness that you have ever experienced)	**OCD**: BDP 2.8 (0.8), placebo 2.6 (0.9), **VAS** 6.0 (1.9) placebo 6.2 (2.0); not significant differences	Only male patients	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			excluded if not stable state. Age 69.7 (SD 5.7)					
Milman, J Intern Med 1994 [202]	RCT, double blind	n= 21 (3 drop outs after 6 months) 5 subjects had to take additional oral prednisolone during treatment due to disease progression (2 in budesonide group)	pulmonary **sarcoidosis** (radiological stage I-III) with normal or slightly reduced lung function	▪ Intervention: inhaled budesonide 1.2 - 2.0 mg/day (n = 9) or ▪ Control: placebo (n = 12) for 12 months given in two doses (1x morning, 1x evening)	▪ cough, chest pain, dyspnoea at rest and during exercise ▪ chest X-ray, gallium scintigraphy, pulmonary function tests, Erythrocyte sedimentation rate (ESR), haemoglobin, leucoytes, neutrophilocytes, eosinophilocites, lymphocytes, plasma (P-) creatinine, P-calcium, P-phosphate, P-aspartate aminotransferase, P-alkaline phophatase, P- immunoglobulins (Ig) G, A, M, E Outcomes measured before treatment, after 1, 3, 6, 9, 12 months during treatment, and 6 months after treatment had been discontinued	No difference in any outcome between groups (P>0,1 minimum)	▪ small sample size and not enough power to detect differences ▪ strange way to create subgroups ▪ confounding effects due to additional use of oral prednisolone possible ▪ majority of subjects were male ▪ not enough details on how outcomes were measures (e.g., dyspnea, cough, chest pain) ▪ no data shown for dyspnea, cough, chest pain only p-values	1-
Rice, Am J Respir Crit Care Med 2000 [203]	RCT double-blind	n=38 (11drop-outs)	**COPD** (criteria of AmThSoc) with steroid maintenance therapy of at least 5 mg prednisone equivalent ("steroid dependent")	• 1st arm: Prednisone reduction of 5 mg/week and withdrawal • 2nd arm: continuation of prednisone maintenance therapy	1.O: ▪ exacerbations (resulting in rescue cortisone administration, antibiotic administration, first-aid provision, unscheduled clinic visit.for dyspnea) 2.O: ▪ Dyspnea index (Mahler 1984), HRQoL	Spirometric results, **dyspnea**, and **health-related quality** of life did not differ significantly in the two groups.	Conflict of Interest not mentionned. Only male patients.	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Sayiner, Chest 2001 [204]	Randomised single-blind study	n = 36 (2 drop-outs)	severe **airway obstruction** (FEV1 < 35% predicted), presented with an exacerbation necessitating hospitalization	▪ Intervention: Methylprednisolone (MP) 0.5 mg/kg 6 hourly for 3 days ▪ Control: Methylprednisolone (MP)0.5 mg/kg 6 hourly for 3 days, then tapered and terminated on day 10	1.O: ▪ FEV1 and PaO2 levels on day 3 and day 10 2.O: ▪ symptom scores (dyspnoea, cough with physical and emotional function on a 7-point scale, higher scores represent better function), recurrence of exacerbation in the following 6 months, and adverse events	Both groups showed significant improvements in PaO2 and FEV1 levels, but these were more marked in group 2 (p 5 0.012 and p 5 0.019, respectively). Significant improvements in **shortness of breath** at daytime, at night, and on exertion. Improvement in dyspnoea on **exertion** observed in group 2 was significantly better than that obtained in group 1 [GROUP 1: Day 0: 3.0± 0.3; Day 3 5.4 ± 0.3; Day 10: 5.5 ± 0.2; GROUP 2: Day 0: 2.8 ± 0.3; Day 3: 5.1 ± 0.3 Day 10: 6.3 ± 0.2 (p=0.024)]. This was associated with the fact that, although both groups had similar increases in this symptom score at day 3, further significant improvement occurred between day 3 and day 10 in group 2 only (p < 0.01)	Predominantly male patients	1-
Shmelev & Kunicina, Clin Drug Invest 2006 [205] **I** (Part II see below)	RCT plus… (see below)	122 patients assigned to either RCT (part I) or observational study (part II, see below)	Patients with **COPD** stage 1 and 2 without active therapy (stable or with exacerbation) Note: No indication on which criteria	In addition to bronchodilator therapy with ipratropium bromide/fenoterol hydrobromide (based on individual level of bronchoconstriction, doses not	• Symptoms (dyspnea, cough, rales, sputum, nightly symptoms) • lung function (FEV1, FVC) • 6min walking test (6MWT)	• The most significant reduction in respiratory symptoms with fenspiride related to sputum parameters, which showed a decrease in mean ± SD values from	• very small sample sizes and not enough power to detect differences • too many statistical tests for the small Ns (=inflation of alpha errors)	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
		In RCT: **58 patients** with stable COPD stage 1 oder 2, of which 35 divided into 3 groups with Ns </= 13 and 23 patients in 2 control groups (Out of the 122 patients, 38 drop outs in intervention groups; 26 drop outs in control groups) Drop outs were examined in additional observational study (see below)	COPD stages were based. FEV1% values suggest staging was not conform to GOLD stages Some patients were stable, others had non-infectious exacerbations	further specified) patients received either: • F1: fenspiride (2xdaily 80mg for 6 months) in COPD patients stage 1 • F2: fenspiride (2xdaily 80mg for 6 months) in COPD patients stage 2 • B2: beclomethasone inhalation (2xdaily 200mg for 6 months) in COPD patients stage 2 • C1: only bronchodilator therapy with ipratropium bromide/fenoterol hydrobromide for 6 months in COPD patients with stage 1 • C2: only bronchodilator therapy with ipratropium bromide/fenoterol hydrobromide for 6 months in COPD patients with stage 2	outcomes measured before treatment, after 1 month and then every 2nd month up to 6 months total	2.58 ± 0.27 to 0.33 ± 0.18 ($p < 0.001$). • somewhat greater improvements in symptoms in both fenspiride groups compared to control or beclomethasone • effects seem more pronounced in COPD stage 1 patients compared to stage 2 patients • only very small reductions in **dyspnea** after beclomethasone • Dyspnoea decreased significantly by the second month of treatment in stage 1 COPD patients receiving fenspiride (from 1.67 ± 0.18 to 0.83 ± 0.18; $p < 0.001$) • after fenspiride improved lung function) in COPD stage 1 patients • after fenspiride improved 6MWT in COPD stage 1 patients (walking distance increased by 14.22%: from 403.83 ± 18.60m to 461.25 ± 14.7m; $p < 0.05$ • reduced number of exacerbations in fenspiride groups and	• Strange way to create these subgroups. Looks like as if groups were build post-hoc • high drop outs and no explanation for it • No indication on which criteria COPD stages were based FEV1% values suggest staging was not conform to GOLD stages and rather stage 2 or 3 than 1 and 2 • no details on lung function measurements • baseline differences in group characteristics (e.g FEV1%) could be confounders • remains unclear who rated symptoms (patient or clinician) • not enough patient characteristics presented	

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
						beclomethasone groups compared to control groups		
Shmelev & Kunicina, Clin Drug Invest 2006 [205] **II**	additional observational controlled study without mentioning whether randomized or not (but presumably not)	64 patients with COPD with exacerbations divided into 3 groups	Idem (see above)	• F: fenspiride (2xdaily 80mg for 2 weeks) • C: only bronchodilator therapy with ipratropium bromide/fenoterol hydrobromide for 2 weeks • SC: prednisolone (20 mg daily for 1 week than gradually reduced in week 2)	Symptoms (dyspnea, cough, rales, sputum, nightly symptoms) after 2 weeks	• Symptoms improved similar after 2 weeks of beclomethasone and fenspiride compared to control during exacerbation phases	(continuation:) • no description on what exact statistics were performed→ impossible to judge effects	
Tashkin, Drugs 2008 [206]	Randomised double-blind, double-dummy placebo controlled parallel group multicentre study	n = 1704	age ≥ 40 years, **COPD**, symptoms > 2 years, history of at least one COPD exacerbation treated with course of oral steroids and/or antibacterials within 1-12 months before screening; FEV1 predicted ≤ 50%MRC dyspnoea scale ≥ 2, BCSS ≥ 2/day for at least half of the 2 weeks run-in period	Intervention: 5 different treatments twice daily 1) BUD/FMpMDI 160/4.5 µg x 2 inhalations (320/9 µg bd; 2) BUD/FMpMDI 80/4.5 µg x 2 inhalations (160/9 µg bd; 3) BUDpMDI 160 µg x 2 inhalations (320 µg) bd + FMDPI 4.5 µg x 2 inhalations (9 µg) bd; 4) BUDpMDI 160 µg x 2 inhalations (320 µg) bd 5)FMDPI 4.5 µg x 2 inhalations (9 µg) bd Control: Placebo BUD= budesonide FM = formoterol pMDI = pressurized metered-dose inhaler	1.O: ▪ pre-does FEV1 and 1-hour-post-dose FEV1 2.O: ▪ dyspnoea (Breathlessness diary based on BCSS, 0-4), HR-QoL, COPD exacerbations	Both budesonide/ formoterol dosage strengths experienced significantly greater improvements in **dyspnoea** scores compared with budesonide, formoterol and placebo (p ≤ 0.044). No sign. improvement in dyspnea scores between budesonide and placebo. Improvements in dyspnoea were clinically meaningful (i.e. reduction of ≥ 0.2 units [MID]) for all active treatment groups compared with their baseline values, although neither budesonide/formoterol dosage strength reached the pre-specified		1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				DPI=dry powder inhaler		MID compared with placebo (based on comparison of least squares mean changes from baseline).		
Vestbo, Thorax 2005 [207]	Randomised, double blind, placebo-controlled study	n = 1465/ 75 drop outs/ 456 withdrawals after randomisation	**COPD** (ERS definition), age 40–79 years, .10 pack-years, pre-bronchodilator FEV1 25–70% predicted, FEV1/forced vital capacity (FVC) <70%, poor short term reversibility (<10% predicted FEV1 30 minutes after inhaling 400 mg salbutamol), and chronic bronchitis with exacerbations in the last 3 years	▪ 1st arm: salmeterol / fluticasone propionate combination (50/500 µg twice daily) ▪ 2nd arm: salmeterol alone (50µg twice daily) ▪ 3rd arm: fluticasone propionate (500 µg twice daily) ▪ 4th arm: Control: Placebo	1.O: ▪ peak expiratory flow: time at which treatment effect was first observed in three treatment arms 2.O: ▪ dyspnoea time at which treatment effect was first observed in three treatment arms	After 14 days: OR for **dyspnoea** improvement: combination treatment significantly better than other treatments; OR salmeterol group 1.4 (95% CI 1.0 to 1.9, p=0.035) and compared with fluticasone propionate OR 1.7 (95% 1.3 to 2.3, p<0.001) No sign. Difference between fluticasone and placebo (p=0.111)	Text about change of dyspnoea scores is not reflected in data provided in table	1-
Worth, Resp Med 2010 [208]	RCT doppelblind crossover	n=111 (20 drop-outs)	**COPD** (FEV1<50% of predicted normal value)	• 1st arm: Budenoside/Formoterol • 2nd arm: Formoterol • 3rd arm: Placebo for 1 week	• Exercise Endurance Time 1h and 6h after medication • Spirometry • inspiratory capacity during exercice (ICex)) • Borg CR10-scale	**Breathlessness score** only sig. better after 1h for Budenoside/Formoterol vs placebo (but not vs. Formoterol and not after 6h). Budesonide/formoterol resulted in a significant improvement in **endurance time** 1 h after the last morning dose in a 1-week treatment period versus formoterol [by	Steroid only in combination with other drugs. 3/6 of the authors by Astra/Zeneca	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
						69 s (P < 0.005)] and placebo [by 105 s (P < 0.0001)].		
Wouters, Thorax 2005 [209]	RCT, double-blind, parallel group design	n=497 patients enrolled: 373 randomized 293 completions	**COPD** age 64 y Current smokers ca 50% Pack-years ca 37 Mean FEV 1.44	1 year withdrawal after a 3 months run-in randomized to • Fluticasone/Salmeterol 500/50µg twice daily • Salmeterol 50µg twice daily	• Dyspnoea at rest (0-4) and other symptoms • Spirometry, • exacerbation	An immediate and sustained increase in **dyspnoea score** (scale 0–4; mean difference between groups 0.17 (0.04), p 0.001) and in the percentage of disturbed nights (6 (2) percentage points, p 0.001) occurred after withdrawal of fluticasone.	Steroid only in combination with other drug. The effects are small and not clearly clinical relevant. Authors emphasize, however, the importance of ICS in COPD.	1++
Yennurajalingam, J Clin Oncol 2013 [210]	RCT, double-blind, placebo-controlled	N=84	Patients with **advanced cancer** with ≥ three **cancer- related fatigue** symptoms (ie, fatigue, pain, nausea, loss of appetite, depression, anxiety or sleep disturbance) ≥ 4 of 10 Edmonton Symptom Assessment Scale (ESAS) were eligible.	4 mg **dexamethason** or placebo orally twice per day for 14 days	1.O: ▪ Change in the functional Assessment of Chronic Illness-Fatigue subscale 2.O: ▪ **ESAS** (including dyspnea)	No differences were observed for ESAS overall symptom distress (P=0.22) or **dyspnea** (P=0.06).	Dexamethasone is more effective than placebo in improving cancer-related fatigue and quality of life in patients with advanced cancer.	1+
Zhang, Int Heart J 2008 [211]	CCT	n=35	Patients with decompensated congestive heart failure (**DCHF**) Mostly heart failure: IDC n=21 (60%) Mostly medication:	**Prednisone** (1 mg/kg/ day with maximum dosage of 60 mg/day for at least 9 day)	1.O: urine volume (day 1, 2, 3, 4 and 9), renal function (glomerular filtration rate (GFR), fractional excretion of sodium (FENa), serum creatinine and blood uric acid.	Significant improvement in congestive symptoms and global clinical status after 3-days, which was consistent with the changes in daily urine volume. At the end of the study, patient assessed dyspnea was markedly improved in 80% of DCHF	Prednisone to conventional care in the patients with refractory DCHF induced potent diuresis accompanied by a dramatic relief of congestive symptoms and improvements in clinical	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			IV diuretecs n=35 (100%) Median age (years) 52.26±18.07 Male n=17 (48.6%) Comorbidity: Diabetes n=4 (11.4%)		2.O: safety profile. Selfassessed dyspnea and global clinical status consisted of 7-point categorical responses of the patients: Markedly improved (3); moderately improved (2); mildly improved (1); no change (0); minimally worsened (-1); moderately worsened (-2); and markedly worsened (-3)	patients ($P < 0.01$), while global clinical status was markedly improved in 68.6% of DCHF patients at the end of the study ($P < 0.001$). As a result, all but one patient discontinued IV therapies (ie, IV diuretics, IV inotropes, and IV nitroglycerine), and 33 patients (94% vs. 54.3% at baseline, $P < 0.01$) were put on beta-blockers. Prednisone significantly increased the fasting glucose level in patients with diabetes (9.65 ± 0.75 mol/L at baseline vs 12.57 ± 0.57 mol/L after treatment, $P < 0.01$).	status and renal function. Small sample size, heterogenity of study poplulation, no control group, relateveley short study phase,	

6.3.5.4. Primärstudie der Aktualisierung 2019

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Hui, J Pain Symptom Manage 2016 [212]	RCT, double-blind, parallel, placebo-controlled	n=41 (n=35 completed blinded phase)	Patients with **advanced cancer** (n=36, 88%) **with lung involvement** (e.g. metastastic disease, lymphangetic carcinomatosis [non-small cell lung cancer n=31], Average dyspnea numeric rating scale intensity of ≥4/10 over the past week, and Karnofsky performance status ≥40% female 61%, average age of 63 years	First arm: Dexamethasone Blinded Phase: 8mg twice daily, four days 4 mg twice daily, then three days, followed by an Open Label Phase for seven days Second arm: Placebo ·Documentation of change in dyspnea (0-10 numeratic rating scale), spirometry measures, quality of life and toxicities (ESAS dyspnea [average 24 hours], Dyspnea rating scale [now], EORTC QLQ-C30 dyspnea [last week]	1. O: changes in dyspnea 2. changes in nondyspnea outcomes (ESAS drowsiness, ESAS symptoms, EORTC-Core)	**Dyspnea**: Dexamethasone was associated with a significant reduction in ESAS dyspnea numeric rating scale of -1.9 (95% CI -3.3 to -0.5, P=0.01) by day 4 and -1.8 (95% CI -3.2 to -0.3, P=0.02) by Day 7. Placebo was associated with a reduction of -0.7 (95% CI -2.1 to 0.6, P=0.38) by day 4 and -1.3 (95% CI -2.4 to -0.2, P= .03) by day 7. After 7 days of open-label the patients of both arms had an improvement in dyspnea by day 14 (dexamethasone: mean -2.1 [95% CI -3.5 to -0.6], P=0.01; placebo: mean -1.7 [95% CI -2.7 to -0.7), P= .004). Dyspnea numeratic rating scale (now) showed similar trends favouring dexamethasone, but the statistical significance is reached on Day 14 (dexamethasone: mean -1.6 [95% CI -3 to -0.2]; placebo: mean -1.5 [95% CI -2.5 to -0.5]). EORTC dyspnea showed significant improvements in dyspnea in the	▪ Limits of the generalizibility because the patients are from a single tertiary care cancer center ▪ small sample size	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
						dexamethasone arm by yay 4 (mean -15.6 [95% CI -29.3 to -1.8, P= .04])		

6.4. Sauerstoff

6.4.1.1. Systematic Reviews

Studie	Studientyp (SR=Systematic Review MA=Meta-analyse) Titel	Untersuchte Studien/ Materialien	Population	Welche Interventionen wurden geprüft	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Ergebnisse	Bemerkungen	LoE
Cranston, Cochrane Review 2008 [213]	SR, MA	8 RCT´s, cross-over (incl. unblinded)	Participants with **chronic terminal illness (excluding COPD)** and breathlessness at rest or on mild exertion: Cancer (97), CHF (35), Kyphoscoliosis (12), n=144	Oxygen (30%, 50% or 100%), control: medical air or compressed air or room air or placebo air	1.O: subjective measures of breathlessness: verbal categorical scales, VAS, NRS, modified BORG test or BORG test. Various physiological parameters were tested as well: SpO2, respiratory rate, heart rate, cardiac output, VO2max	No consistent beneficial effect of oxygen inhalation. Some cancer study participants appeared to feel better during oxygen inhalation.(oxygen inhalation at rest, Peto Odds Ratio (95% CI); 4.94 (1.48 to 16.43) and during exercise, Peto Odds Ratio (95% CI); 2.62 (1.00 to 6.85)	Low volume of research studies, small sample sizes of the studies, variations in study methodologies.	1++
Uronis, Brit J Cancer 2008 [214]	SR, MA	5 studies (n=134)	Participants with **cancer** and dyspnoea	Oxygen versus medical air	1.O: dyspnea (oxygen at rest or 6MWD – standard mean difference (SMD) were used to combine scores)	Oxygen failed to improve dyspnea in mildly- or non-hypoxaemic cancer patients (SMD=-0.09, 95%CI; -0.22-0.04; P=0.16) In this small meta-analysis, oxygen did not	Further study of the use of oxygen in this population is warranted given its widespread use.	1+

Studie	Studientyp (SR=Systematic Review MA=Meta-analyse) Titel	Untersuchte Studien/ Materialien	Population	Welche Interventionen wurden geprüft	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Ergebnisse	Bemerkungen	LoE
						provide symptomatic benefit for cancer patients with refractory dyspnoea, who would normally qualify for home oxygen therapy.		
Uronis, Cochrane Review 2011 [215]	SR, MA	SR: 28 RCT´s, n=702 (of which MA: 18 RCT´s, n=431)	Mildly or non-hypoxaemic people with **COPD**, who would not qualify for home oxygen therapy	Oxygen versus medical air	1.O: VAS, modified BORG, NRS or any other validated scale for measuring dyspnoea. For those studies measuring dyspnea during exercise, isotime scores were used when available. 2.O: 1. Quality of life, 2. Patient preference, 3. Functional status as recorded on a recognised scale	Oxygen was effective reducing dyspnoea in mildly and non-hypoxaemic people with COPD who would not otherwise qualify for home oxygen therapy, with a standardised mean difference (SMD) of -0.37 (95% CI -0.50 to -0.24, P < 0.00001) translating into a reduction of 0.78 cm on a 10 cm visual analogue scale (VAS) and a reduction of 0.9 points on a 0 to 10 numerical rating scale (NRS). . Impact on QoL cannot be determined from currently available data.	Small sample sizes and heterogeneity amongst studies included in this review make it difficult to provide general recommendations.	1++

6.4.1.2. Primärstudie

Studie	Studientyp/ Design	Anzahl der Patienten/ Drop-out	Patienten-merkmale	Intervention/Kontrolle	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure • Follow up	Ergebnisse	Bemerkungen	LoE
Abernethy, Lancet 2010 [216]	RCT, double-blind	Oxygen (n=120, drop out=8), room	239 adults form outpatient clinics with life-limiting	1st arm: oxygen 2nd arm: room air for 7 days.	1.0: „breathlessness right now“ with NRS (0=not breathless at all,	No additional symptomatic benefit of O2 for relief of refractory dyspnoea	• ITT analysis • Full-powered study	1++

Studie	Studientyp/ Design	Anzahl der Patienten/ Drop-out	Patienten-merkmale	Intervention/Kontrolle	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure • Follow up	Ergebnisse	Bemerkungen	LoE
		air (n=119, drop out=20)	illness, refractory dyspnoea, and partial pressure of oxygen in arterial blood (paO2) more than 7-3 kPa from Australia, USA and the UK. **COPD** 64 %, Primary and secondary **cancer** 16%. Restrictive lung disease 5,9% Bronchiectasis 2,9% Primary pulmonary hypertension 1,3% End-stage cardiomyopathy 2,9% Other 7,5%		10=breathlessness as bad as you can imagine), twice daily. 2.0: average dyspnoea in the previous 24h, worst breathlessness in previous 24h, relief of dyspnoea during the previous 24h (0-10 NRS), and ordered categorical scales for functional impact, sleep, disturbance, drowsiness, anxiety, nasal irritation and nose bleeds, QoL (MQoLQ), functional changes (MRC)	in patients with life-limiting illness compared with room air: Over the 7-day period, **dyspnea** decreased by -0.8 (95% CI: -1.1, -0.5) and -0.4 (CI: -0.7, 0.1), respectively (p<0.001), regardless of intervention. Baseline dyspnea predicted improvement with medical gas; participants with moderate (4-6 NRS) and severe (7-10 NRS) baseline dyspnea had average decreases in morning dyspnea of -0.7 (CI: -1.1, -0.4) and -2.4 (CI: -3.0, -1.8), resp. There was no clinically meaningful difference between interventions in **side effects**, and few adverse effects.	• Adequate randomisation, concealment and blinding • It is possible that palliative oxygen is more beneficial than medical air for some sub-groups (e.g., COPD patients vs. cancer patients), and that our study was not adequately powered to identify these patients	

7. Tumorschmerz

7.1. Anwendung verschiedener Opioid-Klassen

7.1.1. WHO-Stufe-II-Opioide

7.1.1.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Tassinari, Pall Med, 2011a [217]	SR / no MA Aim: To analyse the evidence supporting the widespread use of modified analgesic ladders or oral tramadol as alternatives to codeine/ paracetamol for mild to moderate cancer pain.	18 studies (n = 2974) ▪ 11 RCT (n = not given) ▪ 7 CT (n = not given)	Adult patients with **mild to moderate cancer pain** resistant to NSAID ± adjuvants and intervention with oral tramadol	1. Efficacy of 3rd-step opioids vs. 2nd followed by 3rd-step opioids 2. Efficacy of oral tramadol in patients pretreated with oral NSAIDs and not previously treated with opioids vs. placebo or codeine/paracetamol	1.O: ▪ Pain modification (efficacy) 2.O: ▪ Safety	▪ **Pain modification**: weak negative recommendation for the use of modiefied analgesic ladder or the use of oral tramadol in the second step. ▪ The risk / benefit ratio was considered uncertain.	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality of evidence ▪ Low statistical power ▪ Endpoints have not been well defined	1 + Body of evidence SIGN: 1- (most results based on low quality RCTs)

7.1.1.2. Primärstudie

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Leppert, Int J Clin Pract 2010 [218]	RCT, cross-over Aim: to assess the impact of tramadol and DHC treatment on quality of life (QL) and performance status (PS) of patients with cancer pain.	n=40 Drop outs=10 (n=5 in tramadol group and n=2 in DHC group discontinued the study because of insufficient analgesia)	opioid-naïve adult patients with nociceptive **cancer pain**, VAS>40 during non-opioids therapy (NSAIDs, paracetamol, metamizol); mean age: 70.47 ± 8.97; 19 women and 11 men.	• 1st arm: Controlled release tramadol=TR (n=15) (starting dose: 100 mg b.i.d – max. dose: 600 mg/d) versus • 2nd arm: Controlled release dihydrocodeine=DHC (n=15) (starting dose: 60 mg b.i.d – max. dose: 360 mg/d) for 7 days, then cross-over	• Analgesia (VAS), assessed daily • QoL (EORTC QLQ C 30), assessed weekly • Performance status (PS ECOG, Karnofsky), assessed weekly • Adverse events (EAs) reported in another study • Patients' preferences	Mean daily doses on the 7th and on the 14th day: TR= 286.67 ± 157.35 mg; 256.20 ± 109.33 mg; DHC=138.87 ± 40.77 mg; 172.53 ± 95.19 mg. • **Analgesia**: During all but 2 days, DHC analgesic effect sign. superior to TR. More patients in the tramadol group (12) than in the DHC group (8) used rescue analgesics. • **Preferences**: 19 patients preferred DHC treatment, 4 TR; 7 indifferent • **QoL**: **Functional scale**: TR: better emotional functioning; DHC: better global QL and cognitive functioning. **Symptom scale**: DHC: less fatigue, pain and sleep disturbances, less nausea and vomiting, better appetite. TR: less constipation, less financial problems • **Performance status**: ECOG and Karnofsky PS low in both groups • **AEs**: no serious adverse events reported.	No ITT-analysis No sample size calculation No description of concealment or randomisation No wash-out	1-

7.1.2. WHO-Stufe-III-Opioide der ersten Wahl

7.1.2.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Caraceni, Pall Med 2011 [219]	SR + MA (Cochrane review up-date 2010, first version 2007) Aim: To address the question: In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that oral morphine is better than placebo, or other oral/ transdermal opioids in the management of pain?	21 studies (n=2478) ▪ 17 RCTs (n=2053) ▪ 1 Meta-analysis (4 RTCs, n=425) .	**Patients with chronic cancer pain** (most not opioid naïve) ▪ 17 RCTs with 2053 patients in total ▪ The Meta-analysis included 4 RCTs with 425 patients in total	**oral morphine vs other orally or transdermal administered opioids** oral Morphine vs. other orally administered opioids (8 RCTs) ▪ 1st Arm: Morphine ▪ 2nd Arm: Oxycodone (4 RCTs) . Hydromorphone (3 RCTs), Methadone (1 RCT) oral IR Morphine vs. other orally administered opioids (4 RCTs) ▪ 1st Arm: IR Morphine ▪ 2nd Arm: Brompton Cocktail (1 RCT), Methadone (1 RCT), Oxycodone (1 RCT) oral Morphine vs. transdermal administered opioids (5 RCTs) ▪ 1st Arm: Morphine ▪ 2nd Arm: Buprenorphine TTS (1 RCT), Fentanyl TTS (3 RCTs), Fentanyl TTS +	1.O: ▪ Pain modification (efficacy) 2.O: ▪ Adverse events /Side effects Meta-analysis 1.O ▪ Adverse events /Side effects *	Studies published in between 2007/2009 did do not add significant information to the previous Cochrane review **Pain modifiation** ▪ oral morphine, oxycodone and hydromorphone seem to have similar **efficacy**. **Adverse events/side effects** ▪ oral morphine, oxycodone and hydromorphone seem to have have similar **toxicity**	Except the given MA of 4 RCTs, MA not possible due to clinical and methodological heterogeneity and limitations of the identified 17 RCTs The available evidence suggests that oral mo, hydromorphone, oxycodone and methadone offer similar pain relief in this patient population with a similar pattern of side effects. On the other hand, limitation of efficacy and tolerability data on opioid-naive and non-selected populations of cancer patients treated with morphine: • Population mostly-non-naive	1++ Body of evidence (SIGN): 1-

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				Methadone (1 RCT) Meta-analysis (4 RCTs) ▪ Oral Morphine vs. transdermal administered opioids (Fentanyl/ Buprenorphine TTS)			• Risk of bias in most of the studies (above all lost of follow-up) 8 studies were (partly) sponsored by pharmaceutical companies (for 8 other studies no funding details given)	
King, Pall Med 2011a [220]	SR (incl. 1 MA was possible) Aim: to identify and assess the quality of evidence for the use of oxycodone for cancer pain in adults	29 Studies ▪ 1 MA (including 4 RCTS, n=160 patients) ▪ 14 RCTs. ▪ 14 CTs (observational studies:10 prospective, 4 retrospective)	Adult **cancer patients** with **moderate to serve cancer related pain**	**Oxycodone** (Ox) in cancer pain treatment (different release and routes) MA (4 RTCS): (n=160) ▪ 1st Arm: oxycodone ▪ 2nd Arm: morphine (3 RCTS), hydromorphone (1 RCT) 14 RCTs: (n=34/28) ▪ 1st Arm: oxycodone ▪ 2nd Arm: morphine ▪ 3rd Arm: codeine Controlled release (CR) (n=32/23) Mo vs. Ox CR (n=44/31) Ox vs HydroMo CR (n=45/27) Ox vs. HydroMo Titration with patient controlled IV analgesia (n=20/19): ▪ 1st Arm: IV morphine ▪ 2nd Arm: IV oxycodone CR (n=101/79) Ox vs. Mo IM vs. oral Ox (n=17/13) CR Ox vs MR Ox (n=45)	1.O: ▪ **Pain modification** (efficacy) 2.O: **Adverse events** /Side effects	**Pain modification** no significant difference in analgesia or adverse effects of oxycodone compared to other opioids (data from one MA: pooled standardized mean difference, 0.04; 95% CI _0.29 to 0.36, p=0.8, I2=62%) **Adverse events:** no significant difference in adverse effects of oxycodone compared to other opioids - Oxycodone ▪ seems to be effective for first-line opioid therapy ▪ possibly less expensive ▪ close monitoring and conservative dose selection inevitable due to propensity to sedation and dose accumulation inevitable	MA for 4 RCTs, well conducted and unlikely to have been significantly biased in its conclusions RCTs found in addition to the MA: significant limitations; therefore, lower quality evidence and MA not possible. However, consistency of the results. considerable number of studies were (partly) funded by pharmaceutical companies broad systematic search strategy, incl. reference screening and hand search GRADE approach to assess study quality	1++ Body of evidence: 1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				Immediate release (IR) vs CR Ox (n=180) CR Ox vs. CR Mo (n=26) IV vs. rectal oxycodone (n=12) CR vs. immediate release (IR) oxycodone (n=111) CR vs. IR oxycodone (n=40) CR vs. IR Ox (n=50) 14 CTs (10 prospective, 4 retrospective)		oxycodone might be an alternative treatment option to morphine or hydromorphone for cancer-related pain	information on funding of included studies	
Pigni, Pall Med 2011 [221]	SR (MA not possible) Aim: to evaluate the scientific evidence for the efficacy and side effects of hydromorphone in the management of moderate to severe cancer pain.	13 studies (n=1208): ▪ 9 RCTs ▪ 2 CCTs ▪ 2 observational studies (OS)	Adults patients with chronic **moderate to severe cancer pain** (most non-naïve)	**Hydromorphone** (HM) by any route: -7 RCTs/CCTs: HM vs. other drug ▪ 1st Arm: HM ▪ 2nd Arm: Mo (5), Oxycodone (1), Fentanyl/Buprenorphine (2), -4 RCTs comparing various routes (sc, iv, po, im) or release forms (slow/intermediate) -2 OS: administration of HM	1.O: ▪ Pain modification (efficacy) 2.O: ▪ Side effects	▪ **Pain modification**: similar analgesic results showed by RCTs comparing HM with morphine and oxycodone > evidence that HM can be used as an alternative to mo. ▪ The comparison of **side effects** showed minor differences, not consistent across studies.	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality ▪ No MA due to heterogeneity ▪ Most non-naive patients	1+ (no details to study quality assessment) Body of evidence SIGN: 1-

7.1.2.2. Primärstudie

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Mercadante, Clin J Pain 2010 [222]	RCT, Aim:. It was hypothesized that OX could have some advantages over MO in terms of efficacy and dose escalation in pancreatic cancer pain.	n=60 Drop outs=21 (MO n=20; OX n=19)	**Pancreatic cancer** patients with a pain intensity of 4/10 requiring opioids	• 30 mg/d sustained release oral morphine (MO) versus • 20 mg/d sustained release oral oxycodone (OX) Opioids increased according to the clinical needs	• daily doses of opioids • pain intensity • symptom intensity recorded at admission (T0) and at weekly intervals for the subsequent 4 weeks (T1, T2, T3, and T4), with an extension at 8 weeks (T8). • Opioid escalation index (OEI) as percentage (OEI %) and in mg (OEI mg)	**Pain and symptom intensity**: no sign. difference **OEI** at T4 and T8: no sign. difference	The experimental hypothesis that OX would be superior to MO in the clinical model of pancreatic cancer pain was not confirmed.; Power Analysis: Sample Size Analysis: min 25 patients. Sample power dropped to 65% at the end of the study (4wk), limiting the statistical validity Blinding not possible; Drop Outs: 35%; not clear if ITT-analysis. A certain number of patients developed bowel obstructions and could not continue to take the study drugs orally	1+

7.1.2.3. Systematic Review der Aktualisierung 2019

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Wiffen, Cochrane 2017 [223]	SR of SR (overview of reviews) To provide an overview of the analgesic efficacy of opioids in cancer pain, and to report on adverse events associated with their use	9 Cochrane Reviews with 152 included RCTs (13.524 participants)	Adults with **cancer pain**	Opioid drugs for the treat-ment of cancer pain in adults: buprenorphine, codeine with or without paracetamol, fentanyl, hydromorphone, methadone, morphine, oxycodone, tapentadol, and tramadol with or without paracetamol, covering the range of opioids commonly prescribed for cancer pain, at least in England (PCA 2016).	1.O: ▪ Proportion of participants reporting no worse than mild pain on treatment by 14 days after start of treatment ▪ Patient Global Impression of Change (PGIC) of much or very much improved. ▪ Withdrawals due to adverse events These outcomes were also extracted when reported as moderate or substantial improvement according to the relevant Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) criteria 2.O: Description of adverse events including: ▪ withdrawals due to lack of efficacy ▪ participants experiencing any adverse event ▪ participants experiencing any serious adverse event, including death. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-	No worse than mild pain on treatment by 14 days after start of treatment Patient global impression of change (PGIC) of much or very much improved, and withdrawals due to adverse events Only the reviews of oral morphine and transdermal fentanyl reported the important outcome for people with cancer pain of having only mild or no pain within a reasonable time (14 days) after treatment started. 2 reviews demonstrated that 96% of participations achieved this outcome (856 participants). Another review of oxycodone reported average pain scores that were so low that most people would have had no worse than mild pain There were no results for the PGIC outcome and inconsistent results for the number of adverse event withdrawals, although these were always below 20%. The number of participants experiencing any	The most studies were small, compared many different praparations, had different study design and pain results. Outcome of importance to people with cancer pain were often not reported. Quality of evidence: At one level these are encouragging results, and generally agree with surveya of how well the WHO advice works in cancer. On another level, the quality of studies in the reviews was generally poor	1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
					threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the patient, or may require an inte rvention to prevent one of the above characteristics or consequences; specific adverse events, such as thirst, reduced appetite, somnolence and dizziness, as reported	adverse event was inconsiste ntly reported, and when reported occurred inconsistently, with event rates between 11% and 77%.		

7.1.2.4. Primärstudie der Aktualisierung 2019

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Corli, Ann Oncol 2016 [224]	RCT, four-arm multicenter, comparative To compare the analgesic efficacy,	n=520 (44 Italian centers)	Superiority, phase IV trial oncological patients with moderate to severe pain requiring WHO step III opioids	28 day follow-up : 1st arm: oral **controlled-release (CR) morphine** (active comparator; ITT) 2nd arm: **CR oxycodone** 3rd:arm: **Transdermal (TD) fentanyl**	1.O: analgesic properties of oral morphine with three other commonly used strong opioids 2.O: dose escalation, opioid rotation, use of adjuvant analgetic and side-effect	The main finding were the similarity in pain control, reponse rates and main adverse reactions among opioids. **Pain intensity**: CR morphine, CR oxycodone, TD	▪ Short phase of recruitment and control ▪ Limit of the evaluation of ADRs	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
	changes of therapy and safety profile over time of four strong opioids given for cancer patients		Diagnostic evidence of locally advanced or metastatic tumor; persistent moderate to severe cancer pain [average pain intensity (API) experienced in the last 24 h ≥4 points on a 0–10 Numerical Rating Scale (NRS)]; need for WHO step III strong opioids never previously given Age >18 years	4th arm: TD bubrenorphine At each visit (6 visits on days 1, 3, 7, 14, 21, 28), pain intensity, modifications of therapy and adverse drug reactions (ADRs) were recorded. The primary efficacy end point was the proportion of nonresponders (NR), meaning patients with worse or unchanged average pain intensity (API) between the first and last visit, measured on a 0–10 numerical rating scale R=responder PR=poor responder		fentanyl and TD buprenorphine seemed to achieve similar levels of pain NRs/Rs: At end of study 8.9%-14.4% of patients were classifiable as NRs and 11%–15.3% as PRs, meaning that 22%–26.4% had poor responses with <30% reduction of pain intensity (NRs: morphine/oxycodone): p=.430; bruprenorphine p=.270; fentanyl: p= .959; Rs: morphine/oxycodone p=.744; bruprenorphine p=.635; fentanyl:.942) **Dose**: Dose escalation was greater with fentanyl, and switches and discontinuations were more frequent with morphine (baseline: mg/day: 45.7 mg/day, final dose 58.9 mg/day)		

7.1.3. Levomethadon in der Tumorschmerztherapie

7.1.3.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Cherny, Pall Med 2011 [225]	SR (MA not possible) Aim: To address the question: is oral methadone better than placebo, or other oral/transdermal opioids in the management of cancer pain?	5 studies (RCTs) (n=301 patients, group size 18-108)	most adult **cancer patients** with **moderate to severe cancer** related pain; 1 study: patients with **neuropathic pain** (variety of disease)	oral methadone vs. other oral/transdermal opioids 4 RTCs :methadone vs. oral/ transdermal Opioids, among them 2 RCT oral morphine vs. oral methadone treatment. ▪ 1st Arm: oral morphine ▪ 2nd Arm: oral methadone and 1 RCT: intravenous (IV) followed by oral application of methadone/morphine ▪ 1st Arm: IV methadone, followed by oral methadone ▪ 2nd Arm: IV morphine followed by oral morphine 1 RCT oral methadone vs. oral/transdermal morphine (with access to immediate release oral morphine for each patient)	1.O: ▪ **Pain modification** (efficacy) 2.O: ▪ **Adverse events** /Side effects (1 RCT)	**Pain modification** ▪ no evidence that methadone provides more effective analgesia than oral morphine, or transdermal fentanyl ▪ comparable, but not superior, analgesia achieved Over all the RCTs indicate **comparable adverse effects**	No MA due to clinical and methodological heterogeneity/limitations possible Authors state that no studies comparing methadone to placebo for cancer pain were identified. But: The application of placebo seems to be more than ethically questionable in moderate to severe cancer pain. search strategy limeted to MEDLINE + CANCERLIT, 1966–2009; low sensibility; no information on funding of included studies	1- Body of evidence SIGN: 1-

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				▪ 1st Arm: oral morphine ▪ 2nd Arm: transdermal fentanyl ▪ 3rd Arm: oral methadone				

7.2. Opioid-Titration

7.2.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Klepstad, Pall Med 2011 [226]	Narrative SR / no MA (papers published until the end of 2009) Aim: to analyse the evidence regarding the start of treatment with opioids and dose titration in adults pts with	14 studies ▪ 2 RCTs (n=102) ▪ 12 clinical/ observational studies (1 additional paper reported results of an extended analysis of a CT included in the review)	**adult cancer patients** with **moderate to severe pain**	Starting Step III opioids (dose titration) 2 RCTs comparing titation strategies with different routes/releases of morphine oral vs. intraveanous morphine (1RCT) ▪ 1st Arm: tritation with intravenous (IV) morphine ▪ 2nd Arm: tritation with immediate release (IR) oral morphine	1.O: ▪ **Pain modification**/ control (efficacy) 2.O: ▪ **Adverse events** /Side effects	**Pain modification** ▪ faster onset of pain relief with IV morphine compared to oral morphine – but similar pain relief after 24 hours, ▪ no difference in onset pain relief or adverse effects in tritation with oral IR morphine compared to oral sustained release (SR) morphine According to the CTs all treatment strategies resulted in acceptable pain control	empirical evidence low 2 RCTs published until the End of 2009 only, MA not possible due to the diversity of methods and serious study limitations of 1 RCT (not blinded, no sample estimation) With the exception of the 2 RCTs research mostly focuses on descriptive studies (CTs of different quality)	2++ Body of evidence SIGN: 1-

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	moderate to severe cancer pain			Oral IR morphine vs. sustained release oral morphine (1 RCT) ▪ 1st Arm: oral IR morphine ▪ 2nd Arm: sustained release (SR) oral morphine 12 CTs opioid on tritation with ▪ oral morphine (6 studies) ▪ intravenous morphine (2 studies) ▪ transdermal fentanyl (4 studies).		**Adverse events /Side effects** RCTs indicate ▪ apart from drowsiness after IV titration no serious adverse effects reported ▪ no difference in adverse effects in titration with oral IR morphine compared to oral sustained release (SR) morphine apparent all treatment strategies were well tolerated.	broad search strategy but limited to Medline) GRADE approach to assess study quality Study limitations discussed No information on funding of included studies.	

7.3. Applikationsformen

7.3.1. Die Rolle transdermaler Opioide

7.3.1.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Tassinari, Pall Med, 2011b [227]	SR / no MA Aim: To assess the role of transdermal opioids	13 studies (total n not provided) ▪ 11Randomized clinical trials	Adult patients with moderate to severe cancer pain requiring stable doses of strong opioids	Efficacy of **transdermal** opiods (fentanyl and buprenorphine) in comparison with oral morphine.	1.O: ▪ Pain modification (efficacy) 2.O: ▪ Safety	▪ **Pain modification:** weak negative recommendation for the use of transdermal fentanyl and strong negative for	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality	1- Body of evidence SIGN: 1-

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	as a front-line approach to moderate to severe cancer pain.	▪ 2 Metaanalyses				transdermal buprenorphine. ▪ **The risk / benefit ration** was considered uncertain. Weak data report on less side effects with the use of transdermal opioids (constipation, diarrhoe, nausea, urinary retention).	▪ Low statistical power ▪ Most non-naive patients	

7.3.1.2. Primärstudien der Aktualisierung 2019

Siehe Corli et al. Corli et al. 2016 [224], Kapitel 7.1.2.4

7.3.2. Alternative systemische Applikationsformen für Opioide

7.3.2.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Radbruch, Pall Med, 2011 [228]	SR / no MA planned because of differences in the outcome indicators Aim: to update the EAPC recommendations on	72 studies; 18 included a total of n = 674 patients ▪ 3 SR (n = 916) ▪ 11 CCS (n = 537)	Adult patients with moderate to severe pain **cancer pain** who are unable to take oral opioids	Efficacy and safety of alternative routes of opioid application	1.O: ▪ Efficacy of pain modification 2.O: ▪ Safety	▪ **Pain modification**: good evidence for subcutaneous administration of morphine. ▪ The risk/benefit ratio was considered low.	▪ Methodological limitations of most of the studies (missing data), resulting in a low quality ▪ Low statistical power ▪ Various medications compared	1++ Body of evidence SIGN:

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	opioids in cancer pain management.	▪ 2 crossover non-randomized study (n = 58) ▪ 2 crossover RCTs (n= 38) ▪ 7 CS (n = 230) ▪ 1 CR (n =1) ▪ 1 crossover randomized trial (n = 23) ▪ 2 sequential cohort series (n =70)						sc route, iv titration: 1+; switch from iv or oral to ohter route: 3

7.3.3. Rückenmarksnahe Verabreichung von Opioiden

7.3.3.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Kurita, Pall Med, 2011 [229]	SR / no MA Aim: to analyse analgesic efficacy and side effects of spinal opioids in adult cancer patients	44 studies: (n= 2126): ▪ 9 RCTs (n = 639) ▪ 28 uncontrolled prospective	Adults patients with **severe cancer pain** (mostly patient havew been pretreated with opioids)	Morphine by the spinal route: - implantable pump system in 5 of 9 in RCTs. - implantable pump system in 16 of 28	1.O: ▪ Pain modification (efficacy) 2.O: ▪ Side effects	▪ **Pain modification**: weak recommendation for the use of spinal opioids, in the RCT 6 did not show a significant difference between oral or epidural application.	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality ▪ No MA due to heterogeneity	1+ Body of evidence SIGN: 1-

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	previously treated with systemic opioids.	studies (n = 1378) ▪ 2 non-randomised cohort studies (n= 24) ▪ 5 CS (n = 85)		uncontrolled prospective studies - implantable pump system in 4 of the non-randomized cohort studies and CS In the remaining studies morphine has been delivered by epidural route via spinal tap.		▪ The comparison of **side effects** showed minor differences with an advantage of the spinal route.	▪ Most non-naive patients	

7.3.3.2. Primärstudie

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Lauretti, BJC 2013 [230]	RCT, double-blind Power of 80% Aim: to evaluate the role of epidural methadone-lidocaine in cancer pain combined or not to epidural dexamethasone.	n=72 (n=12/group) Drop-out=14	Aged 32 – 67 years; with a diagnosis of **cancer**, documented history of moderate/severe chronic cancer pain, classified as Tumour-Node-Metastasis stage III or IV, requiring round-the-clock opioid Exclusion criteria: Clinically unstable; clinically significant gastro-intestinal disease, cyclic	Regular medication: oral morphine and oral amitriptyline (Oral mo regimen individually adjusted to a maximal oral dose of 80-90 mg per day, in order to keep the VAS score <4/10; oral amitriptyline 25 mg at bedtime) Patients randomised to one of 6 arms if they complained of pain (VAS >=4/10): • Controll Group (CG):	Daily: • Analgesia (Pain average - VAS) • Morphine consumption Weekly evaluation (yes/no) of side effects: (1) daily somnolence (2) nocturnal insomnia (3) nausea (4) occurence of vomiting (5) constipation (6) diminished appetite (7) fatigue (8) sadness Follow-up during 21 days	**Analgesia**: overall daily VAS scores <4cm in all groups **Morphine consumption**: • CG, DG and 2.5MetG: gradual increase in mo intake, without sign. difference between groups • 5MetG and 7.5MetG: patients took 3±1 and 5±1 days, respectively, to restart oral morphine. • 7.5MetDG: patients took 14±2 to restart oral morphine (P<0.001). > shows dose-dependent effect of methadone and	Randomisation not clear described 19,4% drop-outs; no ITT-analysis described Study powered The groups showed no differences regarding gender, weight, age and height , distribution of the primary site of the cancer pathology and incidence of metastasis	1+

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
			chemotherapy within 3 weeks before visit or planned during the core study; radiotherapy that would influence bowel function or pain, refusal, allergy to any of the drugs used or inability to ingest the oral rescue analgesic morphine	Epidural 40 mg lidocaine diluted to 10 ml volume with saline. • Dexamethasone group (DG): 40 mg lidocaine + 10 mg dexamethasone • 2.5 MetG: 2,5 mg epidural methadone + 40 mg lidocaine • 5MetG: 5 mg epidural methadone + 40 mg lidocaine • 7.5MetG: 7.5 mg epidural methadone + 40 mg lidocaine • 7.5Met-DG: 7.5 mg epidural methadone + 40 mg lidocaine + 10 mg dexamethasone		enhancement with dexamethasone **Adverse effects**: Daily somnolence and appetite improved in the 7.5MetDG during 2-week evaluation (P<0.005). Fatigue improved for both DG and 7.5MetDG during 2-week evaluation (P<0.005). By the third week of evaluation, all patients were similar.		

7.4. Opioid-Wechsel

7.4.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Dale, Pall Med 2011 [231]	SR / no MA (Cochrane review up-date 2004-2010, first Version 2004) Aim: to address the question: what is the evidence of opioid switching resulting in improved analgesia or reduced adverse effects in adult patients suffering from cancer pain?	11 studies (MA not possible) uncontrolled prospective observational studies (n=280 patients, (group size 10–32).	mostly **adult cancer patients** with inadequate relief of **moderate to serve pain** and/or intolerable opiode associated adverse/side effects	Opioid switch (variety of opioids, routes and switching strategies) ▪ transdermal Buphrenophine → transdermal Fentanyl (vice versa) ▪ transdermal Fentanyl → Methadone ▪ Morphine→ transdermal Fentanyl ▪ Morphine → Methadone ▪ Methadone → transdermal Fentanyl ▪ transdermal Fentanyl → Methadone ▪ transdermal Fentanyl → Methadone or Morphine and and Morphine → Methadone ▪ Morphine → transdermal and parentetral Fentanyl ▪ transdermal Fentany/ Morphine or Hydromorphone → Methadone	1.O: ▪ **Pain modification** (efficacy) 2.O: ▪ **Adverse events** /Side effects (reduction)	▪ **Pain modification:** significant **reduction of pain intensity** in the majority of studies ▪ **Adverse events**: significant **reduction of** serious **adverse events/side effects** in the majority of studies	All in all still low level of evidence due to methological study limitations: open uncontrolled studies with bias risk and data imprecision (GRADE D) Quantitative review (and MA) not possible due to lack of RCTs Search and assessment strategy described no information on funding of included studies	2++ Body of evidence SIGN: 3

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				▪ Morphine → Oxycodone ▪ Morphine →transdermal Fentany				
Mercadante, Pall Med, 2011 [232]	SR / no MA Aim: to describe the results of a systematic search of the literature on conversion ratios during opioid switching	31 studies (n =) ▪ 26 uncontrolled, non-randomized, prospective (n = 1505) ▪ 2 non-randomized crossover (n = 33) ▪ 6 RCT (n = 267)	Adult patients with chronic **cancer pain** with opiod treatment	Efficacy and reliability of conversion rates of **opiod switching** during opioid treatment	1.O: Efficacy and reliability of opioid switching rates in treatment of pain	▪ **Switiching an opioid**: no specific generalized recommendation can be made. Use of established available evidence of conversion ratios. ▪ Opioid switching to methadone should needs more experience	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality ▪ Low statistical power ▪ Various opioid administration route	1+ Body of evidence SIGN: ORmo/ TDfe to TDbu: 3; ORmo to ORhy: 3; ORox to ORhy: 1++ (only 1 RCT, but high quality); ORmo to TDfe: 2-; ORmo to ORox: 1+

7.4.2. Primärstudie

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Moksnes, Eur J Cancer 2011 [233]	RCT, phase II trial, parallel groups, multicentre Aim: We investigated whether patients switched to methadone by the stop and go (SAG) strategy have lower pain intensity than the patients switched over three days (3DS), and whether the SAG strategy is as safe as the 3DS	n=42 Drop outs=7 (n=2 in 3DS group; n=5 in SAG group)	**Cancer** patients >18y, treated with morphine or oxycodone >1week and having increasing pain considered to be untreatable with further opioid titration and/or having opioid related adverse effects	Switch strategy from morphine or oxycodone to methadone: • Stop and Go (SAG) versus • switch over 3 days (3DS) The methadone dose was calculated using a dose-dependent ratio. Rescue dose: 1/6 of the baseline opioid dose.	1.O: Average pain intensity (PI) on day 3 (BPI) 2.O: • Average pain intensity (PI) on day 14 (BPI) • PI now on day 3 and 14 • Adverse events (AEs) on day 3 and 14 • Number of serious adverse events (SAEs)	Mean preswitch morphine doses: 900mg/d in SAG; 1330mg/d in 3DS; The two study groups had similar patients' characteristics except time on WHO step 3 opioids (SAG mean 9.1 months and 3DS 23.6 months, mean difference 14.4 (CI) 26.6 to)2.3)). **Average PI day 3/PI now**: no sign. difference, but trend of more pain in the SAG group **Mean AEs**: no sign. difference between groups **SAEs**: 3 in SAG (2 deaths, 1 severe sedation)	The SAG group had sign. more dropouts and three SAEs (two deaths and one severe sedation). The SAG strategy should not replace the 3DS when switching from high doses of morphine or oxycodone to methadone Sample size calculation, concealment and randomisation described. ITT-analysis?	1+

7.5. Prophylaxe und Behandlung von Nebenwirkungen

7.5.1. Behandlung von opioidbedingter Übelkeit und Erbrechen

7.5.1.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Laugsand, Pall Med, 2011 [234]	SR / no MA Aim: to review the existing literature on management of opioid-induced nausea and vomiting in cancer patients and summarize the findings into evidence-based	55 studies (n = 5741) ▪ 19 RCT (n = not given) ▪ 13 case reports or case series (n = not given) ▪ 18 studies with nausea as primary outcome (with 8/18 studies opioid-induced nausea) ▪ 37 studies with nausea not primary outcome	Adult patients with cancer pain receiving opiods for cancer pain addressing nausea and vomiting either as a primary or secondary outcome	• use of analgetics for opiod sparing • change of opiod • change of route • other	1.O: ▪ Nausea and vomiting (opiod induced emesis) 2.O: ▪ Nausea and vomiting 3.O: ▪ Nausea and vomiting	▪ **Nausea and vomiting**: weak recommendation for changing the opiod or the opiod administration route. ▪ Too less evidence for a prioritization between symptomatic treatment and adjustment of opiod treatment	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low to very low quality (C-D) ▪ No MA due to heterogeneity ▪ Most non-naive patients ▪ Lack of consistency	1++ Body of evidence SIGN: 1-

7.5.2. Behandlung opioidbedingter Obstipation

7.5.2.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Candy, Cochrane 2011 [235]	SR (MA not possible) Cochrane Review up date 2010 (first version 2006) Aim: to determine (1) the effectiveness of laxatives and methylnaltrexone for the management of constipation in PC patienss and (2) the differential efficacy of laxatives used to manage constipation	7 studies (n=616) 7 RTCs, among them 2 crossover design	**palliative care / hospice patients** (most with advanced cancer and (anticipated) **opioid induced constipation)**	**Methylnaltrexone** (MN) and/or **conventional laxatives** -4 RCTs: senna (+ lactulose) vs various other laxatives -1 RCT (n=91/75) ▪ 1st Arm: starting dose daily of 15 ml (10 g) lactulose, up to max. 60ml (40 g) ▪ 2nd Arm: starting dose daily of 0.4 ml (12 mg) senna, dose increase up to max. 1.6ml -1 RCT (n=36) ▪ 1st Arm: misrakasneham (starting dose 2.5 ml) ▪ 2nd Arm: senna (starting dose 24 mg) -1 RCT (crossover) (n=118): ▪ 1st Arm: magnesium hydroxide + liquid paraffin 2nd Arm: senna + lactulose -1 RCT (crossover) (n=51): ▪ 1st Arm: senna + lactulose ▪ 2nd Arm: co-danthramer	1.O: ▪ Constipation management (relief) 2.O: ▪ Adverse effects ▪ opioid withdrawal ▪ quality of life (1 study)	**Constipation management:** subcutaneous methylnaltrexone seems to be effective in opioid-induced constipation and where conventional laxatives have failed (odds ratio 6.95; 95% confidence interval 3.83 to 12.61) **Adverse effects:** in total no difference in the occurrence of side effects (although higher proportion of flatulence and dizziness under methylnaltrexone) but drug safety of methylnaltrexone not yet fully evaluated (serious adverse events possible, i.e. severe diarrhoea, subsequent dehydration and cardiovascular collapse) **Opioid withdrawal:** evidence of opioid withdrawal was found **Quality of life** results not reported	MA not possible, due to clinical and methodological heterogeneity and study limitations ▪ evidence remains limited due to insufficient RCTs ▪ All RCTs under-reported key design features (randomisation, allocation, incomplete outcome data) > unclear risk of bias ▪ further rigorous, independent trials needed (6 of 7 studies were funded by pharmaceutical companies) broad search strategy, summary and discussion of study limitations information on funding of included studies	1++ Body of evidence SIGN: 1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				MN dose ranging: 1 RCT: sc MN (n=33, out of them 29 on conventional laxatives) ▪ 1st Arm: sc MN 1 mg ▪ 2nd Arm: sc MN 5 mg ▪ 3rd Arm: sc MN 12.5 mg 2 RCTs: sc MN vs.placebo 1 RCT: dose variation (n=154) ▪ 1st Arm: single sc injection MN (0.15 mg/kg) ▪ 2nd Arm: single sc injection MN (0.3 mg/kg) ▪ 3rd Arm: placeo 1 RCT: (n=133) ▪ 1st Arm: sc MN (0.15 mg/kg) ▪ 2nd Arm: placebo				

7.5.2.2. Systematic Reviews der Aktualisierung 2019

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
LAXATIVES						
Candy, Cochrane 2015 [236] *(Partial update of review 2006/ 2011)*	SR To evaluate laxatives for constipation in people receiving palliative care	Databases: CENTRAL; *The Cochrane Library*), MEDLINE, EMBASE, CINAHL and Web of Science (SCI & CPCI-S) for trials to September 2014. Design: RCTs Population: Patients in palliative care and advanced or end-stage irrespective of care setting	Interventions: any laxative Outcomes: 1.O: - Laxation response - Adverse events 2.O: - Participant preference - Relief of other constipation-associated symptoms (abdominal pain, nausea, vomiting and loss of appetite)	Study number: 5 RCTs (n=370 participations) Population: cancer only Intervention: laxatives lactulose, senna, co-danthramer, misrakasneham, docusate and magnesium hydroxide with liquid paraffin Outcomes: Docusate plus senna versus placebo plus senna: **Laxation response**: No statistical difference (in volume, difficulty, and complettness of defecation, and having a bowel movement on 50 % of the study days (for instance the OR was 0.52 (95% CI 0.17 to 1.57)). Bristol Stoll charts: between the trial arms significant difference (P= .001) in stool consistency; with more participants in the placebo plus senna group having Type 4 (smooth and soft) or Type 5 (soft blobs) stools, and more participants in the docusate plus senna group having Type 3 (sausage like) or Type 6 (mushy) stools. **Need for additional laxatives**: One type of additional laxative was given to 74% of participants in the placebo plus senna group and 68.6% of participants in the docusate plus senna group. The difference was not significant (P = .77).	Method: Well conducted systematic review of double blinded RCTs Content Low to moderate QoL (most small sample size)	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				Constipation-associated symptoms: measured symptoms (as shortness of breath and drowsiness, using the Edmonton Symptom Assessment System) had no significant difference between the trial arms		
OPIOIDANTAGONISTS						
Candy, Cochrane 2018 [237] *(Partial update of review 2006/ 2011)*	SR, MA To assess the effectiveness and safety of MOA (Mu-Opioid-Antagonist) for opioid-induced bowel dysfunction (OIBD) in people with cancer and people receiving palliative care	Databases: Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL, andWeb of Science to August 2017; clinical trial registries and regulatory websites Design: double-blind RCTs Population: Patients with cancer or people at a palliative stage; and patients on a stable opioid regimen and had opioid-induced bowel dysfunction (OIBD) that had not resolved from taking laxatives	Interventions: mu-receptor opioid antagonists that were either peripherally or systemically acting for opioid-induced bowel dysfunction Outcomes: 1.O: - Laxation response n the first 24 hours and between days one and 14 - effect on analgesia - Adverse events (AE) 2.O: - dropped out due to adverse events - Participant preference - Relief of other constipation-associated symptoms (abdominal pain, nausea, vomiting and loss of appetite)	Study number: 8 RCTs (n=1022 participations) Population: mostly (advanced) cancer Quality of studies: 4 trials with high risk of bias by small sample Intervention: oral naldemedine and naloxone (alone or in combination with oxycodone), and subcutaneous methylnaltrexone Outcomes: Naldemedine (1 RCT, n=225): **Spontaneous laxations**: sign. more over the 2-week treatment for naldemedine (risk ratio (RR) 1.93, 95% CI 1.36 to 2.74; moderate-quality evidence). **Opiate withdrawal:** no sign. effect (moderate-quality evidence) **Serious AE**: 5, all were in people taking naldemedine (low-quality evidence). **Non-serious AE**: sign. Increase in the naldemedine group (RR 1.36, 95% CI 1.04 to 1.79, moderate-quality evidence). The most common adverse event was diarrhoea.	Method: Well conducted systematic review of double blinded RCTs Content Moderate to low LoE; There is moderate-quality evidence to suggest that, taken orally, naldemedine improves bowel function over two weeks in people with cancer and OIBD but increases the risk of adverse events. The trials on naloxone did not assess laxation at 24 hours or over two weeks. There is moderate-quality evidence that MNTX improves bowel function in people receiving palliative care in the short	1++ (Body of evidence: 1+)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				Naloxone alone or with oxycodone (3 RCTs): **Laxation response over the first 2 weeks**: no results **Effect on analgesia**: no sign. effect (very low-quality evidence for naloxone alone, moderate-quality evidence for oxycodone/naloxone) **(Serious) AE**: not increased by nal./oxyc. Methylnaltrexone, MNTX (4 RCTs): Results of MA: **Laxations within 24 hours** (2 RCTs, n=287): sign. higher in MNTX -group (RR 2.77, 95% CI 1.91 to 4.04. I^2 = 0%; moderate-quality evidence). **Rescue free laxation within 4h** (3 RCTs): sign. higher in MNTX-group (RR 3.87 [95% CI 2.83, 5.28, moderate LoE) **Laxation responses over 2 weeks** (2 RCTs): sign. higher (RR 9.98, 95%CI 4.96 to 20.09. I^2 = 0%; moderate-quality evidence). Opioid withdrawal: not affected (moderate-quality evidence) **Serious AE** (2 RCTs): fewer in the intervention arm (RR 0.59, 95% CI 0.38 to 0.93; I^2 = 0%; moderate-quality evidence). **AE** (3 RCTs): n.s. (RR 1.17, 95% CI 0.94 to 1.45; I^2 = 74%; low-quality evidence). **Symptoms**: increased abdominal pain and flatulence in MNTX -group.	term and over two weeks, and low-quality evidence that it does not increase adverse events.	
Esmadi, J Gastrointestin Liver Dis 2019 [238]	MA to perform a meta-analysis of existing clinical trials to estimate the efficacy	Databases: PubMed, CINAHL, Scopus, Cochrane database of systematic reviews, and ClinicalTrials.gov until March 2018; hand search	Intervention: naldemedine (NAL) Control: placebo Outcomes:	Study number: 6 RCTs incl. in MA (n=2,762) Population: not stated Quality of studies: low risk of bias	Well-conducted systematic review, comprehensive search strategy	1++ (Body of evidence: 1+)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
	and safety of naldemedine in opioid-induced constipation	Design: RCTs placebo-controlled Population: patients treated for opoioid-induced constipation (OIC)	1.O: spontaneous bowel movement (SBM) responder rates (≥3/wk, ≥1 increase from baseline/wk) 2.O: change in SBM (spontaneous bowel movement) frequency per week from baseline during the treatment period, change from baseline in the frequency of complete SBM (CSBM was defined as an SBM with the feeling of complete evacuation), and the incidence of treatment-emergent adverse events (AE).	Outcomes: **SBM responder rate** (5 RCTs): sign. higher in NAL-group (OR 3.0 [95% CI 1.93, 4.65]) **Change in SBM frequency from baseline/wk.** (3 RCTs): sign. higher (SMD 6.46 [95% CI 4.73, 8.20]) **Change in CSBM from baseline** (3 RCTs): SMD 5.93 [95% CI 4.9, 6.96] **AE** (6 RCTs): n.s. increased (OR 1.18 [95% CI 0.89, 1.55]). AE were: diarrhea (most common), abdominal pain, vomiting, decreased appetite, decreased white blood cells count, nasopharyngitis, decreased total protein, hypertension, increased blood alkaline phosphatase and increased blood lactate dehydrogenase.	Of the 6 studies done, a total of 43% of patients reached the primary end point The RCTs varied in time for which patients were followed, ranging from 2 weeks to 52 weeks Calculated effect considerably higher than in other MA; AE were here not significant higher, in constrast to the conclusions of other MA.	
Hanson, Gastroenterology 2018 [239]	Technical review (SR/MA) To provide evidence-based information to guide patients, clinicians, and policy makers in the management of adults with OIC.	Databases: MEDLINE (1950 to February 2017), EMBASE and EMBASE Classic (1947 to February 2017), and the Cochrane Central Register of Controlled Trials, and health technology assessments; update until May 2018 Design: RCTs, English Population: adult patients with OIC (with and without cancer)	Interventions: pharmacological therapies: laxatives, methylnaltrexone, naloxegol, alvimopan, naldemedine, prucalopride, and lubiprostone Only trials with at least a 4-week duration of treatment were considered, with the exception of	Study number/interventions: 20 RCTs (1 laxative, 3 naloxegol, 3 alvimopan, 3 naldemedine, 2 methylnaltrexone, 3 lubiprostone, and 2 prucalopride) Population: non-cancer patients Outcomes: *We report here only results of MA for opioidantagonists* Naldemedine (4 RCTs, n=2463, all non-cancer): **SBM responder rate** (≥3/wk, ≥1 increase from baseline/wk) (3 RCTs): sign. higher (RR 1.51 [95% CI 1.32 to 1.72]; high LoE)	Well-conducted SR and MA Results of MA for non-cancer patients only	1++ (Body of evidence: see single drugs)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
			methylnaltrexone (2-week minimum)	**Change in SBM frequency from baseline** (3 RCTs): sign. more in NAL-group (MD 1.38 [95% CI 1.03, 1.73], high LoE) **Change in frequency of BMs without straining** (3 RCTs): sign. more in NAL-group (MD 0.82 [95% CI 0.44, 1.21], high LoE) **AE with treatment discontinuation** (3 RCTs): n.s. difference (RR 1.44 [95% CI 1.03, 2.03], high LoE) Naloxegol (3 RCTs, n=1559; non-cancer): **SBM responder rate** (≥3/wk, ≥1 increase from baseline/wk) (2 RCTs): sign. higher (RR 1.43 [95% CI 1.19, 1.71]; moderate LoE) **Change in SBM frequency** from baseline (2 RCTs): sign. more (MD 1.02 [95% CI 0.67, 1.37]; moderate LoE) **Severity of straining** (5-point scale) (2 RCTs): sign. lower (MD 1.02 more (0.67, 1.37); high LoE) **Stool consistency** (2 RCTs): sign. better (MD 0.33 (0.20 to 0.46); moderate LoE) **AE with treatment discontinuation** (4 RCTs): sign. less (RR 2.33 (1.62 to 3.35); moderate QoE) Methylnaltrexone (all non-cancer): **Rescue-free bowel movement (RFBM) response** (≥3 RFBM/wk) (2 RCTs): sign. more (RR 1.43 [95% CI 1.21 to 1.68]; low QoE) **Laxation response** (=BM within 4h) (2 RCTs): sign. more (RR 3.16 [95% CI 2.18 to 4.58]; moderate QoE)		
Luthra,	SR, network MA	Databases: MEDLINE (2012 to December 2017), EMBASE and	Interventions: pharmacological therapies	Study number: 27 RCTs (n=9149), all Against placebo; no trials making head-to-	Well conducted SR and network MA;	1++ (body

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Gut 2019 [240]	To evaluate the efficacy of pharmacological treatement for OIC (opioid-induced constipation) und to compare these drugs	EMBASE Classic (2012 to December 2017), PUBMED (2012 to December 2017) and the Cochrane central register of controlled trials; clinicaltrials. gov Design: RCTs Population: Adult OIC patients	(methylnaltrexone, naloxone, alvimopan, naldemedine, naloxegol, bevenopran, lubiprostone, prucalopride, naronapride, velusetrag, linaclotide or plecanatide) Outcomes: Efficacy; AE	head comparisons of one drug versus another Population: most non-cancer Quality of evidence: 11 RCTs with low risk of bias Outcomes: *P-score (0-1) = probability of each treatment being ranked as best in the network analysis* **Failure to achieve an average of ≥3 BMs per week with an increase of ≥1 BM per week over baseline or an average of ≥3 BMs per week** (22 RCTs, 8500 patients, I^2=58.8%): ranking according to P-score: 1. Naloxone (2 RCTs): highest ranking (P-score=0.84); sign. more effective than placebo (PL) (RR 0.65, 95% CI 0.52 to 0.80; NNT=4, 95% CI 3 to 8) 2. Naldemedine (5 RCTs): P=0.8; sign. more effective than PL (RR 0.67, 95% CI 0.59 to 0.77; NNT=5, 95% CI 4 to 7) 3. Alvimopan (3 RCTs): P=0.79; sign. more effective than PL (RR 0.67; 95% CI 0.57 to 0.80, NNT=5; 95% CI 4 to 8) 4. s.c. methylnaltrexone (2 RCTs): P=0.61; sign. more effective than PL RR 0.74; 95% CI 0.58 to 0.94, NNT=6; 95% CI 4 to 26) 5. Prucalopride (2 RCTs): P=0.60; sign. more effective than PL RR 0.74; 95% CI 0.58 to 0.96, NNT=6; 95% CI 4 to 39) 6. Bevenopran (2 RCTs): P=0.51 7. Naloxegol (2 RCTs): P=0.35 8. Methylnaltrexone (1 RCT): P=0.23	Risks of bias not reported for single outcomes Moderate levels of global statistical heterogeneity in some of our analyses Limited data for naloxegol: 2 phase III RCTs and a phase II trial of the drug did not reported dichotomous data and those could not be obtained	of evidence: 1+)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				9. Lubiprostone (3 RCTs): P=0.22 Indirect comparison of drugs: sign. differences were seen with naloxone compared with oral methylnaltrexone or lubiprostone; naldemedine compared with naloxegol, oral methylnaltrexone or lubiprostone and alvimopan compared with lubiprostone **Failure to achieve an average of ≥3 BMs per week with an increase of ≥1 BM per week over baseline** (14 RCTs, n=6011, I^2=70.6%): ranking according to P-score: 1. Naldemedine (5 RCTs): ranked as the most effective treatment (P-score=0.91); sign. more effective than PL (RR 0.66; 95% CI 0.56 to 0.77) 2. Alvimopan (2 RCTs): P=0.71; sign. more effective than PL (RR 0.74; 95% CI 0.57 to 0.94) 3. Bevenopran (2 RCTs): P=0.60 4. Methylnaltrexone s.c. (1 RCT): P=0.58 5. Naloxegol (2 RCTs): P=0.44 6. Lubiprostone (1 RCT): P=0.34 7. Methylnaltrexone (1 RCT): P=0.31 Indirect comparison of active drugs: n.s. differences **Failure to achieve an average of ≥3 BMs per week** (9 RCTs, n=2949; I^2=0%): Alvimopan ranked as the most effective treatment (P=0.96), followed by naloxone (P=0.79), methylnaltrexone s.c. (P=0.52), prucalopride (P=0.52) and lubiprostone (P=0.19)		

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				Indirect comparison of active drugs: sign. differences were seen with alvimopan compared with s.c. methylnaltrexone or lubiprostone and with both naloxone and s.c. methylnaltrexone compared with lubiprostone		
Metha, Postgrad Med J 2016 [241]	SR, MA To evaluate the efficacy of methylnaltrexone for the treatment of OIC	Databases: Cochrane Collaboration Databases and MEDLINE from 2007 to present Design: RCTs, English Population: patients treated with methylnaltrexone (MNTX) for OIC	Intervention: MNTX Outcomes: 1.O: RFBM within 4 hours	Study number: 6 RCTs, n=1239 patients Population: cancer, chronic nonmalignant pain, other advanced illness, and OIC following orthopedic surgery Treatment: duration ranged from a single injection to up to 4 weeks Outcomes: **RFBM within 4 hours**: sign. more (risk difference 0.33, 95% CI 0.21 to 0.39; p= <0.0001). Similar sign. results for subgroup analysis (0.15 or 0.30 mg/kg)	Literature search might be little sensitive (few databases, data and language limitation, few hits) Data on study assessment/risk of bias not reported	1- (body of evidence: not stated)
Nee, Clin Gastroenterol Hepatol 2018 [242]	SR, MA to evaluate the effectiveness of treatments of OIC; to update a previous metaanalysis by including additional studies published for the treatment of OIC	Databases: MEDLINE (1950 to March 2017), EMBASE (Elsevier Science: 1975–present) and EMBASE Classic (1947 to March 2017), Web of Science (1900 to March 2017), and the Cochrane Central Register of Controlled Trials (update software: 1996 to March 2017). Design: RCTs Population:OIC (not further described)	Outcomes: efficacy of the therapy to fail compared with placebo; AE	Study number/interventions: 27 RCTs (naloxone, n=5; alvimopan, n=4; naloxegol, n=3; methylnatrexone, n=7; naldemedine N=4; axelopran (TD-1211), n=1; lubiprostone, n=3; prucalopride, n=1) Interventions: methylnaltrexone, naloxone, naloxegol, alvimopan, prucalopride, lubiprostone, axelopran (TD-1211), and naldemedine Outcomes: *We report here only results of MA for opioidantagonists*	Well-conducted SR Although a limitation of this study was the significant heterogeneity across 27 studies, we have shown through sensitivity analysis and meta-regression the potential factors contributing to this heterogeneity. This is likely owing to the inclusion of multiple	1++ (Body of evidence: see single drugs)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				The most common primary outcome (efficacy) was 3 or more complete SBMs/wk over the trial period: Methylnaltrexone (6 RCTs, n=1622, I^2=77,2%) **Failure to respond**: sign. lower (Cancer-related pain: RR 0.51 (95% CI 0.41–0.63); non-cancer-related pain: RR 0.75 (95% CI 0.63–0.90); high LoE Naloxone (5 RCTs, n=838, I^2=0,0%): **Failure to respond**: sign. lower (RR, 0.63 (95% CI 0.56–0.71); moderate LoE Naldemedine (4 RCTs, n=1525, I^2=79,6%): **Failure to respond**: sign. lower (RR, 0.65 (95% CI 0.52–0.82); moderate LoE Naloxegol (3 RCTs, n=1522, I^2=86,4%): **Failure to respond**: sign. lower (RR, 0.77 (95% CI 0.61–0.97) Treatment overall: **AE (any)**: RR 1.10 (95% CI 1.05 to 1.16); NNH 20.6 (95% CI 14.3 to 36.8)	agents, varying baseline opioid use, and different subject populations (cancer vs non-cancer-related pain).	
Nishie, J Gastroenterol Hepatol 2019 [243]	SR, MA To identify randomized controlled trials (RCTs) evaluating the role of PAMORA in patients with OIC, and we conducted a meta-analysis to	Databases: PubMed (1946 to the date of search), Embase (1974 to the date of search), and Cochrane databases (from inception through February 12, 2018) Design: RCTs	Intervention: PAMORA (Peripherally acting μ-opioid antagonist) vs. placebo Outcomes: 1.O: change from baseline in spontaneous bowel movement	Study number/interventions: 31 RCTs, n=7849 seven used naldemedine (n = 1399), Seven used methylnaltrexone (n = 605), Four used alvimopan (n = 518), six used naloxegol (n = 547), five used bevenopran (n = 776), and two used axelopran (n = 69). Population: mostly non-cancer	Well-conducted SR; SR includes unpublished data, such as those on axelopran and bevenopran. Risks of bias not reported for single outcomes	1+ (body of evidence: 1+)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
	estimate the effect and safety of PAMORA.	Population: adults receiving opioid or opiate drugs and with diagnosis of OIC or OIBD (opioid-induced bowel dysfunction) with constipation	(SBM) 2.O: QOL, responder rate, and adverse events (AEs)	Outcomes (results of MA): **Change from baseline of SBM** (20 RCTs, n=5622): Overall results: sign. increase in PAMORA groups (MD, 1.43; 95% CI, 1.18–1.68; P < 0.00001). *Subgroup analysis*: all sign. improved Naldemedine (6 RCTs; MD, 1.71; 95% CI, 1.13– 2.28; P < 0.00001) Methylnaltrexone (2 RCTs; MD, 1.49; 95% CI, 1.10–1.89; P < 0.00001) Alvimopan (4 RCTs; MD, 1.17; 95% CI, 0.68–1.67; P = 0.49) Naloxegol (5 RCTs; MD, 1.35; 95% CI, 0.71–1.98; P < 0.00001) Bevenopran (1 RCTs; MD, 1.98; 95% CI, 0.88–3.08; P = 0.00004) Axelopran (2 RCTs; MD, 1.52; 95% CI, 0.72–2.33; P = 0.0002) Moderate heterogeneity ($\chi 2 = 34.67$, P = 0.02, $I^2 = 45\%$) was observed. In sensitive analysis, when we excluded 2 trials in which the dose of the drug was 10 times different, heterogeneity was reduced ($\chi 2 = 24.68$, P = 0.10, $I^2 = 31\%$) **QoL** (8 RCTs, n=2284): sign. improvement in PAMORA groups (MD -0.22; 95% CI, -0.28 to -0.17; P < 0.00001; $I^2 = 2\%$) **Proportion of responders** (21 RCTs, n=4821): sign. greater response in PAMORA groups (RR 1.81; 95% CI, 1.55–2.12; P < 0.00001; $I^2 = 77\%$)	Especially the naldemedine study seemed to show publication bias (funnel plot). In some registries (e.g. clinicaltrials.gov) some trials were found that had not been published yet despite sufficient time passing after the study completion	

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				AE (26 RCTs, n=7715): 4100 AE reported; sign. increased AE in PAMORA groups overall (RR, 1.10; 95% CI, 1.06–1.15; P < 0.00001) **Serious AE** (17 RCTs): n.s. (RR, 1.04; 95% CI, 0.85–1.28; P = 0.68) Gastrointestinal toxicity, diarrhea (25 RCTs; RR, 2.07; 95% CI, 2.14–4.65), abdominal pain (26 RCTs; RR, 2.22; 95% CI, 2.14–4.65), vomiting (22 RCTs; RR, 1.47; 95% CI, 1.17–1.84), and nausea (27 RCTs; RR, 1.39; 95% CI, 1.17–1.65) were significantly increased AEs		
Siemens, Ther Clin Risk Manag 2016 [244]	MA To evaluate the objective and subjective efficacy and the safety of methylnaltrexone (MNTX) in opioid-induced constipation (OIC) patients	Databases: RCTs from a recent systematic review were included. In addition, a PubMed search was conducted for January 2014 to December 21, 2015 Design: RCTs Population: Adult OIC patients (<3 BMs/week); postoperative OIC excluded	Interventions: MNTX Outcomes: 1. O: Objective Outcome measures (OOM): eg, time to laxation 2. O: patient-reported outcomes (PROs): eg, straining global burden measures (GBMs) eg, constipation distress	Study number: 7 RCTs (qualitative synthesis; 1.860 patients) ; 6 RCT (quantitative synthesis; meta-analysis 1.412 patients) Population: mixed cancer and non-cancer population Outcomes: Patients under MNTX had considerably more **rescue-free bowel movement within 4 hours** after the first dose (RR 3.74, 95% CI 2.87 to 4.86; five studies, n=938; *I2*=0). Patients under MNTX had a higher stool frequency and needed less **time to laxation** compared with placebo. Moreover, patients receiving MNTX tended to have better values in patient-reported outcomes and global **burden** measures. Meta-analyses on **safety** revealed that patients under MNTX experienced more abdominal pain (RR 2.38, 95% CI 1.75 to 3.23;	Overall, the risk of bias can be considered as acceptable. However, it should be noted that all studies were sponsored by pharmaceutical companies	1+ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				six studies, n=1.412; *I2*=60%) but showed a nonsignificant tendency in nausea (RR 1.27, 95% CI 0.90 to 1.78; six studies, n=1.412; *I2*=12%) and diarrhea (RR 1.45, 95% CI 0.94 to 2.24; 5 studies, n=1.258; *I2*=45%). The incidence of MNTX-related serious adverse events was 0.2% (4/1.860).		
Sridharan, J Pain Symptom Manage 2018 [245]	SR, Network-MA To compare available interventions for the treatment of opioid-induced constipation	Databases: Medline (through PubMed) and Cochrane CENTRAL, Until June 15, 2017. Design: RCTs Population: Patients from any medical conditions like cancer, arthritis, or orthopaedic surgeries and opioid-induced constipation	Interventions: pharmacological treatment of opioid-induced constipation Outcomes: 1.O: Number of patients with rescue-free bowel movements (RFBM) 2.O: - time for achieving RFBM - adverse events - changes in the analgesic activity of the opioid analgesics	Study number: SR (qualitative synthesis): 23 RCTs, MA (quantitative synthesis): 21 RCTs Population: mixed cancer and non-cancer population Interventions: lubiprostone, naloxegol, naldemedine, alvimopan, prucalopride, senna, oral, and s.c. methylnaltrexone Outcomes: All the interventions were observed to significantly improve the **RFBM** compared with placebo. S.c. methylnaltrexone has the highest odds ratio [95% Confidence Intervalls] among the interventions (Mixed treatment comparison estimates: 0.2 [0.1, 0.4] Naloxegol was observed with a shorter time (42 [68.68, 15.32]) hours than placebo, but not with methyl naltrexone (1.71 [28.72, 25.3]) hours	Review did not include EMBASE database Low or very low quality of evidence for the comparison (body of evidence)	1+ (body of evidence 1-)

7.5.2.3. Primärstudien

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Dropouts	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Ahmedzai, Palliative Medicine 2012 [246] *(included in SR of Candy et al. 2018)*	RCT, double blind Aim: to examine whether oxycodone/naloxone prolonged-release tablets (OXN PR) can improve constipation and maintain analgesia, compared with oxycodone prolonged-release tablets (OxyPR) in patients with moderate/ severe cancer pain.	n=184 Dropouts: n=51 Patients who needed to titrate up to oxycodone PR 120 mg/day and who regularly required two or more rescue doses of OxyIR were withdrawn from the study.	aged 18 years or older, with a diagnosis of **cancer** and a documented history of moderate/severe, chronic cancer pain, requiring round-the-clock opioid therapy (equivalent to OxyPR 20–80 mg/day at the start of the trial).	120 mg/day of **OXN PR** or **OxyPR** over 4 weeks Open-label oxycodone immediate-release capsules (OxyIR) were available to patients as rescue medication, up to a maximum of six doses per 24 h.	**1.O:** Efficacy assessments: • Bowel Function Index (BFI) • Brief Pain Inventory Short-Form (BPI-SF) **2.O:** • laxative use • rescue medication use. • Quality of life (QoL) • safety	**Efficacy**: Mean BFI score was significantly lower with OXN PR [ΔBFI= -11.14; 95% confidence interval [CI]: -19.03 to -3.24; p<0.01)] ; Mean BPI-SF scores were similar for both treatments. Mean total **laxative intake** was 20% lower with OXN PR [(26.10 [27.60] vs. 32.69 [31.26] mg, respectively), (p=0.17)]. The average rate of analgesic **rescue medication** use was low and comparable. **QoL** assessments were stable and comparable with greater improvements in constipation specific QoL assessments with OXN PR. Overall, rates of **adverse drug reactions** were similar.	computerized randomisation power: 80% double-blind primary analysis (superiority testing) of BFI was performed in an intention-to-treat manner on the full analysis II population. dropout-rate: 27%	1+

7.5.3. Behandlung oipoidbedingter ZNS-Symptome

7.5.3.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Stone, Pall Med, 2010 [247]	SR / no MA because of low-quality studies with multiple outcomes) Aim: to examine the management of opioid-induced central side effects.	26 studies (n = 432) ▪ 9 RCT ▪ 20 case series ▪ 3 case reports ▪ 2 uncontrolled prospective trials ▪ 3 retrospective case reviews ▪ 1 uncontrolled pilot study	Adult patients with chronic **cancer pain** and reported side effects	Efficacy of pharmacological treatment of opiod induced side effects.	1.O: ▪ Management of side effects o opiod use: sedation, cognitive impairment, myoclonus, hyperalgesia, insomnia 2.O: ▪ Safety	▪ **Management of side effects**: no recommendation for the use of any of the pharmacological interventions. ▪ The risk / benefit ratio was not reported	▪ Methodological limitations of most of the studies (missing data), resulting in a low quality ▪ Low statistical power ▪ Endpoints have not been well defined, sometimes two endpoints ▪ One study Included also non-adolescents	1+ Body of evidence SIGN: 1-

7.5.4. Verwendung von Opioiden bei Patienten mit Nierenversagen

7.5.4.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
King, Pall Med, 2011b [159]	SR (MA not possible) Aim: to identify and assess the quality of evidence for the safe and effective use of opioids for the relief of cancer pain in patients with renal impairment and to produce guidelines.	15 CTs, among them ▪ 8 prospective CTs ▪ 7 retrospective CTs	adult/older **cancer pain patients** (with moderate to severe pain) with **renal impairment and/or advanced cancer**	Opioid treatment in renal impairment (various opioids + routes) 8 prospective CTs ▪ oral or sc mo treatment (n=18 hospice inpatients) ▪ oral or continuous sc infusion (CSCI) mo (n=36 hospice pts) ▪ oral or parenteral mo (n=109 cancer pain service patients) ▪ oral mo (n=11 cancer pain patients) ▪ mo (n=300 chronic pain patients with cancer) ▪ mo (n=186 patients) ▪ pethidine (n=64 patients with neurological symptoms, 19 cancer pain patients) ▪ mo → oxycodone (n=27 patients, 9 with renal impairment) 7 retrospective CTs ▪ mo (n= 177 pts non-responsive to mo or with intolerable side effects) ▪ afentanil (n=4 patients diamorphone intolerance)	**1.O** **adverse events**/side effects (incl. renal and cognitive functining/impairment	**Adverse events** ▪ fentanyl, alfentanil and methadone seem to be the least likely to cause harm in patients with renal impairment ▪ morphine may be associated with toxicity cancer pain treatment with opioids in renal impairment primarily relies on pharmacokinetic data, extrapolation from non-cancer pain studies and clinical experience no CTs on treatment with diamorphine, codeine, dihydrocodeine, buprenorphine, tramadol, dextropropoxyphene, methadone in the respective data bases .	Very low empirical evidence (GRADE) relating to the use of morphine, alfentanil, pethindine, fentanyl, sulfentanil, oxycodone, hydromorphone (no RCTs available/MA not possible) study quality is limited due to high risk of methodological and publication bias Broad systematic review according to the Cochrane protocol GRADE approach to assess study quality No information on funding of included studies.	2++ Body of evidence SIGN: 3

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				▪ afentanil (n=48 hospital patients) ▪ fentanyl (n=53 hospital palliative care patients) ▪ sufentanil (n= 48 hospital palliative care patient) ▪ hydromo (n=45 pain patients, 26 with renal impairment) ▪ codeine, mo, diamorphone, oxy or combination of opiods (n=40 patients with chronic kidney disease CKD, among them 34 cancer patients)				

7.6. Nicht-Opioide

7.6.1. Verschiedene Medikamentenklassen: Aktualisierung 2019

7.6.1.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Schüchen, J Cachexia Sarcopenia Muscle 2018 [248]	SR, MA To analyse the efficacy, tolerability, and safety of non-opioids in palliative care patients	Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, and EMBASE from inception to 18 February 2018 Design: double blinded RCTs Population: adult palliative patients (any diagnosis)	Interventions: Non-opioid analgesics at any dose, using any application route Outcomes: pain intensity, opioid-sparing effects, safety, and quality of life	Study number: 43 RCTs (n= 2925); 24 RCTs in meta-analyses Study quality: Most RCTs were of medium quality; 4 high quality RCTs Population: cancer only Outcomes: **Acetaminophen** + opioid step III (6 RCTs) or step II (1 RCT): - Pain relief: n.s. in 4 RCTs, sign. relief in 2 RCTs - QoL: not increased with acetaminophen ➔ No convincing evidence for the analgesic efficacy of acetaminophen in cancer pain **Dipyrone** (2 RCTs): cf. evidence table, chapter 7.6.2.1. ➔ can be recommended alone or in combination with opioids - QoL: n.s. increase compared with placebo **Flupirtine** (2 RCTs): - vs Tramadol: Pain relief: n.s. difference between groups; relief in both groups - vs. Pentazocine: Pain relief: sign. higher for flupirtine (p<0.05)	Method: Well conducted systematic review of double blinded RCTs Content Low to moderate QoL (most small sample size)	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				➔ evidence of moderate quality for a satisfactory pain relief in cancer by flupirtine **NSAID:** - + **opoid step III** (6 RCTs): o Pain relief: sign. higher pain relief in NSAID+opioid group in 3 RCTs, n.s. difference in 2 RCTs, sign. reduction of narcotics use in 2 RCTs o Withdrawals due to inadequate pain relief (MA with 4 RCTs): RD 0.00 (95% CI -0.06 to 0.06) o AE: n.s. difference o Withdrawal due to AE (MA with 3 RCTs): RD 0.00 (95% CI -0.06 to 0.06) o Number of patients with AE (MA with 2 RCTs): RD 0.00 (95% CI -0.16 to 0.16) - + **opioid step II** vs. NSAID (2 RCTs): o Pain relief: sign. higer pain relief in NSAID+weak opioid group in 2 RCTs, n.s. difference in 2 RCTs ➔ no substantial evidence for a clear superiority of the combined treatment o AE: more AE in NSAID+opioid in 2 RCTs, no difference in 2 RCTs - **vs. opioid** (7 RCTs) : o Pain relief: moderate quality of evidence for a similar pain reduction by NSAIDs in the usual dosage range compared with up to 15 mg of morphine or opioids of equianalgesic potency o Withdrawals due to inadequate pain relief (MA with 4 RCTs):: RD 0.09 (95% CI -0.02 to 0.21) o AE: lower rate of side effects for NSAID. Symptoms like drowsiness, nausea, and vomiting were more commonly reported		

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				in the opioid groups. The NSAID groups also experienced a lower dropout rate because of adverse events (p<0.00001, RD -0.26, 95% CI -0.36 to -0.16) ○ Withdrawal due to AE (MA with 4 RCTs): RD -0.26, 95% CI -0.36 to -0.16) in favour of NSAID ○ Number of patients with AE (MA with 3 RCTs): RD -0.19 (95% CI -0.27 to -0.11) in favour of NSAID - **vs. placebo or other analgesics** (20 RCTs): ○ Pain relief: no evidence for a superiority of one specific NSAID - **vs. COX-2 inhibitors** (2 RCTs): ○ Pain relief: no evidence for a superiority of NSAID vs. COX-2-Inh.		

7.6.2. Metamizol

7.6.2.1. Primärstudien

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
Duarte Souza, Support	RCT Double-blinded	34 Intention to treat	**Ambulatory cancer pts.**	1.Morphine 6x10 mg p.o. + placebo	1.O: Pain scores (VAS 0-10) at entry, 48 and 96 hrs.	• **Pain scores** at baseline Mo+placebo: 7.31±0.29	The only study administrating dipyrone as co-medication to	1-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
Care Cancer 2007 [249]	Cross-over Placebo controlled	1 patient taking paracetamol+codeine during the study was not excluded	Presence of cancer pain for which analgesia with morphine was indicated. Exclusion criteria: Neuropathic pain, renal, hepatic failure, jaundice, additional analgesic comedication	2.Morphine 6x10 mg p.o. + dipyrone 4x500 mg Crossover after 48 hrs Telephone interview at 48 hrs and 96 hrs.	2.O: • Preference of dipyrone versus placebo versus indifferent • Toxicities (not mentioned in the methods)	Mo+ dipyrone: 6.88±0.28 (p=0.03) 48 hrs Mo+placebo: 7.06±0.32 Mo+ dipyrone:5.5±0.31 (p=0.001) 96 hrs Mo+placebo: 3.18±0.39 Mo+dipyrone: 1.94±0.37 (p=0.03) Dipyrone significantly adds to the analgesic effect of morphine. Pain control was still improved after 96 hrs after switch from dipy. to placebo. • **Preference** Dipyrone 28 pts. (85%) Placebo 4 pts. No preference 2 pts. (p<0.001) • **Toxicities** 48 hrs: n (%) Mo+placebo: 9 (56.2%) Mo+dipyrone: 7 (38.9%) 96 hrs: n (%) Mo+placebo: 15 (93.7%) Mo+dipyrone: 16 (88.9%) No agranulocytosis	morphine. The comedication to an opioid is the standard situation in clinical palliative care practice Randomisation: how? Power analysis? The significant results were only possible due to the low SD. Evaluation only by telephone interview Imbalance in pts. Characteristics Mo+placebo: higher proportion of visceral pain (p=0.02) Mo+dipyrone: higher proportion of bone pain (p=0.02) Higher proportion of pts. who had not yet received oncological treatment (p=0.04)	
Rodriguez, Eur J Cancer 1994 [250]	RCT double-blinded parallel multi-center	149 pts. eligible, 121 analyzed Dropouts not mentioned, maybe these were 7 pts	**Pts. suffering from cancer pain** VAS ≥70 mm Karnofsky performance index >30% Exclusion criteria: Brain –, liver metastasis	1. Dipyrone 3x1g oral + 3x placebo 2. Dipyrone 3x2 g oral + 3x placebo 3. Morphine 6x10 mg oral for 7 days	1.O: Degree of pain relief on VAS 0-100 2.O: • Number of pts. who decided to increase the dose on day	1.O: all groups had significant improvement in **cancer pain** But less pain relieve in dipyrone 1g compared to dipyrone 2g (p<0.05) + morphine (0.01)	Participating centers not mentioned, probably the institutions where the authors come from. Power analysis. No information about blinding procedure /	1-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			Gastric disorders, insufficient mental status, adjuvant therapy at the time of entering the study, radiotherapy or chemotherapy within 15 days prior to study	dose escalation possible on day 4 rescue medication paracetamol+codeine	• Grading of "tolerance" as excellent/ good on day 7 by pts. and observers • Side effects not mentioned in the methods but described I n the results	2.O: • No difference in number of pts. who decided to increase the dose Dipyrone 1g: 17/31 (55%) Dipyrone 2g: 11/27 (41%) Morphine: 12/35 (35%) • Excellent / good tolerance graded by pts. / observers Dipyrone 1g: 77% / 77% Dipyrone 2g: 46% / 47% Morphine 62% / 62% • **Side effects** Dipyrone 1g: 52 side effects in 27 pts. Dipyrone 2 g: 63 bin 25 pts. Morphine: 92 in 34 pts. n.s. more severe side effects in the morphine group (21) than in dipyrone 1g (7) or dipyrone 2 g (14)	appearance of medication. Seems to be liquid. No information on placebo. The taste of drugs allows unblinding. Dugs prepared by whom? Physicians are not explicitly mentioned as blinded. Who were the "observers"? = physicians? Or other persons, who were blinded? Definition of tolerance? In the results al lot of further comparisons between groups are preformed (e.g. grading of efficacy by pts. and observers) which have not been introduced in the method section. Statistics: Correction for multiple testing not mentioned. Investigation of 3 g dipyrone /d does not make much sense (underdosing). It is clear that this cannot be equianalgesic to 60 mg morphine/ day.	
Yalçin,	Cohort study Not randomised	50 pts. 25 per group No dropouts	**Cancer patients experiencing severe pain**.	1. 4x10 mg Ketorolac oral	Not explicitly mentioned; according to the methods:	1.O: Significant decrease in **VAS** scores in both	No ethics approval mentioned,	2-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evi-dence SIGN
Acta Oncologica 1997 [251]	Not blinded Not controlled		Inclusion criteria: no regular analgesic treat-ment before Exclusion criteria: significant impairement of brain, liver, kidney lung	2. 3 x 500 mg dipyrone oral	1.O: decrease in pain scores after 2 days compared to worst pain score for 24 hours before start of the study 2.O: number of patients with complete pain relief, incomplete relief and no benefit	groups with no difference between groups. (p<0.05) 2.O: **Complete pain relief** ketorolac n=13, dipyrone n=4 (p<0.05). **Partial** relief ketoroloac n=7, dipyrone n=17. **No** relief ketorolac n=5, dipyrone n=4	No (written) informed consent mentioned No blinding, no randomisation, No statement whether it was a prospective study No power analysis Ketoroloac not available in Germany (due to severe side effects). Metamizol dose only 1.5 g/d No differentiation pain at rest / movement	
Yalçin, Am J Clin Oncol 1998 [252]	RCT not blinded cross-over	50 pts. included 3 dropouts (1 died, 2 lost to follow-up)	**14 different kind of cancer**, e.g. breast, lung, colorectal, stomach ca; Inclusion criteria: VAS score >5 - No history of long-term analgesic use -ECOG 0,1 or 2 Exclusion criteria: renal or liver impairement, GI malabsorption, hemorrhagic diathesis, intracranial metastasis, active peptic ulcer	1. Dipyrone 3 x 500 mg oral 2. Diflunisal 2 x 500 mg oral Both for 1 week followed by 1 day washout, then cross-over to the other drug for 1 week.	Not explicitly mentioned; 1.0 Decrease in pain scores after 7 days of treatment in the whole group and in subgroups with no metastasis, metastasis and bone metastasis 2.0 Side effects	1.O: **Reduction in VAS** scores: Diflunisal by a mean of 4.65 ± 3.10dipyrone by a mean of 3.25 ± 2.85 ($p < 0.001$) VAS scores in subgroups Pts. with no metastasis no difference, pts. with metastasis no difference, patients with bone metastasis diflunisal: VAS after treatment 5.0±3.9, dipyrone 6.2±3.3; p=0.045 2.O: **Adverse events** Dipyrone 14.8% Diflunisal 17.02% n.s. In no pat. drug withdrawal necessary.	No ethics approval mentioned, No (written) informed consent mentioned No information on randomisation No power analysis No correction for multiple testing Only localization of pain described (extremities, abdomen, face etc.) no characterization of pain (e.g. visceral, neuropathic, bone) Diflunisal not available in Germany Metamizol dose only 1.5 g/d	1-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evi-dence SIGN
							No differentiation pain at rest - movement/ breakthrough pain	

7.6.3. NSAR und Paracetamol als Ergänzung zu Stufe-III-Opioiden

7.6.3.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Nabal, Pall Med, 2011 [253]	SR / no MA due to differences in NSAIDs molecules employed, paracetamol dosages (3–5 g/day), and the different follow-up periods Aim: To perform a systematic literature review of the evidence of the efficacy and toxicity of	7 studies for NSAID (n = 200) ▪ 9 double-blind cross over (n = 150) ▪ Open parallel study (n = 50) 5 studies for paracetamol (n = 200) ▪ 3 double-blind cross over (n = 107)	Adult patients with moderate to severe pain **cancer pain**	Efficacy and safety of NSAID and paracetamol added to step III WHO opioid treatment for cancer pain ds	1.O: ▪ Efficacy of pain modification 2.O: ▪ Safety	▪ **Pain modification**: weak recommendation for the use of NSAID in addition to opioids in WHO ladder step III regimen. ▪ No evidence for the use of paracetamol. ▪ The risk / benefit ratio was considered low.	▪ Methodological limitations of most of the studies (bias, missing data), resulting in a low quality ▪ Low statistical power ▪ Opioid-naive and non-naive patients were evaluated	1+ Body of evidence SIGN: 1-

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	NSAIDs or paracetamol added to WHO Step III opioid treatment for cancer pain.	▪ 2 double-blind (n = 93)						

7.7. Adjuvanzien bei neuropathischen Schmerzen (Antidepressiva und Antikonvulsiva)

7.7.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Bennett, Pall Med 2011 [254]	SR (MA not possible) Aim: to determine the effectiveness of antiepileptics when added to opioids, compared to opioids alone, for the management of pain caused directly by cancer	8 studies ▪ 5 RCTs ▪ 3 BAs (Observational Before-After Studies)	In total 465 adult **cancer patients** with chronic **moderate to severe (neuropathic) pain**, 370 (79.5%) completed the study period (almost non naïve) RCTs included 354 patient (of whom over 80% completed the study period)	Opioid + antiepileptic or antidepressant adjuvants (Gabapentin, Imipramine, Phenytoin) 5 RCT Opioid + adjuvant vs. Opioid alone (2 RCTs) ▪ 1st Arm: Opioid + Gabapentin (1),Imipramine (1) ▪ 2nd Arm: Opioid alone Opioid + adjuvant vs. Opioid + placebo (2 RCTs) ▪ 1st Arm: Opioid + Gabapentin (1), Amitriptyline (1) ▪ 2nd Arm: Opioid + Placebo Opioid + adjuvant vs. Adjuvant alone vs. Opioid alone (1 RCT) ▪ 1st Arm: Opioid + Phenytoin ▪ 2nd Arm: Phenytoin alone ▪ 3rd Arm: Opioid alone 3 BAs	Mainly 1.O: ▪ **Pain modification**/relief (effectiveness) (5 studies) 2.O: ▪ **Adverse events /Side effects** (4 Studies) 3 Studies 1.O: ▪ **Adverse events /Side effects** (In 3 RCTs pain relief and in 1 RCT adverse events not reported)	**Pain modification/relief** ▪ adjuvants improve pain control within 4–8 days when added to opioids for cancer pain (strongest evidence for gabapentin) ▪ overall, the effect size was much less than reported for patients with non-cancer neuropathic pain (unlikely reduction in pain intensity of greater than 1 point on a 0–10/NRS) **Adverse events:** increase likely	MA not possible, due to clinical and methodological heterogeneity Methodological limitation of included studies: ▪ bias/confounding factors, i.e. loss to follow up, opioid dose variation between and within studies, study duration ▪ in 3 RCTs pain intensity/relief and in 1 RCT adverse events not reported ▪ studies on various adjuvants commonly used in non-cancer neuropathic pain are missing (i.e. pregabalin, nortriptyline, duloxetine) No info. on search strategy or on funding of the included studies; no quality assessment reported	1+ Body of evidence SIGN: 1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				▪ Opioid + Gabapentin (2) ▪ Opioid + Sodium valproate (1)				

7.7.2. Primärstudie

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Mishra, Am J Hosp Palliat Med 2011 [255]	Double-blind, placebo-controlled RCT Aim: to evaluate comparative clinical efficacy of pregabaline with amitriptyline and pregabaline in neuropathic cancer pain	n=120	Patients with cancer and severe **neuropathic cancer pain**	• 1st arm: amitriptyline (AT) – 50mg/d (1st week), 75 mg/d (2nd week), 100mg/d (3rd week) • 2nd arm: gabapentine (GB) – 900 mg/d), 1200 mg/d (2nd week), 1800 mg/d (3rd week) • 3rd arm: pregabaline (PG) - 150 mg/d), 300 mg/d (2nd week), 600 mg/d (3rd week) • 4th arm: placebo (PL) • 30 patients each group	1.O.: Level of pain with Visual Analogue Scale (VAS 0-100) daily (ratings averaged over 7 days, i.e. results calculated once a week over 4 weeks) 2.O.: • Intensity of lancinating, dysesthesia, burning (NRS 0-10) • Global Satisfaction Scores (GSS) • Functional capacity (ECOG) • Adverse effects (AEs) (mild, moderate, severe) • morphine-sparing effect (% patients requiring	**Pain intensity**: • Sign. decrease in mean VAS value in all 4 groups as compared to baseline. In all 4 groups, VAS sign. less in every visit as compared to previous visit. • PG: visit 3: mean VAS in group PG sign. less than in group AT (p=.003) and group PL (p=.024). Visit 4: mean VAS in group PG sign. less than in GB (p=.042). **Mo-sparing effect:** • PL: 100% of pts requiring mo in visits 2-4	No drop outs (or not described?) No sample size calculation Mo-sparing effect not described in 4th visit for PG. Data unclear. Nevertheless, the authors conclude that morphine-sparing effect is statistically and clinically significant with PG	1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
				• Oral morphine was used for rescue analgesic for continued pain • 4 weeks study period (4 visits)	rescue morphine) – not described in protocole as outcome but measured	• Visit 3: AT 46.7%; GB 23.3%; PG 16.7%; PL 100% > all study drugs have mo-sparing effect • Mo. needs increased in AT and GB between visit 2 and visit 4. • PG: mo increment was minimum between visit 2 and visit 3. Mo needs in visit 4 not described. **Burning, lancinating pain, dysesthesia:** PL: Sign. higher reduction in burning, lancinating pain, and dysesthesia than in GB, AT and PL **ECOG-GSS:** max. improvement in PG group		

7.8. Opioide bei Schmerzexazerbation und Durchbruchschmerzen

7.8.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Zeppetella, Pall Med 2011 [256]	SR (MA for transmucosal fentanyl) Aim: to determine the evidence for the utility of opioids in the management of breakthrough pain in patients with cancer.	8 RCTs	adult patients with **cancer** and **breakthrough pain** in any setting	Oral transmucosal fentanyl citrate (OTFC): ▪ 2 RCTs: Dose titration ▪ 3 RCTs: OTFC vs placebo (1), normal release Mo (1) or Mo iv (1) Fentanyl buccal tablet (FBT): ▪ 2 RCTs: FBT vs placebo and dose titration Intranasal fentanyl spray (INFS): ▪ 1 RCT: INFS vs placebo and dose titration	▪ Reduction in pain intensity ▪ Adverse effects (AEs) ▪ Patient's satisfaction	▪ **Reduction in pain intensity**: Most studies reported the utility of transmucosal fentanyl products and confirmed their efficacy, safety, and tolerability provided that they are first titrated to a successful dose in the individual patients already using opioids as ATC medication. One study demonstrated the utility of parenteral morphine and its faster onset of action compared with transmucosal fentanyl. ▪ **Meta-analysis** (Weighted mean difference=WMD (95%CI) in pain intensity): 1) at 10 min. following transmucosal fentanyl or comparator: WMD =0.51 (0.91 to 1.65); 2) at 15 min following transmucosal fentanyl or comparator: WMD =0.52 (0.33 to 0.70); 3) at 15 min following OTFC or Mo iv: WMD=0.80 (0.64 to 0.96)	Good quality of the included studies. Most industry sponsored	1+ (no details to study quality assessment) Body of evidence SIGN: 1+; for timing: 1-

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						▪ **AEs:** generally mild and tolerable. Serious adverse events were commonly considered to be related to underlying conditions. All patients were also taking concomitant ATC opioids, thus it was not possible to definitively separate the effects of transmucosal opioids alone.		
Zeppetella, Cochrane 2013 [257]	SR and MA Aim: update of a Cochrane Review (Issue 1, 2006) To determine the efficacy of opioid analgesics given by any route, used for the management of breakthrough pain in patients with cancer, and to identify and quantify, if data permitted, any adverse effects of this treatment	15 trials (1699 paticipants)	1699 cancer patients and BTP in any setting. Patients (both male and female) of all ages who were treated with opioids for cancer pain.	**Opioid analgesics** vs. placebo or other opioids, or both, or other active controls regardless of the dose (single or multiple doses) or mode of administration for the relief of BTP. All studies reported on the utility of seven different transmucosal fentanyl formulations, 5 of which were administered orally and 2 nasally. 8 studies compared transmucosal fentanyl vs. placebo, 4 studies compared them with another opioid, 1 study was a comparison of different doses of the same formulation and two were randomised titration studies.	1. O: • Patient-reported pain • AE 2. O: • rescue analgesia • patient preference in the analysis	Oral and nasal transmucosal fentanyl formulations were an effective treatment for breakthrough pain. When compared with placebo (6 studies: Pain Intensity Difference (PID): 0.39 [0.27, 0.52] or oral morphine (2 studies: PID: 0.37 [0.00, 0.73]), participants gave lower pain intensity and higher pain relief scores for transmucosal fentanyl formulations at all time points. Global assessment scores also favoured transmucosal fentanyl preparations. One study compared intravenous with the transmucosal route and both were effective.	No change to conclusions in this update; 11 new studies were identified through the updated search with 1306 participants. The RCT literature for the management of breakthrough pain is relatively small. Most identified studies were industry sponsored and undertaken for registration of either oral or nasal transmucosal opioids specifically developed for the management of BTP. Two studies were judged at a high risk of bias because of a small size.	1++

8. Fatigue

8.1. Nicht-medikamentöse Verfahren

8.1.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Dittus, Prev Med 2017 [258]	SR; to identify characteristics and benefits of exercise interventions for individuals with advanced cancer with an emphasis on evaluating aerobic fitness, strength, physical function, fatigue, and QOL	- Databases: PubMed, OvidMedline and CINHAL until March 2017 - Design: RCTs, single-arm pre/post interventions, pragmatic studies and prospective cohort studies - Population: patients with **advances cancer** (at least 1/3 of the sample population with advanced cancer)	Intervention: intervention with a component of **exercise** Outcomes: - parameters of physical capacity including aerobic fitness, strength and standard measures of physical function (defined as the ability to complete activities required for independent living - fatigue - overall QoL	Study number: 26 studies, n=2053 (14 RCTs, 10 single-arm pre-post observational studies, 3 descriptive) Interventions: Aerobic capacity (19 studies), strength (12 studies) Outcome **fatigue** (19 studies): Improvement in 11 of 19 studies (45% of total participants reported improvement); - Results for RCTs: 3 RCTs with sign. improvement of fatigue, 1 RCT with sign. slower worsening of fatigue, 6 RCTs with no sign. results. - Results for pre-post-studies: overall sign. improvement of fatigue.	Content: RCT trials did not clearly identify improved fatigue with exercise interventions compared to controls Methods: - No quality assessement of included studies	1- (Body of evidence: not statable)
Mochamat (personal communication)	SR; To evaluate the efficacy of non-pharmacological treatments for fatigue in advanced disease associated with palliative care	- Databases: CENTRAL, MEDLINE, PsycINFO, PubMed, and a selection of journals from inception to March 31st 2017 - Design: RCTs - Population: Palliative care patients ≥ 18, both sexes, with fatigue, suffering from chronic progressive diseases (advanced cancer, HIV/AIDS, multiple sclerosis,	Interventions: - Physical exercise - Energy restoration - Psycho-educational therapy Outcomes: -	Study number: 13 RCTs (9 cancer, 2 ALS, 1 ESRD, 1 cirrhosis) Outcomes: - Primary O.: Patient reported fatigue, improvement of fatigue intensity by 33%, related to the assessment instrument	Precise description of risk of bias assessment for each study. Most studies had relatively small number of participant (only 4 studies > 100; total number of participants included in the	1+ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
		amyotrophic lateral sclerosis, cardiac, lung or kidney failure in advanced stage - Exclusion criteria: Studies comparing different types of cancer-modifying treatment and its effect on the prognosis and quality of life, studies not focusing on non-pharmacological treatment, studies using dietary treatment		- Secondary O.: Asthenia, weakness, tiredness, exhaustion, treatment-related burden Physical exercise (9 RCTs): 2 ALS, 1 cirrhosis, 5 various cancer types, 1 lung or colorectal cancer • Various cancer types: 618 patients - 4 of 5 studies reported a statistically significant positive correlation between change in aerobic performance and fatigue (Largest study (n=269): Estimated improvement in intervention group = −6.6 points (95% confidence interval −12.3 to −0.9, p=0.02; effect size=0.33, CI: 0.04 to 0.6 (EORTC QLQ-C30); Intervention: Supervised exercise comprising high intensity cardiovascular and resistance training, relaxation and body awareness training, massage, nine hours weekly for six weeks in addition to conventional care; Second-largest study (n=231): no significant difference between control and intervention group; Intervention: sixty minutes twice a week physical exercise for 8 weeks) • Lung or colorectal cancer: 66 patients used home-based exercise programs – intervention group demonstrated significantly improved levels of fatigue (p = 0.02) compared to control group (I:4.46 ± 8.65 vs. C:−0.79 ±9.11, p=0.03) • Cirrhosis: 19 patients received exercise training 3 days a week for 8 weeks - fatigue symptoms were significantly improved in the EG compared to the CG (4.64	analysis= 1101). Detection bias of the included studies was rated as relatively poor. Low risk of selection and attrition bias. Inconclusive findings: differences in data reporting, heterogeneous populations, inconsistent symptom assessment (the use of instrument differed greatly) and a consistent definition for a clinically significant reduction in fatigue was missing. Also mode, intensity, and time of exercise differed across the studies. 4 studies used a single-item fatigue assessment	

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				± 1.52 vs. 5.62 ± 0.71, p = 0.03 compared to 4.88±1.12 vs. 4.93 ± 0.93,p = 0.84) • ALS: 52 patients in exercise-therapy evaluated after 6 months - no statistically significant change in the absolute fatigue assessment <u>Energy restoration (1 RCT)</u>: End-stage renal disease (ESRD) - 37 patients performed yoga 30 min/day twice a week for 3 months – significant improvements in the fatigue score (−55%; p = 0.008) <u>Psycho-educational therapy (3 RCTs)</u>: 1 lung cancer, 1 unspecified cancer, 1 breast cancer • Lung cancer: 140 patients – fatigue significantly improved after 12 weeks of psycho-educational intervention (p= 0.011) in the pattern of change in fatigue, with a small effect size (partial eta-squared = 0.033). (I: 3.80 ±2.64 to 3.25± 2.79 vs. C: 4.43±2.84 to 3.97±2.82) • Unspecified cancer: 124 patients - significant relieve in severity of symptoms after cognitive-behavioral intervention; no symptom-specific details • Breast cancer: 45 patients with cognitive therapy over eight weekly sessions - change in the Multidimensional Fatigue Inventory superior in the EG compared to CG (3.29, SE 0.10 vs. 2.94, SE 0.11, p = 0.01)		

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Payne, Cochrane 2012 [259]	SR; To conduct an overview of the evidence available on the efficacy of interventions used in themanagement of fatigue and/or unintentional weight loss in adults with advanced progressive illness	- Databases: Cochrane Database of Systematic Reviews (CDSR); until 2010 - Design: Cochrane Reviews - Population: Adults 18 years or older with an **advanced progressive illness** known to have clinically significant fatigue and/or weight loss in the latter stages of illness	Interventions: intervention on fatigue and/or unintentional weight loss Primary outcomes: - Clinically significant improvements in fatigue and/or unintentional weight loss - Improvements in QoL - Withdrawals due to adverse events	Studies: 27 systematic reviews (302 studies with 31,833 participants Quality: high methodological quality in all but 1 SR Results for **fatigue** by cancer patients, non-pharmacological interventions: - 3 SR (60 studies, n=6459) - Exercise (1 SR): no specific data available for advanced cancer - Breast care nurse management strategies (1 SR): fatigue not assessed as an independent outcome - Psychosocial interventions (1 SR): insufficient evidence supporting the efficacy of the interventions (7 out of 27 studies reported improvement in fatigue); interventions specifically focused on fatigue were more likely to show positive fatigue outcomes. Poor quality of included studies (Results for pharmacological interventions: see chapter “Pharmacological treatment of fatigue”)	Well conducted SR	1++ (Body of evidence: 1-)
Poort, Cochrane 2017 [260]	SR/MA; To assess the effects of psychosocial interventions for fatigue in adult patients with incurable cancer receiving cancer treatment with palliative intent	- Databases: CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, and seven clinical trial registries; handsearch; until Nov. 2016 - Design: RCTs - Population: adults aged 18 years or over undergoing cancer treatment with palliative intent for **incurable cancer** (sample with at	Interventions: **Psychosocial interventions** defined as various kinds of interventions provided to influence or change cognitions, emotions, behaviours, social interactions, or a combination of these	Study number: 14 RCTs, n=3077 Quality of studies: very low quality, small studies Interventions: broad spectrum, different aims and duration Results of meta-analysis:	Well conducted SR; overall quality of evidence for primary and secondary outcomes was very low. Therefore, we have very little confidence in the effect estimate	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
		least 80% of patients with incurable cancer)	Outcomes: 1.O: Fatigue post intervention 2.O: - Fatigue (first and second follow-up) - Social functioning - Role functioning (post intervention) - Emotional functioning (post intervention) - Cognitive functioning (post intervention) - Adverse events	- **Fatigue post-intervention** (12 RCTs, n=535): n.s. (SMD: -0.25, 95% -CI: -0.50 to 0.00) - **Fatigue first follow-up** (4 RCTs,n=147): sign. improved (SMD -0.66, 95% CI -1.00 to -0.32) - **Fatigue second follow-up:** n.s. - **Physical functioning** (7 RCTs, n=307): sign. improved (SMD 0.32, 95% CI 0.01 to 0.63) - **Social, role, cognitive or emotional functioning** (2 to 4 RCTs, n=86 to 143): n.s. - **AE** (3 RCTs): no difference between groups		

8.1.2. Primärstudien

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Warth, Dtsch Arztebl Int 2015 [261]	RCT; examined whether relaxation interventions as part of music therapy could be effective for	I/C: n=42/42; Drop-outs: n=4/12)	Patients receiving **palliative care**	- I: relaxation exercise conducted by trained music therapists, involving voice as well as music played live on a monochord - C: excerpt from the Mindfulness-	1.O: - Relaxation (VAS 1-10) - Well-being (VAS 1-10) - Pain (VAS 1-10) 2.O: - Heart rate variability (photoplethysmography)	- **Relaxation**: sign. improved (F = 13.7; p <0.001) - **Well-being**: sign. improved (F = 6.41; p = 0.01) - **high-frequency oscillations** of the heart	- Sample size did not reached the treshhold for statistical power of (1-β) = .80 - No blinding (except blinding to the study hypotheses)	1-

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
	patients in palliative care			Based Stress Reduction Program, played through headphones, with o musical content or therapeutic relationship two 30-minute sessions were given 2 days apart	- blood volume pulse amplitude (BVP-A) - QoL (EORTC QLQ-C15-PAL) - Fatigue (subscale of EORTC QLQ-C15-PAL)	rate: sign. increased (F = 8.13; p= 0.01). - **fatigue** score on the quality-of-life scale: sign. decreased (F = 4.74; p = 0.03). - **Pain, overall QoL, BVP-A**: n.s.	- ITT - Adequate randomisation - Results were tested for robustness in sensitivity analyses (complete case analysis, CCA): According to CCA, the effect on fatigue failed to reach statistical significance (p = 0.07).	
Pyszora, Support Care Cancer 2017 [262]	RCT; to evaluate the effect of a physiotherapy programme on CRF and other symptoms in patients diagnosed with advanced cancer.	I/C: n=30/30; Drop-outs: n=1/1	Adult patients with: - diagnosis of **advanced cancer** - intensity of fatigue ≥4 in a 10-point NRS obtained - survival expectancy of a month at the very least Exclusion: - anaemia - comorbidities causing fatigue	- I: physiotherapy program: active exercises of the upper and lower limbs, myofascial release and proprioceptive neuromuscular facilitation; 30-min sessions, 3 times a week for 2 weeks - C: no exercise	1.O: severity of fatigue (BFI, Brief Fatigue Inventory, on NRS 0-10) and of sympotoms (ESAS, on NRS 0-10) 2.O: patient satisfaction (satisfaction score -3 to +3)	**Severity of fatigue**: - BFI: sign. reduction of fatigue in intervention group; no sign. change in control group. No numerical data reported. - ESAS: sign. lower (4.6 ± 1.6 vs. 6.3 ± 1.2, p<0.01) **Other sympt. (**ESAS): - Drowsiness: 2.3±2.1 vs. 2.5±2.5, p<0.05 - Well-being: 3.0±1.2 vs. 5.0±1.3, p<0.01 - Other symptoms: n.s. in between-group comparision **Satisfaction**: Mean = 1.6±0.8	- Baseline: sign. more female patients at baseline in control group - Powered despite small patients' collective - No blinding	1-

8.2. Medikamentöse Therapie

Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Mücke, Cochrane 2015 [263]	SR, MA; to evaluate the efficacy of pharmacological treatments for fatigue in palliative care, with a focus on patients at an advanced stage of disease	Databases: CENTRAL (Cochrane Library), MEDLINE, PsycInfo (up to 2014); handsearch Design: RCTs Population: adult palliative care patients with fatigue and estimated life expectancy of 6 month or less (cancer and other chronic diseases)	Interventions: psychostimulants (amphetamines, modafinil, armodafinil, methylphenidate, pemoline), amantadine, corticosteroids (dexamethasone, prednisone, methylprednisolone), donepezil, antidepressants such as selective serotonin reuptake inhibitors (SSRIs; paroxetine), acetylsalicylic acid, megestrol acetate, alfacalcidol and acetyl-L-carnitine. Outcomes: - 1.O: Patient-reported fatigue; improvement of fatigue - 2.O: asthenia, weakness, tiredness, exhaustion, treatment related-burden	Study number: 45 RCTs, 18 drugs analysed Population: n=4.696; study number according to disease:18 cancer, 1 ALS, 1 ESRD, 13 multiple sclerosis, 9 HIV/ AIDS, 1 multi-type advanced disease (hospice patient), 1end-stage COPD Methylphenidate: - Cancer-related fatigue (Metanalysis= MA of 2 RCTs): estimated superior effect: SMD 0.49, 95% CI 0.15-0.83 - HIV-related fatigue (no MA, 1 small RCT): sign. effect Acetylsalicylic acid (2 RCTs, no MA): Multiple sclerosis (MS)-related fatigue: sign. effect Acetyl-L-carnitine (no MA): sign. effect in 1 (end-stage renal disease) out of 4 RCTs (3 with MS patients) Alfacalcidol (1 RCT, MS): sign. effect Amantadine (7 RCTs, no MA): MS-related fatigue: tendency towards improved outcomes Armodafinil (1 RCT, HIV): response rate 75% (to placebo: 26%) Dexamethasone (1 RCT, **cancer**): sign. effect Dextroamphetamine (1 RCT **cancer**; 1 RCT HIV): n.s. Donepezil (1 RCT, **cancer**): n.s. Fluoxetine (1 RCT MS): n.s. Medroxyprogesterone (1 RCT, cancer): n.s.	- Overall, this review demonstrates a lack of evidence rather than a lack of efficacy of the interventions. - high degree of statistical and clinical heterogeneity in the trials - no consensus on threshold values for relief of fatigue or on criteria for the responder - potential bias in the included studies	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				Megestrol acetate (1 RCT, **cancer**): n.s.; lack strong evidence Methylprednisolone (1 big RCT, n=403, **cancer**): sign. effect Mistletoe extract (1 RCT, **cancer**): sign. effect; lack strong evidence Modafinil: - Multiple sclerosis-related fatigue (MA of 2 RCTs): no superior effect - **Cancer**-related fatigue (no MA; 2 RCTs): sign. and n.s. (unconsistant) Paroxetine (1 big RCT **cancer**; 1 small RCT COPD): n.s. Pemoline: - Multiple sclerosis-related fatigue (MA of 2 RCTs): no superior effect - HIV-related fatigue (no MA; 1 small RCT): sign. effect Testosteone (3 RCTs, HIV): n.s.; lack strong evidence Adverse reactions: in general mild and with little or no impact		
Payne, Cochrane 2012 [259]	SR; To conduct an overview of the evidence available on the efficacy of interventions used in themanagement of fatigue and/or unintentional weight loss in adults with advanced progressive illness	- Databases: Cochrane Database of Systematic Reviews (CDSR); until 2010 - Design: Cochrane Reviews - Population: Adults 18 years or older with an **advanced progressive illness** known to have clinically significant fatigue and/or weight loss in the latter stages of illness	Interventions: intervention on fatigue and/or unintentional weight loss Primary outcomes: - Clinically significant improvements in fatigue and/or unintentional weight loss - Improvements in QoL	Studies: 27 systematic reviews (302 studies with 31,833 participants Quality: high methodological quality in all but 1 SR Results for **fatigue** by cancer patients, pharmacological interventions: - 2 SR (56 studies, n=10,883) - EPA (eicosapentaenoic acid) vs. placebo (1 SR): authors of the review were unable to	Well conducted SR	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
			- Withdrawals due to adverse events	perform a meta-review on fatigue outcomes. - Methylphenidate (1 SR): small but significant improvement in fatigue over placebo - Paroxetine: no benefit over placebo (results not limited to participants in the advanced cancer) - Progestational steroids: no benefit over placebo (results not limited to participants in the advanced cancer) (Results for non-pharmacological interventions: see chapter "Non-Pharmacological treatment of fatigue")		
Thiem, Schmerz 2012 [264]	SR; To evaluate the efficacy of glucocorticoids and androgens in the treatment of fatigue by palliative care patients	- Databases: PubMed, Embase and Cochrane until August 2011 - Design: studies with original data - Population: palliative patients	Intervention: - Glucocorticoids - androgens Outcomes: Fatigue, asthenia, sedation, tiredness, weakness, exhaustion, cachexia, drowsiness and wasting	Study number: 39 studies (out of them 11 controlled studies on glucocorticoids and 13 controlled studies on androgens Population and interventions: - Cancer patients (11 controlled studies, of which 4 RCTs): all received corticosteroids - HIV patients (13 controlled studies, of which 5 studies with fatigue as outcome): all received androgens Outcomes: (results reported here only for cancer patients, i.e. receiving teroids): - **QoL**: improved - **Fatigue, weakness**: results inconsistent - **Tiredness, energy**: not improved	- No recommendation for corticoid and androgen in tiredness and weakness in palliative care can be given; however, corticoids in cancer patients and androgens in HIV positive-patients can be used in an individual trial for QoL - Difficulty with nomenclature: differentiation and translation of terms such as fatigue, tiredness, weakness from English to German is challenging and not always possible.	1- (Body of evidence: not deducible)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
					- Methods: No quality assessement of included studies	

9. Schlafbezogene Erkrankungen/Nächtliche Unruhe

9.1. Medikamentöse Therapie

9.1.1. Antidepressiva

9.1.1.1. Primärstudien

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Cankurtaran, Support Care Cancer 2008 [265]	RCT; to compare the effectiveness of mirtazapine and imipramine on distressing symptoms of cancer patients such as pain, nausea, sleep disturbance	n= 53 (I1=20;I2=13; C=20); 19 drop-outs	Adult **cancer** patients with major depressive disorder, anxiety disorder or adjustment disorder No other serious chronic physical illness or psychiatric disorder	- **I1: mirtazapine** T0: 12.2 ±5.7 (7.5–30 mg/d), T2 (after 6 weeks): 18±7.9 (5–30 mg/d), T3: 18.7±9.1 (7.5–30 mg/d); n=20 - **I2: imipramine**; T1: 13.8±7.1 (5–25 mg/d), T2: 26.5±23.2 (5–75 mg/d), T3:29.4 ±34.4 (5–100 mg/d), n=13 - **C (no medication):** n=20	1.O: - Pain - Nausea - vomiting assessed on a single-symptom scale rated by physician; - weights noted during each visit; appetite evaluated by patients; - sleep disturbance evaluated on the Hamilton Depression Rating Scale (HDS) 2.O: Hospital Anxiety Depression Scale (HADS) Measurement: T0 (baseline), T1 (21 days), T2 (42 days)	1. O: **sleep** disturbance: Between-group comparison: n.s. Pre-post comparison in I1: sign. within the mirtazapine group between the different visits (p=0.001, p=0.001, p=0.003); insomnia scores improved; 2. O.: **HADS**: sign. differences within the mirtazapine group in mean total (p=0.03), anxiety (p=0.003) and depression (p=0.025)	- Randomisation only for I1 and I2 = RCT; control group = patients who agreed to participate in the study but did not agree to take any psycotropic drugs = CCT - No description of randomisation - Single blind (evaluation) - high dropout rate (35,8% in total), esp. at third visit in control group (n=10; 50%)	1-

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
							- no intention to treat analysis - not powered	
Palesh, Sleep Med 2012 [266]	RCT; to compare the effects of paroxetine to placebo on fatigue in cancer patients undergoing chemotherapy	n= 549, 123 drop-outs	Adult **cancer** patients 23 – 87 years) receiving chemotherapy	**I: parotexine** (20 mg/d); n= 217 **C: placebo** (identically matched); n=209 Duration: 60 days	Sleep problems (Hamilton Depression Inventory - HDI + 3 extra items); Depression (CES-D) Measurement: T0 (baseline, after chemotherapy cycle 1), T1-T4 (5-7 days after chemotherapy cycle 2 up to cycle 4 maximum)	**Sleep** (HDI): significant superiority of paroxetine compared to placebo group in sleep problems (($X^2(1) = 5.97$, $p = 0.01$, Cohen d = 0.23) at end of study (seven days post Cycle 4); Proportion with sleep problems at Cycle 4: I: 0.79, n=172/217 vs. C: 0.88, n=184/209; Baseline (Cycle 2): I: 80.6%, n=175/217 vs. C: 81.1%, n=171/209. Superiority remained significant even after adjustment for baseline sleep problems and depression ($p < 0.05$). Relative risk of sleep problems at Cycle 4 for patients with sleep problems at baseline = 1.48 ($p<.001$); effect of baseline depression on sleep problems smaller, but still sign., (all $p<.001$) CES-D: n.s.	- not specifically designed to test impact of paroxetine on sleep problems: secondary data analysis of a RCT (so not powered); - Inclusion criteria was fatigue - serotonin antagonists like nefazodone and mirtazapine might produce larger effect than SSRIs in improving patients' sleep - no intent-to-treat analysis	1-

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Tanimukai, Am J Hosp Palliat Care 2013 [267]	Observational study; To report effectiveness of treatment of insomnia and nightmares with trazodone in cancer patients	n= 30 Drop-outs: 0	Adult cancer patients with - **insomnia** - Age: 37 – 84 years	**Trazodone** (starting dose of 12.5 to 25 mg/d): dose was increased to 25 to 50 mg/d until insomnia was improved Duration: open	**O:** Rate of patients whose insomnia improved without a request for an additional hypnotic within 7 days after prescription of trazodone Measurement: T0 (baseline), T1 (7 days), T2 (42 days); BDI and Ham-D not administered at T1	Main results: Effect of trazodone was observed in 15 (50%) patients	- No standardized measure or definition for the change in insomnia	3
Theobald, J Pain Symptom Manage 2002 [268]	Pilot open-label, crossover RCT; To examine the impact of mirtazapine for multiply symptomatic cancer patients	n= 36; 16 drop-outs	Adult advanced cancer patients with - on opioid medication - life expectancy ≥ 3 months - Age: 40 - 83 years	I1: Mirtazapine (dose 15 mg/d) I2: Mirtazapine (dose 30 mg/d) Duration: 49 days	1.O: Pain and other symptoms (Pain: MPAC; Other symptoms: nausea, **insomnia**, anxiety and appetite – rated after Numeric Rating Scales - NRS) 2.O: Depression and Quality of Life (Depression: ZSDS; Quality of Life: FACT-G); weight gain Measurement: T0 (baseline), T1 (28 days), T2 (56 days)	Main results: no significant group differences; RS scales for insomnia (mean = 3.4 to mean = 2.3) (f=1.5, p = 0.25), interpreted as a trend toward improvement from baseline to Week 7.	- Small sample (n=20) because of 44% (16/36) drop out - No wash-out period - No description of randomisation - No significant within-group improvements for pain and other symptoms (nausea, insomnia, anxiety and appetite) - Depression, quality of life and weight gain significantly improved	1-

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
							-	

9.1.2. Benzodiazepine

9.1.2.1. Systematic Review

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); Aim	Inclusion criteria (studies, population)	Interventions evaluated	Results	Comments	LoE SIGN
Hirst, Cochrane, 2002 [269]	SR; To assess the effectiveness and safety of benzodiazepines or benzodiazepine receptor agonists for insomnia in palliative care	- Design: RCT - Databases: Cochrane Library, MEDLINE, EMBASE, BNI, CINAHL, Biological Abstracts, PSYCInfo, CANCERLIT, HealthStar, PubCrawler, Web of Science, SIGLE, Dissertation Abstracts, Index to Theses, ZETOC, metaRegister of Controlled Trials and handsearched references as well as personal communications and pharmaceutical companies, - Population: Palliative care patients ≥ 18 years receiving palliative care or suffering an incurable progressive medical condition with explicit complaint of insomnia	- Drug therapies for the relief of insomnia were any benzodiazepine, Zolpidem, Zopiclone and Zaleplon. - Studies had to compare a benzodiazepine, Zolpidem, Zopiclone or Zaleplon with placebo or active control for the treatment of insomnia	Study Number: No studies included	Thirty-seven studies did not meet the prespecified inclusion criteria and were therefore excluded. Prime reasons for exclusion; - patient population not having progressive incurable medical conditions (17 studies). - No explicit subjective complaint of insomnia by study patients (nine studies).	1++ (Body of evidence: not statable)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); Aim	Inclusion criteria (studies, population)	Interventions evaluated	Results	Comments	LoE SIGN
					- No RCT (six studies).	

9.1.2.2. Primärstudien

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Kaneishi, J Pain Sympt Manag 2015 [270]	Retrospective observational controlled study; To assess the effect of a single-dose subcutaneous benzodiazepines for insomnia in patients with advanced cancer	n=69	Adult patients with: - advanced cancer - on palliative care unit - poor sleep - difficulty taking medic. orally	**I:** (n=61) **midazolam** s.c., single dosis/day (Mean dose: SD 2,2 mg (.28); Median: 2 (1,5-2,5)) or: (n=28) **flunitrazepam** s.c., single dosis/day (Mean dose: SD 0,88 mg (.12); Median: 0,8 (0,6-1))	Rate of patients with > 6 hours sleep/day Adverse events	Midazolam group: 57% Flunitrazepam group: 75% No adverse events	Bias associated with retrospective design No statistical comparison (descriptive design)	3
Matsuo, J Palliat Med 2007 [271]	Multicenter retrospective observational	n= 167; 4 drop-outs	Adult, terminally ill **cancer** patients - with primary insomnia	**I1: midazolam** (median initial-dose 10 mg/d, median max	- Efficacy (sleep description as poor, fair, good or unknown)	No significant differences in **efficacy** (I1: 91% vs. I2: 81%, p =0.084).	- ad-hoc retrospective and observer rating of outcome	2-

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
	controlled study; to compare efficacy, safety, and cost-effectiveness of midazolam and flunitrazepam		- without other indications than primary insomnia (e.g. delirium and sedation) - Age: 52 – 79 years	dose 18 mg/d); n= 104 **I2: flunitrazepam** (median initial dose 2mg/d, median max dose 2 mg/d); n=59 Duration: 1-207 days (median 6 days for midalozam, 9 days for flunitrazepam)	- Safety (defined as: presence or absence of a hangover effect, delirium at night and - the next morning (diagnosed by DSM-IV), respiratory depression, the reason for treatment withdrawal, and treatment-related death) - Tolerance - Cost effectiveness	**Safety**: Flunitrazepam caused respiratory depression significantly more frequently than midazolam (17% vs. 3.8%, p=.0073) **Tolerance**: For patients treated for 14 days or longer, daily escalation dose ratio required for maintaining adequate sleep significantly higher in I1 than in I2 (11% versus 2.6%, p = 0.015). **Cost effectiveness**: costs of initial and maximum administration sign. higher in I1 than in I2 (p=.001)	- difficulties to completely evaluate effects of other medications for insomnia - patients receiving benzodiazepines to palliate physical and psychical symptoms other than primary insomnia excluded - no unification of administration protocol due to large variance in clinical practice in institutions	

9.1.3. Neuroleptika

9.1.3.1. Primärstudie

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Pasquini, Psycho-somatics 2009 [272]	Fall series; To report on patients treated with quetiapine for tamoxifen-related insomnia without depression	n= 6 Drop-outs: 0	Adult female patients with - **breast cancer** (TNM Stage I–IIIA) - receiving **tamoxifen** therapy (20 mg) after a definitive primary therapy suffering from tamoxifen-induced Sleep Disorder - without depression	**Quetiapine** (25 mg/d): dose adjustments upward were made in 25-mg increments, titrated to a maximum dose of 100 mg Duration: 42 days	Italian version of the Insomnia Severity Index scale (ISI) Measurement: T0 (baseline), T1 (7 days), T2 (42 days); BDI and Ham-D not administered at T1	**Main results**: 5of 6 women showed improvement of insomnia, moving from the ISI moderate category to absence	- Very small sample (n=6) - No inference statistical measures reported, just descriptive - Depression could not be excluded safely - Reported side effects at second follow-up were weight gain (N=2) and dizziness (N=1)	3

9.1.4. Phytotherapeutika

9.1.4.1. Primärstudien

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Barton, J Support Oncol 2011 [273]	Double-blind RCT; To evaluate efficacy of a valerian officinalis supplement for sleep in people with cancer undergoing cancer treatment	n= 227 (I: n=62; C: n=57 with 108 drop-outs)	Adult cancer patients - receiving therapy (radiation, chemotherapy, oral anti-tumor agents, or endocrine therapy) - with sleeping difficulty of ≥ 4 (on a scale of 10) - life expectancy ≥ 6 months - ECOG Performance Score (PS) of 0 or 1 - without	- I: Valerian (450 mg/d); n=62 versus - C: Placebo; n=57 Duration: 56 days	1.O: Pittsburgh Sleep Quality Index (**PSQI**), Functional Outcomes of Sleep Questionnaire (**FOSQ**) 2.O: Profile of Moods States (**POMS**), Brief Fatigue Inventory (**BFI**) Measurement: T0 (baseline), T1 (28 days), T2 (56 days)	Total PSQI: n.s. **FOSQ**: n.s. **POMS:** sign. improvement for valerian group for fatigue-inertia subscale in T1 (I: 13.9 vs. C: 2.8, p= =0.004) and T2 (I: 17.5 vs. C: 9.2, p=0.02) **BFI:** sign. improvement for valerian group on categories "fatigue now"- and "usual fatigue" T1 (I: 13.2 vs. C: 1.5, p=0.003 and I: 12.8 vs. C: 4.2 p=0.01) and T2 (I: 22.1 vs. C: 10.5, p=0.02; and I: 19.4 vs. C: 10.0 p=0.046)	- Randomisation and blinding not described - Intent-to-treat-analysis - Powered - Hypothesis related to the inconsistencies in the results: PSQI may measure different dimensions of well-being than the BFI or POMS, the former concentrating on sleep quality measures, while the latter two measures concentrate on daytime symptoms.	1-
Tröger, Dtsch Arztebl Int 2014 [274]	RCT, open-label; to investigate efficacy of mistletoe monotherapy on the survival and quality of life	n= 220; 7 drop-outs	Adult cancer patients with inoperable locally advanced or metastatic pancreatic carcinoma (UICC stage III/IV) and - unsuitability for, or unwillingness	**I: mistletoe** (50 mg/d); n=110 C: control n=110	1. Overall survival 2. O.: Quality of Life (EORTC QLQ-C30); weight loss (CTCAE 3.0); undesired events (GCP)	**Quality of Life**: sign. difference between groups in scores of all 6 functioning-scales (p< .001) including pain, fatigue appetite loss, and **insomnia** (95% CI −45.8	- data of 52 patients could not be analyzed (I: n=14, C: n=38) - patients were not blinded (mistletoe	1-

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
	of patients with locally advanced or metastatic pancreatic carcinoma		to undergo other type of cancer treatment - leukocyte count ≥ 3000/mm³; platelet count ≥ 100 000/mm³ - Exclusion: life expectancy < 4 weeks; weight loss of ≥ 20% in past 6 weeks; brain metastases	Duration: up to 12 months	Measurement: T0 (baseline), T1 (1 month), T2 (2 months), T3 (3 months), T4 (6 months), T5 (9 months), T6 (12 months)	to -28.6). Effect size for insomnia increased with duration of intervention (1 month: 0.93 - 9 month 1.83) **Weight loss**: sign. difference averaged over all follow-up visits - patients in intervention group gained and patients in control group lost weight ($p < .001$) Undesired events: n.s.	treatment supposed to be initiated with dose escalation) - not powered - Results for Insomnia are given for intervention and control group stratified into six strata depending on the time of the last assessment before death.	

9.1.5. Melatonin

9.1.5.1. Primärstudien

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Hansen, Int J Breast Cancer 2014 [275]	Double-blind RCT; To evaluate the effect of melatonin on cognitive function postoperatively in breast cancer patients	n= 54 (I: n=28; C: n=26); 11 drop-outs	Postoperative adult female patients with - Breast **cancer** (ASA I-III)	- **I: Melatonin** (6 mg/d); n=28 versus - **C:** Placebo; n=26	Primary trial endpoint: depressive symptoms Secondary endpoints reported in this study: 1.O: cognitive dysfunction (Neuropsychological	Cognitive dysfunction: n.s. Sleep diary: **sleep efficiency (%):** sign. greater in melatonin group at short term	- Randomization and blinding well reported - Study reports secondary endpoints	1-

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
	Study reports secondary endpoints from a randomized, double-blind, placebo-controlled trial that primarily sought to investigate depressive symptoms		without depression	Duration: 3 months	tests: ISPOCD Test Battery) Measurement: T0 (baseline, preoperatively), T1 (2 weeks postoperatively), T2 (12 weeks postoperatively) 2.O: Sleep quantity (diary) and subjective sleep quality (visual analogue scale ; VAS) Measurement: Period 1 (3 days preoperatively - 8 days postoperatively), Period 2 (2 – 12 weeks postoperatively)	postoperative (T1): mean difference = 4.28% [95% CI 0.57; 7.82]; p = 0.02. Long term (T2): n.s. **Total sleep period:** significantly longer in the melatonin group at long term (T2): mean difference = 37.0 min [95% CI 3.6; 69.7];p=0.03. At short term (T1): n.s. Sleep quality: n.s.	- Not powered - Per-protocol-analysis; drop-out rate significantly lower in the melatonin group - Postoperative patients	
Innominato, Support Care Cancer 2016 [276]	Prospective, non-controlled open-label phase II trial; to assess the effect of melatonin on circadian bio-markers, sleep, and quality of life in breast cancer patients	n= 41; 9 drop-outs	Adult patients with metastatic breast cancer - receiving either no systemic treatment, bisphosphonates, hormonal therapy (tamoxifen, aromatase inhibitors, or progestins), or trastuzumab - no shift work, intake of steroids or beta blockers and ECOG performance status >2	- I: Melatonine (dose 5 mg/d) Duration: 2 months	1.O: sleep and circadian rhythmicity (actigraphy, diurnal patterns of serum cortisol and expression of core clock genes PER2 and BMAL1) 2.O: subjective parameters (European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire) Measurement: T0 (baseline), T1 (21 days), T2 (42 days)	**1. O.: Actigraphy recordings**: Sign. post-treatment decrease in average activity during 6 most active hours (L6), probabilistic metric of activity fragmentation (sAR), and sleep fragmentation index (SFI) (p=.031, p=.033, p=.037); significant increase in total duration of rest (p=.012). No significant difference in the distribution of the circadian parameter before and after treatment with melatonine.	- Some parameters could be calculated only in a smaller number of recordings due to technical issues. - No control group	3

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
						Subjective parameters: Sign. improvement in global quality of life (p=.016), social (p=.013) and cognitive functioning (p=.005) domains and self-rated sleep disturbance (p=.022) and fatigue (p=.011). No further data was reported.		
Kurdi, Ind J Pall Care 2016 [277]	Double-blind RCT; To assess the hypnotic efficacy of oral melatonin in cancer patients with insomnia.	n = 50; 2 drop-outs	Pain clinic patients with malignancies meeting the Diagnostic and Statistical Manual of Mental Disorders 4 th edition criteria for primary insomnia Age: 20-65 years	At 7 pm orally every day for 14 days: I: melatonin (3 mg/d); n= 24 or C: Placebo (vitamine tablet); n = 24 Duration: 14 days	Subjective sleep quality (Athens insomnia scale (AIS) oral questionnaire) Measurement: T0 (baseline), T1 (7 days), T2 (14 days)	Significant differences in favor of I in **insomnia** (improvement I: 46.53%; p = 0.00001 vs. C: 11.30%; p = 0.1026), improvement in sleep from 1 to 7 days (I: 19.91%; p = 0.00001 vs. C: 0.98%; p = 0.2563) and from 7 to 14 days (I: 33.24%; p = 0.00001 vs. C: 10.42%; p = 0.1469).	- Randomization and blinding adequate - Powered, despite relative small sample - No objective measure of sleep (polysomnography, actigraphy) - daily sleep diary and Pittsburgh Sleep Quality Index (PSQI) was not feasible for poorly educated patients - all stages of cancer included	1+

9.1.6. Zolpidem

9.1.6.1. Primärstudie

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Joffe, J of the North-Amercian Menopause Society 2010 [278]	Double-blind RCT; to evaluate the efficacy of hot flash treatment by combining the hypnotic agent zolpidem with an SSRI/SNRI	n= 53; 15 drop-outs	Adult female patients (18 - 65 years) with - **breast cancer** or a high risk for the disease - clinical insomnia syndrome - without previous primary sleep disorders	- **I: venlafaxine** (dose 10 mg/d)/ **SSRI with zolpidem**; n=22 - **C: placebo** (identically matched); n=16 Duration: 35 days	1.O: wake time after sleep onset (WASO), measured with actigraphic watch or subjective sleep quality (PSQI) 2.O: quality of life (QOLI); hot flashes (diary); mood state (BDI) Measurement: daily	**wake time after sleep onset**: n.s. **2.O:** n.s.	- modification of primary endpoint (classifying non-completers as non-responders) as reaction to unanticipated differential drop-out rate - heterogeneous population: women already taking SSRI/ SNRI and women who had started intake with study start	1-

10. Übelkeit und Erbrechen (unabhängig von einer Chemotherapie)

10.1. Erfassung

10.1.1. Systematic Reviews

Es wurden keine Systematic Reviews identifiziert.

10.1.2. Primärstudien

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	1. Tested assessment tool 2. reference assessment tool(s) 3. test procedure	Psychometric properties	Results	Comments	LoE SIGN
Rhodes, Oncol Nurs Forum 1999 [279]	Validation study	n= 159 Drop-outs: 0	Convenience sample of 40 obstetrical, 60 oncological and 59 medical/surgical patients between 18 - 89 years	8. Index of Nausea, Vomiting, and Retching (INVR): - Frequencies of vomiting, nausea and retching - Severity of distress from nausea, vomiting and retching - Duration of nausea - Amount of vomitus each time 9. Index of Nausea and Vomiting Form 2 (INV-2) 10. INVR and INV-2 were administered approximately 30-60 minutes apart. One-half of the subjects completed the INVR first, the other half the INV-2 first.	Reliability	1.O: 79 – 98% agreement between the INVR and the INV-2 (Spearmen Correlation 0.714 – 0,954)		3

Reference	Type of study/ Design	Number of included patients (I/C); Drop-outs	Patients characteristics	1. Tested assessment tool 2. reference assessment tool(s) 3. test procedure	Psychometric properties	Results	Comments	LoE SIGN
Fu, Cancer Nurs 2002 [280]	Integrative translation method; Validation study	n = 177 Drop-outs: 0	Convenience sample of 177 Chinese-speaking participants was accrued from a large teaching cancer institute and a teaching obstetric hospital 75 male, 102 female, average age 38 (range 24 – 76)	1. INVR 2. INV-2 3. test-retest, parallel forms, and crossover design: The INVR and the INV-2 were administered approximately 30-60 minutes apart in the morning and in the evening of the same day	Reliability Validity	1. O:66 – 94% agreement; for the Chinese version of INV-2, the Cronbach's [alpha] for the morning report: 0.951, for the evening report: 0.929 For the Chinese version of INVR, the Cronbach's [alpha] for the morning report was 0.952 and 0.941 for the evening report. Wilcoxon signed rank test was performed by comparing the morning and evening reports regarding both INV-2 and INVR. No recall bias was revealed in Chinese version of INV-2 (P = .0031) and INVR (P = .0123). 2.O: In this study, the established equivalence of the Chinese versions of the INV-2 and INVR represents their validity.		3

10.2. Medikamentöse Therapie

10.2.1. Systematic Reviews von verschiedenen Wirkstoffklassen

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Benze, Schmerz 2012a [281]	SR; to determine the level of evidence for the treatment of nausea and vomiting with prokinetics and neuroleptics in palliative care patients	- Design: No exclusion because of study type - Databases: PubMed and EmBase, published 1966–2011 completed by manual searching - Population: Palliative care patients ≥ 18 years suffering from far advanced cancer and no longer being treated with chemotherapy or radiation therapy	Interventions: - Prokinetics (metoclopramide (**MCP**) - **Neuroleptics** (haloperidol, olanzapine, levosulpiride, levomepromazine, chlorpromazine, prochlorperazine mirtazapine, risperidone) Outcomes: symptom reduction of nausea (duration, intensity) and vomiting (duration, frequency)	Study Number: 22 studies + 8 SR Prokinetics (13 studies): 2 SR, 7 RCT, 2 retrospective + 2 case series on the effectiveness of metoclopramide (MCP); patient numbers from 7 to 280 (Mean=77); *Outcomes* (**nausea**): - SR: MCP is effective (applied separately or in combination) - RCTs: 1 study showed significant nausea reduction (p=0.04), 1 RCT showed significant superiority of retarded MCP compared to MCP (p=0.033), 1 RCT showed levosulpirid significant more effective than MCP in nausea duration (p=0.002) and complete control (p=0.0004), frequency (p=0.002) and complete control (p=0.041) of vomiting; 4 RCTs showed symptom improvement without significance - Uncontrolled studies: positive effect of MCP in nausea and vomiting reduction Neuroleptics (9 studies): Haloperidol: 3 SR found no relevant studies. 3 case series + 1 case study described effectiveness of Haloperidol, 1 in combination with Ondansetron, small study sizes and additional high dropout rate in 1 case series weaken study relevance Olanzapine: 2 studies found a significant reduction of nausea ($p < 0,04$ for 2,5 mg; $p < 0,002$ for 5,0 mg; $p < 0,0001$ for 10 mg)	Author reports partly only marginally undercut significance level Partly interventions with combination of drugs included Partly comparison of different drugs	1+ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				with low patient numbers (5/16), lack of control patients and heterogeneous patient groups Levosulpiride: 1 double-blind randomised cross-over-study with 30 patients showed significant superiority compared to MCP (nausea duration p = 0,002; nausea intensity = 0,0004; complete control of nausea= 0,0034; frequency of vomiting=0,002; complete control of vomiting= 0.041); of treated (3/day, 25 mg) patients (n=30) 48% without nausea, 81% without vomiting Levomepromazine (Methotrimeprazin): 1 Case report, 3 case series, 1 narrative review: good impact on nausea resistant to other antiemetics Chlorpromazine: 2 RCTs: In combination with Dexamethasone superior compared to Metoclopramide with regard to vomiting, but not regarding nausea (After 15 days, total control of emesis was obtained in 23.6% (9 of 38) of MET + DEX patients (dose: 10 mg*4 + 2 mg*1, orally) and 33.3 (13 of 39) of CHL + DEX patients (dose: 25 mg*2 + 2 mg*1, orally). Total control of nausea was achieved in 18.4% (7 of 38) of MET + DEX patients, 17.9% (7 of 39) of CHL + DEX patients) Prochlorperazine: 1 RCT: complete response concerning nausea in 48,9 % compared to 26,7 % with Ondansetron (p = 0,0504); vomiting aggravation with Ondansetron (p = 0,0513); 1 case series showed good impact Mirtazapine: No studies on palliative patients		

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				Risperidone: 1 retrospective study with 20 patients (dose: 1mg/day); In 50% (10/20) nausea disappeared, in 64% (7/11) vomiting; study design does not allow general recommendations		
Benze, Schmerz 2012b [282]	SR; to analyze the current evidence for antiemetic treatment in palliative care patients	Design: no exclusion because of study type Databases: PubMed and EmBase were systematically searched for studies (published 1966–2011) dealing with antiemetic therapy in palliative care and electronic retrieval was completed by manual searching. **Palliative** care patients ≥18 years with far advanced **cancer** not receiving chemotherapy or radiotherapy, suffering from nausea and vomiting	Interventions: **5HT3 receptor antagonists, steroids, antihistamines, anticholinergics, somatostatin analogs, benzodiazepines** and **cannabinoids** Outcomes: Effect on **nausea** (duration, intensity) and **vomiting** (duration, frequency)	Study number: 36 studies + 6 SR 5HT3 receptor antagonists: 9 studies on cancer patients (2 case studies, 2 case series, 1 retrospective cohort study, 4 RCTs with 92 – 280 patients); medication: Granisetron (2), Ondansetron (4), Tropisetron (3): Contradictory results; larger studies showed positive effect and better efficacy, as compared to metoclopramide, dexamethasone and neuroleptics. One case series (n=24 patients) with significant reduction of nausea intensity ($p<0.001$) and frequency of vomiting ($p<0.001$); RCTs: no significant test results Steroids: 9 studies on cancer patients (5 RCTs, 4 case series) + 1 SR: Heterogeneous results, positive trend but no significant differences in the RCTs. Antihistamines: Insufficient data Anticholinergics: 4 Studies (3 RCTs, 1 Case report) on malignant gastrointestinal obstruction, which was covered in another section of the guideline and therefore excluded for this search Benzodiazepines: No studies identified. Cannabinoids: (2 case studies, 1 observational study): Relieve of nausea and vomiting but with notable side effects. Comparison of cannabinoids to less recent	The author stated that regarding symptom control of nausea and vomiting in patients with COPD, progressive heart failure and ALS no studies were undertaken in patients receiving palliative care. Recommendations in the literature are mainly based on studies in patients with cancer. The overall strength of evidence is described as low.	1+ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				antiemetic drugs but not, for example to 5HT3 receptor antagonists.		

10.2.2. Cannabinoide

10.2.2.1. Systematic Review

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Mücke, J Cachexia Sarcopenia Muscle 2018 [283]	SR/MA; To assess the efficacy, tolerability, and safety of cannabinoids in palliative medicine	Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, PubMed, Scopus and Clinicaltrials.gov until March 2017 Design: parallel or cross-over RCTs with a duration of ≥ 2 weeks and ≥ 10 participants per study arm Patients of any age, suffering from advanced or end stage diseases (**palliative**)	Interventions: **Cannabis/ Cannabinoids** vs. placebo or active control Outcomes: Efficacy: 1.O: responder (pain reduction ≥30%), body weight, appetite, caloric intake, and **nausea/ vomiting** 2.O: sleeping dysfunction, fatigue, mood disorders, and health-related quality of life at the end of each medication phase. Tolerability: nb. of patients who discontinued the	Study number: 9 RCTs; Meta-analysis: 8 RCTs, n=1561 Population: advanced cancer (5 RCTs, n=758), HIV (3 RCTs, n=251), Alzheimer (1 RCT, n=15); 90.8% male; Median study duration by cancer patients = 8 weeks (16 days–11 weeks) Quality of evidence: 3 RCTs of moderate quality; 6 of low quality Outcomes: Cancer patients: - **Nausea/vomiting** (2 RCTs, n=420, moderate to low quality of evidence): n.s. (SMD: 0.21; 95 % CI: − 0.10 to 0.52; p = 0.19) - **>30% decrease in pain, appetite, caloric intake, sleep problems**: n.s. - **Tolerability, side effects, safety**: n.s. HIV patients: - **Weight gain, appetite**: sign. increased	- Few retrieved publications from the database search suggesting low sensitivity of the search strategy - Nausea and vomiting always assessed together with other symptoms like pain	1+ (Body of evidence: 1+)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
			study because of adverse events; dizziness, mental health symptoms, and cognitive dysfunction. Safety: AE, death during medication	- **Nausea/vomiting**: n.s. - **Tolerability, safety**: n.s. - **Side effects**: sign. increase in mental health symptoms Too little data to recommend a favored use of cannabis or cannabinoids		

10.2.3. Neuroleptika / Antipsychotika

10.2.3.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Cox, Cochrane 2015 [284]	SR; to evaluate the efficacy of, and adverse events associated with levomepromazine for the treatment of nausea and vomiting in palliative care patients.	Design: RCTs Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE, up to 2/ 2015. Clinical trial registers on 7/10/2015 for ongoing trials Patients: Adults receiving **palliative care**	Interventions: **Levomepromazine** Primary outcomes: 1. Patient-reported nausea severity 2. Patient-reported vomiting severity 3. Patient-reported relief of symptoms of nausea and vomiting	No study included	Twelve studies were excluded because of study design (1 case report, 1 case series, 2 trials without randomization, 4 reviews, 4 on chemo-induced nausea and vomiting)	1++ (Body of evidence: not statable)
Dietz, BMC Palliative Care	SR; to determine the level of evidence	Design: SR, RCTs, prospective trials, cohort studies, case series or case reports	Interventions: **Levomepromazine**	Included studies on nausea and vomiting: 2 SR, 3 prospective studies, 2 open-label prospective studies, 1 case report	Further regarded outcomes: Sedation, delirium, agitation, pain	2+ (Body of

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
2013 [285]	for the use of levomeproma-zine in palliative symptom control, and to discover gaps in evidence	Search: Medline, Embase, Cochrane, PsychInfo and Ovid Nursing, up to 4/ 2012 together with hand-searching and cross-referencing Adults patients treated in the **palliative care** setting	Dose range: 3.12 – 30mg/ 24h Outcomes: Treatment of symptoms	Outcomes: - Open-label prospective study: 60 (86%) responders of 70 patients with digestive cancer treated with levomepromazine for **nausea and vomiting**, Pearson test: no association between levomepromazine dose and response to treatment - 1 quasi-experimental prospective study (n= 65 patients): o day 2: 33/53 (62%) of patients evaluable for response showed some improvement in **nausea or vomiting** o day 5: improvement in 20/34 (58%) -> levomepromazine as efficient first line antiemetic in indeterminate patho-physiological causes of nausea and vomiting, and second line for all other causes	In total included studies: 33; 9 SR, 6 case reports, 2 survey studies, 9 retrospective studies, 7 prospective studies; Most papers (n = 22) were categorized as level 3 (non-randomized, non-consecutive or cohort studies), only 2 studies on nausea reached level 2 according to the Oxford Centre for Evidence-Based Medicine LoE	evidence: 2-)
Murray-Brown, Cochrane 2015 [286]	SR; to evaluate the efficacy and adverse events associated with the use of haloperidol for the treatment of nausea and vomiting in palliative care patients	Design: RCTs Search: Updated searches of CENTRAL, EMBASE and MEDLINE in 11/2013 and 11/2014, con-trolled trials registers in March 2015 No language restrictions. For the original review, database searching was performed in 8/2007, including CENTRAL, MEDLINE, EMBASE, CINAHL and AMED. Handsearching complemented the electronic searches Adults patients receiving **palliative** care or suffering from an incurable progressive medical condition.	Intervention: **Haloperidol** Primary outcome: Patient-reported nausea severity / vomiting severity; Secondary outcomes: Quality of life measurement, acceptability of treatment, need for rescue antiemetic medication, adverse events, withdrawal from study because of side effects	Included studies: 1 RCT of moderate quality: ABH gel (including haloperidol, diphenhydramine + lorazepam) vs. placebo (n=22): n.s superior (Mean change in nausea score (baseline to 60 minutes after treatment): ABH gel group = 1.7 ± 2.05; placebo group = 0.9 ±2.45 (not statistically different). Non-inferiority test through a paired t-test significant (p = 0.0115). One ongoing trial of haloperidol for the management of nausea and vomiting in patients with cancer, with initial results published in a conference abstract suggesting that haloperidol is effective for 65% of patients.	27 studies from the 2007 search were excluded, as well as further 37 studies from the 2013/2014 update search. Intervention with combination of drugs included	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
		Exclusion criteria: Nausea or/ and vomiting thought to be secondary to pregnancy or surgery				
Storrar, Cochrane 2014 [287]	SR; to evaluate the efficacy and adverse events (both minor and serious) associated with the use of droperidol for the treatment of nausea and vomiting	Design: RCTs Search: CENTRAL,MEDLINE, EMBASE, CINAHL and AMED, trial registers, and the WHO International Clinical Trials Registry Platform up to 11/2013 Adults patients receiving **palliative** care or suffering from an incurable progressive medical condition	Intervention: **Droperidol** Outcomes: **Nausea** and **vomiting**	No study included	- In the 2010 search 23 studies were excluded on the full text level,in the 2013 search 18 studies - No registered trials of droperidol for the management of nausea or vomiting in palliative care was found.	1++ (Body of evidence: not statable)

10.2.4. Glucocorticoide

10.2.4.1. Systematic Review

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Vayne-Bossert, Cochrane 2017 [288]	SR/MA; to assess the effects of corticosteroids on nausea and vomiting not related to chemotherapy, radiotherapy, or surgery in	Design: RCTs (extension to prospective controlled studies, if no RCTs found) Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, EMBASE, CINAHL, Science Citation Index Web of Science, Conference	Interventions: - any **corticosteroid** - Comparison: placebo, other antiemetics, no intervention, usual treatment, alternative treatment for nausea/vomiting	Study number/desing: 3 RCTs Population: n=451 Drugs: dexamethasone PO (4 or 20 mg/d) vs. placebo; or combination of oral drugs (dexamethasone, chlorpromazine, metoclopramide, tropisetron)	Method: Good conducted Sys-Rev Content: Low LoE (high risk of bias); There is insufficient evidence to support	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
	adult cancer patients	Proceedings Citation Index - ScienceWeb of Science, LILACS, up to 8/ 2016. Patients: Adults participants with **cancer** suffering from nausea, vomiting or both not related to chemotherapy, radiotherapy, or surgery	Primary outcomes: Patient-reported nausea intensity and relief using validated scales (visual analogue scales (VAS), numerical rating scales (NRS), verbal rating scales (VRS), or a combination), and the number of vomiting episodes in a predefined time interval. Secondary outcomes: - AE - QoL - Patient satisfaction	Metaanalysis (n=127; 2 studies, dexamethasone vs. placebo or metoclopramide; data at day 8 of therapy): - **Nausea intensity** (scale 0-10): n.s. trend to reduction of nausea at day 8 (MD -0.48, 95% CI -1.53 to 0.57; p =0.37) - **Nausea relief**: no data Narrative analysis: - **Number of vomiting episodes (**1 RCT): n.s.difference between dexamethasone and placebo; improvement in both groups - **AE** (3 RCTs): n.s. difference between groups - **Total score of QoL** (2 RCTs): inconsistent results (sign. improvement in 1 RCT; n.s. in other RCT).	or refute the suggestion that corticosteroids have any efficacy in nausea and vomiting. This is particularly relevant when considering the toxicity of corticosteroids, especially following prolonged use.	

10.2.5. Opioidwechsel

10.2.5.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Laugsand, Pall Med, 2011 [234]	SR; to review the existing literature on management of opioid-induced nausea and vomiting in cancer patients and summarize the findings into evidence-based	Design: no limitation Databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials Patients: Adult patients with **cancer** pain receiving opiods for cancer pain addressing nausea and vomiting either as a primary or secondary outcome	Interventions: - use of analgetics for opiod sparing - change of opiod - change of route - other Primary outcomes: Nausea and vomiting (opiod induced emesis)	Study number: 55 studies; 17 studies to opioid switch Population: n=3379 Swith: - 7 studies (4 RCTs) showed no difference in prevalence or intensity of nausea/vomiting - 2 studies (1 RCT) did not provide sufficient clinical evidence to form recommendations - 2 case reports - 6 studies (2 RCTs, 4 prospective OS) showed difference in intensity or prevalence of nausea/vomiting. Based on this evidence, a weak recommendation for changing the opiod could be formulated: switching from morphine to opoid as oxycodone or hydromorphone; or from fentanyl to methadone.	Method: Well conducted SysRev Content: Low LoE (high risk of bias)	1++ (Body of evidence: 1-)
Sande, J Palliat Med 2018 [289] *(Update of Laugsand et al. 2011)*	SR; To evaluate the evidence for the management of opioid-induced nausea and vomiting	Study design: RCTs Databases: MEDLINE (1966–2017) and EMBASE (1980–2017) Patients: Adult patients with **cancer** pain on opiods for cancer pain and with nausea and vomiting assessed either as a primary or secondary outcome (tumortherapy or MBO related nausea excluded)	Interventions: - switching from one - opioid to another; studies on antiemetics - studies on change of administration route for the opioid(s) Outcomes:	Study number: 15 RCTs (n=1524) Opioid switching (8 RCTs; low quality of evidence): - 1 RCT (n=20): oxycodone (vs. morphine): sign. less nausea - 1 RCT (n=177): codeine or hydrocodone (vs. tramadol): vomiting sign. less - 1 RCT (n=52): buprenorphine + tramadol (vs. morphine + tramadol): sign. less nausea	Method: - a quality appraisal of the included studies is mentioned, but no results are reported for the single trials, only an overall conclusion of a low quality of evidence Content:	1- (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
			Nausea and vomiting (opioid induced)	- 1 RCT (n=62): controlled-release morphine and oxycodone vs. transdermal buprenorphine and fentanyl: n.s. difference in nausea (but trend for a greater severity of nausea in morphine group) - 1 RCT (n=42): stop-and-go vs. 3-day switch from morphine/oxycodone to methadone: n.s. difference in nausea - 3 RCTs did not report clear conclusions on nausea/vomiting <u>Author's recommendations</u>: - A weak recommendation is given for switching from morphine to oxycodone in cancer patients with nausea. - A weak recommendation is given for switching from tramadol to either codeine or hydrocodone for pain in cancer patients with nausea. - A weak recommendation is given for switching from morphine/oxycodone to methadone using the three-day switch method in patients with increasing pain considered untreatable with further opioid titration and/or with opioid-related side effects	Low LoE (high risk of bias)	

11. Obstipation

11.1. Medikamentöse Therapie

11.1.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN (justification)
Bader, Schmerz 2012 [290]	SR (MA not possible)	10 studies (n=1136): 4 RCTs 6 controlled trials	Patients in end-of-life situations (most patients in these studies had cancer; n=994)	4 RCTs: 3 x methylnaltrexone vs. placebo 1 x naloxone/ oxycodone vs. placebo/ oxycodone 6 controlled trials: 1 x senna vs. lactulose 1 x Ayurvedic preparation (Misrakasneham) vs. senna 1 x Codanthramer vs. lactulose with senna 1 x senna vs. senna/ docusate 1 x naloxone 1 x polyethylene glycol (PEG), sodiumpicosulfate, lactulose	QoL reduction of symptoms frequency of defacation	Only for methylnaltrexone and naloxone evidence exists for opioid-induced constipation in patients with no risk of bowel perforation, which confirms the efficacy and safety of patients in palliative care settings. The studies on conventional laxatives approved the tolerance of lactulose, PEG, senna, sodiumpicosulfate and docusate in this population, but results of the included studies suggest, there is no evidence for the efficacy of one of these agents.	Evidence on medical treatment of constipation in palliative care is sparse and guidelines have to refer to evidence from outside of the palliative care setting and to expert opinions. Results from other studies with other patient groups can only be transferred with limitations to very ill patients at the end of life who might have a higher risk for potential side effects such was gastrointestinal perforation in case of abdominal tumour manifestation.	1+
Becker, Lancet 2009 [291]	SR; MA of McNicol included [292]	7 studies (with **methylnaltrone**; n=269): 5 RCTs 2 controlled trials	Studies with **methylnaltrexone**: Patients with incurable cancer or other end-stage disease n=133	Studies with **methylnaltrexone**; 5 RCTs: Placebo vs. mophine+placebo vs. morphine+methylnaltrexone	Effectiveness and safety of methylnaltrone and alvimopan: Transit time Time to bowel movement	**Methylnaltrexone** and alvimopan are better than placebo for reversal of opioid-mediated increase of gastrointensinal transit time and constipation.	• Alvimopan seems to have higher pharmacological potency than methylnaltrexone, but methylnaltrexone can be given	1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN (justification)
		12 studies (with **alvimopan**; n=4574) 12 RCTs	Healthy volunteers n=37 Patients with chronic methadone-induced constipation n=34 Patients with potoperative ileus n=65 Studies with **alvimopan** Healthy volunteers n=70 Patients with chronic methadone-induced constipation or opioid-induced bowel dysfunction n=765 Patients with postoperative ileus n=3739	Placebo vs. morphine vs. morphine+methylnaltreone 3xPlacebo vs. methylnaltrexone 2 controlled trials: methyl-naltrexone in different doses: 0.64mg/kg vs. 6.4mg/kg vs. 19.2mg/kg) 0.3mg/kg vs. 1mg/kg vs. 3mg/kg Studies with **alvimopan** Placebo vs. morphine vs. alvimopan Alvimopan+morphine vs. placebo+morphine vs. placebo Morphine+placebo vs. morphine+alvimopan 10 x placebo vs. alvimopan in different doses	Proportion of patients that laxated within 4 h of first dose Colonic motility Time to recovery of gastrointestinal functions	Based on included MA of McNicol [292] gastrointestinal transit time in patients given methylnaltrexone was reduced by 52 min (95% CI inal transit time s at the en Placebo - Methylnaltrexone reduced the mean transit time to 93altrexone was reduced by 52 min (95% CI) **Methylnaltrexone** (intravenous doses of 0.3–0.45 mg/kg and oral doses up to 19 mg/kg) is well tolerated and able to relieve constipation in methadone dependent individuals and patients with advanced illnesses who need high doses of opioids. **Methylnaltrexone** should be used in patients with opioid-induced bowel dysfunction who do not have a response to a reasonable laxative regimen, in combination with the laxative regimen. Recommended dose: 8 mg (38–61kg); 12 mg (62–114 kg) every 2 days. Outside these weight ranges: 0.15mg/kg. Defaecation can be expected within 4 h after the first dose in about 50% of patients.	via different routes, which might be beneficial for early postoperative or terminally ill patients, whereas alvimopan is available only orally. • External validity of the studies to the general population of patients is low.	

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN (justification)
						Alvimopan is effective in patients with postoperative ileus at doses of 6 mg or 12 mg daily.		
Candy, Cochrane 2011 [235]	SR; MA	7 RCTs (n=616)	• Participants at an advanced stage of disease (most participants had a cancer diagnosis). • Most common primary cancer site was the lungs. Participants with other diagnoses included advanced cardiovascular disease, AIDS and dementia. • Average age 61 to 72 years.	4 studies: laxatives lactulose, senna, co-danthramer, misrakasneham, magnesium hydroxide with liquid paraffinen 3 studies: methylnaltrexone	Change in frequency of defacation Ease of defacation Relief of systemic and abdominal symptoms related to constipation Change in quality of life Use of rescue laxatives	No differences in effectiveness were demonstrated between **lactulose** and **senna**, lactulose with **senna** compared to **magnesium hydroxide and liquid paraffin**, or between **misrakasneham and senna**. Between **lactulose and senna** versus **co-danthramer** was a significant difference, favouring the group who took lactulose and senna, in stool frequency. No significant difference between **lactulose and senna** compared with **co-danthramer** in participants' assessment of bowel function. All studies that compared different laxatives (one to three) participants suffered side effects. Most commonly reported events: nausea, vomiting, diarrhoea and abdominal pain. Subcutaneous **methylnaltrexone** is effective in	In studies comparing the different laxatives evidence was inconclusive. Evidence on subcutaneous methylnaltrexone was clearer Safety of subcutaneous methylnaltrexone is not fully evaluated. Large, rigorous, independent trials are needed. The study comparing lactulose and senna with magnesium hydroxide and liquid paraffin emulsion a participant from each group withdrew because of intolerable nausea and gripping abdominal pain. Participant preferences were only reported in two studies; one showed a preference for lactulose plus senna over magnesium hydroxide combined with liquid paraffin. The other found no difference in preference.	1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN (justification)
						inducing laxation after 4 hours in palliative care patients with opioid-induced constipation and where conventional laxatives have failed compared to placebo. Rescue free laxation within 4 hours: OR 6.95 (95% CI: 3.83 to 12.6). Rescue free laxation within 24 hours: OR 5.42 (95% CI: 3.12 to 9.41)		

11.1.2. Systematic Reviews der Aktualisierung 2019

Hier werden nur Systematic Reviews zu herkömmlichen Laxantien dargestellt. Für die Systematic Reviews zu Opioidrezeptorenantagonisten, siehe Kapitel Systematic Reviews der Aktualisierung 2019 und Primärstudien der Aktualisierung 2019.

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Candy, Cochrane 2015 [236] *(Partial update of review 2006/ 2011)*	SR To evaluate laxatives for constipation in people receiving palliative care	Databases: Design: double blinded RCTs Population: Patients in palliative care and advanced or end-stage irrespective of care setting	Interventions: any laxative Outcomes: 1.O: - Laxation response - Adverse events 2.O:	Study number: 5 RCTs (n=370 participations) Study quality: Population: cancer only	Method: Well conducted systematic review of double blinded RCTs Content	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
			- Participant preference - Relief of other constipation-associated symptoms (abdominal pain, nausea, vomiting and loss of appetite)	Intervention: laxatives lactulose, senna, co-danthramer, misrakasneham, docusate and magnesium hydroxide with liquid paraffin Outcomes: Docusate plus senna versus placebo plus senna: **Laxation response**: No statistical difference (in volume, difficulty, and complettness of defecation, and having a bowel movement on 50 % of the study days (for instance the OR was 0.52 (95% CI 0.17 to 1.57)). Bristol Stoll charts: between the trial arms significant difference (P= .001) in stool consistency; with more participants in the placebo plus senna group having Type 4 (smooth and soft) or Type 5 (soft blobs) stools, and more participants in the docusate plus senna group having Type 3 (sausage like) or Type 6 (mushy) stools. **Need for additional laxatives**: One type of additional laxative was given to 74% of participants in the placebo plus senna group and 68.6% of participants in the docusate plus senna group. The difference was not significant (P = .77). **Constipation-associated symptoms**: measured symptoms (as shortness of breath and drowsiness, using the Edmonton Symptom Assessment System) had no significant difference between the trial arms	Low to moderate QoL (most small sample size)	

12. Maligne intestinale Obstruktion (MIO)

12.1. Nicht-medikamentöse Verfahren: Parenterale Ernährung

12.1.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Naghibi, Clin Nutr 2015 [293]	SR; MA to establish an evidence base, of clinically relevant outcomes (survival time, QOL and cost effectiveness) in the palliative malignant inoperable bowel obstruction (IBO) patient group to help inform and guide clinical practice for HPN therapy.	Databases: MEDLINE, EMBASE, Web of Knowledge, CINAHL from 1970 onwards; English language only; handsearch Design: any design, except case reports/series Population: Palliative care adult patients confirmed diagnosis of malignancy with IBO treated with parenteral nutrition ± chemotherapy - Exclusion: studies with <80% of patients with inoperable bowel obstruction	Interventions: home parenteral nutrition (HPN) Outcomes: - QoL, measured by specific validated tools; - Survival length data - Complication - cost-effectiveness - …	Study number/design: - 1 retrospective cohort - 1 prospective pre-post study - 5 prospective case series - 5 retrospective case series Quality: variable quality and potentially subject to moderate risk of bias Population: n=437 Metaanalysis (n=244; 7 studies): - **Survival length**: median: 83 days (95% CI 67 to 100 days); mean: 116 days. 55% mortality at 3 months and 76% mortality at 6 months. I.e. only 45% of the patients treated with HPN for palliative MBO survive to 3 months Narrative analysis: - **QOL (**4 studies; validated tools in only 1 study): Limited evidence suggests that QOL deteriorated before death in a highly symptomatic group. - **Complications**: central venous catheter sepsis rate (5 studies): 0.4-2.89 per 1000 days; metabolic (3 studies): 0.32-1.37 per 1000 days	Content: - Meta-analyses reveal a short survival and health economic analysis demonstrates high associated costs - On current evidence, the identification of patients who are most likely to benefit from HPN should take account, but not depend entirely on the performance status at the time of starting HPN Quality incl. studies: - Limited quality of evidence - In 6 out of 12 studies, confounder chemotherapy; and in 8 out 12, confounder metastasis weren't reported	1+ (Body of evidence: 3)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				- **Re-admission rate** (1 study): 1.3 re-admissions per patient (8% directly related to PN) - **Survival by patient characteristics:** o Type of malignancy (3 studies): survival by GI malignancy > by gynecologic malignancy o Karnofsky performance status (2 studies): KPS>50 survived longer o Concomitant palliative chemo-radiotherapy (2 studies): no sign. difference between survival length of patients receiving therapy or not - **Cost effectiveness**: high cost	- In 5 out of 12 studies representativeness of cohort is not stated - QOL was measured with different tools, only 1 using a validated one Method: - Wide search strategy, clear inclusion criteria - variable definition for the starting point for measuring survival length (not necessarily from the start of PN)	
Sowerbutts, Cochrane 2018 [294]	SR; To assess the effectiveness of home parenteral nutrition (HPN) in improving survival and quality of life in people with inoperable MBO	Databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), Embase (Ovid), BNI, CINAHL, Web of Science and NHS Economic Evaluation and Health Technology, ClinicalTrials.gov and in the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal; handsearch; until January 2018 Design: any study with more than 5 participants Population: people over 16 y with inoperable MBO	Interventions: home parenteral nutrition (HPN) via a central venous catheter Outcomes: 1.O: - Survival length - QoL 2.O: - GI symptoms - Nutritional status - AE	Study number/design: 13 studies (n=721), of which 12 were uncontrolled; Quality of studies: high risk of bias Outcomes: **Overall survival length** (13 studies): - median survival intervals: 15 to 155 days (range: 3 to 1278 days) - mean survival intervals: 85 to 164 days (range 8 to 1004 days) **QoL** (3 studies with validated measures): results equivocal: - 1 study reported improvements up until three months	Well conducted systematic review; MA not possible due to heterogeneity of data Outcomes heterogeneity: - varying definition of overall survival - QoL: 3 studies with validated measures; different scales; measured at different time points	1++ (Body of evidence: 3)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				- 2 studies reported approximately similar numbers of participants with improvements and deterioration **AE** (8 studies): central venous catheter infection by 32 of 260 (12%) patients	Author conclusions: Due to the very low certainty of evidence, we are very uncertain whether parenteral nutrition (PN) improves length and quality of life in people with malignant bowel obstruction (MBO).	

12.1.2. Primärstudien

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Aria Guerra, Nutr Hosp 2015 [295]	Prospective pilot case series; To identify the effects of parenteral nutrition in these patients regarding prognosis	n=55 mean age: 60±13y	Patients with advanced cancer and intestinal occlusion with peritoneal carcinomatosis, considered candidates for chemotherapy	Parenteral Nutrition (PN) aimed 20-35kcal/kg/day	- Survival rate from the start of PN - Hospital discharge - Continuation with home parenteral nutrition and ambulatory chemotherapy - Performance status (ECOG) - Body mass index (BMI) - Weight loss	Median **survival** from start of nutrition = 40 days (range:2-702) - Survival from the start of PN did not vary significantly with regard to the baseline ECOG, BMI or previous chemotherapy - Survival in patients who received PN after hospital discharge was higher than of those	- PN in oncologic patients with intestinal occlusion and peritoneal carcinomatosis might enhance survival when associated with a response to chemotherapy - Small sample - Descriptive design	3

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
					- The Malnutrition Universal Screening Tool (MUST)	who stayed in-hospital (log rank = 7.090, P= 0.008) - Survival of patients who received chemotherapy during or after PN was higher than those who did not (log rank = 17.316, P < 0.001) - Multivariate Cox proportional hazards test: BMI, home PN and ambulatory chemotherapy after hospital discharge as the significant factors associated with survival		
Chouhan, J Cancer Med 2016 [296]	Retrospective case series; to examine a large dataset to describe outcomes associated with concurrent TPN and systemic chemotherapy for persistent MSBO after conservative management	n=82 51 women; median age: 55 age range: 17 to 85 y.	Patients with Malignant Small Bowel Obstruction (**MSBO**) who receivend concurrent systemic chemotherapy and TPN ≥8 days	Intravenous systemic chemotherapy + TPN ≥8 days n=82 (+ surgery n=6)	- overall survival - Radiographic response to chemotherapy - MSBO resolution - hospitalization - duration of stay in hospital - TPN-related AE (hyperbilirubinemia, infections) - …	- MSBO resolution: n=10 (attributable to: surgery=3; chemotherapy=5; none=2); recurrence: n=6/10 - Median overall survival: 3.1 months (0.03–69.4) - One year overall survival rate: 12,6% - 1 year survival: 12.2% - 76,8% rehospitalized - Median in patient stay: 26.5 days - TPN-related AE: 32.9%	Content: Concurrent chemotherapy + TPN resulted in low efficacy and a high morbidity and mortality, and thus should not represent a standard approach. Method: - Relative small sample - Heterogeneity in patient population, tumors and treatment - Retrospective design	3

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Diver, Gynecolog Onc 2013 [297]	Retrospective case series (chart review); to review a single institution's experience with gastrostomy tubes (GTs) performed for malignant bowel obstruction by gynecologic cancer	n=115 - median age: 57 - age range: 26-88y. n=41/115 TPN (± chemotherapy)	Female patients with gynecologic cancer (84% ovarian cancer)	Gastrostomy tube (GT) placement for palliation of symptoms MBO: n=115 + TPN only: n=19 + chemotherapy only: n=23 + TPN and chemoth.: n=22	- Overall survival after GT - Overall survival by TPN after GT	- Median time for GT placement after cancer diagnosis: 2.2 years - Overall survival after GT placement: 5.57 weeks (1day - 5.5 y.; n=115) - **Median survival by TPN** after GT (± chemotherapy): 9.6 weeks (4 days- 4.7 years); no TPN: 4.3 weeks; p<0.003 - Median survival by chemotherapy (±TPN) after GT: 13.3 weeks (5 days- 5.5 years)	Content: - GT near the end of life had a high rate of complications requiring medical intervention. - TPN was independently associated with a survival benefit - Chemotherapy associated with better survival Method: - TPN investigated in association with GT ± chemotherapy - Small sample - Descriptive design	3
Hu, Eur Rev Med Pharmacol Sci 2014 [298]	Cohort controlled study (unclear if prospective or retrospective); ; unclear whether randomized or not – selection criteria for both groups are unclear To build a quantitative	n=60 (study group: n=30; control: n=30)	Patients with MBO - I: n=30 (n=26 incomplete MBO) - C: n=30 MBO radiologically confirmed (X-Ray, US or CT)	- I: small intestinal decompression + enteral nutrition - C: nasogastric decompression + parenteral nutrition (PN)	- Body weight - Albumin, prealbumin Measurement: T0 and T1 (=14 d after intubation) - Complication rate during treatment (Vomiting, diarrhea, abdominal distension, metabolic disorders and liver damage)	**Body weight:** sign. higher in Intervention group - I (kg, $x + s$): 1.96+1.38 - C: 0.66+0.87 - t= -4.35, p<0.05 **Gain of albumin and prealbumin**: sign. improved in Intervention group - Albumin: t = -4.789, p<0.001 - Prealbumin: t = -2.218, p<0.05	- Unclear if recruitment occurred pro- or retrospectively, randomized or not in both groups - Radiological diagnosis for inclusion was not always CT (gold standard) - No patient-related outcomes - No baseline data on outcomes - Type of complications not reported - Conclusion on effect of PN very	2-

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
	assessment system for normative cancer pain management					**Complication rate:** sign. lower in Intervention group - I: n=8 - C: n=26 - $\chi 2 = 21.9910$, $p<0.01$	limited, as PN combined with tube	
Rath, Gynecol Oncol 2013 [299]	Retrospective case series; To evaluate peri-operative and survival outcomes of ovarian cancer patients undergoing percutaneous upper gastrointestinal decompression for MBO	n=53	Patients with ovarian, peritoneal, or fallopian tube cancer who underwent palliative decompressive treatment for MBO	palliative decompressive treatment (PDT) for MBO; TPN after PDT: n=21 (39.6%)	Outcomes associated with TPN: Survival (General outcomes associated with PDT: - Complications - Symptom relief (nausea, vomiting) - Oral intake)	- **Survival**: Those who received TPN, with or without chemotherapy, had similar survival to those who did not receive TPN	- Small sample of patients receiving TPN - Retrospective design - Effects of TPN not the primary focus of the study; TPN always associated with PDT	3

12.2. Medikamentöse Therapie

12.2.1. Sekretionsinhibitoren (Somatostatin-Analoga, Scopolamin)

12.2.1.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Klein, Schmerz 2012 [300]	SR; To investigate the current evidence of pharmacological treatment for MBO during the last days of life.	Databases: Medline, Embase, from 1966 to 2011; handsearch Design: no inclusion criteria mentioned Population: Patients with intestinal obstruction and cancer, MS, AIDS/ HIV, heart or lund disease, or AML	Interventions: - **Antisecretory drugs** - Corticosteroids Outcomes: effect on symptoms	Population: all cancer Antisecretory drugs: - Study number: 3 RCTs + 14 uncontrolled prospective studies - Outcomes: RCTs (octreotide vs. Butylscopolamine): sign. superiority of octreotide in reducing **nausea/vomiting** and **GI secretions**. Uncontrolled studies: overall positive effect of octreotide on symptoms Steroids: see “Glucocorticoids”	- Sensitive search strategy - Inclusion criteria not described - Interventions with fixed combination of drugs included - Study quality assessment not described	1- (Body of evidence: not statable)
Obita, J Pain Symp Manag 2016 [301]	SR; To evaluate the evidence of effectiveness of somatostatin analogues compared with placebo and/or other pharmacologic agents in relieving vomiting in patients with inoperable MBO	Databases: Medline, Embase, Cinahl, Cochrane Trials from 1979 to August 2015; handsearch Design: RCTs and quasi-RCTs; consecutive cohort studies included for toxicity Population: Adults with inoperable MBO	Interventions: Somatostatin analogues (SAs) Outcomes: Change in symptoms; toxicity	Study number: 7 RCTs: - octreotide vs. placebo (2) - lanretotide vs. placebo (1) - octreotide vs. hyoscine butylbromide (HB) (4) Population: total of 427 patients (220 administered SAs) Doses: - octreotide (6 RCTs): 300 to 800 µg/d, sc infusion - lanreotide (1 RCT): 30mg im, every 10 days - HB: 60-80mg/d, sc infusion Outcomes: **Vomiting**:	- MA not possible because of heterogeneity of studies - 5 RCTs with high or unclear risk of bias; 2 RCTs with low risk of bias - no agreed clinically relevant outcome measure or time point for nausea and vomiting in the palliative care setting	1++ (Body of evidence: 1+)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				- 2 RCTs with low risk of bias: no benefit of SAs vs. placebo - 4 RCTs with high/unclear risk of bias: benefit of SAs over HB, but in general effect not sustained **Pain**: - 2 RCTs with low risk of bias and 2 with high/unclear risk: no benefit of SAs vs. placebo (2) or HB (2) - 2 RCTs with high risk of bias: benefit of SAs on continuous (but not on colicky) pain **Adverse effects**: In general, SAs well tolerated with a few mild adverse events (i.a. cases of diabetes mellitus, dry mouth, minor skin reaction)	- Natural history of MBO largely unknown - Role of SAs requires further clarification	

12.2.1.2. Primärstudien

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
De Conno, J Pain Sympt Manag 1991 [302]	Case series; (no aim mentioned)	n=3	Patients with inoperable MBO caused by advanced ovarian cancer cancer ; nasogastric tube (NGT)	**hyoscine butylbromide** (HB) via subcutaneous infusion Doses: 80 to 120mg/d until death	- Volume of GI fluids through NGT - Colicky pain - Adverse events	**GI fluids**: sign. reduction for every single patient, with p< 0.05. NG tube removed after 1 week	- Very small sample - Limitations of descriptive case series	3

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
						Colicky pain: reduction during 1st week of treatment **Adverse effects**: xerostomia by all patients; no sedation; 1 case of visual and micturition disturbance		
Mercadante, Support Care Cancer 2000* [303]	RCT; here: pre-post results for hyoscine butylbromide (HB)	n=6 (HB arm) per protocol	Patients with inoperable bowel obstruction	Hyoscine butylbromide (HB): 60mg/d sc for 72h (RCT: HB vs. Octreotide: see SysRev Obita et al.)	- Episodes of vomiting - Nausea - Drowsiness - Dry mouth - Continuous and colicky pain Measure: Likert scale (0-3) Period: before (T0), 24 h (T1), 48 h (T2) and after (72 h) (T3)	Pre-post comparison for HB (mean ±SD): - **Vomiting**: - T0: 5.3±0.9 - T3: 2.4±0.7 (P<0.05) - **Nausea, drowsiness, dry mouth, pain**: n.s.	- Very small sample - Unclear risk of bias	3
Peng, J Surg Oncol 2015* [304]	RCT; here: pre-post results for scopolamine butylbromide (SB)	n=49 (SB arm)	advanced ovarian cancer patients with inoperable MBO	Scopolamine butylbromide (SB): 60 mg/d for 3 days, continuous sc infusion	- Daily volume of GI secretions through NGT - episodes of vomiting - nausea - dry mouth - drowsiness - continuous pain - colicky pain Measure: Likert scale (0-3)	Pre-post comparison for SB (mean ±SD): - **GI secretions** (ml): - T0: 1,48± 432.4 - T3: 783.4± 258.6 - (P<0.05) - **Vomiting** : - T0: 5.4±0.8 - T3: 2.0 ±0.8 (P<0.05) - **Other symptoms**: n.s.	- Primary outcome unclearly defined - Outcome assessment not clearly stated	3

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O=secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
					Period: before (T0) and 24 h (T1), 48 h (T2), and 72 h after (T3)			
Ripamonti, J Pain Sympt Manag 2000* [305]	RCT; here: pre-post results for scopolamine butylbromide (SB)	n=8 (SB arm)	patients with a decompressive NGT and MBO	Scopolamine butylbromide (SB): 60mg/24h for 3 days, continuous sc infusion (RCT: SB vs. Octreotide: see SysRev Obita et al.)	- Daily volume of GI secretion through NGT - Symptom intensity: - Continuous pain - Colicky pain - Nausea - Dry mouth - Thirst - Dyspnea - Abdominal distention - Drowsiness Measure: VRS 0-3 Period: T0, daily for 3 days (T1, T2, T3)	Pre-post/within-group comparison for SB: - **NGT secretions** (n=5): n.s. - **Continuous pain** (n=8; means): - T0: 1.37 - T3: 0.37 - (P=0.039) - **Colicky pain** (n=8; means): - T0: 0.87 - T1: 0.37 - (T0 vs. T1:P=0.046); - T0 vs. T3: p<0.05) - **Other symptoms**: not data reported	- Very small sample - Unclear risk of bias	3

* Diese drei im Systematic Review von Obita et al. [301] eingeschlossenen RCTs vergleichen Octreotid und Scopolamin. Da diese Studien einen Prä-Post-Vergleich des Studienarmes Scopolamin durchführen, die Ergebnisse davon aber im Systematic Review nicht beschrieben sind, wurden sie hier gesondert extrahiert und wie prospektive Prä-Post-Studien bewertet. Für die Ergebnisse zum randomisierten Vergleich von Octreotid und Scopolamin, siehe Obita et al. in der oben aufgeführten Evidenztabelle (Kapitel 12.2.1.1). Diese Prozedere wurde gewählt, da die Literaturrecherche keine Studie identifizieren konnte, die Scopolamin gegen Placebo vergleicht. So wurden Studien niedrigerer Evidenzklasse eingeschlossen (Beobachtungsstudien).

12.2.2. Glucocorticoide

12.2.2.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Klein, Schmerz 2012 [300]	SR; To investigate the current evidence of pharmacological treatment for MBO during the last days of life.	Databases: Medline, Embase, from 1966 to 2011; handsearch Design: no criteria mentioned Population: Patients with **intestinal obstruction and cancer, MS, AIDS/ HIV, heart or lund disease, or AML**	Interventions: - **Corticosteroids** - Antisecretory drugs Outcomes: effect on symptoms	Population: all cancer Steroids: - Study number: 3 RCTs (same as in Feuer et al.) + 2 prospective uncontrolled - Results: vgl. Feuer et al. Antisecretory drugs: see "antisecretory drugs"	- Sensitive search strategy - Inclusion criteria not described - Interventions with fixed combination of drugs included - No study quality assessment	1- (Body of evidence: not statable)
Feuer, Cochrane 2000-2006 [306]	SR, MA; To locate, appraise and summarise evidence from scientific studies on intestinal obstruction due to advanced gynaecological and gastrointestinal cancer, in order to assess efficacy of corticosteroids	Design: RCTs, cohort, case-control, longitudinal, case series Databases: Medline, Embase, CancerCD, Cochrane, CINAHL from inception to 2006; handsearch Population: Patients with MBO due to **advanced gynaecological and gastrointestinal cancer**	Interventions: **Corticosteroids** Outcomes: 1.O: clinical resolution within 10 days 2.O: - time to resolution of symptoms of pain, nausea and vomiting, - reduction in further episodes of bowel obstruction, - mortality, - morbidity, - QoL	- Study number: 10 (3 RCTs, 1 prospective uncontrolled; 6 retrospective uncontrolled) - Population: 89 patients included in RCTs - Drug: iv dexamethasone 16 mg/d; iv methylprednisolone 40 to 240mg/d (RCTs) - Control: Placebo Metaanalysis : Included studies: 3 RCTs Results: 1.O (**resolution**): n.s. but positive trend (Random effects model: OR=0.51; 95% CI 0.19, 1.43); NNT: 6 2.O: - **Mortality**: n.s. (OR=.91; 95% CI .37, 2,23) - **Others**: MA not possible Narrative results (all trials): **morbidity** associated with steroids very low	- Older RCTs good quality with inclusion in meta-analysis; other studies poor quality. - Good methodical quality of the SR - Small patient's collective -	1++ (Body of evidence: 1+)

12.2.2.2. Primärstudien

Das Update des Cochrane Review von Feuer et al. [306] ergab keine weiteren Primärstudien.

12.2.3. Antiemetika (5HT3-Antagonisten, H1-Antagonisten, Antipsychotika, Prokinetika)

12.2.3.1. Primärstudien

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Kaneishi, J Pain Sympt Manag 2012 [307]	Single-center, retrospective uncontrolled observational study; To explore the antiemetic activity of olanzapine against nausea and vomiting in cancer patients with incomplete bowel obstruction.	n=20 (7 male; mean age 64.7 ±14.9, range 35-90 y.)	**Cancer** patients **with incomplete bowel obstruction** receiving olanzapine for the relief of nausea/ vomiting, from medical records 2007-2009	**Olanzapine**: - average dose: 4.9 ± 1.2mg - average treatment duration: 23.4 ± 16.2 days	- Intensity of nausea - Frequency of vomiting per day - Adverse effects (AE) - Measure : assessed daily by nurses for all patients; at the point before starting treatment and for 3 days after administration of the drug; translated retrospectively as four scales (scores)	- Incomplete bowel obstruction in the upper (n=11) and lower (n=9) intestines - **Nausea**: sign. improvement (Pre: mean 2.4 ±0.7 SD; Post: 0.2 ±0.4; P<0.001) - **Vomiting**: sign. decrease: Pre: mean 1.1 ±1.3 SD times/d (median 0.5; range 0-4); Post: 0.3 ±0.5 times/d (median 0; range 0-1); P<0.01) - **AE**: drowsiness (n=2) and dizziness (n=1)	- Small patient sample - Retrospective and uncontrolled (selection, performance, detection bias) - Unclear if mechanical obstruction or paralytic ileus	3

12.2.4. Kombination aus verschiedenen Wirkstoffklassen

12.2.4.1. Primärstudien

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Analytic experimental studies								
Tuca, J Pain Sympt Manag 2009 [308]	Multi-center, prospective, uncontrolled phase II clinical trial; To assess antiemetic efficacy of granisetron in inoperable intestinal obstruction caused by advanced cancer	n=24 (10 male; mean age 61,3 [SD 13.0; 40-83] Drop-out: 1	Adult patients with inoperable MBO on palliative care unit and with nausea/ vomiting (clinical and radiological diagnosis)	- I: **Granisetron** (3mg iv every 24h) + **Dexamethasone** (4mg iv every 12h) for 96h. Dexamethasone administered because of potential effect on resolution of MBO. - If adequate response, treatment continued for 7 days. - C: no - Rescue: haloperidol, morphine; after 96h, antisecretory drug allowed. - Nasogastric drainage not allowed - Co-medication: analgesics (Baseline: nonopioid n=7; weak opioid n=1; strong opioid n=16. Switch on morphine at trial begin, if patients were on a non-morphine strong opioid therapy prior to intervention)	- Symptoms (nausea, continuous pain, colic pain, anorexia, asthenia) on NRS (0-10) - Number of vomiting episodes - Need for antiemetic or analgesic rescue doses in the last 24 hours - Adverse effects Measure at baseline and every 24h during 96h; follow-up period: max. 7 days Treatment failure defined as nausea >4 on NRS, vomiting 2/day or more, and rescue therapy with haloperidol at 5 mg/day or more	Scores in mean ±SD at baseline and at 96h: - **Nausea**: sign. decrease (6.9 ±1.7 vs. 0.8 ±1.9; P < 0.001) - **Episodes of vomiting**: sign. decrease (5.3 ±2.99 vs. 1.0 ±1.7; P < 0.001) - **Continuous pain**: sign. decrease (4.4 ±3.2 vs. 1.2 ±2.2; P<0.001) - **Colic pain**: sign. decrease (3.3 ±3.6 vs. 0.4 ±1.0; P<0.001) - All significant results were already significant at 24 h - **Asthenia, anorexia**: n.s. - 3 patients (12.5%) were considered treatment failures - n.s. trend toward greater efficacy in	- Relative small patient sample - Selection bias through consecutive enrollment of patients reduced - Antiemetic effect of dexamethasone as potential confounder - 23 patients on antiemetic treatment prior to trial. Washout only if pre-intervention treatment was ondansetron - Switch on morphine at trial begin (n=16), if patients were on a non-morphine strong opioid therapy prior to intervention to enhance comparability	3

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
						the lower and multiple levels of MBO		
Ventafridda, Tumori 1990 [309]	Prospective uncontrolled pre-post trial; To assess vomit and pain control in terminal cancer patients with Inoperable gastrolntestinal obstruction, using a pharmacologlc symptomatic treatment which prevents recourse to nasogastrlc tube placement and Intravenous hydration	n=22 16 women; age range: 40 to 80y.; mean± SD: 57.9 ± 10.6).	Patients with inoperable MBO (clinical and radiological diagnosis)	**Scopolamine butylbromide**, **morphine** and **haloperidol:** combination of 2 or 3 drugs according to symptoms. Continuous sc or iv infusion	- Pain - Episodes of vomiting - Adverse effects: dry mouth, drowsiness, thirst sensation Measure: - Pain: 5 points NRS x daily hours of pain = score range 0-240 - Dry mouth, drowsiness: 4 points Likert scale Period: T0, 48h (T2), 2 days before death (T-2)	Drug combination: - 3 drugs: n=9 - 2 drugs: n=9 - 1 drug: n=4 **Pain**: sign. decrease - T0-T2: t=8,06; df=21; p<0.001) - T2-T-2:t=2,25; df=21; p<0.05 - Vomiting: - T0: 12 patients with ≥4 episodes/d; 5 pts. with 2-3 times/d - T2: 8 patients with 0 episodes; 4 with 1 episode/d; 3 pts. with treatment failure - T-2: results maintained **Dry mouth**: sign. increase (chi square=6, df=1, p<0.05) **Drowsiness**: sign. increase (chi=20,8; df=1; p<0.001)	- Intervention not identical for all patients - Small sample - Heterogeneous symptom level at baseline	3
Descriptive case series								
Berger, Am J Hosp Palliat	Retrospective case series (chart review);	n=12 MBO (clinical and radiological diagnosis)	Patients with MBO (clinical and radiological diagnosis) or MBD	Octreotide, MCP and dexamethasone combined	- Nausea - Pain (subjective improvement)	Results for MBO patients: - **Nausea**: 11/11 patients with	- Small sample - Descriptive design - Drug doses not reported	3

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Med 2016 [310]	To describe the effect of octreotide, metoclopramide, and dexamethasone in combination on symptom burden and bowel function in patients with malignant bowel obstruction and dysfunction	n=7 malignant bowel dysfunction (MBD) suggesting MBO, but no radiological diagnosis	MBO group: - 11/12 with moderate/ severe nausea; - 7/12 with mod./ severe pain - 8/12 with evaluable data on resumption of oral intake		- Time to resumption of oral intake	mod./severe nausea had subjective improvement at day 1 - **Pain**: 7/7 patients with mod./severe pain had tolerable pain at day 1 - **Time to oral intake** (8 patients evaluated): median=2 days (1-6 days)		
Ibister, J R Coll Surg Edinb 1990 [311]	Prospective case series; (no aim mentioned)	n=24	Patients with MBO managed conservatively (radiological or previous operative evidence of MBO); Mean age: 63 y. (range 40-82)	MCP and morphine - mean dose of morphine infused: 9.2mg/h (95% CI 8.2-10.2) - mean dose of MCP: 6.9mg/h (95% CI 5.1-8.7)	- Pain - Vomiting - Survival	**Mean survival rate**: 29.2 days (95% CI 11.2-47.2; range 2-100 days) No descriptive statistics on symptoms	- few data reported - descriptive study	3
Laval, J Pain Sympt Manag 2006 [312]	Single-center, prospective descriptive case series; (no aim mentioned)	n=75 (with 80 episodes of MBO); 51 women; median age: 64 y.(22-99 y.)	Patients with inoperable MBO (clinical and radiological diagnosis)	Step therapy: 1) **Antipsychotics** (haloperidol or chlorpromazine) + **Anticholinergic** (scopolamine) + Corticosteroids (CS) + Analgesics (WHO) for 5 days 2) No obstruction relief: **octreotide** for 3 days	- Obstruction relief - Symptom control	No statistical pre-post comparison; Descriptive results: - Step 1: 31% obstruction relief; 31% satisfactory symptom control without obstruction resolution	- Consecutive recruitement - Relative large sample - Descriptive study	3

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
				(stop scopolamine, stop or reduce CS) 3) No vomiting stop: **venting PEG**		- Step 2: 14% satisfactory symptom control - -> 76% symptom control - Step 3: 12% PEG - -> 90% symptom control - -> 10% refractory vomiting and long term NGT necessary		
Mercadante, J Pain Symptom Manage 2004 [313]	Prospective descriptive case series; (no aim mentioned)	n=15	Patients with inoperable MBO (clinical and radiological diagnosis)	**Octreotide** 0.3 mg/ day, **metoclopramide** (MCP) 60 mg/day, and **dexamethasone** 12 mg daily, in iv infusion + initial bolus of 50 mL of **amidotrizoate** po Co-medication: **opioids** (n=11/15)	- episodes of vomiting - time to achieve an effective bowel movement - survival	- Recovery of intestinal **transit** within 1-5 days (more commonly within 2 days) - **vomiting** generally disappeared within 24 h; sustained until death - mean **survival**: 44.9 days (13–187)	- Small sample - Consecutive recruitment - Descriptive study	3
Porzio, Support Care Cancer 2005 [314]	Prospective descriptive case series	n=11	Patients with inoperable MBO treated at home (clinical diagnosis only)	**octreotide** (0.3 mg/24 h; escalation if necessary), **metoclopramide (MCP)** (1 mg/kg/24 h) and **morphine** (dose patient-tailored) mixed in sc infusion; and **dexamethasone** (16 mg/day iv bolus)	- Episodes of vomiting/day - Survival - Doses of octreotide	- Resolution of gastrointestinal **symptoms** and recovery of **bowel movements** within 5 days - 2 patients with recurrence successfully re-treated - No NGT needed - No pain exacerbation after MCP observed	- Small sample - No radiological diagnosis of MBO - Consecutive recruitment - Descriptive study	3

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
						- Survival: 10 days to 8 weeks		
Weber, Am J Hosp Palliativ Care 2009 [315]	Case series; (no aim mentioned)	n=4	Patient with MBO (clinical and radiological diagnosis)	**Octreotide** (300-1500 mcg/8h bolus sc), **corticosteroids** sc (dexamethasone or prednisone), **antiemetics** (ondansetron iv or MCP sc) and **opioids** sc, transdermal or intrathecal (3/4 patients)	- Pain (VAS 0-10) - Need for NGT insertion - Survival	- **Pain**: very good control (VAS: 0 to2/10) - Mean **survival**: 57 days (51-64) - Need for long-term **NGT**: 1/4 patients	- Very small sample - No baseline values for pain - Descriptive	3
Descriptive case reports								
Mercadante, J Pain Symptom Manage 1998 [316]	Case report; To demonstrate the value of combining scopolamine butylbromide, and octreotide in a patient with a high level of obstruction, whose GI symptoms were uncontrolled when either drug was administered alone	n=1	Patient with inoperable MBO (clinical and radiological diagnosis);	**Octreotide** (0.3 mg/d) and **scopolamine** (80 mg/d) combined (after treatment failure with each drug alone) and **fentanyl** (1mg/h) + **ketamine** (200-40 mg/d) **iv**	- Vomiting - Pain	- Episodes of **vomiting** stopped by combination of octreotide and scopolamine (each drug alone had failed to reach symptom control) - Satisfactory **pain** control under combination of fentanyl and ketamine	Case report design	3
Thaker, Indian J Palli Care	Case report; (no aim mentioned)	n=1	Patient with MBO (clinical and radiological diagnosis)	**Octreotide** (100 mcg/ 8h sc), **MCP** (10 mg/ 8h sc) and **dexamethasone** (4 mg/12h sc)	- Vomiting - Pain - Abdominal distention	- Symptom improvement after 2-3 days (vomiting; abdominal distention; pain)	Case report design	3

Reference	Type of study/Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
2010 [317]				Co-medication: **Morphine** sc				

13. Maligne Wunden

13.1. Medikamentöse Therapie

13.1.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Adderley, Cochrane 2014 [318]	SR; to review the evidence of the effects of dressings and topical agents on quality of life, and symptoms that impact on quality of life, in people with fungating malignant wounds.	Databases: CENTRAL (Cochrane Library), MEDLINE, EMBASE, CINAHL (until 2013); handsearch Design: RCTs, CCTs Population: patients of any age with **fungating wounds** due to any type of carcinoma	Interventions: - Topical agents: all agents, including antimicrobial drugs and topical cytotoxic agents. - Dressings - Dressing system: combination of topical agent and dressings Outcomes: 1.O: QoL 2.O: - Containment or regression - Malodour - Cutaneous pain - Exudate - Haemorrhage - Cost	Study number: 4 RCTs Miltefosine 6% solution vs. placebo (1 RCT, 52 patients): - **Containment/regression**: time to treatment failure sign. longer compared to placebo: median 56 d (range: 8-234) vs. 21 d (8-197), p=0.007 - **Pain**: n.s. Honey-coated vs. sliver-coated dressings (1 RCT, 75 patients): - **Containment/regression** : n.s. median decrease in wound size (15 cm^2 vs. 8 cm^2, p=0.563) - **Malodour**: n.s. - **Pain**: n.s. - **Exudate**: n.s. Metronidazole gel vs. placebo (1 RCT, 11 patients): - **Malodour**: n.s. difference between groups Foam dressings with silver vs. without silver (1 RCT, 26 patients): - **Malodour:** sign. decrease in 76,9% of patients vs. 30,8%, p=0,049 QoL, haemorrage: no data	Method: - Good conducted SysRev Content: - Quality of included studies: all RCTs had high risk o bias; small to very small sample size - Weak evidence (1 RCT) that 6% miltefosine solution applied to superficial fungating breast lesions <1cm (previous radiotherapy, surgery, hormonal therapy or chemotherapy for breast cancer) may slow disease progression. - Very weak evidence that foam dressings containing silver may be effective in reducing malodour.	1++ (body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
					- Insufficient evidence with regard to improving quality of life or managing pain, exudate or haemorrhage	
Da Costa, J Pain Sympt Manag 2010 [319]	SR; to collect evidence about topical treatments to control the odor of MFW (malignant fungating wounds)	Databases: MEDLINE, EMBASE, CINAHL, Thesis Bank, Capes, Digital Library of Theses and Dissertations, Proquest Dissertation and Theses, Current Controlled Trials, PsycInfo, Scopus, and Web of Science, Lilacs, EBM Reviews, until 2006; handsearch Design: any design, except qualitative and narrative reviews Population: Patient: individuals with **malignant neoplasms** who developed MFWs	Interventions: different topical agents and/or dressings available Outcomes: control or improvement of **odor**	Study number/design: 2 RCTs, 5 uncontrolled trials, 5 case series, 8 case reports Metronidazole topical, 0.75-0.8% (1 RCT, n=11; 3 uncontrolled trials; 6 descriptive case series/studies): n.s. reduction of odor in RCT; reduction in other studies. Mesalt® dressing (absorbent material with NaCl) (1 RCT): sign. improvement of odor (n=6; T=0) Curcumin ointement (1 OS, non-controlled, n=111): reduction of odor in 90% of patients Activated carbon dressings (1 uncontrolled OS, n=12; 1 case report, n=2): reduction of incidence of odor from 67% to 42% Essential oils (4 case series/report, n=36): reduction of odor (no further data stated) Topical arsenic trioxide (1 case report, n=2): reduction of odor Green tea extract (1 case series, n=4): reduction of odor Hydropolymer dressings (1 case report, n=1): complete resolution of odor	Methods: No mention of independent review of study selection by a second author Content: few studies, few RCTs, small sample sizes, absence of measurement instruments or scales - Higher LoE for Metronidazole and Mesalt® (RCTs and observational studies) - Low LoE for activated carbon dressing and curcumin ointment (uncontrolled OS) - Very low LoE (descriptive studies) for other interventions	1+ / 2+ (Body of evidence: variable, according to the intervention type)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				Antiseptic solutions (1 case report, n=2): in combination with other agents; resolution of odor Hydrogels (1 case report; n=2): reduction of odor Debridement enzymes (1 case report; n=2): reduction of odor		
De Castro, JHPN 2015 [320]	SR; The use of metronidazole as a topical therapy for odor control in malignant fungating wounds	Databases: MEDLINE, Cochrane Library, Lilacs, EMBASE, CINAHL until July 2013 Design: clinical trials Population: patients with malignant fungating wounds (with order)	Intervention: Topical metronidazole Outcomes: **Odor** control	Study number/design: - 1 RCT (n=9) - 2 uncontrolled studies (n=16 and n=5) Intervention: Metronidazole gel: 0,75 to 0,8% Outcome: - RCT (metronidazole vs. placebo): n.s. trend in favour of metronidazole in RCT in between group comparison (sign. reduction of odor in in-group comparison) - Uncontrolled trials: odor reduction in 24h or absence in 5 to 14 days	Method: uncomplete description of study design and results Content: - Very small samples of included trials; - Randomization of RCT not described; limited conclusions on significance of results by sample of n=9; - The poor available evidence does not allow to draw conclusions on the effectiveness of topical metronidazole 0,75% to 0,8% to control the odor of malignant fungating wounds	1+ to 2+ (Body of evidence: variable, according to the intervention type)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Dissemond, J Dtsch Dermatol Ges 2017 [321]	SR; to review the scientifi c basis of wound treatment using silver, taking into account the numerous studies of recent years as the basis for a practical recommendation for its clinical use.	Databases: Pubmed, Embase, and Cochrane databases, manual search; till 2015 Design: RCTs, comparative studies Population: **any type of wound** (not clearly defined in the inclusion criteria)	Intervention: wound treatment using silver Outcomes: wound resolution (healing, wound closure, wound size/area reduction, completed repithelialization), quality of life including pain; cost-effectiveness; and three, reduction of bacterial load (bioburden)	Study number: 157 studies: - 34 SysRev and meta-analyses - 31 RCTs and 8 comparative studies - 32 case series or case studies - 31 preclinical studies (in vitro, animal) - 21 studies on biofilm > Only the RCTs and comparative studies were included in the narrative analysis Quality of clinical studies (RCTs/ comparative studies): evalutation not performed Population of the 28 clinical studies with sign. results (other studies not described): - Burn injuries (8 RCTs, 1 comparative study) - Venous leg ulcers (9 studies) - Pressure ulcers (3 studies) - Chonic wounds (2 studies) - Diabetic foot ulcer (1 study) - Other wounds (5 studies) Outcomes: - **Wound resolution**: sign. improved in 16 clinical studies - **QoL (incl. pain)**: sign. improved in 12 studies - **Cost-effectiveness**: sign. improved in 8 studies - **Bioburden**: sign. reduced in 8 studies	Method: - Unclear terminology: no meta-analysis performed, despite being the title of the article - inclusion criteria not clearly defined - Diverging reporting of the number of included studies between abstract and fulltext - CoI by all authors - Quality evaluation of the included studies not performed “as all studies included had been published in peer-reviewed journals” - Out of the included SysRev and meta-analysis, only the main conclusion was mentioned, but not integrated in the narrative analysis - Uncomplete report of the non sign. results in the narrartive analysis. Content: - No results on malignant wounds	1- (Body of evidence: not statable)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Finlayson, ONF 2017 [322]	SR; to explore topical opioids, antimicrobials, and odor reducing-agents for preventing or managing malignant wound pain, infection, and odor	Databases: MEDLINE, EMBASE, Cochrane Library, CINHAL, and reference lists identify relevant studies; till 2015 Design: RCT, nonrandomized Intervention Studies with pre/post-Outcomes Population: Patients with cancer and a **malignant wound** (fungating, infiltrative, ulcerating)	Intervention: **topical analgesics** with/ without additional inert substances for the management of pain and/or **topical antimicrobials** with/ or without additional odor-reducing topical agents for the prevention or management of infection and infection-related-odors. Outcomes: 1.O: - Pain - Use of adjuvant pain medications or breakthrough medications 2.O: - Indicators of infection - Subjective measures of odor	Study number/design: 4 RCTs, 1 nonrandomized study Metronidazole gel - 0.8% vs. placebo (Double-Blind RCT, n=9): n.s. differences in **odor** between groups - 0.75% (Open-label, single-arm study, n=16): significant decrease in **odor** in pre-post comparison ($p < 0.05$) Green tea: (Unblinded RCT, n=30): n.s. difference in **odor** Manuka honey-coated vs. silver-coated bandages (RCT, n=69): n.s. difference in **malador**, **exudate** or **pain** Hypertonic dressing of dry mesalt vs. isotonic dressing of continuous wet saline (Crossover RCT, n=11): - **Odor**: sign.increase in control in intervention group - **Infection**: n.s. No study evaluating opioid use.	Method: good conducted SysRev Content: - Small to very small samples - Heterogneity did not allow pooling - Moderate to high risk of bias - Topical antimicrobials, like metronidazole, is the most studied intervention. - No studies on opidoid use - Current evidence is limited and does not allow drawing firms conclusions	1++
Graham, Pain 2013 [323]	SR (critical review); to critique clinical practice as reported in the literature and provide insights into the use of topical opioids in the	Databases: Medline, CINAHL, Cochrane Library, Biomed Central, NHS Evidence and British Nursing Index (BNI), grey literatures; till 2012 Design: all types of design except reviews	Intervention: **topical opioids** Outcomes: pain relief, adverse events, impact on systemic medication	Study number: 27 studies (n=170): Population: wide variation in the size and aetiology of the wounds in the studies reporting positive responses to topical opioids. Outcomes: **Pain relief**:	Method: - Results not reported systematically, focus on controlled studies. - Quality assessement of included studies not mentioned, so that a body of	1- (Body of evidence: not statable)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
	management of painful cutaneous lesions.	Population: patients with **painful cutaneous skin lesions**		- 3 RCTs and 3 case studies with a large number of patients reported statistically sign. reduction in pain scores (pressure ulcers). - 3 RCTs found that topical opioids were not effective (arterial and/or venous leg ulcers). - 17 case studies indicated that topical opioids are clinically useful for reducing pain for patients with cutaneous lesions but did not conduct statistical analyses of their results - No mention of other studies - Most commonly analgesic relief was achieved for patients with pressure and malignant wounds (no further details mentioned) **Local adverse events:** itching, burning i.a. not attributable to the topical morphine **Systemic absorption**: 6 studies found systemic uptake of topical opioids at levels considered safe; absorption probably dependent on wound surface area. **Use of systemic medication**: 4 studies reported patients were able to reduce or withdraw their systemic medications after applying topical opioids. One study found that analgesia was maintained without escalation of systemic doses.	evidence can't be deduced from the SR - Particular conclusion on malignant wounds not possible	
Le Bon, J Pain Sympt Manag 2010 [324]	SR; to assess the quality of published literature and to examine whether	Databases: Medline, Embase, Cinahl, Cancerlit, St. Christopher's Hospice Library database, www.controlled-trials.com, and	Intervention: **topical** application of **opioids** Outcomes:	Study number: 19 studies (6 RCTs, 13 case series or reports): Quality of RCTs: 3 moderate/high quality of evidence; 3 low quality	Method: No evidence tables with details on studies and patient population; particular	1+ (body of evidence: 1+)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
	topical opioids are effective in controlling pain in palliative care settings	Evidence-Based Medicine Reviews; till 2006 Design: no limit (except reviews) Population: patients in **palliative care** setting	1.O: pain relief 2.O: - time to onset of analgesia - duration of analgesia - side effects	Population: patients with both malignant and nonmalignant wounds, as well as oropharyngeal mucositis Opioids: diamorphine, morphine (sulfate and hydrochloride), methadone, oxycodone, and meperidine Outcomes: **Pain relief**: - 5 of 6 RCTs reported a statistically sign. analgesic effectiveness of topical opioids. 3 RCTs on skin lesions demonstrated that morphine and diamorphine gel obtained by mixing with IntraSite gel can be effective in painful pressure ulcers, and that once daily application may not be sufficient for the optimal maintenance of pain relief. 2 RCTs in mucositis also showed analgesic benefit of topical morphine mouthwashes. - 1 RCT in painful skin (mainly leg) ulcers did not show statistically sign. pain relief. **Time to onset of pain relief** (9 studies): immediate to 60 min. **Duration of pain relief** (10 studies): - Diamorphine: between 24 and 48 hours in two case reports - Morphine: ranged from 2 to 45 hours - in ulcers and 1 to 4 hours in mucositis **Local AE** (2 studies): itching, burning. Attributable to opioid in mucositis.	conclusion on malignant wounds not possible Content: - In summary, this review concludes that there is support for the use of topical opioids, but does not permit us to make clear recommendations for clinical practice in terms of the ideal opioid, the starting dose, interval of administration, methods of titration, or carrier, nor are we able to identify which wounds are most suitable for this treatment. - 14 studies used objective measures to evaluate pain relief	

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Montroy, Transfus Med Rev 2018 [325]	SR, MA; to investigate the efficacy and safety of topically applied tranexamic acid (TXA) compared to both placebo, and the intravenous administration.	Databases: MEDLINE, EMBASE, Cochrane Library (Trials), ISI Web of Science, PubMed, Clinicaltrials.gov and grey literature; till 2016 Design: RCTs Population: **adult** patients (surgical and non-surgical)	Intervention: **Topical TXA**; Control: placebo or systemic TXA Outcomes: 1.O: - Risk of blood transfusion (OR of receiving transfusion) 2.O: - Blood loss - Adverse events	Study number: 67 RCTs (n=6.034): - Topical TXA versus placebo = 42 RCTs - Topical versus iv =14 RCTs - Topical TXA versus iv TXA versus placebo = 11 RCTs Population: - Surgical patients: 66 RCTs (43 orthopedics) - Epistaxis: 1 RCT - Malignant wounds: 0 RCT Outcomes: Meta-analysis (56 RCTs): 1) Topical TXA versus placebo: - **Risk of receiving blood transfusion**: sign. reduced (pooled OR 0.28, 95% CI 0.20 to 0.38; P <0.001) - **Mean blood loss**: sign. reduced (WMD -276.6, 95% CI -327.8 to -225.4; P <0.0001) - **Risk of thromboemboly**: n.s. (pooled OR=0.78, 95% CI 0.47 to 1.29; P=0.33) 2) TXA topical versus iv: - **Risk of receiving blood transfusion**: n.s. (pooled OR 1.03, 95% CI 0.72 to 1.46; P=0.88) - **Mean blood loss**: n.s. (WMD -21.95, 95% CI -66.61 to 27.71; P=0.34) - **Risk of thromboemboly**: n.s. when compared to placebo (pooled OR=0.75, 95% CI 0.39 to 1.46;P=0.40)	Method: Good conducted systematic review and meta-analysis Content: - unclear risk of bias for at least on methodological criterion (due to under reporting of methodological details) > moderate risk of bias - substantial statistical heterogeneity in our clinical outcomes of blood transfusion and blood loss. But the variation seen in these outcomes were in the magnitude of effect, and not the direction - few trials reported data on the rate of mortality, stroke or MI, making the effect estimates for these outcomes very imprecise and preclude definitive conclusions	1++ (body of evidence: 1+)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Norman, Cochrane 2016 [326]	SR, MA; To assess the effects of systemic and topical antibiotics, and topical antiseptics on the healing of infected and uninfected pressure ulcers	Databases: Cochrane Wounds Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid MEDLINE (In-Process & Other Non-Indexed Citations), Ovid EMBASE,and EBSCOCINAHL Plus, three clinical trials registries and the references of included studies; till 2015 Design: RCTs Population: adults diagnosed with **a pressure ulcer** of category 2 or above	Intervention: topical **antiseptic** agents or antibacterial (antibiotic) agents delivered either systemically or topically. Control: placebo, therapy, standard care or no treatment Outcomes: 1.O: - Time to complete wound healing - Proportion of wounds completely healed during follow-up - AE 2.O: - Change in wound size - Changes in infection status; signs or symptoms of clinical infection - Changes in bacterial (antibiotic) resistance - HRQOL	Study number/design: 12 RCTs (n=576) Quality of evidence: moderate to very low Outcomes: **Wound healing** (6 RCTs, 5 compared an antiseptic to a non-microbial comparator): - Some moderate and low quality evidence that fewer ulcers may heal in the short term when treated with povidone iodine compared with non-antimicrobial alternatives (protease-modulating dressings (risk ratio (RR) 0.78, 95% confidence interval (CI) 0.62 to 0.98) and hydrogel (RR 0.64, 95%CI 0.43 to 0.97)); - no clear difference between povidone iodine and a third non-antimicrobial treatment (hydrocolloid) (low quality evidence). - Pine resin salve may heal more pressure ulcers than hydrocolloid (RR 2.83, 95% CI 1.14 to 7.05) (low quality evidence). - No clear difference between cadexomer iodine and standard care, and between honey and a combined antiseptic and antibiotic treatment (very low quality evidence). **AE** (6 RCTs): 4 reported no adverse events; there was very low quality evidence from one RCT showing no clear evidence of a difference between cadexomer iodine and standard care; in one trial it was not clear whether data were appropriately reported **Wound size** (5 RCTs): did not report any clear evidence favouring any particular antiseptic/anti-microbial treatments	Method: well conducted systematic review; meta-analysis not possible Content: - relative effects of systemic and topical antimicrobial treatments on pressure ulcers not clear. Where differences in wound healing were found, these sometimes favoured the comparator treatment without antimicrobial properties. - The trials are small, clinically heterogenous, generally of short duration, and at high or unclear risk of bias. - The quality of the evidence ranges from moderate to very low; evidence on all comparisons was subject to some limitations.	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				Changes in infection satuts: - **Pain** (1 RCT): comparison of polyhexanide dressing with a polyhexanide swab: patients in the dressing group also reported less pain (MD −2.03, 95% CI −2.66 to −1.40). - **Infection resolution** (3 RCTs): no clear evidence of a difference between interventions in infection resolution		
Norman, Cochrane 2016 [327]	SR; To assess the effects of systemic and topical antibiotics, and topical antiseptics on the healing of infected and uninfected pressure ulcers	Databases: Cochrane Wounds Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid MEDLINE (In-Process & Other Non-Indexed Citations), Ovid EMBASE, and EBSCO CINAHL, three clinical trials registries and the references of included studies; till 2015 Design: RCTs Population: adults with a **surgical wound healing by secondary intention**	Intervention: **antiseptic** agents or antibiotic (antimicrobial) agents delivered either systemically or topically Control: placebo, therapy, standard care or no treatment Outcomes: 1.O: - Time to complete wound healing - Proportion of wounds completely healed during follow-up - AE (incl. wound infection) 2.O: - Change in wound size	Study number/design: 11 RCTs (n=886) Quality of evidence: moderate to very low Outcomes: Iodine preparations vs. no antiseptic tratement (2 RCTs, low quality): no clear evidence of effects Zinc oxide mesh dressing vs plain mesh dressing (1 RCT, low quality): - **Time to healing**: n.s. - **Smell** (as infection sign): 1/33 (3%) of participants with foul smell in the zinc oxide mesh group compared with 8/31 (26%) in the placebo group: RR 0.12, 95%, CIs 0.02 to 0.89. Sucralfate cream vs. petrolatum cream following haemorrhoidectomy over 3 weeks (1 RCT, moderate quality): - **Likelihood of healing**: sign. increased (RR: 1.50, 95% CI 1.13 to 1.99) - **Wound pain**: sign. reduced	Method: well conducted systematic review; meta-analysis not possible Content: - There is no robust evidence on the relative effectiveness of any antiseptic/ antibiotic/ anti-bacterial preparation evaluated to date for use on surgical wounds healing by secondary intention. - Where some evidence for possible treatment effects was reported, it stemmed from single studies with small participant numbers and was classed as moderate or low quality evidence.	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
			- Changes in bacterial (antibiotic) resistance - HRQOL - Mean pain score - Number of wounds closed surgically - Ressource use and costs	Triclosan vs. standard sodium hypochlorite solution following haemorrhoidectomy (1 RCT, low quality): **Time to healing**: sign. reduced (mean difference -1.70 days, 95% CI -3.41 to 0.01) Honey-soaked gauze vs.EUSOL-soaked gauze for 3 weeks after excision of pyomyositis abscesses (1 RCT, moderate quality): **Proportion of wounds healed**: sign. higher (RR: 1.58, 95% CI 1.03 to 2.42) Dermacym® vs. iodine for post-operative foot wounds in people with diabetes (1 RCT, moderate quality): **Proportion of wounds healed**: sign. higher (RR 0.61, 95%CI 0.40 to 0.93)		
Norman, Cochrane 2017 [328]	SR, MA; To assess the effects and safety of antiseptics for the treatment of burns in any care setting	Databases: Cochrane Wounds Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid MEDLINE (In-Process & Other Non-Indexed Citations), Ovid EMBASE, and EBSCO CINAHL, three clinical trials registries and the references of included studies; till 2016 Design: RCTs Population: participants of any age with **burn** wounds.	Intervention: topical **antiseptic** agents Control: placebo, an alternative antiseptic, another therapy such as antibiotics or isolation of the patient, standard care or no treatment Outcomes: 1.O: - Time to complete wound healing - Proportion of wounds completely healed during follow-up	Study number/design: 56 RCTs (n=5.807); 44 RCTs included in meta-analysis Quality of evidence: unclear or high risk of bias for 2 or more domains Outcomes: **Antiseptics versus topical antibiotics**: Silver-based antiseptics vs. SSD (silver sulfadiazine) (3 RCTs, low quality): **Chance of healing (HR)**: n.s. **Mean time to healing**: sign.reduced **Number of healing events (RR)**: sign. increased **Infection**: n.s: RR 0,84 [95% CI 0,48-1,49] Honey vs. topical antibiotics:	Method: well conducted systematic review Content: - It was often uncertain whether antiseptics were associated with any difference in healing, infections, or other outcomes.	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
			- change in wound infection status 2.O: - AE - HRQOL - Pain (including pain at dressing change) - Resource use, costs - Mortality (overall and infection-related)	**Chance of healing (HR)** (5 RCTs, moderate evidence): sign. higher (HR 2.45, 95% CI 1.71 to 3.52; I2 = 66%; n=140) **Infection** (4 RCTs): sign. lower (RR: 0,16; 95% CI 0,08 – 0,34) Sodium hypochlorite vs. SSD and merbromin vs SSD: **Mean time to healing**: slightly sign. reduced (low quality) **Antiseptics vs alternative antiseptics:** Povidone iodine vs chlorhexidine: There may be some reduction in **mean time to healing** for wounds treated with povidone iodine (MD -2.21 days, 95% CI 0.34 to 4.08). Other evidence showed no clear differences and is of low or very low certainty. **Antiseptics vs non-antibacterial comparators**: Honey: **Mean time to healing** (4 RCTs, n=1156, high level of evidence): sign. reduced (but this comparison included some unconventional treatments): difference in means -5.3 days, 95% CI -6.30 to -4.34; I^2 = 71%; **Likelihood of wounds healing** (2 RCTs, n=154, moderate evidence): sign. higher (HR 2.86, 95% C 1.60 to 5.11; I2 = 50% (but unconventional comparison treatment). Silver dressings vs. Vaseline gauze: **Mean time to healing** (2 RCTs, n=204, moderate evidence): slightly sign. reduced		

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				(difference in means -3.49 days, 95%CI -4.46 to -2.52; I^2 = 0%;) Silver xenographt vs. paraffin gauze: **Healing events** (1 RCT, n=32, low evidence): n.s. Other comparisons represented low or very low certainty evidence It is uncertain whether **infection** rates in burns treated with either silver-based antiseptics or honey differ compared with non-antimicrobial treatments (very low certainty evidence). There is probably no difference in infection rates between an iodine-based treatment compared with moist exposed burn ointment (moderate certainty evidence). **Mortality** was low where reported.Most comparisons provided low certainty evidence that there may be little or no difference between many treatments.		
O'Meara, Cochrane 2014 [329]	SR, MA; To determine the effects of systemic antibiotics and topical antibiotics and antiseptics on the healing of venous ulcers	Databases: CENTRAL (Cochrane Library), Cochrane Wounds Specialised Register, Ovid MEDLINE, Ovid EMBASE, EBSCO CINAHL Design: RCTs Population: people with **venous leg ulcers**	Intervention: systemic or topical antibiotics or topical **antiseptics** in the treatment of venous ulcers Outcomes: 1.O: - Time to complete wound healing - Proportion of wounds healed during follow-up	Study number/design: 45 RCTs (n= 4.486); 44 RCTs included in meta-analysis Quality of evidence: Many RCTs were small, and most were at high or unclear risk of bias Outcomes (results on antiseptics only): Cadexomer iodine: **Proportion of healing** - vs. standard care (4 RCTs): sign. higher - vs. hydrocolloid dressing; paraffin gauze dressing; dextranomer; or silver-impregnated dressings: n.s.	Method: well-conducted SysRev Content: - At present, no evidence is available to support the routine use of systemic antibiotics in promoting healing of venous leg ulcers. - In terms of topical preparations, some evidence supports the use of	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
			- change in wound size 2.O: - Changes in signs and/or symptoms of clinical infection - Changes in bacterial flora - Development of bacterial resistance - Ulcer recurrence rates - AE - Participant satisfaction - HRQOL - Costs	Povidone iodine vs. hydrocolloid; moist or foam dressings; or growth factor: **complete healing**: n.s. Peroxide-based preparations vs. usual care (4 RCTs): surrogate healing outcomes (**change in ulcer area):** sign. better Honey-based preparations vs. usual care: - **time to healing** or **complete healing**: n.s. - **infection:** n.s. 0.71 [95% CI: 0.49, 1.04] Silver-impregnated dressings vs. standard care, placebo, tripeptide copper complex, non-antimicrobial dressings: **complete healing**: n.s.	cadexomer iodine. Current evidence does not support the routine use of honey- or silver-based products. - Very few results on infection (relevant for our guideline)	
Ramasubbu, Cochrane 2017 [330]	SR; to assess the effects of systemic antibiotics for treating malignant wounds	Databases: CENTRAL (Cochrane Library), Cochrane Wounds Specialised Register, MEDLINE, EMBASE, CINAHL plus, EBSCO, (WHO) International Clinical Trials Registry Platform, OpenSIGLE, ProQuest Dissertations & Theses Global (until 2017); handsearch Design: RCTs, CCTs Population: people of any age with a clinically diagnosed malignant wound resulting from any type of cancer	Intervention: **any systemic antibiotic** used in the treatment of any type of malignant wound Outcomes: 1.O: - malodour - AE 2.O: - Health-related QoL - Exudate/ haemorrhage - Pain relief - containment or regression	Study number/design: 1 cross-over double-blind RCT (n=6): metronidazole vs. placebo, with very high risk of bias Outcomes: - **Malodour**: n.s.: smell score graded 0-3; mean score in metronidazole group: 1.17 (SD 1.60); mean score in placebo group: 3.33 (SD 0.82); MD -2.16 (95% CI -3.60 to -0.72) - **AE**: not reported - **Other outcomes**: not measured	Method: good conducted SysRev Content: Very limited evidence (1 very small RCT with high risk of bias); No conclusion possible on the effectiveness of systematic metronidazole	1++ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Verleumen, J Hosp Infect 2010 [331]	SR; To investigate the possible beneficial and harmful clinical effects of iodine in the treatment of all kinds of (contaminated) wounds	Databases: Cinahl, Embase, Medline and the Cochrane Controlled Trials Register (until 2008); handsearch Design: RCTs Population: patients with any kind of (more or less contaminated) wound.	Intervention: local wound care product containing iodine vs. any type of control treatment Outcomes: 1.O: - bacterial load and wound infection - wound healing (expressed as time to complete healing, change in wound surface, survival rate of split-thickness skin grafts, and wound ready for surgical closure 2.O: - adverse events (AE) (such as pain and erythema), - costs - length of hospital stay	Study number/design: 27, n=4495 RCTs Quality: low quality (high risk of bias) Relevant outcomes (bacterial load and wound infection): Chronic ulcers: - **Bacterial load** (1 RCT): n.s. Pressure ulcers: **Infection** (2 RCTs): favour control Acute wounds: - **Infection occurring** (4 RCTs): 3/4 favour control - **Infection cured** (1 RCT): favours iodine Burn wounds: no infection outcome Skin grafts: - **Infection** (1 RCT): favours iodine **AE** including thyroid function derailment, did not occur more frequently with iodine	Well conducted systematic review Author conclusions: The antiseptic effect of iodine is not inferior to that of other (antiseptic) agents and does not impair wound healing Low quality of evidence Results for the outcome wound infection inconclusives	1++ (Body of evidence: 1-)

13.1.2. Primärstudien

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Ashford, Lancet 1980 [332]	Case report; To identify the reduce of anaerobic infection in ulcerate tumour-lesion	n=1 men age: 48 year	Patient with a **axillary tumour**, recurrent after mastectomy	200 mg **metronidazole**/3 times daily	1.0=Within a week the putrid **odour** disappears 2.=However some smell of the dressed lesion	When other measures fail metronidazole can prove to control the smell	Method: Case report with only 1 patient Content: - Limitation of the retrograde description case report - Cause of the weak data, however the positive results of provement metronidazole reduce the putrid odour, a double blind cross-over study is started	3
Ashford, Lancet 1984 [333]	RCT, double-blind; To explore the use of metrodinazole to reduce the maladour of ulcerate tumours	n=9 6 patients (I)	- Patients with maladour ulcerating tumours (**breast cancer**) - Not with irritation or chemotherapy - Abstain from alcohol	- I:200 mg **metronidazole**/3 times daily for 14 days - C: Placebo/3 times daily for 14 days 14 days wash out	- Smell: In each visit the patient, doctor and nurse graded the smell (absent (0) till offensive and intolerable (4)) - Bacterial colonisation: before and after each treatment is taken swaps of the tumour	**Smell**: significantly less after metronidazole than after placebo ($p<0.01$, *t-test*[2]). **Anaerobic isolates**: significant difference ($p<0.005$). - No anaerobes or anaerobic product are identify	Method: - Small sample Content: - Metronidazole eliminates anaerobes and reduces the smell of ulcerating tumours - Patients who abstain from alcohol can be offered metronidazole	1+
Brusis, Laryngol Rhinol Otol	Case series; To reduce foetor	n=6 treated with metronidazole; (n=7, clindamycine)	Patients with incurable **tumours of head and neck** region (oral cavity, oropharynx and	Oral (or feeding tube) **metronidazole**: 250 mg 5 times daily (Oral (or feeding tube) clindamycine:	- **Foetor** and anaerobic germs dissapeared or sparingly detectable after 24 hours	- Fetid smell is caused of microbial activity of anaerobic bacteria, which settle the tumors secondly	Method: - Case series < 10 - Relative heterogenity in patients and diagnosis	3

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
1986 [334]			recurrance of hypopharynx- and larynxcarcinoma.	150 mg 4 x 2 times daily/ 4 x 3 daily)		- Antibiotic treatment improve the unpleasant foetor		
Dankert, Lancet 1981 [335]	Case series; To explain the use of metrodinazole to reduce the smell of fungating tumours	n=4	Patients with smelly fungating **gynaecological tumours**	**Metronidazole** 500 mg three times daily	smell (no data on measurement tool)	The **smell** was reduce or disappeared after 5 - 10 days	Method: Small case series, no description of outcome measurement	3
Sparrow, Lancet 1980 [336]	Prä-post-Studie	n=9	patients with fungating **breast carcinoma** causing offensive smell	**Metronidazole** 400 mg three times a day orally	Smell, assessed by the patient, a nurse, and a doctor, and, in some cases, by a close relative before and 7 days after treatment start; No instrument described	**Smell** reduced considerably in all patients after 7 days (no furter data reported)		

14. Angst

14.1. Erfassung

14.1.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Tools evaluated; psychometric criteria	Results	Comments	LoE SIGN
Luckett, Support Care Cancer 2010 [337]	SR; To identify all PROMs used to assess anxiety, depression and general distress in RCTs of psychosocial interventions for people with cancer	Databases: Medline, PsycINFO, Embase, AMED, CENTRAL and Cinahl, 1999-2009 Design: RCTs (to identify PROMs) Population: **cancer patients**	Candidate PROMs used to assess **anxiety, depression and general distress** were evaluated for content, evidence of reliability and validity, clinical meaningfulness, comparison data, efficiency, ease of administration, cognitive burden and track record in identifying treatment effects in RCTs of psychosocial interventions	Study number: 132 psychosocial RCT interventions assessing anxiety, depression and/or distress by means of 30 PROMs Study quality: variable Scores **HADS**: scored highest overall due to many evidence on its psychometric properties (weighted score=77.5); we recommend continued use of the HADS-D in combination with the HADS-A and HADS-T where mixed affective disorders are the outcome of interest **POMS-37** (Profile of Mood States-37): second score due to consistent evidence for its validity and responsiveness (weighted score=60)	Exclusion of PROMs considered unsuitable for undergoing active treatment for cancer of any type and stage (items judged as problematic); only English-speaking patients included; Results for anxiety not specifically reported	1+ (Body of evidence: 1-)
Plummer, J Natl Cancer Inst 2016 [338]	SR; MA To systematically review the accuracy of the GAD-7 and GAD-2 questionnaires for identifying anxiety disorder	Databases: MEDLINE, PsycINFO, CINAHL and the Cochrane library, until 2014; grey literature Design: cross-sectional validation studies	Administration of the **GAD-7** or **GAD-2** questionnaire to screen for any anxiety disorder (GAD, panic disorder, agoraphobia, social	Study number: 14 studies (12 independent samples); Sample sizes ranged from 103 to 2011 Population: general population (3 samples); primary care (3 samples), secondary care (4 samples), a community drugs treatment service, an occupational health service	Well conducted systematic review; Indirect evidence (no palliative patients) The GAD-7 had acceptable properties	1++ (Body of evidence: 3)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Tools evaluated; psychometric criteria	Results	Comments	LoE SIGN
		Population: adults aged 16 years and older in **any setting**	phobia, specific phobia, OCD or PTSD); Reference test: recognized 'gold standard' instrument (SCID, CIS-R); Where sufficient studies were found (n≥4), pooled estimates [and 95% confidence interval (95% CI) values] of sensitivity, specificity, positive likelihood ratios, negative likelihood ratios and summary diagnostic odds ratios were produced for each cutoff point	Study quality: variable; Only two studies were judged to have a low risk of bias across all domains Accuracy: - GAD-7 for identifying GAD (11 samples): a cutoff score of 8 had the highest sensitivity and specificity balance (results MA) - GAD-7 for identifying any anxiety disorder (4 samples): At a cutoff point of 8, sensitivity and specificity values were high - GAD-2 for identifying GAD (6 samples): A cutoff score of 3 had the highest sensitivity and specificity balance; however, between-study heterogeneity was high (I2=75.6%). - GAD-2 for identifying any anxiety disorder (3 samples): At a cutoff score of 3, sensitivity values were moderate ranging from 0.65 to 0.72. Specificity at this cutoff point was high in two studies (0.92 and 0.88) but low in one (0.39).	for identifying GAD at cutoff scores 7–10. The GAD-2 had acceptable properties for identifying GAD at a cutoff score of 3.	
Vodermaier, J Natl Cancer Inst 2009 [339]	SR; To examine the psychometric properties of the existing tools used to screen patients for emotional distress	Databases: PubMed, PsycINFO, until August 2008 Design: validation studies Population: **cancer patients**	Tools used to screen patients for **emotional distress** - number of validation studies identified - number of participants - generalizability across cancer types and/or disease stages - reliability	Study number: 106 validation studies describing 33 screening tools for distress Study quality: variable Anxiety tools (9 tools measuring anxiety or with subscale for anxiety): Ultra-short (1-4 items): - Most studies on palliative patients - **Anxiety question** (1 item, 1 study, n=79): poor quality (insufficient specificity to rule out nonanxious patients) - **ESAS** (1 sub-item, 2 studies, n=295): fair quality (moderate validity)	- Well conducted systematic review - Few (sub-)scales for anxiety in palliative care	1++ (Body of evidence: 3)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Tools evaluated; psychometric criteria	Results	Comments	LoE SIGN
			- type of the criterion measure - validity - sensitivity - specificity - positive or negative predictive value	Short (5-20 items): - 2/15 studies on advance cancer - **BSI-18** (6 sub-items for anxiety): good quality (Internal consistency was high for the anxiety subscale) - **HADS** (7 sub-items for anxiety): good quality (The internal consistency of each subscale and of the total scale were shown to be adequate) - **MAX-PC** (Memorial Anxiety Scale for Prostate Cancer): prostate cancer anxiety, prostate-specific antigen anxiety, and fear of recurrence (18 items, 3 studies, n=930); poor quality (Long (21-50 items): not reported here, as not used in the clinical praxis)		
Ziegler, J Pain Sympt Manag 2011 [340]	SR; To examine the performance of self-report measures for identifying clinically significant levels of psychological distress across the cancer patient trajectory	Databases: Medline, PsychInfo, CINAHL, EmBase, The Cochrane Library, AMED, BNI, ASSIA, and Web of Science (search period not reported) Design: validation studies exploring the validation of a self-report measure alongside a structured clinical interview for psychiatric disorder Population: **cancer patients**	validation of a self-report measure for **psychological distress** alongside a structured clinical interview for psychiatric disorder - cut-off score for target disorder, - sensitivity, - specificity, - positive - predictive and negative predictive value, - reliability scores, - item structure, - feasibility	Study number: 85 validation studies (of which 22 reported findings at a specific point on the illness trajectory) reporting 48 different self-report measures Tools for anxiety related to disease trajectory: At Diagnosis and Prior to Treatment: No tool with adequate sensitivity/specificity During Active Treatment: HADS (cut-off-score 10 for anxiety, but do not provide sensitivity and specificity scores at these levels) Post-treatment: BAI (Beck Anxiety Inventory): adequate sensitivity but insufficient specificity	Well conducted systematic review Few results specific for anxiety; There were clear knowledge gaps identified in the validated assessment of anxiety, adjustment and undifferentiated distress pretreatment, depression during treatment, and anxiety and distress both after treatment and at recurrence.	1++ (Body of evidence: 3)

14.2. Nicht -medikamentöse Verfahren

14.2.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN

Fulton, J Palliat Med 2018 [341]	SR, MA;
	To examine the effect of psychotherapy on depression and anxiety among individuals with any condition appropriate for palliative care
		Databases: PubMed, PsycINFO, Cochrane Library, and EMBASE databases until August 2017
		
		Design: RCTs (peer-reviewed)
		
		Population: adults with **any condition appropriate for palliative care**
			Interventions:
			Psychotherapy (PT), defined as: psychological interventions conducted by trained individuals and involve direct verbal and interactive communication to improve distress, that involved at least two sessions or a minimum of 60 minutes
			
			Outcomes: depression, anxiety symptoms or QoL as continuous variables
				The following results apply exclusively to the outcome anxiety:
				Study number: 21 RCTs (n=1983)
				
				Study quality: Most RCTs were of medium quality; 4 high quality RCTs
				
				Population: cancer (16 RCTs), mixed palliative patients (2), other (3)
				
				Interventions:
				CB-based Therapies (CBT, PST Problem Solving Therapy, IPT Interpersonal Therapy), existential therapies (DT Dignity Therapy, Legacy, LR life review, MM meaning making therapy) Other Therapies (ACT, MBSR, Supportive expressive therapy, Outlook intervention)
				
				Outcome Anxiety:
				Overall effect: sign. reduced with small effect: mean effect size (ES): -0.38 (-0.52, -0.24)
				
				Categorical moderators:
				- Psychotherapy type:
				  ○ CBT, CT, CET, PST, IPT (11) : ES by class sign.: -0.44 (p<0.001)
				  ○ DT, LR, MM, Ex (7): ES by class n.s.: -0.12
					Method:
					Good conducted systematic review according to PRISMA
					
					Content:
					- Medium quality of included studies
					- metaanalysis for both depression and anxiety showed similar effects
						1++ (Body of evidence: 1+)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				○ Other: MBSR, Outlook, ACT (3): ES by class sign.: -0.67 (p<0.001) ○ Between-class effect: sign. (Q_B = 10.16 (p<0.01) - Provider type: ○ Mental health Provider (16): ES by class sign.: -0.43 (p<0.001) ○ Other (5): ES by class n.s.: -0.22 ○ Between-class effect: n.s. - Treatment modality: ○ Individual: ES by class sign.: -0.48 (p<0.001) ○ Group: ES by class sign.: -0.25 (p<0.05) ○ Between-class effect: n.s. - Study quality: ○ Low: ES by class n.s.: -0.25 ○ Medium: ES by class sign.: -0.35 (p<0.001) ○ High: ES by class sign.: -0.59 (p<0.001) ○ Between-class effect: n.s. - Population condition: ○ Cancer: ES by class sign: -.38 (p<0.001) ○ Other or mixed: ES by class sign.: -0.39 (p<0.01) ○ Between-class effect: n.s. <u>Interventions/control groups (only RTCs with cancer or mixed patients)</u> - CBT vs. supportive Therapy (2 RCTs, 137 patients) Outcome: POMS, ES: -0.32/-0.23 - CBT vs. Waitlist control (2 RCTs, 87 patients) HAM-A, HADS-A / HADS-A; Result: ES: -0.69/-1.34 - CBT vs. Social support vs. control group (1 RTC, 78 patients) Outcome: SCL-90-R, ES: 0,0		

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				- Cognitive therapy vs. Biofeedback vs. No-treatment control (1 RTC, 19 patients) Outcome: STAI-S, ES: -1.39 - Cognitive-existential therapy + relaxation classes vs. Relaxation classes (1RTC, 303 patients) Outcome: HADS-A, MACS, ES: -0.26 - Meaning-centered therapy vs. Supportive group therapy (1 RTC, 90 patients) Outcome: HADS-A, ES: 0.29 - Meaning centered therapy vs. massage (1 RTC, 120 patients) Outcome: HADS-A, Result: ES: -0.33 - Meaning-making intervention vs. Waitlist control (1 RTC, 28 patients) Outcome: HADS-A; Result: ES: -0.12 - Dignity therapy vs. Supportive therapy vs. standard palliative care (1 RTC, 229 patients) HADS-A; Result: ES: 0.15 - Dignity therapy + standard palliative care vs. standard palliative care (2 RCTs, 105 patients), Outcome: HADS-A/HADS-A; Result: ES: -0,15/-0.41 - Adjuvant psychological therapy vs. standard medical care (1 RTC, 73 patients) Outcome: HADS-A; Result: ES: -0.38 - Adjuvant psychological care vs. Supportive counseling (1 RTC, 57 patients) Outcome: HADS-A, STAI-S, MACS; Result: ES: -0.65 - ACT (Acceptance and commitment therapy) vs. usual care (1 RTC, 47 patients) Outcome: BAI; Results: ES: -1.20 - MBSR vs. Waitlist control (1 RTC, 109 patients) Outcome: POMS-A, SOSI-A; Result: ES: -0.64		

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
				- Outlook intervention vs. Attention control vs. no treatment control (1 RTC, 78 patients) Outcome: POMS-A; Result: ES: -0.56		
Grossman, Palliat Med 2018 [342]	SR; To assess quantitative studies on interventions for adult patients with advanced cancer suffering from death anxiety	Databases: MEDLINE, PsycINFO, Embase and CINAHL until Dec. 2016; handsearch Design: Any intervention study design which included quantitative measures Population: adult patients with **advanced cancer**	Interventions: Any intervention targeting death anxiety or related existential aspects of distress in a systematic fashion Comparison: Usual care, no intervention or other control population Outcomes: All outcome measures for death anxiety or related existential aspects of distress	Study number: 9 (5 RCTs, 4 pre-post studies) Study quality: moderate to high risk of bias Interventions: 'Life Review', 'Dignity Therapy', 'Meaning-Centred' or 'Meaning-Making' therapy, 'Couples Therapy with Existential Focus' and 'Managing Cancer and Living Meaningfully (CALM)' psychotherapy; no pharmacological intervention identified. Duration: from two sessions over 2–3 days, to up to eight sessions over 6 months Outcomes: large variation of outcome measures and results - CALM psychotherapy was the only intervention shown to significantly decrease death anxiety ($p < 0.009$) on a validated measure (DADDS) in patients with advanced cancer - Dignity therapy/life review: results for existential distress variable (in 1 study sign., in 1 study not sign.) - Meaning-centered therapy: sign. improvements in desire for hastened death and spiritual well-being as well as physical symptom distress; death anxiety not directly measured	Well conducted SR despite wide concept of death anxiety with consecuently inclusion of inhomogeneous studies Only 1 study measured death anxiety with validated scale (DADDS); the others used a non-validated tool or surrogates High risk of bias of included studies	1+ (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Wang, Palliat Med 2017 [343]	SR; MA To evaluate the effects of therapeutic life review on spiritual well-being, psychological distress, and quality of life in patients with terminal or advanced cancer	Databases: CINAHL, Cochrane Library, PsycINFO, PubMed, and Web of Science until Feb. 2017; handsearch Design: RCTs Population: patients with **terminal or advanced cancer**	Interventions: therapeutic life review Outcomes: spiritual well-being, psychological distress, and/or QOL	Study number: 9 reports on 8 RCTs (n=955); 7 RCTs included in MA Study quality: all but 1 RCT with high risk of bias Interventions: short-term life-review, life review, dignity therapy, meaning-making intervention, meaning of life intervention, and meaning-centered psychotherapy. Frequencies of intervention ranged from single session to 7 sessions, Outcomes: Results of MA: **Anxiety** on HADS subscale, pooled results: - Anxiety at post-intervention (4 RCTs): n.s. (SMD: 0.11; 95% CI: -0.10; 0.33) - Anxiety at follow-ups (3 RCTs): n.s. (SMD: -0.04; 95% CI: -0.42; 0.33) **Psychological distress** on HADS scale, pooled results: - Distress at post intervention (3 RCTs): sign. improved (SMD: -0.32; 95% CI: -0.55, -0.09). High statistical heterogeneity (I2=93%); after removing the trial responsible for inconsistency, results were not sign. - Distress at follow-ups (1 RCT): n.s. **Overall spiritual well-being** and **QoL**: n.s.	Well-conducted SR and MA; positive conclusions reported by authors do not always correlate with the well-described results of the MA, that show high inconsistency by sign. results.	1+ (Body of evidence: 1-)

14.3. Medikamentöse Therapie

14.3.1. Systematic Reviews

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
Salt, Cochrane 2017 [344]	SR; to identify RCTs examining the effectiveness of drug therapy for symptoms of anxiety in adult palliative care patients	Databases: CENTRAL (Cochrane Library), MEDLINE, CINAHL, PsycLit and PsycInfo until May 2016; handsearch Design: RCTs Population: adult palliative care patients whose symptoms of anxiety were described by the trial authors as beyond what could be seen as normal in this patient group. Anxiety assessed as symptom on a validated scale or as disorder (adjustment, obsessive-compulsive, phobia, panic, post-traumatic, generalized anxiety disorder).	Interventions: - 5-HT3 receptor antagonists - anxiolytics - antiepileptics - antidepressants - antipsychotics - benzodiazepines - butyrophenones - phenothiazines - antihistamines - barbiturates, - sedative hypnotics - antiepileptic drugs - beta-blockers Outcomes: all validated forms of measurement of anxiety alone or on a subscale	Study number: 0 RCTs	insufficient evidence to draw a conclusion about the effectiveness of drug therapy for symptoms of anxiety in adult palliative care patients	1++ (Body of evidence: not statable)
Nübling, Schmerz 2012 [345]	SR; to identify the current evidence of pharmacological treatment of anxiety in palliative care	Databases: PubMed, Embase, PsycLIT, PsycINFO, CINAHL from inception to Jan. 2012; handsearch Design: no limitation Population: - Palliative care adult patients	Interventions: - Anxiolytics - Hypnotics - Antidepressants - Antipsychotics - Antihistaminics - beta-blockers	Study number/design: - 4 RCTs - 3 prospective uncontrolled - 2 retrospective uncontrolled - 1 case report - 1 Cochrane review (no study included) - 1 review (not systematic) Study quality: low	Content: - With the existing evidence, no general recommendations for pharmacological treatment of anxiety in palliative care can be given. - Low study quality	1- (Body of evidence: 1-)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated; outcomes	Results	Comments	LoE SIGN
		- Exclusion: studies on depression, fatigue or on symptoms other than anxiety (anxiety as secondary outcome)	Outcome: **anxiety**, measured by specific tools for anxiety or by tools with a subscale anxiety.	Population: cancer patients, except 1 prospective uncontrolled study with HIV/AIDS Interventions: Benzodiazepines: n.s. in 2 RCTs (alprazolam vs. placebo or progressive muscle relaxation); improvement in 1 retrospective study (alprazolam). Other drugs: - 3 prospective descriptive studies with no standardized drug therapy -> conclusion not possible - 2 RCTs and 1 case report evaluated other drugs than those systematically searched (mazindol, methylprednisolone, ketamine)	- Few conclusions possible Method: - Sensible search strategy - Discrepancy between inclusion criteria and finally included studies (some drugs not included in search strategy, no outcome measurement, intervention with unclear drug therapy, mixed palliative and non-palliative population in 2 RCTs) - No LoE stated (although mention of quality assessment with Oxford)	

14.3.2. Primärstudien

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Majumdar, J Palliat Med 2015 [346]	Case report; (no aim mentioned)	n=1	Man with large B-cell lymphoma (Stage IV DLBCL), significant pain, anxiety and agitation, on conventional therapies for anxiolysis	**Dexmedetomidine** 0.3 mcg/kg/hr iv. gradually increased to 0.7 mcg/kg/hr over a 35-hour period; combined with **fentanyl** and **midazolam** infusions, all titrated to agitation	agitation and confusion (no validated scale)	Patient responsive and comfortable after 36 hrs	- 1 patient - Unclear symptoms (delirium? anxiety?)	3
Razavi, J Int Med Res 1999 [347]	Pilot double-blind RCT; To investigate the efficacy and safety of trazodone vs. clorazepate in the treatment of adjustment disorders in cancer patients	n=18 , (n=11 trazodone; n=7 clorazepate); +9 drop-outs before taking medication and are not included in the efficacy analysis; 1 drop-out during investigation	Adult female patients with - **breast cancer** (55,6% life expectancy < 6 months), - and DSM-a**djustment disorders** with anxious or depressed mood and/or mixed disturbance of emotion and conduct, - and HADS score ≥ 14 - and no history of serious psychiatric disorders	- **I: trazodone** (mean dose 111.5 ± 36.3 mg/d); n=11 versus - **C: clorazepate** (mean dose 17.5 ± 7.5 mg/d); n=7 - Duration: 28 days	1.O: Clinical Global Impression (CGI); success defined as score 1-3, very much to minimally improved (total of 7-items) 2.O: Improvement in: - HADS - Revised Symptom Checklist (SCL-90-R) - QoL (QLQ-C30) - Safety - Measurement: T0 (baseline), T1 (14 days), T2 (28 days)	**Success in CGI**: n.s. - I: 90.9% (10/11) - C: 57.1% (4/7) - **Total HADS**: - T1: sign. improvement in between-group comparison for trazodone group (p<0.001) – no further data reported - T2: n.s. between-group comparison (pre-post improvement in both groups) - **Anxiety** and **Phobic Anxiety** (subscore of SCL-90-R): n.s. between-group comparison (decrease in both groups, greater in trazodone in comparison with clorazepate group) **Safety**: n.s. difference between groups; 1 withdrawal in trazodone group (severe	- Pilot study, very small sample - 55,6% of patients with life expectancy < 6 months; no details about other patients - No differences at baseline - ITT - No significant between-group improvement of anxiety	1-

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
						vertigo); 1 dose adjustement necessary in trazodone group and 3 in clorazepate group (seepiness, aggressiveness, disinhibition).		
Stockler, Lancet oncology 2007 [348]	Double-blind RCT; to identify the effects of sertraline on symptoms and survival in patients with advanced cancer and without major depression	n=189; Drop-outs in sertraline arm: - at week 4: n=36; - at week 8: n=35; Drop outs in placebo arm: - at week 4: n=17; - at week 8: n=21	Palliative patients with **advanced cancer** and without major depression	- **I: sertraline** 50 mg/d (n=95) - **C:** placebo (n=94), once per day Duration: no limit	1.O: Depression (Centre for Epidemiologic Studies Depression scale (CES-D) 2.O: - Anxiety (HADS-A) - Overall QoL and fatigue (FACT-G and FACT-F) - Clinicians' ratings of QoL (Spizter's Quality of Life Index (SQLI)) - Survival - Etc. - Measurement: T0 (baseline), weeks (=w) 4, 8, 12, 16, 26, 39, and 52	**Anxiety, Depression, fatigue, overall QoL, clinician rating**: n.s. **Drug discontinuation**: sign. earlier in sertraline group (hazard ratio: 1.46 [1·03–2·06], p=0.03) **Survival**: - sign. lower in sertraline group at first planned interim analysis (adjusted hazard ratio 1·62 [1·06–2·41], Cox model p=0·02) - n.s. at final analysis (adjusted hazard ratio 1·27 [0·87–1·84], Cox model p=0·20)	- Validated outcome measures - ITT for efficacy analysis - Per-protocol-analysis for frequency of serious adverse events - Judgement of major depression as exclusion criteria was left to the responsible oncologist - Suspension of the study because of ruling out a sign. benefit of sertraline (and because of shorter survival in the sertraline group at the first planned interim analysis, although the difference did not reach the prespecified rule for stopping.) - Sample size (n=440) not reached due to study interruption	1+

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Suzuki, Int J Gynecol Cancer 2011 [349]	Prospective unconrolled study; To investigate the safety/ efficacy of fluvoxamine in cancer patients for anxiety and depression	n=10	**Gynecologic cancer** patients with HADS score ≥ 11 (with either adjustment disorder=AD, n=5; or major depression=MD, n=5) after diagnosis of cancer (at least 2 weeks); Stage: - FIGO I-II: n=7 - FIGO III: n=3 (30%)	Fluvoxamine p.o.: Week 1: 25 mg/d Week 2: 50 mg/d Week 3: 100 mg/d Week 4: 150 mg/d From week 5: according to patient's condition Total duration: 8 weeks	1.O: improvement in - HADS score - QoL (SF-36) 2.O: improvement in the Clinical Global Impression (CGI) - - Measurement: - HADS: T0 (baseline), at T2 (week 2), T4 (week 4), T6 (week 6), T8 (week 8); - SF-36: T0,4,8	AD group: HADS, subscore Anxiety: sign. reduction in pre-post comparison, at T6 ($p < 0.05$) and T8 ($p < 0.01$) (MD group: not relevant; exclusion criteria)	- Very small sample, statistics not applicable - Mixed population with early (70%) and advanced cancer (30%)	3

15. Depression

15.1. Screening, Diagnose und Assessment

15.1.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Meijer, PLoS ONE 2011 [350]	SR; no MA to evaluate the potential benefits of depression screening in cancer patients	19 studies (Sample size ranged from 16 to 361)	8 studies of patients with **breast cancer** patients. 11 studies of patients with **mixed cancer** sites across the spectrum of cancer stages. Number of cases of major depressive disorder (MDD) ranged from 6 to 74 (median=17).	Screening instrument vs. a valid MDD criterion standard ▪ HADS;-D ▪ EPDS	Assessing accuracy With: ▪ Sensitivity ▪ Specificity ▪ PPV ▪ NPV (95% CI)	• The main finding of this systematic review was that there are no RCTs that have evaluated whether screening for depression among cancer patients would improve depression outcomes. • The result shows that the recommendation statement of the NIH panel, IOM, clinical guideline of NCCN and NICE are not supported by evidence from RCTs that screening cancer patients for depression would improve patients' mental health beyond existing psychological services that are offered in oncology settings.		1-
Mitchell, J Clin Oncol 2007 [351]	SR, MA; Accuracy of distress thermometer (DT) and other	38 analyses about diagnostic validity studies	**Cancer** settings N=6414 patients	Ultra-short screening tools (DT, single-question, VAS) involving fewer than five questions	Utilizing an accepted psychiatric interview or a standardized ratings scale for assessing: ▪ Depression	Pooled ability of ultra-short methods to detect depression was given by: ▪ Sensitivity=78.4% ▪ Specificity=66.8%		1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	ultra-short methods of detecting cancer-related mood disorders				▪ Anxiety ▪ Distress	▪ PPV=34.2% ▪ NPV=93.4% Thus these tools were very good at excluding possible cases of depression but poor at confirming a suspected diagnosis. Their rule-in ability was poorer than their rule-out ability. Ultra-short methods cannot be used alone to diagnose depression, anxiety, or distress in cancer patients but they may be considered as a first-stage screen to rule out cases of depression.		
Mitchell, Brit J Cancer 2008 [352]	SR, MA; to examine the value of one or two simple verbal questions in the detection of depression	Seventeen analyses were found. Of these, 13 were conducted in late stage palliative settings.	**Cancer** settings	▪ Single depression question ▪ Single interest question ▪ Two questions (low mood and low interest)	The majority of studies defined depression using a psychiatric interview (applied in a semi-structured or clinical interview) but a minority utilised standardised rating scales.	(1) Single depression question (9 studies): prevalence of depression = 16%, sensitivity = 72%, specificity = 83%. PPV = 44%, NPV =94%. (2) Single interest question (3 studies): Prevalence=14%, sensitivity= 83%, specificity=86%, PPV= 48%, NPV =97%. (3) Two questions (5 studies): prevalence=17%, sensitivity= 91%, specificity= 86%, PPV = 57%, NPV =98%. Simple verbal methods perform well at excluding depression in the non-depressed but perform poorly at confirming		1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						depression. The 'two question' method is significantly more accurate than either single question but clinicians should not rely on these simple questions alone and should be prepared to assess the patient more thoroughly.		
Mitchell, J Affect Disorders 2010 [353]	SR, MA; To examine the validity of the HADS in the identification of psychiatric complications of cancer, as defined by robust criterion standard	50 analysis	**Cancer and palliative setting**	50 analyses tested the HADS-S (depression), HADS-A (anxiety)or HADS-T (both) against syndromal (clinical) depression (n=22), syndromal anxiety (n=4) or any mental ill health/distress, all defined by semi-structured psychiatric interview.	1.O: Syndromal (clinical) depression defined by ICD10 or DSM-IV. 2.O: Syndromal anxiety disorder defined by ICD10 or DSM-IV. 3.O: Any mental ill health (usually distress or adjustment disorder) defined by ICD10or DSM-IV.	Overall it appeared to perform marginally better in non-palliative cancer settings. In the identification of depression the HADS-T, HADS-D and HADS-A had a pooled sensitivity and specificity of 82.0%, 77.0%; 71.6%, 82.6% and 80.5%, 77.8%, respectively. All versions performed poorly in case-finding but well in a screening capacity. For the identification of depression, anxiety or distress in cancer settings, the HADS (including subscales) is not recommended as a case-finding instrument but it may, subject to concerns about its length, be a suitable addition to screening programme.		1+
Mitchell, J Affect Disord 2012	SR, MA; To examine the validity of screening and	63 studies involving 19 tools	**Cancer** patients in ▪ **Palliative settings**	To examine the validity of screening and case-finding tools used in the identification of	Validation of diagnostic accuracy with: ▪ Sensitivity	Across 16 analyses (n=4138) the weighted prevalence of depression	The main cautions are the reliance on DSM-IV definitions of major depression,	1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
[354]	case-finding tools used in the identification of depression as defined by an ICD 10/DSM-IV criterion standard Plus panel recommendation of Depression in Cancer Care consensus group		▪ Non-palliative settings	depression as defined by an ICD10/DSM-IV criterion standard. ▪ BDI ▪ BDI fast screen ▪ DT ▪ EPDS ▪ PHD ▪ PHQ-2 ▪ Two stem questions ▪ GHQ-12 and GHQ-24 ▪ CES-D ▪ Zung ▪ HADS ▪ HDS ▪ Several other tools	▪ Specificity ▪ I^2 ▪ Bayesian Plot (post-test and pre-test probabilities)	in palliative settings was 19% (CI95% CI=17.5-19.5). In terms of case-finding, the two stem questions had level 1b evidence and one stem question had level 2b evidence. We gave both methods a grade B recommendation. Two stem questions also had level 1b evidence in screening and also had high acceptability. For every 100 people screened in advanced cancer, the two questions would accurately detect 18 cases, while missing only 1 and correctly reassure 74 with 7 falsely identified.	the large number of small studies and the paucity of data for many tools in specific settings.	
Nelson, J Clin Oncol 2010 [355]	SR;no MA To determine which depression instruments are appropriate	53 depression scales were identified, 8 tools were selected	**Geriatric cancer** patients	Patient reported scales ▪ BDI ▪ BSI-18 ▪ CES-D ▪ GDS-15 ▪ HADS ▪ PHQ-9 ▪ POMS-SF ▪ Zung SDS	▪ General properties: conceptual framework ▪ Instrument development ▪ Validation and psychometric properties ▪ Symptom profile analysis	We could not locate any validation or psychometric information of these measures specifically in elderly patients with cancer. The validation evidence for use of common depression instruments in geriatric patients with cancer is lacking.		1+
Vordermaier, Support Care Cancer 2011 [356]	SR, MA; to examine the scale's accuracy in assessing any type of clinically relevant mental	28 studies	**Cancer** Mixed cancer sites: 10 studies, N=2828 Breast cancer: 8 studies, N=1407 Mixed cancer sites in palliative settings: 3 studies	▪ HADS total and its subscale scores against ▪ semi-structured or structured clinical interview as a reference standard with regard to its screening efficacy for any mental	▪ Sensitivity ▪ Specificity on the HADS total and/or subscales and had any type of mental disorder and/or any type of depressive disorder as the criterion.	Respective thresholds for depression screening were 15 for the HADS total (sensitivity 0.87; specificity 0.88), 7 for the HADS depression subscale (sensitivity 0.86; specificity 0.81), and 10 or 11 for the HADS anxiety subscale		1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	disorder in cancer patients, as well as determining cut-off rates for clinical use.		N=388 Lung cancer: 3 studies, N=219 Head and neck cancer: 2 studies, N=167 Laryngeal cancer: 1 study, N=250 Otolaryngologic cancer: 1 study, N=50	disorders and depressive disorders alone		(sensitivity 0.63; specificity 0.83). The HADS anxiety subscale performed worse than the total and the depression subscales for both indicators. Diagnostic accuracy varied widely by threshold but was consistently superior for depression screening than for screening of any mental disorder.		
Wasteson, Palliative Med 2009 [357]	SR ; no MA Assessment tools and classification systems	202 full-length articles: ▪ 128 observational study ▪ 61 prevalence studies ▪ 42 intervention studies (Depression outcome) ▪ 46 validation studies (depression assessment) ▪ 27 validations studies (other assessment) ▪ 15 intervention studies (other outcome) ▪ 18 other or not specified studies	**Palliative cancer care** patients	▪ What are the assessment methods that have been used according to the type of study, year of study, sample size and geographical region? ▪ In studies that report on depression cases, what are the classification systems that have been used to define caseness and how have the criteria of duration and functional consequences of symptoms been met?	▪ Assessment methods ▪ Type of study ▪ Sample size ▪ Geographical region ▪ Classification systems ▪ Duration and functional consequences ▪ Criteria modification	Large number of assessment methods in identified papers for depression (N=106), many of which were unique to one paper (N=65). The content of the assessment methods varied greatly and included different types (i.e. structured diagnostic interviews, specific questionnaires, general questionnaires). All together, the HADS was the most commonly used assessment method. There were regional differences: HADS dominated in Europe it was quite seldom used in Canada or in the USA. Few prevalence and intervention studies used assessment methods with an explicit reference to a diagnostic system. There were in total few case		1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						definitions of depression. Among these, the classifications were in general based on cut-off scores (77%) and not according to diagnostic systems. The full range of the DSM-IV diagnostic criteria was seldom assessed, i.e. less than one-third of the assessments in the review took into account the duration of symptoms and 18% assessed consequences and impact upon patient functioning. Although heterogeneity in assessments was expected the diversity in the reviewed papers was pronounced. Depression and distress are rarely conceptualized explicitly and it is often unclear why a given measure was chosen.		

15.2. Nicht-medikamentöse Verfahren: Aktualisierung 2019

15.2.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Fulton, J Palliat Med 2018 [358]	MA To examine the effect of psychotherapy on depression and anxiety among individuals with any condition appropriate for palliative care	32 RCT with 36 samples including n=1536 participants ▪ psychotherapy that involved at least two sessions or a minimum of 60 minutes of intervention ▪ randomized design	**Palliative patients** (Cancer, MS, HIV/AIDS, advanced illness)	Psychotherapy focusing on marital functioning, physical symptom reduction (e.g. pain, or health behavior change) Psychotherapy type: CB-based Therapies (CBT, PST Problem Solving Therapy, IPT Interpersonal Therapy), existential therapies (DT Dignity Therapy, Legacy, LR life review, MM meaning making therapy) Other Therapies (ACT, MBSR, Supportive expressive therapy, Outlook intervention) Treatment modality ▪ Individual ▪ Group ▪ Family	1.O: reduce depression symptoms (large effect) 2.O: reduce anxiety symptoms (small effect) 1.O: Improve quality of life (small effect)	**Depression and anxiety:** The mean effect was significant: Depression (n=35): Mean ES (effective size) -0.82 <0.001, 95% CI -1.02 to -0.62), **anxiety** (n=21): Mean ES -0.38 p<0.001, 95% CI -0.52 to -0.24, **QoL** (n=9): Mean ES 0.47 p<0.01, 95% CI 0.17 to -0.78 **Cancer**: ES by class -0.80; wthin class effect 81.83, p<0.001	Limited methodological quality of research designs and reporting, quality rating is medium	1+

15.3. Medikamentöse Therapie

15.3.1. Antidepressiva

15.3.1.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Rayner, Cochrane 2010 [359]	SR; MA to determine the efficacy of antidepressants in the treatment of depression in patients with a physical illness	51 RCTs included in qualitative analyses (n=3603; adults older than 18 years with depression in the context of a physical illness) 44 studies (n=3372) contributed data towards the efficacy analyses included in quantitative synthesis of primary outcome	• 11 trials (stroke) • 7 trials (HIV/AIDS) • 6 trials (Parkinson's disease) • 4 trials (cancer) • 3 trials (COPD) • 3 trials (diabetes) • 3 trials (myocardial infarction • 2 trials (renal failure) • 1 trial (rheumatoid arthritis) • 1 trial with: brain injury/ asthma/ coronary artery disease/ chronic heart failure/ epilepsy/ chronic prostatitis • 3 trials with mixed diagnoses Average age: 33-82 years	All types of antidepressants were eligible for inclusion in this review: • Selective serotonin reuptake inhibitors • Tricyclic antidepressants • Monoamine oxidase inhibitors • Serotonin noradrenaline reuptake inhibitors • Noradrenergic specific serotonergic antidepressant • Serotonin2 antagonists • Noradrenaline reuptake inhibitor • Norepinephrine and dopamine reuptake blockers • Tetracyclic antidepressants • Heterocyclic antidepressants Control condition was placebo	1.O: • Antidepressant efficacy at 6-8 weeks after randomisation • dichotomous outcome of individuals who attained a 50% improvement of depressive symptomatology at 6 to 8 weeks from randomisation (HDRS, MADRS, HADS) • continous measures of depression expressed as mean values at 6 to 8 weeks from randomisation (HDRS, MADRS, HADS) 2.O: • Depression scores and symptomatology defined by validates measures • Number of drop-outs • Number of adverse events	1.O: • response to treatment: Odds of response were greater with antidepressants than with placebo (OR 2.33, 95CI 1.8 to 3.0, p<0.00001; 25 studies involving 1674) • Antidepressants were also more efficacious than placebo at the other time-points. • Mean depression score: Antidepressants were more efficacious than placebo in reducing depressive symptoms (SMD -0.66, 95% CI -0.94 to -0.38, p<0.00001; 22 studies involving 1214 patients). 2.O: • Mean depression score (4-5 weeks): Antidepressants were more efficacious than placebo in reducing depressive symptoms (SMD -0.46, 95% CI		1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						-0.88 to -0.04, p=0.03; 6 studies, n=365) • Number of drop-outs (4 to 5 weeks): Similar numbers of patients dropped out of the treatment and control group (OR1.11, 95% CI 0.48 to 2.57, p=0.86; 5 studies, n=365) • Tolerability: dizziness, dry mouth, headache, nausea, constipation, insomnia, sexual dysfunction, sedation, hypotension, appetite change.		
Rayner, Pall Med 2011 [360]	SR; MA to determine the efficacy of antidepressants for the treatment of depression in palliative care	SR: 25 studies MA: 21 studies	• 7 trials (HIV/AIDS) • 6 trials (Parkison´s disease) • 4 trials (cancer) • 3 trials (COPD) • 2 trials (multiple sclerosis) • 2 trials (renal failure) • 1 trial (chronic heart failure)	antidepressants vs. placebo in the treatment of depression in palliative care	1.O: • Efficacy assessed using dichotomous and continuous measures of depression: dichotomous outcome response to treatment' is defined conventionally and widely reported as a 50% or greater improvement in depressive symptomatology according to a validated scale, such as the HDRS, the MADRS or the HADS. Continuous measures expressed as mean depression score values and standard deviations, according to a validated scale. Outcomes were assessed at three time-points: 4–5 weeks, 6–	At each time-point antidepressants were more efficacious than placebo: 4–5 weeks odds ratio (OR) 1.93 (1.15–3.42) p=0.001; 6–8 weeks OR 2.25 (1.38–3.67) p=0.001; 9–18 weeks OR 2.71 (1.50–4.91) p=0.001. This review provides evidence that antidepressants are effective in treating depression in palliative care. Their superiority over placebo is apparent within 4–5 weeks and increases with continued use.	• It is probable that the effect sizes yielded in this review overestimate the efficacy of antidepressants due to biases such as selective reporting and publication. • the magnitude and consistency of the effect suggests genuine benefit.	1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
					8 weeks and 9–18 weeks from randomization. 2.O: • Acceptability, tolerability, quality of life and functional status.			
Ujeyl, Schmerz 2012 [361]	SR; MA Aim was to assess the evidence of the efficacy and safety of different classes of antidepressants depending on the type and severity of physical illness.	40 trials: • 35 double-blind RCT´s • 3 doubleblind crossover RCT´s • 1 simpleblind RCT • 1 CT not blinded	• 3 trials (multiple sclerosis; n=133) • 6 trials (Parkisnon´s disease; n=187) • 7 trials (Alzheimer´s disease; n=625) • 8 studies (cancer; n=819) • 11 studies (HIV/AIDS; n=664) • 5 studies (COPD/CHF; n=568)	• Nonselective monoamine reuptake inhibitors (tri- and tetracyclics) • Selective serotonin reuptake inhibitors • mirtazapine • nefazodone • trazodone compared with placebo, other antidepressants, benzodiazepines, psycho-stimulants or psychotherapy	Outcomes: • response rate • change from baseline • remission rate	Due to heterogeneous study designs no conclusions can be drawn if efficacy or tolerability of AD is dependent on disease severity. In most cases, studies might have been too small to detect limited treatment effects. As a lack of superiority over placebo was predominantly shown in larger trials, publication bias might have been present. In most of the reviewed internal medicine diseases study results were heterogeneous. In contrast to the popularity of the treatment approach, results suggest that SSRIs are not effective in Alzheimer's disease. In Parkinson's disease, negative studies are too small to prove lack of efficacy of SSRIs as present in the majority of trials.	This review allows only limited conclusions concerning the use of antidepressants in physical illness at the end of life. The reviewed evidence does not allow direct conclusions to be drawn concerning the use of antidepressants in different disease severities and its benefits compared to other treatment options (psychotherapy, benzodiazepines etc.).	1+

15.3.1.2. Systematic Review der Aktualisierung 2019

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Ostuzzi, Cochrane 2018 [362]	SR to assess the efficacy, tolerability and acceptability of antidepressants for treating depressive symptoms in adults	10 RCTs (n=885) ▪ 7 of which contributed to the meta-analysis for the primary outcome ▪ 4 of these compared antidepressants and placebo, ▪ 2 compared two antidepressants, ▪ 1 three-armed study compared two antidepressants and placebo This update included one additional unpublished study. These new data contributed to the secondary analysis, while the results of	Patients with primary diagnosis of cancer (confirmed with appropriate clinical and instrumental assessment) and depression (including major depressive disorder, adjustment disorder, dysthymic disorder or depressive symptoms in the absence of a formal diagnosis; Diagnostic systems DSM/ICD, Hamilton Rating Scale for Depression (HRSD), Beck Depression Inventory (BDE), Montgomery-Asberg Depression Rating Scale (MADRS), or the Hospital Anxiety and Depression Scale (HADS) Age ≥18 years In- and outpatients	Antidepressants for the treatment of depression in people with cancer Antidepressants, reported in the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) Index (updated to December 2017) from the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology website (www.whocc.no)	1.O:Efficacy as a continuous outcome 2.O:Efficacy as a dichotomous outcome Social adjustment Health-related quality of life Dropouts:	**Acute Phase**: For acute-phase treatment response (6 to 12 weeks), no difference between antidepressants as a class and placebo on symptoms of depression measured both as a continuous outcome (standardised mean difference (SMD) −0.45, 95% confidence interval (CI) −1.01 to 0.11, 5 RCTs (n=266 participants); very low certainty evidence) and as a proportion of people who had depression at the end of the study (risk ratio (RR) 0.82, 95% CI 0.62 to 1.08, 5 RCTs, 417 participants; very low certainty evidence). No trials reported data on follow-up response (more than 12 weeks). In head-to-head comparisons where only retrieved data for selective serotonin reuptake inhibitors (SSRIs) vs. tricyclic antidepressants, showing no difference between these two classes (SMD −0.08, 95% CI −0.34 to 0.18, 3 RCTs (n=237 participants); very low certainty evidence).	Downgrading of the certainty (quality) of the evidence because the included studies were at an unclear or high risk of bias due to poor reporting, imprecision arising from small sample sizes and wide confidence intervals, and inconsistency due to statistical or clinical heterogeneity.	1++

Study	Type of study (SR=Systematic Review; MA=Meta-analysis); Aim of study	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
		the primary analysis remained unchanged.				No clear evidence of a beneficial effect of antidepressants versus either placebo or other antidepressants emerged from our analyses of the secondary efficacy outcomes (dichotomous outcome, response at 6 to 12 weeks, very low certainty evidence). In terms of dropouts due to any cause, no difference between antidepressants as a class compared with placebo (RR 0.85, 95% CI 0.52 to 1.38, 7 RCTs (n=479 participants); very low certainty evidence), and between SSRIs and tricyclic antidepressants (RR 0.83, 95% CI 0.53 to 1.30, 3 RCTs (n=237 participants).		

15.3.2. Andere Wirkstoffe

15.3.2.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Abbasowa, Nord J Psychiatry 2013 [363]	SR /no MA Exploring the efficacy of psychostimulants (PS) in the treatment of major depressive disorder (MDD) to clarify the current empirically founded evidence for clinical approaches	18 RCTS (N=1407)	Patients suffering from ▪ MDD (n=1038) ▪ Bipolar depressed patients (n=342) ▪ Mixed samples of bipolar and unipolar patients (n=27)	▪ Modafinil ▪ Methylphenidate ▪ Dexamphetamine ▪ Methylamphetamine ▪ Pemilone were administered orally/intravenously, as monotherapy/adjunct therapy and in comparison to placebo (n=1311) or to antidepressants/mood stabilizers (n=96)	A priori defined efficacy measures (change and scores) of: ▪ HAM-D ▪ MADRS ▪ ESS ▪ IDS and non-predefined efficacy outcomes	▪ Two studies examining modafinil demonstrated significant ameliorating characteristics pertaining to symptoms of depression. ▪ No clear evidence for the effectiveness of traditional PS in the therapeutic management of MDD was found.	▪ In general the quality of included trials was poor since the majority was of short-term duration, comprising relatively small sample sizes and some, especially older studies, were methodologically flawed. ▪ Clearly larger well designed placebo-controlled studies with longer follow-up accompanied by evaluations of tolerance/ dependence are warranted before PS can be recommended in routine clinical practice for the treatment of MDD.	1-
Candy, Cochrane 2008 [364]	SR (24 RCTs); MA (13 trials) To determine the effectiveness of PS in the treatment of depression and to assess adverse	24 RCTs • 15 parallel design • 9 cross-over design	Patients (>16 years) receiving psychostimulants as a treatment of depression (diagnosis was made according to any edition of DSM or ICD or when a clinician made the diagnosis)	Psychostimulants (PS): • dexamphetamine • methylphenidate • methylamphetamine • pemoline • modafinil (trials using modafinil were evaluated separately) Main comparisons:	1.O: Examine the effectiveness of PS on depressive symptoms or diagnosing using: • Continous measures (Hamilton Depression Scale or Montgomery Asberg Scale) • Dichotomous measures (proportion of people who respond to treatment	▪ 3 trials (n=62) demonstrated that oral psychostimulants, as a monotherapy, significantly reduced short term depressive symptoms in comparison with placebo (SMD -0.87, 95% CI -1.4, -0.33) with non-significant heterogeneity.	• 15 trials were performed over 20 years ago. • 4 trials declared pharmaceutical funding or interests. • Some evidence in the short-term, PS reduce symptoms of depression. Whilst this reduction is statistically	1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	events associated with PS.			• PS vs. monotherapy vs. placebo • PS vs. monotherapy vs. other treatment (medication, psychological therapy) • PS vs. other treatment as a adjunctive treatment	(categorisation of HAM-D score or any other validated depression scale into a 50 response or less. 2.O: • Changes in other symptoms associated with depression • Remission criteria • Social adjustment and functioning • HRQL • acceptability	▪ Similar effect was found for fatigue. ▪ No statistically significant difference in depression symptoms was found between modafinil and placebo.	significant, the clinical significance is less clear. • Larger high quality trials with longer follow-up and evaluation of tolerance and dependence are needed to test the robustness of these findings and to explore which PS may be more beneficial and in which clinical situations they are optimal.	

15.3.2.2. Primärstudie

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
Kerr, J Pain Symptom Manag 2012 [365]	RCT, double-blind, placebo-controlled To evaluate the response of fatigue and	n=34 4 drop-outs: • 3 died • 1 withdrew	hospice patients • 12 male; 18 female • diagnosis of terminal illness including cancer (n=26) and	1st arm: 5mg methylphenidate twice a day 2nd arm: placebo Doses were titrated every three days	Influence of methylphenidate on the symptom of fatigue on ▪ Piper-Fatigue-Scale (PFS) ▪ VAS-F ▪ ESAS and on depression with	Fatigue: ▪ PFS: reduction of 66% (day 0 mean intensity of 6.2; day 14=2.1±2.5) ▪ VAS-F: reduction of 55% (day 0=4.9±2.7; day 14=2.2±3.1), although significant was noted		1-

Study	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/ control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure Follow up	Results	Comments	Level of Evidence SIGN
	depression in patients with advanced illness		noncancer diseases (n=4) • absence of significant cognitive impairment • presence of fatigue for at least two weeks	according to response and adverse effects	▪ ESAS ▪ CES-D ▪ BDI-II from days 0-14	until day 7 (P=0.05) ad day 14 (P=0.0007) ▪ ESAS: reduction of 64% from baseline index of fatigue (day 0=7.4±2.0 and day 14=2.7±1.3) Depression: ▪ ESAS: reduction of 35%, P=0.002 (day 0=2.9±3.1 and day 14=1.9±2.0) ▪ CES-D: reduction of 33%, P=0.002 (day 0=25.0, day 14=16.7±9.5 • BDI-II: reduction of 22%, P=0.028 (day 0=15.1, day 14=11.8±9.1)		

16. Todeswünsche

16.1. Das Phänomen „Todeswunsch“

16.1.1. Systematic Review

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	LoE SIGN
Rodriguez-Prat, BMJ, 2017 [366] *(Update meta-ethnography 2012)*	SR and meta-ethnography; To explore the wish to hasten death (WTHD) as expressed by patients with advanced disease; describe suffer	Databases: PubMed MEDLINE, Web of Science, CINHAL and PsycInfo from 2000 to January 2016 Design: primary qualitative studies (ie, studies using recognised methods of both qualitative data collection and qualitative data analysis) Population: adult patients with **advanced disease** that express a wish to hasten death (WTHD)	The synthesis followed the seven steps proposed by Noblit and Hare as follows: 1. Definition of the research question 2. A literature search for references to studies for inclusion in the synthesis. 3. Reading the studies in order to identify key and secondary concepts in each of them. 4. Determining how the studies are related. To this end we created a chart showing the categories that emerged from the studies (more descriptive level), and this ser ed as the basis for abstracting themes and	Study number: 14 studies (n=255) Population: cancer (ambulatory/ terminally)/palliative patients in 9 studies; not specified in 2 studies; HIV/AIDS in 1 study; terminal ill elders in 1 study; different diagnoses in 1 study) Study designs: 3 studies used grounded theory, 1 study used mixed-methods, 1 used phenomenological approach, 3 studies used a combination of phenomenological and hermeneutical methods, 1 study design is unclear; most studies with in-depth or semistructured interviews, 1 with narrative interviews Results: 5 main themes were identified (suffering [overarching theme], reasons, meanings, functions, live experience of a timeline towards dying and death. WTHD emerges as a reaction to physical, psychological, social and existential suffering, all of which impacts on the patient´s sense of self, of dignity and meaning in life. WTHD can hold different meanings for each individual	- proportion of patients (sample sizes from 2 to 35 patients, total sample size of 255) - Different populations - Well-conducted qualitative SR	3

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	LoE SIGN
			subthemes from each study 5. To perform translation across studies, in other words, to ‘deconstruct’ the studies, identifying different metaphors or concepts on the basis of words or statements in the original articles.			

16.2. Erfassung

16.2.1. Systematic Review

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	LoE SIGN
Bellido-Pérez, Palliat Medicine 2017 [367]	SR; To identify and analyse existing instruments for assessing the wish to hasten death (WTHD) and to rate their reported psychometric properties	Databases: CINAHL, PsycINFO, Pubmed and Web of Science databases from inception to November 2015 Design: no restrictions; language: English, French, Spanish Population: adult patients with **advanced disease** and/or who were being cared for in any **palliative** care facility	Measurement tools: **any instrument used to assess the WTHD** (validation studies, assessment of WTHD as main purpose, or WTHD as outcome among others)	Study number: 50 studies Population: cancer patients in 39 studies; HIV/AIDS or MND in 7 studies Instruments: 7 tools (scales, questionnaires or VAS), item number between 1 and 20: - SAHD (Schedule of Attitudes toward Hastened Death): most widely used; originally developed for use in research rather than in clinical practice - DDRS (Desire for Death Rating Scale) or modified DDRS: designed for clinician administration in the context of a clinical interview - 3 instruments developed ad hoc for study purpose	- Lack of conceptual clarity appears to have led to the development of different assessment methods that focus on different aspects of the WTHD - Low proportion of patients, from among those who were eligible for inclusion, who finally participated - Methodological quality of validation studies (COSMIN): ratings between fair and excellent; but lacking data, so that only some of the criteria could be evaluated	3

16.3. Proaktives Thematisieren

16.3.1. Systematic Review

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	LoE SIGN
Blades, Clin Psychol Rev 2018 [368]	SR, MA; To examine whether asking about suicide or exposure to suicide-related content in research studies led to changes in three relevant outcome variables: levels of distress, levels of suicidal ideation, and likelihood of attempting suicide following research participation.	Databases: PsycINFO, MEDLINE, and ERIC from 2000 to November 2017 Design: original, empirical articles; language: English; effect size reported Population: study participants (children and adults, healthy or sick) being asked about suicide or exposed to suicide-related content in research studies	Exposition: suicide assessment or screening, or exposition to suicide-related content Outcomes: - levels of distress - levels of suicidal ideation - likelihood of attempting suicide following research participation	Study number: 18 studies; 12 studies with Single group- Pre/Post data; 18 studies with 2 groups- Post data. No further details on study design Population: from healthy volunteers (incl. children/adolescents) to psychiatric patients Outcomes in MA: **Distress**: - Pre-post within-group comparison (8 studies, n=5562): n.s. Hedges' g=−0.09, p=.165, 95% CI [−0.21, 0.04]; high heterogeneity I^2=92.04, explained as being caused by the format of exposure (one-on-one interview vs. non-interview context, with sign. reduction of distress with one-on-one interview, vs. n.s. change with non-interview) - Post between-group comparison, **immediate effects** (6 studies, n=3430): n.s. Hedges' g=−0.01, p=.894, 95% CI [−0.16, 0.14]; high heterogeneity I^2= 64.81 - Post between-group comparison, **delayed effects 2 days later** (2 studies, n=2319): n.s. Hedges' g=0.04, p=.293, 95% CI [−0.04, 0.13]; I^2=0.00 **Suicidal ideation** - Pre-post within-group comparison (4 studies, n=3699): small sign. reduction, Hedges' g=−0.13, 95% CI [−0.16, −0.10], p < .001; I^2=0.00	- In part, high statistical heterogneneity between studies; or very few study number, so that I^2 may not reflect true heterogeneity. - Few studies identified through the search strategy (261 hits) > search strategy sensitive enough? - High heterogeneous population - No details on study design - No mention of assessment of evidence quality	1- / 3 (body of evidence: not statable: between 1 and 3)

Reference	Type of study (SR=Sys Review; MA=Meta-analysis); aim	Databases; Inclusion criteria (study design, population)	Interventions evaluated, outcomes	Results	Comments	LoE SIGN
				- Post between-group comparison (6 studies, n=7398): n.s.: OR=0.973, 95% CI [0.83, 1.15], p=.749; I^2=28.61 **Suicide attempt** - Post between-group comparison (4 studies, n=5261): sign. reduction, OR=0.714, 95% CI [0.56, 0.91], p < .05; I^2=0.00		
DeCou, Suicide Life Threat Behav 2018 [369]	SR, MA; To synthesize research concerning the iatrogenic risks of assessing suicidality	Databases: Academic Search Complete, MedLine, PsycINFO, PubMed, and SCOPUS until December 15, 2016 Design: RCTs, experimental or single sample longitudinal designs Population: not stated	Exposition/ intervention: suicide assessment Outcomes: suicidal ideation, suicidal behaviour, emotional or psychological distress (e.g., negative affect, symptoms of depression, global distress).	Study number: 13 studies, n=4,406 (out of them 4 RCTs) Population: from healthy volunteers (incl. children/adolescents) to psychiatric patients Outcomes in MA: **Suicidal Ideation**: - Within 2 Days of Assessment (4 studies): n.s., *d*=-0.081, 95% CI -0.222 to 0.061, I^2=0.00% - 2 to 4 weeks postassessment (3 studies): n.s., *d*=0.079, 95% CI -0.143 to 0.301, I^2=19.38% - 2 months to 2 years postassessment (3 studies): n.s., *d*=-0.064, 95% CI - -0.513 to 0.385, I^2= 64.05% - Among high-risk/vulnerable patients (7 studies): n.s., *d*=0.093, 95% CI -0.315 to 0.129, I^2=43.81% **Psychological distress**: - Overall (8 studies): n.s., *d*=-0.0128, 95% CI -0.332 to 0.076, I^2= 85.91% - Among high-risk/vulnerable patients (6 studies): n.s., *d*=0.052, 95% CI -0.146 to 0.250, I^2=56.99% **Suicidal behavior** (3 studies): no MA; no higher suicidal behavior in 1 study; not statable in the other 2 studies	- No mention of assessment of evidence quality - Sensitive search strategy - In part high heterogeneity between studies - High heterogeneous population	1+/3 (body of evidence: not statable (between 1 and 3)

16.3.2. Primärstudien

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Crawford, BJPsych 2011 [370]	Multicenter, single-blind RCT; To examine whether screening for suicidal ideation increases the short-term incidence of feeling that life is not worth living	n=443 (I: n=230; C: n=213) Drop outs =92 (I: n=43 C: n=49)	People who attend **primary care** services and have a positive 2-item screening for **depression** Mean age: 48.5 y (SD = 18.4, range 16–92); 30.9% were male	**I: early screening** for suicidal ideation **C**: control questions on health and lifestyle	1.O: thinking that life is not worth living 2.O: wish to be dead, thoughts of taking one's life, serious consideration of taking one's life, attempt to take one's life (adapted from a questionnaire on suicide risk) Comparison: OR Measurement: - I: T0 and T1 (10-14 days) - C: T1 only	**Thinking that life is not worth living**, wish to be dead, thoughts of taking one's life, attempt to take one's life: n.s. Screening for suicidal ideation in primary care among people who have signs of depression does not appear to induce feelings that life is not worth living.	- Randomised and single blinded - Study powered - ITT mentionned but appears not clearly in the results - Intervention and outcome measurement identical, due to study question - No validated outcome measurement scale	1-
De Beurs, Arch Suicide Res 2016 [371]	RCT; To investigate the effect of the questions from the Beck Scale for Suicide Ideation on psychological well-being among healthy participants	n=301 (I: n=150; C: n=151)	**Healthy** participants	**I: BSS** (Beck Scale of Suicide Ideation) + standard questionnaires **C:** WHOQOL (World Health Organization Quality of Life abbreviated) + standard questionnaires	- Positive affect subscale - Negative affect subscale on the Positive and Negative Affect Schedule (PANAS); total score range: 10-50 Measurement: T0 and T1 (immediately after intervention); no follow up	**Negative affect (NA)**: sign. higher in BSS-group at T1 in comparison with control. No statistical data reported **Positive affect**: n.s. Multivariate analyses showed that the 24 participants with elevated NA were characterized by significant higher scores on loneliness compared to the other 273 participants. Answering	Content: Results differ from other studies that showed no negative effect of questions about suicide Method: - Sign. results reported without statistical data - Questionable generalizability of results from healthy	1-

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
						questions about suicide does result in distress for a small minority of more vulnerable individuals.	participants on patients - No follow up - No blinding - Not powered	
Harris, Int J Ment Health Nurs, 2016 [372]	Double-blind RCT; To test the emotional impact of suicide assessment on participant	n=267 (I: n=127; C: n=140) Drop outs =8 (I: n=5 C: n=3)	Singapore **adults volunteers** Aged 18–57 years (M = 24.96, SD = 8.18) -	**I: SABCS** (Suicidal Affect-Behavior-Cognition Scale) + **RFL/RFD** (Reasons for Living and Dying) + standard questionnaires **C:** WHOQOL (World Health Organization Quality of Life abbreviated) + standard questionnaires (Design based upon de Beurs et al. 2016)	- Positive affect subscale - Negative affect subscale on the Positive and Negative Affect Schedule (PANAS); total score range: 10-50 <u>Measurement:</u> T0 and T1 (immediately after intervention); no follow up	**Negative affect**: n.s. **Positive affect**: - Total sample: n.s. - Subgroup analysis for depressive participants: o n.s. for between-group comparison o sign. decrease in pre-post comparison for intervention group The study supported the null hypothesis that asking people suicide-related questions would not lead to a significant increase in emotional distress.	<u>Content</u>: Results confirm other studies that showed no negative effect of questionning about suicide <u>Method</u>: - Double blinding - Not powered - No follow up - Questionable generalizability of results from healthy participants on patients - No ITT	1-

16.4. Umgang mit Patienten mit Todeswünschen

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Breitbart, Palliat Psycho-Oncology 2010 [373]	Pilot RCT; To examine the impact of Meaning Centered Group Psychotherapy (MCGP)	n=90 (I: n=49; C: n=41) Drop outs =35 (I: n=14 C: n=21)	Patients with diagnosed **stage III or IV solid tumor** cancers or **non-Hodgkin's lymphoma**, ambulatory, over 18 years old; Mean age: 60.1 y (SD=11.8; range: 21-84); Males: 48.9%	**I: Meaning Centered Group Psychotherapy (MCGP):** focus around themes related to meaning and advanced cancer; 8-week duration **C**: supportive psychotherapy intervention (SGP) : discussion of issues themes that emerge for patients coping with cancer; 8-week duration	- FACIT Spiritual Well-Being Scale (SWB) - Beck Hopelessness Scale (BHS) - Schedule of Attitudes toward Hastened Death (SAHD) - Life Orientation Test (LOT) - Hospital Anxiety and Depression Scale (HADS) <u>Measurement</u>: - T0 (baseline) - T1 (8 weeks at post-intervention) - T2 (2 months, follow-up)	*We report here only results on Desire for Death:* **Desire for death** (SAHD): - Between-group: n.s. - Pre-post MCGP group: sign o T0-T1: d=0.29; p=0.09 o T1-T2: d=0.63, p=0.04 - Pre-post SGP group: n.s.	- block randomization - no blinding possible - No ITT feasible, because no a priori threshold existed for identifying 'improvement' on many of the study outcome measures (e.g. spiritual well-being, hopelessness, desire for hastened death), and participants were not selected based on meeting a threshold level of distress - Participants in MCGP attended significantly more sessions than SGP participants - No sample size calculation (pilot) - Most sign. results only for pre-post comparison inside a group and not for between-group comparison	1-
Breitbart, J	RCT;	n=253 (I: n=132;	Patients with diagnosed **stage IV**	<u>I:</u> **Meaning Centered Group**	<u>1.O</u>:	*We report here only results on Desire for Death:*	- Clustered randomization	1+

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
Clin Oncol 2015 [374]	To test the efficacy of MCGP to reduce psychological distress and improve spiritual well-being in patients with advanced or terminal cancer	C: n=121) Drop outs (at post-intervention): =126 (I: n=63 C: n=63)	**cancers** (or III if poor-prognosis disease), ambulatory, over 18 years old Mean age: 58.2 y (SD=11); Males: 30.4%	**Psychotherapy (MCGP):** focus around themes related to meaning and advanced cancer; 8-week duration C: supportive psychotherapy intervention (SGP) : discussion of issues themes that emerge for patients coping with cancer; 8-week duration	- spiritual well-being (FACIT-WBS) - QoL (McGill) 2.O: - Depression (BDI) - Hopelessness (Hopelessness Assessment in Illness Questionnaire) - desire for hastened death (SAHD) - anxiety (HADS) - physical symptom distress (MSAS) Measurement: - T0 (baseline) - T1 (8 weeks at post-intervention) - T2 (2 months, follow-up)	**Desire for death** (SAHD): Per protocol analysis: - Between-group: n.s. - Group x time: sign.: B = -0.22 (95% CI: -0.39 to -0.05) - Pre-post MCGP group: sign o T0-T1: d=-0.31; p=<0.05 o T1-T2: d=-0.27, p=<0.05 - Pre-post SGP group: n.s. ITT: Group x time: sign., although effect was smaller	- No blinding possible - Large sample; no sample size calculation described - lack of a threshold for distress as an entry criterion, which likely resulted in the inclusion of some participants with relatively little distress and hence less opportunity for improvement - Some baseline differences - High drop-out rate	
Breitbart, Cancer 2018 [375]	RCT; To examine the effectiveness of individual meaning-centered psychotherapy (IMCP) in comparison with supportive psychotherapy (SP)	n=321 (IMCP: n=132 SP: n=108; EUC: n=104) Drop outs (at post-intervention): =114	patient had to be at least 18 years old and English-speaking, have a **stage IV solid tumor cancer**, and have at least moderate distress Mean age: 58.2 y (SD=11); Males: 30.4%	I: IMPC (**individual meaning-centered psycho-therapy**) C1: SP (supportive psychotherapy): widely used in oncology settings C2: EUC (enhanced usual care)	1.O: existential distress and QoL: - spiritual well-being (FACIT-WBS) - Personal Meaning Index of the Life Attitude Profile–Revised (LAP-R) - QoL (McGill) 2.O: psychological distress:	*We report here only results on Desire for Death:* Analysis of patients achieving 3 or more sessions (n=264): - Group x treatment interaction: n.s. but trend: F(2,589)=2.55; P=0.08) - Between-group IMPC vs. EUC: sign. greater improvement - Between-group IMPC vs. SP: n.s.	- No blinding possible - Sample size calculation and adequate statistical power - ITT (and analysis with participants attending 3 or more sessions) - Some participants (in all 3 arms) were also on concomitant psychotropic medications	1+

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
	and enhanced usual care (EUC)				- Hopelessness Assessment in Illness Questionnaire (HAI) - desire for hastened death (SAHD) - anxiety and depression (HADS) - physical symptom distress (MSAS) Measurement: - T0 (baseline) - T1 (4 weeks mid- intervention) - T2 (8 weeks at post-intervention) - T3 (16 weeks, follow-up)	ITT: - Group x treatment interaction: n.s. - Time x treatment arm effects: o IMPC vs. EUC: sign. greater improvement (-0.9; CI 95% -0.17 to -0.01) o SP vs. EUC, IMCP vs. SP: n.s.	(whether prescribed for psychiatric symptoms or other reasons, eg, sedation or neuropathic pain	
Chochinov, Lancet Oncol 2011 [376]	RCT; To investigate whether dignity therapy could mitigate distress or bolster the experience in patients nearing the end of their lives	n=441 (DT: n=165; CCC: n=136; SPC: n=140) Analysis: n=326 (DT: n=108,; CCC: n=111; SPC: n=107)	Patients (aged ≥18 years) with a **terminal prognosis** (life expectancy ≤6 months) who were receiving **palliative care** in a hospital or community setting (hospice or home)	I: **dignity therapy** (DT) C1: client-centred care (CCC) C2: standard palliative care (SPC) Duration: 7 to 10 days	1.O: - reductions in various dimensions of distress (FACIT-WBS) - Patient Dignity Inventory - Hospital Anxiety and Depression Scale - items from the Structured Interview for Symptoms and Concerns: dignity, desire for death, suff ering, hopelessness, depression, suicidal - ideation, and sense of burden to others	*We report here only results on Desire for Death:* **Desire for Death**: n.s.	- Computer-generated table of random numbers in blocks of 30 to allocate patients - Assessment blinding - Sample size calcualation. Despite this, the authors conclude that the study might be underpowered - No screening for critical distress at baseline and so lower likelihood of showing differences	1+

Reference	Type of study/ Design; aim	Number of included patients (I/C); Drop-outs	Patients characteristics	Intervention (I)/ control (C)	Outcomes (1.O=primary; 2.O= secondary) Outcome measure Follow up	Results	Comments	LoE SIGN
					2.O: addressing to what extent the intervention might have aff ected the participants' end-of-life experiences			
Juliao, Palliat Support Care 2017 [377]	Phase II RCT; To determine the influence of Dignity Therapy on demoralization syndrome, the desire for death, and a sense of dignity in terminally ill inpatients experiencing a high level of distress	n=80 (I: n=41 C: n=39) Drop-outs: n=12 at day 4 (I: n= 8 C: n=4)	Adult patients having a **life-threatening disease** with a prognosis of 6 months or less (inpatients on **palliative** care unit)	I: **Dignity Therapy** (DT) C: Standard Palliative Care (SPC)	2.O (The present paper reports only the following 2.O; 1.O reported in another publication): - Demoralization prevalence (5 items-screening) - Desire for death prevalence (DDRS: Desire for Death Rating Scale; variable with cut-off: ≥ 4) - Sense of dignity (PDI: Patient Dignity Inventory) Measurement: - T0 (baseline) - T1 (post DT,day 4)	*We report here only results on Desire for Death:* **Desire for death=DfD prevalence** (DDRS ≥ 4): T0: 20% (no sign. difference between groups) T1: sign. decrease in DT group (p=0.054) - DT: 0% - SPC: 14.3%	- No blinding possible - Adequate randomization - analysis was applied to all patients who had at least one complete evaluation at any given follow-up point - No sample size calculation, no statistical power - DfD prevalence as categorical variable with fix cut-off questionable	1-

17. Sterbephase

17.1. Das Sterben diagnostizieren

17.1.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Eychmüller, E J Pall Care 2013 [378]	SR; To provide an overview of evidence supporting timely recognition of entry into the dying phase of cancer patients	12 trials: • 11 Cohort Studies • 1 Cross-sectional • 10 prospective and 2 retrospective 2 explicitly conducted with the goal of identifying the dying phase through signs	younger patients (18 to 55 years) to predominantly geriatric patients studies: 7 cancer 2 non-cancer 3 mixed population	SR focused on two research questions (see col. outomes)	1.O: ▪ signs, symptoms, tools or other technologies that can identify (diagnose) the last days of life of a cancer patient 2.O: ▪ evidence that these signs, symptoms, tools or technologies can accurately identify (diagnose) that a cancer patient has entered the dying phase	1.O: Two out of the three studies found the following phenomena in common: ▪ fatigue (80 – 93% of patients) ▪ Dyspnoea (45 – 50%) ▪ Pain (> 40%) ▪ Confusion, reduced consciousness (25 – 50%) Other phenomena, described only in a single study are: ▪ Being totally bedbound ▪ Anxiety/dysphoria ▪ Feeling alone ▪ Nausea 2.0: one study addressed last days of life in cancer patients and integrated “significant factors for predicting dying” into a computer-assisted predicting model	▪ most important finding: the literature did not provide a basis for a systematic review: There is a need of more and better-designed studies to address the lack of data in the field. ▪ the seven-day limit may have excluded important phenomena, if dying is considered as a process that begins more than a week before death ▪ A bias might have been caused by the clinical background of all researchers, who favour the use of the Liverpool care pathway in the last days of life ▪ Based on this systematic literature search there is low	1-

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
							evidence for both phenomena of approaching death in the literature, and for tools to diagnose the imminence of death, within a few days.	
Kehl, Am J Hosp Palliat Med 2012 [379]	SR; no MA to identify commonly occurring signs of impending death and symptoms that occur in the last 2 weeks of life and to estimate their overall prevalence.	12 peer-reviewed empirical studies which reported the prevalence of physical signs and symptoms in the last 2 weeks of life in multiple settings	Patients (n=2146) with physical signs or symptoms in the last 2 weeks of life	physical signs or symptoms in the last 2 weeks of life	1.O.: ▪ signs and symptoms ▪ documented and the overall prevalence of those signs and ▪ symptoms across the studies, both weighted and unweighted.	• In total, 62 signs and symptoms in the final 2 weeks of life were identified across all the studies. Of the 43 unique symptoms, symptoms with the highest prevalence are • dyspnea (56.7%) • pain (52.4%) • respiratory secretions/death rattle (51.4%) • confusion (50.1%)	4 signs and symptoms, agitation/ delirium/ restlessness (20.8%, range 5.8%-51%), anxiety (10.8 %, range 1.4%-45.5%), depression (8.3%, range 0.9%-38.6%), and sleep problems/insomnia (9.0%, range 3.2%-28.4%) were somewhat lower than previously reported ranges.	1-
Kennedy, BMJ, Support Pall Care 2014 [380]	SR; MA not possible	23 articles included: Findings on "characteristics of dying": 1 SR 7 retrospective chart reviews 2 qualitative studies 1 structured interview 1 quantitative study 1 literature review	Population due to findings "Characteristics of dying": Review included all research relevant to death, terminal care and bereavement; 2 studies focused on older people in nursing home setting; 4 studies focused on cancer; one study focused on stroke; 3 studies on cancer and long-term	No interventions.	Findings on "characteristics of dying". Findings on "treatment orientation".	'characteristics of dying' involve dying trajectories that incorporate physical, social, spiritual and psychological decline towards death 'treatment orientation' where decision making related to diagnosing dying may remain focused towards biomedical interventions rather than systematic planning for end-of-life care.	SR about "diagnosing dying" but no interventions. Including retrospective and qualitative studies.	3

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
		1 survey Findings on "treatment orientation": 2 case reviews 1 exploratory interview study 2 mixed methods 1 quantitative study 1retrospective cross-sectional survey of bereaved relatives 1 qualitative study 1 action research study 1 case review	conditions, one on ALS and one on medical decision making at the end of life.			The findings of this review support the explicit recognition of 'uncertainty in diagnosing dying' and the need to work with and within this concept. Clinical decision making needs to allow for recovery where that potential exists, but equally there is the need to avoid futile interventions.		

17.1.2. Primärstudien

Study	Study Aim	Study type	Delphi group size	Rounds	Nature of Subjects	Scoring	Consens criteria	Response	Results	Level of evidence SIGN
Domeisen Benedetti, Support Care Cancer 2013 [381]	to provide expert consensus on phenomena for identification and prediction	Delphi Study; part of the OPCARE9 project	252 in the first cycle; Second Cycle: N=36 questionnaires;	3 cycles: Each cycle included: (1) development of the questionnaire, (2) distribution of the	health care professionals, volunteers, public	▪ Cycle 1: generated 194 different phenomena, perceptions and observations. ▪ Cycle 2_ these phenomena were checked for their specific ability to diagnose the last hours/days of life. Fifty-eight phenomena achieved more than 80 % expert	▪ Cycle 1: The definitive decision on inclusion of phenomena was made by the synthesis group. ▪ Cycle 2: output 2 included phenomena that received more than 80 % expert consensus on agreement	▪ Cycle 1: response rate 100 % ▪ Cycle 2: response rate 72%	The seven categories included after the third cycle were: "breathing", "consciousness/cognition", "emotional state", "general deterioration", "intake of fluid, food other", "non-observations/ expressed opinions/other"	4

Study	Study Aim	Study type	Delphi group size	Rounds	Nature of Subjects	Scoring	Consens criteria	Response	Results	Level of evidence SIGN
	of the last hours or days of a patient's life		Third cycle: 78 palliative care experts	Delphi questionnaire and (3) review and synthesis of findings		consensus and were grouped into nine categories. ▪ Cycle 3: these 58 phenomena were ranked by a group of palliative care experts (78 professionals, including physicians, nurses, psycho-social-spiritual support.)	▪ Cycle 3 incorporated phenomena and respective categories that achieved more than 50 % expert consensus on "high relevance" in predicting that someone would die within the next few hours/days		and "skin". The categories "mobility" and "communication" were discarded after this process.	

17.1.2.1. Primärstudie der Aktualisierung 2019

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
Hui, Oncologist 2014 [382]	Longitudinal observational study to determine the frequeny and onset of 10 clinical signs	n=357 (n=203 drop out because died; 52 of 151 in the USA, 151 of 206 in Brazil))	**Adult cancer patients** Average age 58 years, Female n= 99 Cancer: Breast n=20, Gastrointestinal n=68, Genitourinary n=21, Gynecological n=16, Head and neck n=16, Hematological n=10, Others n=23, Respiratory n=29 Comorbidies: Chronic obstructive pulmonary disease n=4, Heart failure n=9, Coronary artery disease n=4, Stroke n=4, Chronic kidney	Not applicable	1.O: Frequency and onset of 10 clinical signs assocciated with impending death (i.e., apnoe periods, Cheyne-Stokes breathing, death rattle, dysphagia of liquids, decreased level of consciousness, Palliative Performance Scale (PPS) ≤ 20%, peripheral cyanosis, pulselessness of radial artery, respiration with mandibular movement, and urine output over the last 12 hours ,100 mL) in cancer patients admitted to APCUs 2.O: Diagnostic performance for impending death in 3 days	**Frequency and Onset of Clinical Signs:** PPS ≤ 20 %, RASS – 2 or lower, and dysphagia of liquids had a substantial proportion of patients over the last 7 days of life, occurring in a majority of decendents 12 hours before death (PPS ≤ 20 % were Specifity 81.3 (95% CI: 80.9–81.7); RASS – 2 or lower were 89.3 (95% CI: 88.9–89.7 and dysphagia of liquids were 78.8 (95% CI: 78.3–79.2) **Diagnostic Performance of Clinical Signs:** Positive LRs were 15.6 (95% CI: 13.7-17.4) for pulselessness of radial artery, 15.2 (95% CI 13.4 -17.1) for	Cancer patients where admitted in two APCUS, where their received intensive symptom management and interprofessional support Underestimated the frequency of some signs because of active interventions in the APCUs (e.g., death rattle) Variations in the prevalence of some signs may be related to patient differences, cancer diagnoses, and/or	3

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			disease n=1, Diabetes n=28 Months between cancer diagnosis and PC (median) 13, P= . 002 duration of PC (median) 5, P<.001			decreased urine output, 12.4 (95% 10.8 -13.9) for Cheyne-Stokes beathing, 10 (95% CI: 9.1-10.9) for repiration with mandibular movement, and 9 (95% CI: 8.1 – 9.8) for death rattle	how they were interpreted The data were highly compatible when analyzed by study site, demonstrating similar specificities and sensitivities for each sign. No documentation of the clinical sign of physicians	

17.2. Therapie der häufigsten Symptome

17.2.1. Delir

17.2.1.1. Primärstudien

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
Boettger, Aust N Z J Psychiatry 2011, I [383]	Case control study	n=42	▪ Mean age 69.6, SD +/-11.9 yrs, range: 36-85) ▪ patients referred for delirium management to a Cancer Center Psychiatry Service ▪ Cancer diagnoses and etiologies were diverse in both groups and did not significantly differ (as by authors)	**Oral Aripiprazole (AR) vs. Oral Haloperidol (HP)** ▪ Cases: AR, Mean start dose: 15.2mg ▪ Controls: OZ, start dose: 4.9mg ▪ initial diagnosis of delirium (T1) and repeated at 2 – 3 days (T2) and 4 – 7 days (T3)	1.O: ▪ **Treatment efficacy** as measured by improvement in MDAS and delirium resolution (MDAS cut-off score <=10) 2.O: ▪ **Physical performance ability** measured by Karnofsky Performance Status Scale (KPS) ▪ **Side effects** as measured by Udvalg Kliniske Undersogelser Side Effect Rating Scale (UKU) scores	**Treatment efficacy:** ▪ No sign. difference between groups. ▪ MDAS scores declined from 18.1 at baseline to 10.8 at T2 and 8.3 at T3 in AR patients (Friedman: chi square 31.87, df = 2, p < 0.001); from 19.9 at baseline to 9.9 at T2 and 6.8 at T3 (Friedman: chi square 38.3, df = 2, p < 0.001) in HP patients. ▪ No sign. difference in the MDAS scores of AR and HP patients at T2 and T3. ▪ Resolution of delirium symptoms did not differ significantly between AR and HP patients at either subsequent observation point. **Physical performance ability** ▪ KPS scores improved from 28.1 at baseline to	▪ No breakdown of cancer diagnoses and distribution ▪ population not clearly defined as “palliative”	2+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
						35.2 at T2 and 41.0 at T3 in AR patients (Friedman: chi square 20.11, df = 2, p < 0.001) and 22.4 at baseline to 28.1 at T2 and 31.9 at T3 in HP patients (Friedman: chi square 20.83, df = 2, p < 0.001). ▪ No sign. differences between AR and HP at T2 and T3. ▪ greater frequency of EPS. **Side effects** ▪ No extrapyramidal side effects (EPS) were encountered in AR group. ▪ 19% of patients experiencing EPS in HP group. ▪ HP group: Parkinsonism in 19.0% and dystonia in 9%. ▪ HP group: hyperactive delirium with significantly higher doses of HP showed		
Breitbart, Am J Psychiatry 1996, I [384]	RCT, double-blind, parallel	n=30	▪ AIDS patients with treatment for AIDS-related medical problems ▪ Patients met DSM-III-R criteria for delirium and scored 13 or greater on the	**Haloperidol (HP) vs. Chlorpromazine (CP) vs. Lorazepam (LO)** ▪ Three drug study utilizing dose level protocol. Assessment done every hour until stabilization. **Mean**	1.O: ▪ **Efficacy of treatment** of delirium measured by ▪ Delirium Rating Scale [DRS] (0-32; >13=delirious) 2.O: ▪ **Cognitive status** as measured by MMSE:	▪ significant decrease in DRS scores from baseline to day 2 for the HP/CP groups but not for LO group ▪ HP: F=27.S0, df=1.27, p<O.OO1 ▪ CP: F=37.02, df=1.27, p<0.001	▪ Placebo control group not included on ethical grounds ▪ All six patients who received LO developed treatment-limiting side-effects, including oversedation, disinhibition, ataxia, and	1+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			Delirium Rating Scale ▪ 77% men/23% women ▪ Mean age 39.2 yrs (SD=8.8, range=23-56) ▪ Mean Karnofsky Performance Status score n=30 was 52.3 (SD=21.3, range=10-90).	**drug doses during the first 24 hours:** ▪ 1. Arm: HP 2.8 mg (SD = 2.4) ▪ 2. Arm: CP 50 mg (SD = 23.1) ▪ 3. Arm: LO 3 mg (SD = 3.6) ▪ **Average maintenance doses:** ▪ HP 1.4 mg (SD = 1.2) ▪ CP 36 mg (SD = 18.4) ▪ LO 4.6 mg (SD = 4.7). ▪ LO arm stopped early due to adverse effects.	▪ score of 28-30 = 0 (no deficits) on item 6 of the Delirium Rating Scale ▪ score of 25-28 = 1 (very mild deficits) ▪ score of 20-24 = 2 (focal deficits) ▪ score of 15-19 = 3 (significant deficits) ▪ score of 15 or less = 4 (severe deficits) ▪ **Extrapyramidal Symptoms** as measured by ▪ Extrapyramidal Symptom Rating Scale (questionnaire, rating instrument and global impression rating)	▪ LO: F=0.23, df=1.27, p<O.63). ▪ Cognitive functioning (MMSE) improved significantly from baseline to day 2 for patients receiving CP, and trend toward a significant improvement for patients receiving HP. ▪ **DRS Scores:** ▪ ALL (n 30) baseline: 20.1 (SD 3.5, range 14 to 28) Day 2: 13.3 (SD 6.1, range 3 to 26) End of therapy: 12.8 (SD 6.4, range 3 to 26) ▪ HP (n 11) Baseline: 13.45 (SD 6.95) Day 2: 17.27 (SD 8.87) End of Therapy: 17.18 (SD 12.12) ▪ LO (n 6) Baseline: 15.17 (SD 5.31) Day 2: 12.67 (SD 10.23) End of Therapy: 11.5 (SD 8.69)	increased confusion, leading to refusal to take the drug or requiring discontinuation.	
Breitbart, Am J Psychiatry 1996, II [384]						▪ **Extrapyramidal Symptom Rating Scale Scores:** ▪ CP (n 13) Baseline: 7.42 (SD 8.08) End of Therapy: 5.08 (SD 4.48)		

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
						▪ HP (n 11) Baseline: 7.0 (SD 6.8) End of Therapy: 5.54 (SD 6.76) ▪ LO (n 6) Baseline: 7.6 (SD 10.11) End of Therapy: 12.2 (SD 8.93)		
Breitbart, Psychosomatics 2002, I [385]	Cohort study, uncontrolled	n=82 dropout = 3	▪ Mean KPS score 37 (SD 9.9; range 20-85) ▪ Mean age = 60.6 yrs (SD 17.3; range 19-89) ▪ Cancer diagnoses: lung (21%, n = 17); gastrointestinal (18%, n =14); lymphoma (11%, n =9); breast (10%, n = 8); head and neck (6%, n = 5), ovarian (2%, n = 2), brain (2%, n = 2), sarcoma (2%, n = 2), and other cancers (25%, n = 20) ▪ stage of cancer: metastatic (80%, n = 63), localized (15%, n = 12), terminal (5%, n = 4)	**Olanzapine administered orally either as a single bedtime does or twice a day** Mean starting dose at baseline: 3.0 mg (SD 0.14; range, 2.5–10); Mean dose at T2: 4.6 mg (SD 0.27; range, 2.5–15); Mean dose at T3 or end of study: 6.3 mg (SD, 0.52; range, 2.5–20)	1.O: ▪ **Treatment efficacy** as measured by improvement in MDAS and delirium resolution (MDAS cut-off score <=10) 2.O: ▪ **Physical performance ability** measured by Karnofsky Performance Status Scale (KPS) ▪ **Side effects** (clinician documentation and rating)	▪ **Treatment efficacy:** Significant treatment effect Wilks A = 0.345, F (1, 78) = 53.1, P = 0.001. Mean baseline MDAS score (19.85, SD 3.79), significantly lower (improved) at T2 (12.73, 6.87), t (78) = 16.9, P = 0.001, even lower (more improved) at T3 (10.78, SD 7.31), t (78) = 17.6, P = 0.001. Mean MDAS scores between T2 and T3 were also significantly improved, t (78) = 8.6, P = 0.001 ▪ **delirium resolution:** 45% (n = 36) of patients at T2 and 76% (n = 57) of patients at T3 Age was the strongest predictor of treatment	▪ No control group/placebo ▪ No randomization ▪ no blinding ▪ population not clearly defined as “palliative” ▪ Only study so far which identifies predictors of treatment efficacy	2+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			▪ history of brain metastases (20%, n = 16) or a history of dementia (17%, n = 14)			response (odds ratio [OR] = 171.5) (with patients age >70 yrs demonstrating significantly poorer response than patients age <70 yrs) subtype of delirium significant predictor of delirium treatment outcome (OR = 11.3): hyperactive delirium responding better to olanzapine treatment than hypoactive delirium		
Breitbart, Psychosomatics 2002, II [385]			▪ etiologies for delirium: opioid analgesics (63%, n = 50), corticosteroids (34%, n = 27), systemic infection (33%, n = 26), hypoxia (25%, n = 20), CNS spread of cancer (14%, n = 11), dehydration (11%, n = 9), other medications (2.5%, n = 2), and other (unclassified) etiologies (17%, n = 13)			▪ **Side effects** most common: sedation (30% of patients reporting at T2 and T3) 1.3% (n=2 pts) olanzapine appeared to worsen delirium and was discontinued 3.8% of pts experienced other side effects of mild severity (rash, pruritus, nausea, stomach ache, dizziness, light	▪	

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			▪ delirium mild 17% (n = 13) (MDAS <=15); moderate 61% (n = 48) (MDAS 15–22); severe 23% (n = 18) (MDAS >= 23) ▪ subtype of delirium: 46% (n = 36) ''hypoactive'' delirium; 54% (n = 43) ''hyperactive'' delirium (based on MDAS item 9)			headedness, blurring of vision, and headache)		
Lin, J Intern Med Taiwan 2008 [386]	RCT, unblinded, parallel	n=30	▪ Patients from one hospice and palliative care center with advanced cancer who had been referred to the consultation-liaison psychiatry service ▪ Included pts had to meet DSM-IV criteria for delirium ▪ Mean age 61.13, SD +/-16.5 yrs, range: 23-87) ▪ Equal gender distribution	**Oral Haloperidol (HP) vs. Oral Olanzapin (OZ)** ▪ 1. Arm: HP, start dose: 5mg ▪ 2. Arm: OZ, start dose: 5mg Clinical Re-Evaluation after 24hours (T1), 48hours (T2) and 1 week (T3). Dosage titration by psychiatric specialist if no sign of improvement. Maximum dosage given for HP/OZ: 15mg orally.	1.O: **Treatment efficacy** as measured by improvement in MDAS-c (0-33) and CGI (Global Impression-Severity) scale 2.O: **Side effect** assessed by clinical records review and assessor observation	▪ **Treatment efficacy:** ▪ OZ: statistical sign. improvement on DRS-c at T3 (p=0.042); and CGI-S at T1 (p=0.040) ▪ HP: statistical sign. improvement on DRS-c at T1(p=0.008); T2 (p0.044); T3(p=0.043) and CGI-S at T1(p=0.012) ▪ No sign. differences between groups across time for DRS-c (T1, p=0.123; T2, p=0.240; T3, p=0.414) and for CGI-S (T1, p=0.581; T2, p=1.000; T3, p=0.618) ▪ **Side effects**	▪ No blinding ▪ Selection bias (initial inclusion screening done by the same physician who titrated the antipsychotic drugs) ▪ No information on drop-outs ▪ No information on allocation concealment ▪ No information on cancer types ▪ No mention of side-effects	1-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
						No reported side-effects		

17.2.1.2. Systematic Review der Aktualisierung 2019

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Burry, Cochrane 2018 [387]	SR To assess and compare the efficacy of antipsychotic vs. nonpsychotics or placebo on delirous patients	9 RCTs, quasi-randomised trials comparing 4 trials included a comparison of an antipsychotic to a nonantipsychotic drug or placebo 7 trials included a comparison of a typical to an atypical antipsychotic	Adult hospitalised (medical, surgical, and palliative, not critical ill) delirious patients	• antipsychotics to nonantipsychotics or placebo ▪ typical to atypical antipsychotics for the treatment of delirium in adult hospitalised patients	1.O: Assess the treatment efficacy of antipsychotics vs. nonantipsychotics or placebo on the duration of delirium 2.O: Compare the treatment efficacy of: • antipsychotics vs. nonantipsychotics or placebo on delirium severity and resolution, mortality, hospital length of stay, discharge disposition, health-related quality of life, and adverse effects • atypical vs. typical antipsychotics for reducing delirium duration, severity, and resolution, hos pital mortality and length of stay, dis charge disposition,	**Antipsychotic treatment:** not reduce delirium severity compared to nonantipsychotic drugs (standard mean difference (SMD) -1.08, 95% CI -2.55 to 0.39 **Typical/atypical antipsychotics:** 4 studies (n=494 participants; very low-quality evidence); nor was there a difference between typical and atypical antipsychotics (SMD -0.17, 95% CI -0.37 to 0.02 7 studies (n=542 participants) low-quality evidence): no evidence antipsychotics resolved delirium symptoms compared to nonantipsychotic drug regimens	• Poor quality of evidence • No evidence to support or refute • No evidence to support or refut the suggestion that antipsychotics shorten hospital length of stay or improve health-related quality of life. Side effects were rarely reported in the studies	

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
					health-related quality of life, and adverse effects	(RR 0.95, 95% CI 0.30 to 2.98; 3 studies (n= 247 participants; very low-quality evidence); nor was there a difference between typical and atypical antipsychotics (RR 1.10, 95% CI 0.79 to 1.52; 5 studies (n=349 participants; low-quality evidence). The pooled results indicated that antipsychotics did not alter mortality compared to nonantipsychotic regimens (RR 1.29, 95% CI 0.73 to 2.27 3 studies (n=319 participants; low-quality evidence) nor was there a difference between typical and atypical antipsychotics (RR 1.71, 95% CI 0.82 to 3.3 4 studies (n=342 participants; low-quality evidence). **EPS:** antipsychotics did not have a higher risk of extrapyramidal symptoms (EPS) compared to nonantipsychotic drugs (RR 1.70, 95% CI 0.04 to 65.57;		

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
						3 studies (n=247 participants; very-low quality evidence); no increased risk of EPS with typical antipsychotics compared to atypical antipsychotics (RR 12.16, 95% CI 0.55 to 269.52);		

17.2.1.3. Primärstudien der Aktualisierung 2019

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
Agar, JAMA 2017 [388]	RCT, multi-site, double-blind, parallel-arm, dose-titrated, placebo-controlled	n=247 Drop out: n=75	▪ Palliative patients with **life-limiting illness** and the 3 criterias **delirium** diagnosed via DSM-IV criteria for delirium, Memorial Delirium Assessment Scale (MDAS) of 7 or more, and presence of the target symptoms of delirium associated with distress, defined as a delirium symptom score of 1 or	1st Arm: **risperidone** 2 nd Arm: **haloperidol** 3rd Arm: placebo Age-adjusted titrated doses every 12 hours for 72 hours, based of symptoms of delirium	1.O: Improvement in mean group difference of delirium symptom score (severity range, 0-6) between baseline und day 3 2.O: Delirium severity, midazolam use, extrapyramidal effects, sedation, and survival	1. Arm: delirium symptom scores were significantly higher than in the placebo arm (on average 0.48 Units higher; 95% CI, 0.09-0.86: p=0.02) 2. Arm: delirium symptom scores were on average 0.24 Units higher (95% CI, 0.06-0.42, p=0.009) than in the placebo arm Patients in both arms had more extrapyramidal effects (risperidone, 0.73, 95% CI, 0.009-1,37; p=0.03; haloperidol, 0.79; 95% CI, 0.17-1.41; p=0.01) then the placebo arm	- The neuroleptic doses were rather low and not quipotent (chlorpromazine equivalents) - The incidence of extrapyramidal symptoms was surprisingly high (especially for the very small doses). - Dose adjustments were infrequent and 12-hour intervals might be too short to oversee an effect. - Short study duration - The difference in "delirium symptom scores" (primary	1+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			more (sum of the scores from items 2 [inappropriate behavior], 3 [inappropriate communication], and 4 [illusions and hallucinations on the Nursing Delirium Screening Scale [NuDESC] [severity range, 0-6]) ▪ Mean age 74,9 SD +/- 9,8 yrs 85 women (34,4%), 218 with cancer (88,3%)			3. Arm: better overall survival than the patients with haloperidol (hazard ratio, 1.73; 95% CI, 1.20-2.50; p=0.003), but this was not significant for placebo vs. risperidone (hazard ratio, 1.29; 95% CI, 0.91-1.84, p=0.14)	outcome) only reflects some symptoms of delirium. Importantly, patients were comparably "delirious" in all treatment arm (secondary outcome: Delirum intensity)	
Hui, JAMA, 2017 [389]	RCT, double-blind, parallel group, placebo-controlled, randomized, single-center; To compare the effect of lorazepam vs placebo as an adjuvant to haloperidol for persistent agitation in patients with delirium in the setting of	n=90 Drop outs: 32	▪ Palliative patients with a diagnosis of **cancer** and with hyperactive or mixed de**lirium** (DSM-IV and a history of agitation with Richmond Agitation-Sedation Scale (RASS) score of 2 or more over the past 24 hours despite receiving scheduled haloperidol of 1 mg to 8 mg per day)	Treatment of a single episode of restlessness or agitation: 1st Arm: **lorazepam** (3 mg, single dose iv) + haloperidol 2nd Arm: placebo (single dose iv) + haloperidol Standardized open-label regimen with haloperidol (2 mg) every 4 hours intravenously and another 2 mg every hour as needed for agitation; then, by episode of agitation/restlessness, administration of lorazepam or placebo	1.O: The RASS score (range, -5 [unarousable] to 4 [very agitated or combative]) from baseline to 8 hours after treatment administration The RASS score were monitored every 2 hours until the score was 2 or more and required 2.O. rescue neuroleptic use, delirium recall, comfort (perceived by cargivers and nurses), communication capacity, delirium severity, adverse effects, discharge outcomes, and overall survival	lorazepam + haloperidol: resulted in a significantly greater reduction of **RASS** score at 8 hours (-4.1 points) than placebo + haloperidol (-2.3 points) (mean difference, -1.9 points [95% CI, -2.8 to -0.9]; p<0.001) Required less median **rescue neuroleptics** (2.0 mg') than the placebo + haloperidol group (4.0 mg) (median difference, -1.0 mg [95%CI, -2.0 to 0],	▪ High doses for "rescue" medication (Haloperidol 2mg i.v., up to >10mg/d). ▪ short overall survival, high mortality: Difficult to distinguish "(terminal-) delirium" from "restlesness" ▪ A single dose of study medication was examined instead of repeated dosing because of the very short survival rate among our patient population	1+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
	advanced cancer		▪ Mean age, 62 yrs, women, 42 (47%), 58 (64%) received the study medication and 52 (90%) the trial ▪			p=0.009) and was perceived to be more comfortable by both blinded caregivers and nurses (caregivers: 84% for the lorazepam + haloperidol group vs. 37% for the placebo + haloperidol grpup; mean difference, 47% [95% CI, 14% to 73%], p=0.007, nurses 77% for the lorazepam + haloperidol group vs. 30% for the placebo + haloperidol group, mean difference, 47% [95% CI, 17% to 71%], p=0.005) No significant between group differences were found in delirium-related **distress** and **survival** The most common **adverse effects** was hypokinesia: lorazepam + haloperidol group n=3 [19%], placebo haloperidol group n=4 [27%]	(ie, hours to days) and the uncertain risks associated with lorazepam in a frail population ▪ A single lorazepam dose of 3 mg might be to high for some patients, especially those with severe liver failure who cannot metabolize lorazepam ▪ Small sample size and thus wide CIs in many measures ▪ Modified intention-to-treat analysis including only patients who started the study interventions was specified a priori (because of high number of patients who died before receiving study medication) ▪ Adequate randomization method ▪ Double-blinding	

17.2.2. Rasselatmung

17.2.2.1. Systematic Reviews

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Pastrana, Schmerz 2012 [390]	SR (no MA)	6 studies (n=593): ▪ 4 RCTs (of which 1 phase-III RCT und 1 phase II pilot-RCT) ▪ 2 cohort studies	Adult patients with **cancer**	2 cohorts, 1 RCT: ▪ Scopolamine vs. glycopyrrolat 3 RCTs: ▪ Scopolamine vs. Placebo ▪ Scopolmaine vs. Butylscopolamine vs. atropine ▪ Scopolamine vs. octreotid	Effect on noisy breathing (not nearly specified) Adverse events	▪ Few studies ▪ Contradictory results in the cohort studies (once glycopyrrolat, once scopolamine more effective) ▪ Sign. results in only 1 RCT (glycopyrrolat more effective than scopolamine) ▪ Anticholinergic drugs seem to be more effective if applicated early	Insufficient evidence to support the administration of one or the other anticholinergic agent	1- (no adequate description of outcomes used; no information about the quality assessment of the studies)
Wee, Cochrane Rev 2008 [391]	SR (MA not possible)	4 studies (n=398): ▪4 RCTs	▪ **Cancer** patients in **terminal phase** (last 48-72 hours of life)	Hyoscine hydrobromide (HH) by any route: 4 RCTs: HH vs. other drugs ▪ 1st Arm: HH (4) ▪ 2nd Arm: normal Saline (placebo control) (1); Octreotide (1); Glycopyrronium (1); Atropine (1) ▪ 3rd Arm: Hyoscine butylbromide (1) 1 RCT with cross-over design	1.O: ▪ Any subjective or objective **change in noise intensity**. ▪ Complete **cessation of noise**. 2.O: ▪ The number of different types of interventions (including varying doses and types of anticholinergics) needed to achieve a reduction in noise intensity. ▪ The number of times an intervention has to be repeated to achieve or maintain a reduction in noise intensity.	▪ **Change in noise intensity:** no evidence that any intervention, be it pharmacological or non-pharmacological, was superior to placebo in the treatment of noisy breathing ▪ Higher efficacy (stronger decrease in death rattle) in the group of patients given glycopyrronium (n=6) compared to hyoscine hydrobromide (n=7), but not consistent over studies. ▪ No difference in effectiveness (37-42%)	▪ No Metaanalysis: insufficient data ▪ Small sample size for 3 out of 4 RCTs (n=13-31) ▪ Observer bias is a relevant limitation to the interpretation of results (scorer = involved palliative care nurse) ▪ blinding-bias through open label design in 1 RCT with the highest number of included participants, n=333	1+

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
				▪ 1st Arm: HH followed by Octreotide ▪ 2nd Arm: Octreotide followed by HH	▪ Measurable documented **reduction in relatives' distress** relating to the noisy breathing (death rattle) and **reduction in patients' distress** relating to the noisy breathing (death rattle).	between scopolamine (hyoscine hydrobromide), atropine and hyoscine butylbromide after 1h ▪ **Patients' distress**: Statistically significant reduction of pain in one placebo control study. No statistically significant reduction in restlessness. ▪ No data to support a **reduction in relatives' distress**.		

17.2.2.2. Primärstudie

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
Likar, Wien Klin Wochenschr 2008 [392]	RCT, double-blind	n=13 (1st Arm: n=7, 2nd Arm: n=6)	**Cancer patients** in terminal phase **with death rattle** Age: 1st Arm 71,3 + 3,8 years, 2nd Arm 71,8 + 5,4 years	First arm: scopolamine hydrobromide (0.5 mg intravenously/every 4 hours/period of 12 hours) Second arm: glycopyrronium bromide (0.4 mg/every 6 hours/period of 12 hours)	1.O: Death rattle 2.O: Side effects (restlessness, expressions of pain)	**Death rattle:** Both drugs shown a reduction of death rattle after 12 hours. Glycopyrronium bromide had a significant greater reduction after 12 hours (p= .029) in comparission with scopolamine hydrobromide.	Very small sample size -> underpowered No placebo group	1-

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	Outcomes (1.O=primary outcome; 2.O= secondary outcome) Outcome measure	Results	Comment	Level of Evidence SIGN
			Mass: 1st Arm 70,9 + 5,5 kg, 2nd Arm 71,7 + 4,2 kg Gender: 1st Arm 5 male, 2 female, 2nd Arm 5 male, 1 female	If necessary subcutaneously or intravenously in equipotent doses. Every 2 hours death rattle was assessed and rated on a scale of 1 to 5 (1= audible breathing noises, 5 = very severe rattling noises). In addition, restlessness and expressions of pain were assessed and rated on a scale of 1 to 3 (1=mild, 2=moderate, 3=severe).		**Side effects**: No differences of restlessness and expressions of pain between both substances		

17.2.3. Mundtrockenheit

17.2.3.1. Primärstudie

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure	Results	Comment	Level of Evidence SIGN
Davies, Palliat Med 2000 [393]	RCT, unblinded, cross-over	n=41 completed phase 1=30 completed phase 2=26 total drop-out=15	▪ Inpatient and outpatient adults with malignant disease from two specialist palliative care institutions ▪ Estimated prognosis of more than 2 weeks ▪ Mean age = 66 yrs (range 32-87) ▪ 28% own teeth ▪ 37% partial set of dentures ▪ 26% full set of dentures ▪ 7% partial set of dentures but did not use them ▪ 2% no teeth/no dentures ▪ 84% receiving concomitant xerostomic drugs (M=2; range 0-4)	**Saliva stimulant versus saliva substitute** 1. Arm: **AS**+2 days washout+**CG** 2. Arm: **CG**+2 days washout+**AS** **AS**: 5 days artificial saliva spray (mucin-based Saliva Orthana) 4x/day (before meals+bedtime), **CG**: 5 days chewing gum (low-tack, sugar-free Freedent) 4x/day for 10mins (before meals+bedtime)	1.O: ▪ **Reduction of xerostomia** assessed by VAS mouth dryness (1 to 100) and xerostomia questionnaire 2.O: ▪ **patient preference** ▪ **adverse effects** ▪ both assessed by questionnaire	No statistically significant difference between treatments for **reduction of xerostomia** (Fisher's exact test; P = 0.33) ▪ 89-90% of participants felt that either intervention had helped their xerostomia ▪ 74% from AS group wanted to continue with it ▪ 86% from CG group wanted to continue with it ▪ No statistically significant difference for **patient preference** ▪ No statistically significant difference for **adverse effects**	▪ Population/patient characteristics not clearly depicted/no primary diagnoses ▪ Some risk of bias through missing blinding (not possible) ▪ potential selection bias (insufficient information about allocation concealment)	1-

17.3. Flüssigkeit/Ernährung

17.3.1.1. Systematic Review

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
Raijmakers, Ann Oncol 2011 [394]	SR / no MA Aim to address the following research questions: (i) how and how often are artifical nutrition (AN) and artificial hydration (AH) provided in the last week of life of cancer patients; (ii) what is the effect of AN and AH during the last week of life on symptoms, comfort and quality of life of cancer patients and (iii) does providing or not providing AN and AH	15 studies/design: • 9 prospective observational • 1 prospective observational • 5 retrospective observational Fokus of studies: • 4 papers on frequencies of AN in the last week of life • 7 papers on frequencies of AH in the last week of life • 4 papers on withholing/ withdrawing AN/AH in the last week of life • 1 paper about the effect of AN/AH on quality of life	**Cancer** patients (mean age > 54) in their last 7 days, or last 48 hours of life	• Artifical nutrition (AN) in the last week of life • Artifical hydration (AH) in the last week of life	• effects on symptoms and comfort/quality of life • effect on survival	• AH/AN are a substantial part of medical in the last week of cancer patients esp. in hospital up to 50-88%. • No significant relationship between AH and general comfort or quality of life measures. • ANH is not associated with any changes of comfort in 75% (n= 145 whole population) two days before death. • Effect of AH in the last week of life on quality of life: no significant effects in controlling several symptoms except for chronic nausea. No differences in pleural drainage or ascites in the latter studies. Two found more ascites in the AH group • Using AN/AH is not a significant determinant of survival.	Providing AN or AH to cancer patients who are in the last week of life is a frequent practice. The effects on comfort, symptoms and length of survival seem limited. Further	2-

Study	Type of study (SR=Systematic Review; MA=Meta-analysis)	Included studies	Population	Which interventions were evaluated?	Outcomes (1.O=primary outcome; 2.O= secondary outcome)	Results	Comments	Level of Evidence SIGN
	hasten death or prolonge life?	• 5 paper about the effect of AH on symptoms • 1 paper about effect of AN/AH on survival						

17.3.1.2. Primärstudien

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure	Results	Comment	Level of Evidence SIGN
Bruera, JCO 2013 [395]	RCT, double blind	n = 129 hydration (n=63) placebo (n=66) (9 drop outs)	▪ diagnosis of advanced cancer (i. e. locally recurrent or metastatic disease) ▪ > 18 years ▪ life expectancy >= 1 week	▪ parenteral hydration (normal saline 1l per day) ▪ placebo=PL (normal saline 100 ml per day) daily over 4 hours	1.O: • change in the sum of four dehydration symptoms (fatigue, myoclonus, sedation and hallucinations, 0 = best and 40 = worst possible) between day 4 and baseline 2.O: • Edmonton Symptom Assessment Scale (ESAS) • Memorial Delirium Assessment Scale (MDAS) • Nursing Delirium Screening Scale (NuDESC)	• no significant differences between hydration and placebo for change in the sum of four dehydration symptoms(-3.3 v -2.8, P = 0.77) by day four • hydration at 1l per day did not improve symptoms, quality of life or survival compared with placebo. • ESAS (all non-significant) • MDAS (1 v 3.5, P = .084)	Intention-to-treat analysis was conducted to examine the change by day 4±2 and day 7±2 between groups ▪ Hydration at 1l per day did not improve symptoms, QoL, or survival compared with PL ▪ pts with severe dehydration were excluded because they tend to be acutely ill, making it difficult to obtain informed consent	1+

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure	Results	Comment	Level of Evidence SIGN
					• Unified Myoclonus Rating Scale (UMRS), • Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) • Dehydration Assessment Scale • creatinine • urea • overall survival	• NuDESC (0 v 0, P = .13) • UMRS (0 v 0, P = .54) by day 4. • Results for day 7, including FACIT-F, were similar. • Overall survival did not differ between the two groups (median, 21 v 15 days, P = .83).	▪ The power to detect statistical significance given the found values and sample sizes was 4.8%	
Nakajima, J Pall Med 2013 [396]	Descriptive; to explore the influence of hydration volume on the signs during the last three weeks of life in terminally ill cancer patients.	N=75	▪ Terminally ill cancer patients with abdominal incurable malignancies ▪ life expectancy estimated by a physician to be <3 months	▪ Hydration group (n=32) receiving 1000ml or more of artificial hydration per day, on and three wekks before death. ▪ Nonhydation group (n=43)	▪ dehydration and fluid retention signs in the last three weeks of life.	▪ percentage of patients with deterioration in dehydration score in the final three weeks was significantly higher in non-hydration group than in the hydration group (35% versus 13%, p = 0.027), while the percentages of patients whose symptom scores for edema, ascites, and bronchial secretion increased were significantly higher in the hydration group than in the nonhydration group (57% versus 33%, p = 0.040; 34% versus 14%, p = 0.037; 41% versus 19%, p = 0.036, respectively). ▪ There were no significant differences in the degree of pleural effusion or the	▪ The potential benefits of artificial hydration therapy should be balanced with the risk of worsening fluid retention signs.	3

Study (Author, journal, year)	Type of study/ Design (RCT/CCT, blinded, cross-over/parallel)	Number of included patients/ Drop-outs	Patients characteristics	Intervention/Control	• Outcomes (1.O=primary outcome; 2.O= secondary outcome) • Outcome measure	Results	Comment	Level of Evidence SIGN
						prevalence of hyperactive delirium between these groups.		

18. Literaturverzeichnis

1. Adler, K., et al., *Integration der Palliativmedizin in die Intensivmedizin: Systematische Übersichtsarbeit.* Anaesthesist, 2017 **66**: p. 660-66.
2. Dalgaard, K.M., et al., *Early integration of palliative care in hospitals: A systematic review on methods, barriers, and outcome.* Palliat Support Care, 2014. **12**(6): p. 495-513.
3. Davis, M.P., et al., *A review of the trials which examine early integration of outpatient and home palliative care for patients with serious illnesses.* Ann Palliat Med, 2015. **4**(3): p. 99-121.
4. Gaertner, J., et al., *Effect of specialist palliative care services on quality of life in adults with advanced incurable illness in hospital, hospice, or community settings: systematic review and meta-analysis.* BMJ, 2017. **357**: p. j2925.
5. Haun, M.W., et al., *Early palliative care for adults with advanced cancer.* Cochrane Database Syst Rev, 2017. **6**: p. CD011129.
6. Hui, D., et al., *Integration of oncology and palliative care: a systematic review.* Oncologist, 2015. **20**(1): p. 77-83.
7. Hui, D., et al., *Referral Criteria for Outpatient Palliative Cancer Care: A Systematic Review.* Oncologist, 2016. **21**(7): p. 895-901.
8. Tassinari, D., et al., *Early Palliative Care in Advanced Oncologic and Non-Oncologic Chronic Diseases: A Systematic Review of Literature.* Reviews on Recent Clinical Trials, 2016. **11**(1): p. 63-71.
9. Candy, B., et al., *Interventions for supporting informal caregivers of patients in the terminal phase of a disease.* Cochrane Database of Systematic Reviews, 2011(6): p. CD007617.
10. Harding, R. and I.J. Higginson, *What is the best way to help caregivers in cancer and palliative care? A systematic literature review of interventions and their effectiveness.* Palliat Med, 2003. **17**(1): p. 63-74.
11. Harding, R., et al., *How can informal caregivers in cancer and palliative care be supported? An updated systematic literature review of interventions and their effectiveness.* Palliative Medicine, 2012. **26**(1): p. 7-22.
12. Lorenz, K.A., et al., *Evidence for improving palliative care at the end of life: a systematic review.* Annals of Internal Medicine, 2008. **148**(2): p. 147-59.
13. Fegg, M.J., et al., *Existential behavioural therapy for informal caregivers of palliative patients: a randomised controlled trial.* Psychooncology, 2013. **22**(9): p. 2079-86.
14. Hudson, P., et al., *Reducing the psychological distress of family caregivers of home-based palliative care patients: short-term effects from a randomised controlled trial.* Psychooncology, 2013. **22**(9): p. 1987-93.
15. McLean, L.M., et al., *A couple-based intervention for patients and caregivers facing end-stage cancer: outcomes of a randomized controlled trial.* Psychooncology, 2013. **22**(1): p. 28-38.
16. Northouse, L.L., et al., *Randomized clinical trial of a brief and extensive dyadic intervention for advanced cancer patients and their family caregivers.* Psychooncology, 2013. **22**(3): p. 555-63.
17. Yun, Y.H., et al., *Use of a decision aid to help caregivers discuss terminal disease status with a family member with cancer: a randomized controlled trial.* J Clin Oncol, 2011. **29**(36): p. 4811-9.
18. Gauthier, L., *Bereavement Interventions, End-of-Life Cancer Care, and Spousal Well-Being: A Systematic Review.* Clin Psychol Sci Pract, 2012. **19**: p. 72-92.
19. Wittouck, C., et al. *The prevention and treatment of complicated grief: a meta-analysis (Structured abstract).* Clinical Psychology Review, 2011. 69-78.
20. Guldin, M.B., et al., *Bereavement care in general practice: a cluster-randomized clinical trial.* Fam Pract, 2013. **30**(2): p. 134-41.
21. Garcia-Perez, L., et al., *A systematic review of specialised palliative care for terminal patients: which model is better?* Palliat Med, 2009. **23**(1): p. 17-22.
22. Higginson, I.J. and C.J. Evans, *What is the evidence that palliative care teams improve outcomes for cancer patients and their families?* Cancer J, 2010. **16**(5): p. 423-35.
23. Higginson, I.J., et al., *Is there evidence that palliative care teams alter end-of-life experiences of patients and their caregivers?* Journal of Pain & Symptom Management, 2003. **25**(2): p. 150-68.
24. Thomas, R.E., D. Wilson, and S. Sheps, *A literature review of randomized controlled trials of the organization of care at the end of life.* Canadian Journal on Aging, 2006. **25**(3): p. 271-93.
25. Zimmermann, C., et al., *Effectiveness of specialized palliative care: a systematic review.* JAMA, 2008. **299**(14): p. 1698-709.

26. Candy, B., et al., *Hospice care delivered at home, in nursing homes and in dedicated hospice facilities: A systematic review of quantitative and qualitative evidence.* Int J Nurs Stud, 2011. **48**(1): p. 121-33.
27. Gomes, B., et al., *Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers.* Cochrane Database Syst Rev, 2013. **6**: p. CD007760.
28. Hall, S., et al., *Interventions for improving palliative care for older people living in nursing care homes.* Cochrane Database Syst Rev, 2011(3): p. CD007132.
29. Shepperd, S., B. Wee, and S.E. Straus, *Hospital at home: home-based end of life care.* Cochrane Database Syst Rev, 2011(7): p. CD009231.
30. Davies, E. and I.J. Higginson, *Systematic review of specialist palliative day-care for adults with cancer.* Supportive Care in Cancer, 2005. **13**(8): p. 607-27.
31. Stevens, E., C.R. Martin, and C.A. White, *The outcomes of palliative care day services: a systematic review.* Palliative Medicine, 2011. **25**(2): p. 153-69.
32. Bakitas, M.A., et al., *Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial.* J Clin Oncol, 2015. **33**(13): p. 1438-45.
33. Maltoni, M., et al., *Systematic versus on-demand early palliative care: results from a multicentre, randomised clinical trial.* Eur J Cancer, 2016. **65**: p. 61-8.
34. Rugno, F.C., B.S. Paiva, and C.E. Paiva, *Early integration of palliative care facilitates the discontinuation of anticancer treatment in women with advanced breast or gynecologic cancers.* Gynecol Oncol, 2014. **135**(2): p. 249-54.
35. Temel, J.S., et al., *Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial.* J Clin Oncol, 2017. **35**(8): p. 834-41.
36. Dunt, D.R., *The cost-effectiveness of the Citymission Hospice Programme, Melbourne.* Palliat Med 1989. **3**(2): p. 125-34.
37. Kane, R.L., et al., *A randomised controlled trial of hospice care.* Lancet, 1984. **1**(8382): p. 890-4.
38. Kane, R.L., et al., *Hospice effectiveness in controlling pain.* JAMA, 1985. **253**(18): p. 2683-6.
39. Kane, R.L., et al., *The role of hospice in reducing the impact of bereavement.* J Chronic Dis, 1986. **39**(9): p. 735-42.
40. Wales, J., et al., *UCLA hospice evaluation study. Methodology and instrumentation.* Med Care, 1983. **21**(7): p. 734-44.
41. Zimmermann, C., et al., *Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial.* Lancet, 2014. **383**(9930): p. 1721-30.
42. Greer, D.S., et al., *An alternative in terminal care: results of the National Hospice Study.* J Chronic Dis, 1986. **39**(1): p. 9-26.
43. Greer, D.S., et al., *National hospice study analysis plan.* J Chronic Dis, 1983. **36**(11): p. 737-80.
44. Morris, J.N., et al., *The effect of treatment setting and patient characteristics on pain in terminal cancer patients: a report from the National Hospice Study.* J Chronic Dis, 1986. **39**(1): p. 27-35.
45. Morris, J.N., et al., *Last days: a study of the quality of life of terminally ill cancer patients.* J Chronic Dis, 1986. **39**(1): p. 47-62.
46. Birnbaum, H.G. and D. Kidder, *What does hospice cost?* Am J Public Health, 1984. **74**(7): p. 689-97.
47. Mor, V. and S. Masterson-Allen, *A comparison of hospice vs conventional care of the terminally ill cancer patient.* Oncology (Williston Park), 1990. **4**(7): p. 85-91; discussion 94, 96.
48. Powers, J.S. and M.C. Burger, *Terminal care preferences: hospice placement and severity of disease.* Public Health Rep, 1987. **102**(4): p. 444-9.
49. Reuben, D.B., V. Mor, and J. Hiris, *Clinical symptoms and length of survival in patients with terminal cancer.* Arch Intern Med, 1988. **148**(7): p. 1586-91.
50. Goldberg, R., et al., *Analgesic use in terminal cancer patients: report from the National Hospice Study.* J Chronic Dis, 1986. **39**(1): p. 37-45.
51. Wallston, K.A., et al., *Comparing the quality of death for hospice and non-hospice cancer patients.* Med Care, 1988. **26**(2): p. 177-82.
52. Ahlner-Elmqvist, M., et al., *Place of death: hospital-based advanced home care versus conventional care. A prospective study in palliative cancer care.* Palliat Med, 2004. **18**(7): p. 585-93.
53. Ahlner-Elmqvist, M., et al., *Characteristics and quality of life of patients who choose home care at the end of life.* J Pain Symptom Manage, 2008. **36**(3): p. 217-27.

54. Ringdal, G.I., et al., *Health-related quality of life (HRQOL) in family members of cancer victims: results from a longitudinal intervention study in Norway and Sweden.* Palliat Med, 2004. **18**(2): p. 108-20.
55. Axelsson, B. and S.B. Christensen, *Evaluation of a hospital-based palliative support service with particular regard to financial outcome measures.* Palliat Med, 1998. **12**(1): p. 41-9.
56. Bakitas, M., et al., *Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial.* JAMA, 2009. **302**(7): p. 741-9.
57. Bakitas, M., et al., *The project ENABLE II randomized controlled trial to improve palliative care for rural patients with advanced cancer: baseline findings, methodological challenges, and solutions.* Palliat Support Care, 2009. **7**(1): p. 75-86.
58. O'Hara, R.E., et al., *Impact on caregiver burden of a patient-focused palliative care intervention for patients with advanced cancer.* Palliat Support Care, 2010. **8**(4): p. 395-404.
59. Brumley, R., et al., *Increased satisfaction with care and lower costs: results of a randomized trial of in-home palliative care.* J Am Geriatr Soc, 2007. **55**(7): p. 993-1000.
60. Brumley, R.D., S. Enguidanos, and D.A. Cherin, *Effectiveness of a home-based palliative care program for end-of-life.* J Palliat Med, 2003. **6**(5): p. 715-24.
61. Buckingham, R.W., 3rd and S.H. Foley, *A guide to evaluation research in terminal care programs.* Death Educ, 1978. **2**(1-2): p. 127-41.
62. Casarett, D., et al., *Improving the use of hospice services in nursing homes: a randomized controlled trial.* JAMA, 2005. **294**(2): p. 211-7.
63. Cummings, J.E., et al., *Cost-effectiveness of Veterans Administration hospital-based home care. A randomized clinical trial.* Arch Intern Med, 1990. **150**(6): p. 1274-80.
64. Hughes, S.L., et al., *A randomized trial of the cost effectiveness of VA hospital-based home care for the terminally ill.* Health Serv Res, 1992. **26**(6): p. 801-17.
65. Grande, G.E., et al., *Does hospital at home for palliative care facilitate death at home? Randomised controlled trial.* BMJ, 1999. **319**(7223): p. 1472-5.
66. Grande, G.E., et al., *Caregiver bereavement outcome: relationship with hospice at home, satisfaction with care, and home death.* J Palliat Care, 2004. **20**(2): p. 69-77.
67. Grande, G.E., et al., *A randomized controlled trial of a hospital at home service for the terminally ill.* Palliat Med, 2000. **14**(5): p. 375-85.
68. Harding, R., et al., *Evaluation of a short-term group intervention for informal carers of patients attending a home palliative care service.* J Pain Symptom Manage, 2004. **27**(5): p. 396-408.
69. Harding, R., et al., *A multi-professional short-term group intervention for informal caregivers of patients using a home palliative care service.* J Palliat Care, 2002. **18**(4): p. 275-81.
70. Jordhoy, M.S., et al., *A palliative-care intervention and death at home: a cluster randomised trial.* Lancet, 2000. **356**(9233): p. 888-93.
71. Jordhoy, M.S., et al., *Quality of life in palliative cancer care: results from a cluster randomized trial.* J Clin Oncol, 2001. **19**(18): p. 3884-94.
72. Jordhoy, M.S., et al., *Which cancer patients die in nursing homes? Quality of life, medical and sociodemographic characteristics.* Palliat Med, 2003. **17**(5): p. 433-44.
73. Ringdal, G.I., M.S. Jordhoy, and S. Kaasa, *Family satisfaction with end-of-life care for cancer patients in a cluster randomized trial.* J Pain Symptom Manage, 2002. **24**(1): p. 53-63.
74. Ringdal, G.I., et al., *Does social support from family and friends work as a buffer against reactions to stressful life events such as terminal cancer?* Palliat Support Care, 2007. **5**(1): p. 61-9.
75. McCorkle, R., et al., *A randomized clinical trial of home nursing care for lung cancer patients.* Cancer, 1989. **64**(6): p. 1375-82.
76. McCorkle, R., et al., *The effects of home nursing care for patients during terminal illness on the bereaved's psychological distress.* Nurs Res, 1998. **47**(1): p. 2-10.
77. McKegney, F.P., L.R. Bailey, and J.W. Yates, *Prediction and management of pain in patients with advanced cancer.* Gen Hosp Psychiatry, 1981. **3**(2): p. 95-101.
78. Kassakian, M.G., et al., *The cost and quality of dying: a comparison of home and hospital.* Nurse Pract, 1979. **4**(1): p. 18-9, 22-3.
79. Mulligan, J., *Dying at home: An evaluation of a specialist home care service*. 1989, University of Wales, College of Cardiff.
80. Ventafridda, V., et al., *The importance of a home care program for patients with advanced cancer pain.* Tumori, 1985. **71**(5): p. 449-54.
81. Ventafridda, V., et al., *Comparison of home and hospital care of advanced cancer patients.* Tumori, 1989. **75**(6): p. 619-25.

82. Ward, A.W., *Home care services - an alternative to hospices?* Community Med, 1987. **9**(1): p. 47-54.
83. Gade, G., et al., *Impact of an inpatient palliative care team: a randomized control trial.* J Palliat Med, 2008. **11**(2): p. 180-90.
84. Hanks, G.W., et al., *The imPaCT study: a randomised controlled trial to evaluate a hospital palliative care team.* Br J Cancer, 2002. **87**(7): p. 733-9.
85. Jack, B., et al., *Improving cancer patients' pain: the impact of the hospital specialist palliative care team.* Eur J Cancer Care (Engl), 2006. **15**(5): p. 476-80.
86. Norton, S.A., et al., *Proactive palliative care in the medical intensive care unit: effects on length of stay for selected high-risk patients.* Crit Care Med, 2007. **35**(6): p. 1530-5.
87. SUPPORT, *A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). The SUPPORT Principal Investigators.* JAMA, 1995. **274**(20): p. 1591-8.
88. Rabow, M.W., et al., *The comprehensive care team: a controlled trial of outpatient palliative medicine consultation.* Arch Intern Med, 2004. **164**(1): p. 83-91.
89. Rabow, M.W., et al., *The comprehensive care team: a description of a controlled trial of care at the beginning of the end of life.* J Palliat Med, 2003. **6**(3): p. 489-99.
90. Temel, J.S., et al., *Early palliative care for patients with metastatic non-small-cell lung cancer.* N Engl J Med, 2010. **363**(8): p. 733-42.
91. Yoong, J., et al., *Early palliative care in advanced lung cancer: a qualitative study.* JAMA Internal Medicine, 2013. **173**(4): p. 283-90.
92. Goodwin, D.M., et al., *Effectiveness of palliative day care in improving pain, symptom control, and quality of life.* J Pain Symptom Manage, 2003. **25**(3): p. 202-12.
93. Higginson, I.J., et al., *Does a social model of hospice day care affect advanced cancer patients' use of other health and social services? A prospective quasi-experimental trial.* Supportive Care in Cancer, 2010. **18**(5): p. 627-37.
94. Sviden, G.A., et al., *Palliative day care--a study of well-being and health-related quality of life.* Palliative Medicine, 2009. **23**(5): p. 441-7.
95. Clayton, J.M., et al., *Randomized controlled trial of a prompt list to help advanced cancer patients and their caregivers to ask questions about prognosis and end-of-life care.* J Clin Oncol, 2007. **25**(6): p. 715-23.
96. Dyar, S., et al., *A nurse practitioner directed intervention improves the quality of life of patients with metastatic cancer: results of a randomized pilot study.* J Palliat Med, 2012. **15**(8): p. 890-5.
97. Loberiza, F.R., Jr., et al., *Coping styles, health status and advance care planning in patients with hematologic malignancies.* Leuk Lymphoma, 2011. **52**(12): p. 2342-8.
98. Loggers, E.T., et al., *Racial differences in predictors of intensive end-of-life care in patients with advanced cancer.* J Clin Oncol, 2009. **27**(33): p. 5559-64.
99. Mack, J.W., et al., *Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study.* J Clin Oncol, 2012. **30**(35): p. 4387-95.
100. Mack, J.W., et al., *End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences.* J Clin Oncol, 2010. **28**(7): p. 1203-8.
101. Stein, R.A., et al., *Randomized controlled trial of a structured intervention to facilitate end-of-life decision making in patients with advanced cancer.* J Clin Oncol, 2013. **31**(27): p. 3403-10.
102. Wright, A.A., et al., *Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment.* JAMA, 2008. **300**(14): p. 1665-73.
103. Zhang, B., et al., *Health care costs in the last week of life: associations with end-of-life conversations.* Arch Intern Med, 2009. **169**(5): p. 480-8.
104. Butler, M., et al. *Decision Aids for Advance Care Planning. Technical Brief No. 16. AHRQ Publication No. 14-EHC039-EF.* 2015; Available from: http://www.awmf.org/uploads/tx_szleitlinien/021-007OLl_S3_KRK_2014-08-verlaengert.pdf.
105. Stacey, D., et al., *Decision aids for people facing health treatment or screening decisions.* Cochrane Database Syst Rev, 2017. **4**: p. CD001431.
106. Auvinen, A., et al., *A randomized trial of choice of treatment in prostate cancer: the effect of intervention on the treatment chosen.* BJU Int, 2004. **93**(1): p. 52-6; discussion 56.
107. Berry, D.L., et al., *The Personal Patient Profile-Prostate decision support for men with localized prostate cancer: a multi-center randomized trial.* Urol Oncol, 2013. **31**(7): p. 1012-21.
108. Chabrera, C., et al., *A Decision Aid to Support Informed Choices for Patients Recently Diagnosed With Prostate Cancer: A Randomized Controlled Trial.* Cancer Nurs, 2015. **38**(3): p. E42-50.

109. Davison, B.J. and L.F. Degner, *Empowerment of men newly diagnosed with prostate cancer.* Cancer Nurs, 1997. **20**(3): p. 187-96.
110. Heller, L., et al., *Interactive digital education aid in breast reconstruction.* Plast Reconstr Surg, 2008. **122**(3): p. 717-24.
111. Jibaja-Weiss, M.L., et al., *Entertainment education for breast cancer surgery decisions: a randomized trial among patients with low health literacy.* Patient Educ Couns, 2011. **84**(1): p. 41-8.
112. Lam, W.W., et al., *Reducing treatment decision conflict difficulties in breast cancer surgery: a randomized controlled trial.* J Clin Oncol, 2013. **31**(23): p. 2879-85.
113. Leighl, N.B., et al., *Supporting treatment decision making in advanced cancer: a randomized trial of a decision aid for patients with advanced colorectal cancer considering chemotherapy.* J Clin Oncol, 2011. **29**(15): p. 2077-84.
114. Sawka, A.M., et al., *Randomized controlled trial of a computerized decision aid on adjuvant radioactive iodine treatment for patients with early-stage papillary thyroid cancer.* J Clin Oncol, 2012. **30**(23): p. 2906-11.
115. Vodermaier, A., et al., *Contextual factors in shared decision making: a randomised controlled trial in women with a strong suspicion of breast cancer.* Br J Cancer, 2009. **100**(4): p. 590-7.
116. Whelan, T., et al., *Helping patients make informed choices: a randomized trial of a decision aid for adjuvant chemotherapy in lymph node-negative breast cancer.* J Natl Cancer Inst, 2003. **95**(8): p. 581-7.
117. Whelan, T., et al., *Effect of a decision aid on knowledge and treatment decision making for breast cancer surgery: a randomized trial.* JAMA, 2004. **292**(4): p. 435-41.
118. Green, M.J. and B.H. Levi, *Development of an interactive computer program for advance care planning.* Health Expect, 2009. **12**(1): p. 60-9.
119. Smith, T.J., et al., *A pilot trial of decision aids to give truthful prognostic and treatment information to chemotherapy patients with advanced cancer.* J Support Oncol, 2011. **9**(2): p. 79-86.
120. Vogel, R.I., et al., *Development and pilot of an advance care planning website for women with ovarian cancer: a randomized controlled trial.* Gynecol Oncol, 2013. **131**(2): p. 430-6.
121. Volandes, A.E., et al., *Augmenting advance care planning in poor prognosis cancer with a video decision aid: a preintervention-postintervention study.* Cancer, 2012. **118**(17): p. 4331-8.
122. Bausewein, C., et al., *Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases.* Cochrane Database Syst Rev, 2008(2): p. CD005623.
123. Effing, T., et al., *Self-management education for patients with chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2007(4): p. CD002990.
124. Ferreira, I.M., et al., *Nutritional supplementation for stable chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2005(2): p. CD000998.
125. Bausewein, C., et al., *Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial.* BMC Palliative Care, 2010. **9**: p. 22.
126. Galbraith, S., et al., *Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial.* Journal of Pain & Symptom Management, 2010. **39**(5): p. 831-8.
127. Garcia-Aymerich, J., et al., *Effects of an integrated care intervention on risk factors of COPD readmission.* Respiratory Medicine, 2007. **101**(7): p. 1462-9.
128. Nguyen, H.Q., et al., *Randomized controlled trial of an internet-based versus face-to-face dyspnea self-management program for patients with chronic obstructive pulmonary disease: pilot study.* Journal of Medical Internet Research, 2008. **10**(2): p. e9.
129. Wakabayashi, R., et al., *Efficient integrated education for older patients with chronic obstructive pulmonary disease using the Lung Information Needs Questionnaire.* Geriatrics & gerontology international, 2011. **11**(4): p. 422-30.
130. Lau, K.S.L. and A.Y.M. Jones, *A single session of Acu-TENS increases FEV1 and reduces dyspnoea in patients with chronic obstructive pulmonary disease: a randomised, placebo-controlled trial.* Australian Journal of Physiotherapy, 2008. **54**(3): p. 179-84.
131. Mahajan, A.K., et al., *High frequency chest wall oscillation for asthma and chronic obstructive pulmonary disease exacerbations: A randomized sham-controlled clinical trial.* Respiratory Research, 2011. **12**(120).
132. Barton, R., et al., *A randomised trial of high vs low intensity training in breathing techniques for breathless patients with malignant lung disease: a feasibility study.* Lung Cancer, 2010. **70**(3): p. 313-9.
133. Battaglia, E., A. Fulgenzi, and M.E. Ferrero, *Rationale of the combined use of inspiratory and expiratory devices in improving maximal inspiratory pressure and maximal*

expiratory pressure of patients with chronic obstructive pulmonary disease. Archives of Physical Medicine & Rehabilitation, 2009. **90**(6): p. 913-8.
134. Bosnak-Guclu, M., et al., *Effects of inspiratory muscle training in patients with heart failure.* Respiratory Medicine, 2011. **105**(11): p. 1671-81.
135. Ekman, I., et al., *Impact of device-guided slow breathing on symptoms of chronic heart failure: a randomized, controlled feasibility study.* European Journal of Heart Failure, 2011. **13**(9): p. 1000-5.
136. Faager, G., A. Stâhle, and F.F. Larsen *Influence of spontaneous pursed lips breathing on walking endurance and oxygen saturation in patients with moderate to severe chronic obstructive pulmonary disease*. Clinical Rehabilitation, 2008. 675-83.
137. Kunik, M.E., et al., *COPD education and cognitive behavioral therapy group treatment for clinically significant symptoms of depression and anxiety in COPD patients: a randomized controlled trial.* Psychol Med, 2008. **38**(3): p. 385-96.
138. Liddell, F. and J. Webber, *Pulmonary rehabilitation for chronic obstructive pulmonary disease: a pilot study evaluating a once-weekly versus twice-weekly supervised programme.* Physiotherapy, 2010. **96**(1): p. 68-74.
139. Magadle, R., et al., *Inspiratory muscle training in pulmonary rehabilitation program in COPD patients.* Respiratory Medicine, 2007. **101**(7): p. 1500-5.
140. Masanga, L. and L. Fernandez, *Additive effects of high-intensity inspiratory muscle training in pulmonary rehabilitation among COPD patients in the philippines*. Respirology, 2011. **16**: p. 119.
141. Mota, S., et al. *Clinical outcomes of expiratory muscle training in severe COPD patients*. Respiratory Medicine, 2007. 516-24.
142. Mularski, R.A., et al., *Randomized controlled trial of mindfulness-based therapy for dyspnea in chronic obstructive lung disease.* Journal of Alternative & Complementary Medicine, 2009. **15**(10): p. 1083-90.
143. Nield, M.A., et al., *Efficacy of pursed-lips breathing: a breathing pattern retraining strategy for dyspnea reduction.* Journal of Cardiopulmonary Rehabilitation & Prevention, 2007. **27**(4): p. 237-44.
144. Padula, C.A., E. Yeaw, and S. Mistry, *A home-based nurse-coached inspiratory muscle training intervention in heart failure.* Applied Nursing Research, 2009. **22**(1): p. 18-25.
145. Pinto, S., M. Swash, and M. de Carvalho, *Respiratory exercise in amyotrophic lateral sclerosis.* Amyotroph Lateral Scler, 2012. **13**(1): p. 33-43.
146. Suzuki, M., et al., *The effect of acupuncture in the treatment of chronic obstructive pulmonary disease.* Journal of Alternative and Complementary Medicine, 2008. **14**(9): p. 1097-1105.
147. Whale, C.A., et al., *Pilot study to assess the credibility of acupuncture in acute exacerbations of chronic obstructive pulmonary disease.* Acupuncture in Medicine, 2009. **27**(1): p. 13-5.
148. Wu, H.-S., et al., *The psychologic consequences of chronic dyspnea in chronic pulmonary obstruction disease: the effects of acupressure on depression.* Journal of Alternative & Complementary Medicine, 2007. **13**(2): p. 253-61.
149. Singh, V.P., et al. *Comparison of the effectiveness of music and progressive muscle relaxation for anxiety in COPD--A randomized controlled pilot study*. Chronic Respiratory Disease, 2009. 209-16.
150. Chan, A.W., et al., *Tai chi Qigong improves lung functions and activity tolerance in COPD clients: a single blind, randomized controlled trial.* Complement Ther Med, 2011. **19**(1): p. 3-11.
151. Donesky-Cuenco, D., et al., *Yoga therapy decreases dyspnea-related distress and improves functional performance in people with chronic obstructive pulmonary disease: a pilot study.* Journal of Alternative & Complementary Medicine, 2009. **15**(3): p. 225-34.
152. Oh, B., et al., *Medical qigong for cancer patients: Pilot study of impact on quality of life, side effects of treatment and inflammation*. American Journal of Chinese Medicine, 2008. **36**(3): p. 459-472.
153. Yeh, G.Y., et al., *Tai chi exercise for patients with chronic obstructive pulmonary disease: a pilot study.* Respiratory Care, 2010. **55**(11): p. 1475-82.
154. Moullec, G. and G. Ninot, *An integrated programme after pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: effect on emotional and functional dimensions of quality of life.* Clin Rehabil, 2010. **24**(2): p. 122-36.
155. Bonilha, A.G., et al., *Effects of singing classes on pulmonary function and quality of life of COPD patients.* International Journal of Copd, 2009. **4**: p. 1-8.
156. Laviolette, L., et al., *Combined effect of dietary supplementation with pressurized whey and exercise training in chronic obstructive pulmonary disease: a randomized, controlled, double-blind pilot study.* Journal of Medicinal Food, 2010. **13**(3): p. 589-98.

157. Lebowitz, K.R., et al., *Effects of humor and laughter on psychological functioning, quality of life, health status, and pulmonary functioning among patients with chronic obstructive pulmonary disease: a preliminary investigation.* Heart & Lung, 2011. **40**(4): p. 310-9.
158. Jennings, A.L., et al., *Opioids for the palliation of breathlessness in terminal illness.* Cochrane Database Syst Rev, 2001(4): p. CD002066.
159. King, S., et al., *A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project.* Palliat Med, 2011. **25**(5): p. 525-52.
160. Barnes, H., et al., *Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness.* Cochrane Database Syst Rev, 2016. **3**: p. CD011008.
161. Ekstrom, M., et al., *Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review.* Ann Am Thorac Soc, 2015. **12**(7): p. 1079-92.
162. Ekstrom, M., et al., *One evidence base; three stories: do opioids relieve chronic breathlessness?* Thorax, 2018. **73**(1): p. 88-90.
163. Verberkt, C.A., et al., *Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis.* Eur Respir J, 2017. **50**(5).
164. Abernethy, A.P., et al., *Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea.* British Medical Journal, 2003. **327**(7414): p. 523-526.
165. Allard, P., et al., *How effective are supplementary doses of opioids for dyspnea in terminally ill cancer patients? A randomized continuous sequential clinical trial.* Journal of Pain & Symptom Management, 1999. **17**(4): p. 256-65.
166. Bruera, E., et al., *Nebulized versus subcutaneous morphine for patients with cancer dyspnea: a preliminary study.* Journal of Pain & Symptom Management, 2005. **29**(6): p. 613-8.
167. Charles, M.A., L. Reymond, and F. Israel *Relief of incident dyspnea in palliative cancer patients: a pilot, randomized, controlled trial comparing nebulized hydromorphone, systemic hydromorphone, and nebulized saline*. Journal of pain and symptom management, 2008. 29-38.
168. Grimbert, D., et al., *[Dyspnea and morphine aerosols in the palliative care of lung cancer].* Revue des maladies respiratoires, 2004. **21**(6 Pt 1): p. 1091-7.
169. Jensen, D., et al. *Inhaled Fentanyl Citrate Improves Dynamic Airway Function, Exertional Dyspnea And Exercise Endurance In COPD [Abstract].* American Journal of Respiratory and Critical Care Medicine, 2011. A5627.
170. Johnson, M.J., et al., *Morphine for the relief of breathlessness in patients with chronic heart failure - A pilot study.* European journal of heart failure, 2002. **4**(6): p. 753-756.
171. Mazzocato, C., T. Buclin, and C.H. Rapin, *The effects of morphine on dyspnea and ventilatory function in elderly patients with advanced cancer: A randomized double-blind controlled trial.* Annals of Oncology, 1999. **10**(12): p. 1511-1514.
172. Navigante, A.H., et al., *Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer.* Journal of Pain & Symptom Management, 2006. **31**(1): p. 38-47.
173. Navigante, A.H., M.A. Castro, and C. Cerchietti Leandro, *Morphine Versus Midazolam as Upfront Therapy to Control Dyspnea Perception in Cancer Patients While Its Underlying Cause Is Sought or Treated.* Journal of pain and symptom management, 2010. **39**(5): p. 820-830.
174. Oxberry, S.G., et al., *Short-term opioids for breathlessness in stable chronic heart failure: A randomized controlled trial.* European journal of heart failure, 2011. **13**(9): p. 1006-1012.
175. Hui, D., et al., *Impact of Prophylactic Fentanyl Pectin Nasal Spray on Exercise-Induced Episodic Dyspnea in Cancer Patients: A Double-Blind, Randomized Controlled Trial.* J Pain Symptom Manage, 2016. **52**(4): p. 459-468 e1.
176. Hui, D., et al., *Effect of Prophylactic Fentanyl Buccal Tablet on Episodic Exertional Dyspnea: A Pilot Double-Blind Randomized Controlled Trial.* J Pain Symptom Manage, 2017. **54**(6): p. 798-805.
177. Pinna, M.A., et al., *A randomized crossover clinical trial to evaluate the efficacy of oral transmucosal fentanyl citrate in the treatment of dyspnea on exertion in patients with advanced cancer.* Am J Hosp Palliat Care, 2015. **32**(3): p. 298-304.
178. Simon, S.T., et al., *EffenDys-Fentanyl Buccal Tablet for the Relief of Episodic Breathlessness in Patients With Advanced Cancer: A Multicenter, Open-Label, Randomized, Morphine-Controlled, Crossover, Phase II Trial.* J Pain Symptom Manage, 2016. **52**(5): p. 617-625.

179. Allcroft, P., et al., *The role of benzodiazepines in breathlessness: a single site, open label pilot of sustained release morphine together with clonazepam.* J Palliat Med, 2013. **16**(7): p. 741-4.
180. Simon, S.T., et al., *Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults.* Cochrane Database Syst Rev, 2016. **10**: p. CD007354.
181. Hardy, J., et al., *A randomised, double-blind controlled trial of intranasal midazolam for the palliation of dyspnoea in patients with life-limiting disease.* Support Care Cancer, 2016. **24**(7): p. 3069-76.
182. O'Neill, P.A., P.B. Morton, and R.D. Stark, *Chlorpromazine - A specific effect on breathlessness?* British Journal of Clinical Pharmacology, 1985. **19**(6): p. 793-797.
183. Rice, K.L., et al., *Effects of chronic administration of codeine and promethazine on breathlessness and exercise tolerance in patients with chronic airflow obstruction.* British Journal of Diseases of the Chest, 1987. **81**(3): p. 287-292.
184. Stark, R.D., S.A. Gambles, and J.A. Lewis, *Methods to assess breathlessness in healthy subjects: A critical evaluation and application to analyse the acute effects of diazepam and promethazine on breathlessness induced by exercise or by exposure to raised levels of carbon dioxide.* Clinical Science, 1981. **61**(4): p. 429-439.
185. Woodcock, A.A., E.R. Gross, and D.M. Geddes, *Drug treatment of breathlessness: contrasting effects of diazepam and promethazine in pink puffers.* British Medical Journal, 1981. **283**(6287): p. 343-346.
186. Borson, S., et al., *Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease.* Psychosomatics, 1992. **33**(2): p. 190-201.
187. Eiser, N., et al., *Effect of treating depression on quality-of-life and exercise tolerance in severe COPD.* COPD, 2005. **2**(2): p. 233-41.
188. Lacasse, Y., et al., *Randomized trial of paroxetine in end-stage COPD.* Monaldi Archives for Chest Disease, 2004. **61**(3): p. 140-7.
189. Perna, G., R. Cogo, and L. Bellodi, *Selective serotonin re-uptake inhibitors beyond psychiatry: Are they useful in the treatment of severe, chronic, obstructive pulmonary disease?* Depression and Anxiety, 2004. **20**(4): p. 203-204.
190. Smoller, J.W., et al., *Sertraline effects on dyspnea in patients with obstructive airways disease.* Psychosomatics, 1998. **39**(1): p. 24-9.
191. Ström, K., et al. *Effect of protriptyline, 10 mg daily, on chronic hypoxaemia in chronic obstructive pulmonary disease*. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology, 1995. 425-9.
192. Argyropoulou, P., et al., *Buspirone effect on breathlessness and exercise performance in patients with chronic obstructive pulmonary disease.* Respiration, 1993. **60**(4): p. 216-20.
193. Singh, N.P., et al., *Effects of buspirone on anxiety levels and exercise tolerance in patients with chronic airflow obstruction and mild anxiety.* Chest, 1993. **103**(3): p. 800-4.
194. Walters, J.A., E.H. Walters, and R. Wood-Baker, *Oral corticosteroids for stable chronic obstructive pulmonary disease (Review).* Cochrane Database Syst Rev, 2009(3): p. CD005374.
195. Yang, I.A., et al., *Inhaled corticosteroids for stable chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2007(2): p. CD002991.
196. Haywood, A., et al., *Systemic corticosteroids for the management of cancer-related breathlessness (dyspnoea) in adults.* Cochrane Database Syst Rev, 2019. **2**: p. CD012704.
197. Aaron, S.D., et al., *Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease.* N Engl J Med, 2003. **348**(26): p. 2618-25.
198. Choudhury, A.B., et al., *Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial.* Respir Res, 2007. **8**: p. 93.
199. du Bois, R.M., et al., *Randomized trial of inhaled fluticasone propionate in chronic stable pulmonary sarcoidosis: a pilot study.* European Respiratory Journal, 1999. **13**(6): p. 1345-50.
200. Guenette, J.A., et al., *Effect of adjunct fluticasone propionate on airway physiology during rest and exercise in COPD.* Respiratory Medicine, 2011. **105**(12): p. 1836-45.
201. Melani, A.S. and A. Di Gregorio, *Four-week nebulized beclomethasone dipropionate in stable COPD patients with exertional dyspnoea.* Monaldi Archives for Chest Disease, 1999. **54**(3): p. 224-7.
202. Milman, N., et al., *No effect of high-dose inhaled steroids in pulmonary sarcoidosis: a double-blind, placebo-controlled study.* J Intern Med, 1994. **236**(3): p. 285-90.
203. Rice, K.L., et al., *Withdrawal of chronic systemic corticosteroids in patients with COPD: a randomized trial.* American Journal of Respiratory & Critical Care Medicine, 2000. **162**(1): p. 174-8.

204. Sayiner, A., et al., *Systemic glucocorticoids in severe exacerbations of COPD.* Chest, 2001. **119**(3): p. 726-30.
205. Shmelev, E.I. and Y.L. Kunicina, *Comparison of fenspiride with beclomethasone as adjunctive anti-inflammatory treatment in patients with chronic obstructive pulmonary disease.* Clinical Drug Investigation, 2006. **26**(3): p. 151-9.
206. Tashkin, D.P., et al., *Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial.* Drugs, 2008. **68**(14): p. 1975-2000.
207. Vestbo, J., et al., *Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease.* Thorax, 2005. **60**(4): p. 301-4.
208. Worth, H., et al., *Budesonide added to formoterol contributes to improved exercise tolerance in patients with COPD.* Respir Med, 2010. **104**(10): p. 1450-9.
209. Wouters, E.F., et al., *[Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial].* Rev Port Pneumol, 2005. **11**(6): p. 587-9.
210. Yennurajalingam, S., et al., *Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer.* J Clin Oncol, 2013. **31**(25): p. 3076-82.
211. Zhang, H., et al., *Prednisone adding to usual care treatment for refractory decompensated congestive heart failure.* International Heart Journal, 2008. **49**(5): p. 587-95.
212. Hui, D., et al., *Dexamethasone for Dyspnea in Cancer Patients: A Pilot Double-Blind, Randomized, Controlled Trial.* J Pain Symptom Manage, 2016. **52**(1): p. 8-16 e1.
213. Cranston, J.M., A. Crockett, and D. Currow, *Oxygen therapy for dyspnoea in adults.* Cochrane Database Syst Rev, 2008(3): p. CD004769.
214. Uronis, H.E., et al., *Oxygen for relief of dyspnoea in mildly- or non-hypoxaemic patients with cancer: a systematic review and meta-analysis.* Br J Cancer, 2008. **98**(2): p. 294-9.
215. Uronis, H., et al., *Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2011(6): p. CD006429.
216. Abernethy, A.P., et al., *Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial.* Lancet, 2010. **376**(9743): p. 784-93.
217. Tassinari, D., et al., *The second step of the analgesic ladder and oral tramadol in the treatment of mild to moderate cancer pain: a systematic review.* Palliat Med, 2011. **25**(5): p. 410-23.
218. Leppert, W. and M. Majkowicz, *The impact of tramadol and dihydrocodeine treatment on quality of life of patients with cancer pain.* International Journal of Clinical Practice, 2010. **64**(12): p. 1681-7.
219. Caraceni, A., A. Pigni, and C. Brunelli, *Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project.* Palliat Med, 2011. **25**(5): p. 402-9.
220. King, S.J., et al., *A systematic review of oxycodone in the management of cancer pain.* Palliat Med, 2011. **25**(5): p. 454-70.
221. Pigni, A., C. Brunelli, and A. Caraceni, *The role of hydromorphone in cancer pain treatment: a systematic review.* Palliat Med, 2011. **25**(5): p. 471-7.
222. Mercadante, S., et al., *Morphine versus oxycodone in pancreatic cancer pain: a randomized controlled study.* Clinical Journal of Pain, 2010. **26**(9): p. 794-7.
223. Wiffen, P.J., et al., *Opioids for cancer pain - an overview of Cochrane reviews.* Cochrane Database Syst Rev, 2017. **7**: p. CD012592.
224. Corli, O., et al., *Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the variability of response to opioids.* Ann Oncol., 2016. **27**(6): p. 1107-15.
225. Cherny, N., *Is oral methadone better than placebo or other oral/transdermal opioids in the management of pain?* Palliat Med, 2011. **25**(5): p. 488-93.
226. Klepstad, P., S. Kaasa, and P.C. Borchgrevink, *Starting step III opioids for moderate to severe pain in cancer patients: dose titration: a systematic review.* Palliat Med, 2011. **25**(5): p. 424-30.
227. Tassinari, D., et al., *Transdermal opioids as front line treatment of moderate to severe cancer pain: a systemic review.* Palliat Med, 2011. **25**(5): p. 478-87.
228. Radbruch, L., et al., *Systematic review of the role of alternative application routes for opioid treatment for moderate to severe cancer pain: an EPCRC opioid guidelines project.* Palliat Med, 2011. **25**(5): p. 578-96.

229. Kurita, G.P., S. Kaasa, and P. Sjogren, *Spinal opioids in adult patients with cancer pain: a systematic review: a European Palliative Care Research Collaborative (EPCRC) opioid guidelines project.* Palliat Med, 2011. **25**(5): p. 560-77.
230. Lauretti, G.R., et al., *Epidural methadone results in dose-dependent analgesia in cancer pain, further enhanced by epidural dexamethasone.* British Journal of Cancer, 2013. **108**(2): p. 259-64.
231. Dale, O., K. Moksnes, and S. Kaasa, *European Palliative Care Research Collaborative pain guidelines: opioid switching to improve analgesia or reduce side effects. A systematic review.* Palliat Med, 2011. **25**(5): p. 494-503.
232. Mercadante, S. and A. Caraceni, *Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review.* Palliat Med, 2011. **25**(5): p. 504-15.
233. Moksnes, K., et al., *How to switch from morphine or oxycodone to methadone in cancer patients? a randomised clinical phase II trial.* European Journal of Cancer, 2011. **47**(16): p. 2463-70.
234. Laugsand, E.A., S. Kaasa, and P. Klepstad, *Management of opioid-induced nausea and vomiting in cancer patients: systematic review and evidence-based recommendations.* Palliat Med, 2011. **25**(5): p. 442-53.
235. Candy, B., et al., *Laxatives or methylnaltrexone for the management of constipation in palliative care patients.* Cochrane Database Syst Rev, 2011(1): p. CD003448.
236. Candy, B., et al., *Laxatives for the management of constipation in people receiving palliative care.* Cochrane Database Syst Rev, 2015(5): p. CD003448.
237. Candy, B., et al., *Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care.* Cochrane Database Syst Rev, 2018. **6**: p. CD006332.
238. Esmadi, M., D. Ahmad, and A. Hewlett, *Efficacy of naldemedine for the treatment of opioid-induced constipation: A meta-analysis.* Journal of Gastrointestinal & Liver Diseases, 2019. **28**(1): p. 41-46.
239. Hanson, B., et al., *American Gastroenterological Association Institute Technical Review on the Medical Management of Opioid-Induced Constipation.* Gastroenterology, 2019. **156**(1): p. 229-253.e5.
240. Luthra, P., et al., *Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and network meta-analysis.* Gut, 2018. **05**: p. 05.
241. Mehta, N., et al., *Efficacy of methylnaltrexone for the treatment of opiod-induced constipation: a meta-analysis and systematic review.* Postgraduate Medicine, 2016. **128**(3): p. 282-9.
242. Nee, J., et al., *Efficacy of Treatments for Opioid-Induced Constipation: Systematic Review and Meta-analysis.* Clinical Gastroenterology & Hepatology, 2018. **16**(10): p. 1569-1584.e2.
243. Nishie, K., et al., *Peripherally acting mu-opioid antagonist for the treatment of opioid-induced constipation: Systematic review and meta-analysis.* Journal of Gastroenterology & Hepatology, 2019. **34**(5): p. 818-829.
244. Siemens, W. and G. Becker, *Methylnaltrexone for opioid-induced constipation: review and meta-analyses for objective plus subjective efficacy and safety outcomes.* Ther Clin Risk Manag, 2016. **12**: p. 401-12.
245. Sridharan, K. and G. Sivaramakrishnan, *Drugs for Treating Opioid-Induced Constipation: A Mixed Treatment Comparison Network Meta-analysis of Randomized Controlled Clinical Trials.* J Pain Symptom Manage, 2018. **55**(2): p. 468-479 e1.
246. Ahmedzai, S.H., et al., *A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain.* Palliat Med, 2012. **26**(1): p. 50-60.
247. Stone, P. and O. Minton, *European Palliative Care Research collaborative pain guidelines. Central side-effects management: what is the evidence to support best practice in the management of sedation, cognitive impairment and myoclonus?* Palliat Med, 2011. **25**(5): p. 431-41.
248. Schüchen, R.H., et al., *Systematic review and meta-analysis on non-opioid analgesics in palliative medicine.* J Cachexia Sarcopenia Muscle, 2018. **9**(7): p. 1235-1254.
249. Duarte Souza, J.F., et al., *Adjunct dipyrone in association with oral morphine for cancer-related pain: the sooner the better.* Supportive Care in Cancer, 2007. **15**(11): p. 1319-23.
250. Rodriguez, M., et al., *Efficacy and tolerance of oral dipyrone versus oral morphine for cancer pain.* European Journal of Cancer, 1994. **30A**(5): p. 584-7.
251. Yalcin, S., et al., *Ketorolac tromethamine in cancer pain.* Acta Oncologica, 1997. **36**(2): p. 231-2.

252. Yalcin, S., et al., *A comparison of two nonsteroidal antiinflammatory drugs (diflunisal versus dipyrone) in the treatment of moderate to severe cancer pain: a randomized crossover study.* American Journal of Clinical Oncology, 1998. **21**(2): p. 185-8.
253. Nabal, M., et al., *The role of paracetamol and nonsteroidal anti-inflammatory drugs in addition to WHO Step III opioids in the control of pain in advanced cancer. A systematic review of the literature.* Palliat Med, 2011. **26**(4): p. 305-12.
254. Bennett, M.I., *Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review.* Palliat Med, 2011. **25**(5): p. 553-9.
255. Mishra, S., et al., *A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study.* American Journal of Hospice & Palliative Medicine, 2012. **29**(3): p. 177-82.
256. Zeppetella, G., *Opioids for the management of breakthrough cancer pain in adults: a systematic review undertaken as part of an EPCRC opioid guidelines project.* Palliat Med, 2011. **25**(5): p. 516-24.
257. Zeppetella, G. and A.N. Davies, *Opioids for the management of breakthrough pain in cancer patients.* Cochrane Database Syst Rev, 2013. **10**: p. CD004311.
258. Dittus, K.L., R.E. Gramling, and P.A. Ades, *Exercise interventions for individuals with advanced cancer: A systematic review.* Preventive Medicine, 2017. **104**: p. 124-132.
259. Payne, C., P.J. Wiffen, and S. Martin, *Interventions for fatigue and weight loss in adults with advanced progressive illness.* Cochrane Database of Systematic Reviews, 2012. **1**: p. CD008427.
260. Poort, H., et al., *Psychosocial interventions for fatigue during cancer treatment with palliative intent.* Cochrane Database of Systematic Reviews, 2017. **7**: p. CD012030.
261. Warth, M., et al., *Music Therapy in Palliative Care.* Dtsch Arztebl Int, 2015. **112**(46): p. 788-94.
262. Pyszora, A., et al., *Physiotherapy programme reduces fatigue in patients with advanced cancer receiving palliative care: randomized controlled trial.* Support Care Cancer, 2017. **25**(9): p. 2899-2908.
263. Mücke, M., et al., *Pharmacological treatments for fatigue associated with palliative care.* Cochrane Database Syst Rev, 2015. **5**: p. CD006788.
264. Thiem, A., R. Rolke, and L. Radbruch, *[Glucocorticoids and androgens for treatment of tiredness and weakness in palliative care patients : a systematic review].* Der Schmerz, 2012. **26**(5): p. 550-67.
265. Cankurtaran, E.S., et al., *Mirtazapine improves sleep and lowers anxiety and depression in cancer patients: superiority over imipramine.* Supportive Care in Cancer, 2008. **16**(11): p. 1291-8.
266. Palesh, O.G., et al., *Impact of paroxetine on sleep problems in 426 cancer patients receiving chemotherapy: a trial from the University of Rochester Cancer Center Community Clinical Oncology Program.* Sleep Medicine, 2012. **13**(9): p. 1184-90.
267. Tanimukai, H., et al., *An observational study of insomnia and nightmare treated with trazodone in patients with advanced cancer.* American Journal of Hospice & Palliative Medicine, 2013. **30**(4): p. 359-62.
268. Theobald, D.E., et al., *An open-label, crossover trial of mirtazapine (15 and 30 mg) in cancer patients with pain and other distressing symptoms.* Journal of pain and symptom management, 2002. **23**(5): p. 442-447.
269. Hirst, A. and R. Sloan, *Benzodiazepines and related drugs for insomnia in palliative care.* Cochrane Database of Systematic Reviews, 2002(4): p. CD003346.
270. Kaneishi, K., M. Kawabata, and T. Morita, *Single-Dose Subcutaneous Benzodiazepines for Insomnia in Patients With Advanced Cancer.* J Pain Symptom Manage, 2015. **49**(6): p. e1-2.
271. Matsuo, N. and T. Morita, *Efficacy, safety, and cost effectiveness of intravenous midazolam and flunitrazepam for primary insomnia in terminally ill patients with cancer: a retrospective multicenter audit study.* Journal of Palliative Medicine, 2007. **10**(5): p. 1054-62.
272. Pasquini, M., A. Speca, and M. Biondi, *Quetiapine for tamoxifen-induced insomnia in women with breast cancer.* Psychosomatics: Journal of Consultation and Liaison Psychiatry, 2009. **50**(2): p. 159-161.
273. Barton, D.L., et al., *The use of Valeriana officinalis (Valerian) in improving sleep in patients who are undergoing treatment for cancer: a phase III randomized, placebo-controlled, double-blind study (NCCTG Trial, N01C5).* The Journal of Supportive Oncology, 2011. **9**(1): p. 24-31.
274. Troger, W., et al., *Quality of life of patients with advanced pancreatic cancer during treatment with mistletoe: a randomized controlled trial.* Deutsches Arzteblatt International, 2014. **111**(29-30): p. 493-502, 33 p following 502.

275. Hansen, M.V., et al., *Effect of Melatonin on Cognitive Function and Sleep in relation to Breast Cancer Surgery: A Randomized, Double-Blind, Placebo-Controlled Trial.* International Journal of Breast Cancer, 2014. **2014**: p. 416531.
276. Innominato, P.F., et al., *The effect of melatonin on sleep and quality of life in patients with advanced breast cancer.* Supportive Care in Cancer, 2016. **24**(3): p. 1097-105.
277. Kurdi, M.S. and S.P. Muthukalai, *The Efficacy of Oral Melatonin in Improving Sleep in Cancer Patients with Insomnia: A Randomized Double-Blind Placebo-Controlled Study.* Indian Journal of Palliative Care, 2016. **22**(3): p. 295-300.
278. Joffe, H., et al., *Augmentation of venlafaxine and selective serotonin reuptake inhibitors with zolpidem improves sleep and quality of life in breast cancer patients with hot flashes: a randomized, double-blind, placebo-controlled trial.* Menopause, 2010. **17**(5): p. 908-16.
279. Rhodes, V.A. and R.W. McDaniel, *The Index of Nausea, Vomiting, and Retching: a new format of the Index of Nausea and Vomiting.* Oncology nursing forum, 1999. **26**(5): p. 889-894.
280. Fu, M.R., V. Rhodes, and B. Xu, *The Chinese translation of the Index of Nausea, Vomiting, and Retching.* Cancer Nursing, 2002. **25**(2): p. 134-40.
281. Benze, G., et al., *[Treatment of nausea and vomiting with prokinetics and neuroleptics in palliative care patients : a review].* Schmerz, 2012a. **26**(5): p. 500-14.
282. Benze, G., et al., *[Treatment of nausea and vomiting with 5HT3 receptor antagonists, steroids, antihistamines, anticholinergics, somatostatinantagonists, benzodiazepines and cannabinoids in palliative care patients : a systematic review].* Schmerz, 2012b. **26**(5): p. 481-99.
283. Mucke, M., et al., *Systematic review and meta-analysis of cannabinoids in palliative medicine.* Journal of Cachexia, Sarcopenia and Muscle, 2018. **9**(2): p. 220-234.
284. Cox, L., E. Darvill, and S. Dorman, *Levomepromazine for nausea and vomiting in palliative care.* Cochrane Database Syst Rev, 2015(11): p. CD009420.
285. Dietz, I., et al., *Evidence for the use of Levomepromazine for symptom control in the palliative care setting: A systematic review.* BMC Palliative Care, 2013. **12 (1) (no pagination)**(2).
286. Murray-Brown, F. and S. Dorman, *Haloperidol for the treatment of nausea and vomiting in palliative care patients.* Cochrane Database Syst Rev, 2015(11): p. CD006271.
287. Storrar, J., et al. *Droperidol for treatment of nausea and vomiting in palliative care patients*. Cochrane Database of Systematic Reviews, 2014. DOI: 10.1002/14651858.CD006938.pub3.
288. Vayne-Bossert, P., et al., *Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery).* Cochrane Database Syst Rev, 2017. **7**: p. CD012002.
289. Sande, T.A., B.J.A. Laird, and M.T. Fallon, *The Management of Opioid-Induced Nausea and Vomiting in Patients with Cancer: A Systematic Review.* Journal of Palliative Medicine, 2018. **21**: p. 21.
290. Bader, S., M. Weber, and G. Becker, *Is the pharmacological treatment of constipation in palliative care evidence based? : a systematic literature review.* Schmerz, 2012. **26**(5): p. 568-86.
291. Becker, G. and H.E. Blum, *Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus.* Lancet, 2009. **373**(9670): p. 1198-206.
292. McNicol, E.D., et al., *Mu-opioid antagonists for opioid-induced bowel dysfunction.* Cochrane Database Syst Rev, 2008(2): p. CD006332.
293. Naghibi, M., T.R. Smith, and M. Elia, *A systematic review with meta-analysis of survival, quality of life and cost-effectiveness of home parenteral nutrition in patients with inoperable malignant bowel obstruction.* Clin Nutr, 2015. **34**(5): p. 825-37.
294. Sowerbutts, A.M., et al., *Home parenteral nutrition for people with inoperable malignant bowel obstruction.* Cochrane Database of Systematic Reviews, 2018. **8**: p. CD012812.
295. Aria Guerra, E., et al., *Role of Parenteral Nutrition in Oncologic Patients with Intestinal Occlusion and Peritoneal Carcinomatosis.* Nutr Hosp, 2015. **32**(3): p. 1222-7.
296. Chouhan, J., et al., *Retrospective analysis of systemic chemotherapy and total parenteral nutrition for the treatment of malignant small bowel obstruction.* Cancer Med, 2016. **5**(2): p. 239-47.
297. Diver, E., et al., *Modest benefit of total parenteral nutrition and chemotherapy after venting gastrostomy tube placement.* Gynecol Oncol, 2013. **129**(2): p. 332-5.
298. Hu, L.J. and S.Y. Yu, *Management of malignant bowel obstruction with decompression tubes.* Eur Rev Med Pharmacol Sci, 2014. **18**(19): p. 2798-802.
299. Rath, K.S., et al., *Outcomes following percutaneous upper gastrointestinal decompressive tube placement for malignant bowel obstruction in ovarian cancer.* Gynecol Oncol, 2013. **129**(1): p. 103-6.

300. Klein, C., et al., *[Pharmacological treatment of malignant bowel obstruction in severely ill and dying patients : a systematic literature review].* Schmerz, 2012. **26**(5): p. 587-99.
301. Obita, G.P., et al., *Somatostatin Analogues Compared With Placebo and Other Pharmacologic Agents in the Management of Symptoms of Inoperable Malignant Bowel Obstruction: A Systematic Review.* Journal of Pain & Symptom Management, 2016. **52**(6): p. 901-919.e1.
302. De Conno, F., et al., *Continuous subcutaneous infusion of hyoscine butylbromide reduces secretions in patients with gastrointestinal obstruction.* Journal of Pain & Symptom Management, 1991. **6**(8): p. 484-6.
303. Mercadante, S., et al., *Comparison of octreotide and hyoscine butylbromide in controlling gastrointestinal symptoms due to malignant inoperable bowel obstruction.* Supportive Care in Cancer, 2000. **8**(3): p. 188-91.
304. Peng, X., et al., *Randomized clinical trial comparing octreotide and scopolamine butylbromide in symptom control of patients with inoperable bowel obstruction due to advanced ovarian cancer.* World Journal of Surgical Oncology, 2015. **13**: p. 50.
305. Ripamonti, C., et al., *Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: a prospective randomized trial.* J Pain Symptom Manage, 2000. **19**(1): p. 23-34.
306. Feuer, D.J. and K.E. Broadley, *Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer.* Cochrane Database of Systematic Reviews, 2000(2): p. CD001219.
307. Kaneishi, K., M. Kawabata, and T. Morita, *Olanzapine for the relief of nausea in patients with advanced cancer and incomplete bowel obstruction.* Journal of Pain & Symptom Management, 2012. **44**(4): p. 604-7.
308. Tuca, A., et al., *Efficacy of granisetron in the antiemetic control of nonsurgical intestinal obstruction in advanced cancer: a phase II clinical trial.* Journal of Pain & Symptom Management, 2009. **37**(2): p. 259-70.
309. Ventafridda, V., et al., *The management of inoperable gastrointestinal obstruction in terminal cancer patients.* Tumori, 1990. **76**: p. 389-393.
310. Berger, J., P. Lester, and L. Rodrigues, *Medical Therapy of Malignant Bowel Obstruction With Octreotide, Dexamethasone, and Metoclopramide.* American Journal of Hospice & Palliative Medicine, 2016. **33**(4): p. 407-10.
311. Isbister, W.H., P. Elder, and L. Symons, *Non-operative management of malignant intestinal obstruction.* Journal of the Royal College of Surgeons of Edinburgh, 1990. **35**(6): p. 369-72.
312. Laval, G., et al., *Protocol for the treatment of malignant inoperable bowel obstruction: a prospective study of 80 cases at Grenoble University Hospital Center.* Journal of Pain & Symptom Management, 2006. **31**(6): p. 502-12.
313. Mercadante, S., et al., *Aggressive pharmacological treatment for reversing malignant bowel obstruction.* Journal of Pain & Symptom Management, 2004. **28**(4): p. 412-6.
314. Porzio, G., et al., *Can malignant bowel obstruction in advanced cancer patients be treated at home?* Supportive Care in Cancer, 2011. **19**(3): p. 431-3.
315. Weber, C. and G.B. Zulian, *Malignant irreversible intestinal obstruction: the powerful association of octreotide to corticosteroids, antiemetics, and analgesics.* American Journal of Hospice & Palliative Medicine, 2009. **26**(2): p. 84-8.
316. Mercadante, S., *Scopolamine butylbromide plus octreotide in unresponsive bowel obstruction.* Journal of Pain & Symptom Management, 1998. **16**(5): p. 278-80.
317. Thaker, D.A., B.C. Stafford, and L.S. Gaffney, *Palliative management of malignant bowel obstruction in terminally ill patient.* Indian Journal of Palliative Care, 2010. **16**(2): p. 97-100.
318. Adderley, U.J. and I.G. Holt, *Topical agents and dressings for fungating wounds.* Cochrane Database of Systematic Reviews, 2014(5): p. N.PAG-N.PAG.
319. da Costa Santos, C.M., C.A. de Mattos Pimenta, and M.R. Nobre, *A systematic review of topical treatments to control the odor of malignant fungating wounds.* J Pain Symptom Manage, 2010. **39**(6): p. 1065-76.
320. de Castro, D.L.V. and V.L.C.G. Santos, *Odor Management in Fungating Wounds With Metronidazole.* Journal of Hospice & Palliative Nursing, 2015. **17**(1): p. 73-79.
321. Dissemond, J., et al., *Evidence for silver in wound care - meta-analysis of clinical studies from 2000-2015.* J Dtsch Dermatol Ges, 2017. **15**(5): p. 524-535.
322. Finlayson, K., L. Teleni, and A.L. McCarthy, *Topical Opioids and Antimicrobials for the Management of Pain, Infection, and Infection-Related Odors in Malignant Wounds: A Systematic Review.* Oncology Nursing Forum, 2017. **44**(5): p. 626-632.
323. Graham, T., et al., *How are topical opioids used to manage painful cutaneous lesions in palliative care? A critical review.* Pain, 2013. **154**(10): p. 1920-8.

324. LeBon, B., G. Zeppetella, and I.J. Higginson, *Effectiveness of topical administration of opioids in palliative care: a systematic review.* J Pain Symptom Manage, 2009. **37**(5): p. 913-7.
325. Montroy, J., et al., *The efficacy and safety of topical tranexamic acid: A systematic review and meta-analysis.* Transfus Med Rev, 2018.
326. Norman, G., et al., *Antibiotics and antiseptics for pressure ulcers.* Cochrane Database Syst Rev, 2016. **4**: p. CD011586.
327. Norman, G., et al., *Antibiotics and antiseptics for surgical wounds healing by secondary intention.* Cochrane Database Syst Rev, 2016. **3**: p. CD011712.
328. Norman, G., et al., *Antiseptics for burns.* Cochrane Database Syst Rev, 2017. **7**: p. CD011821.
329. O'Meara, S., et al., *Antibiotics and antiseptics for venous leg ulcers.* Cochrane Database Syst Rev, 2014(1): p. CD003557.
330. Ramasubbu, D.A., et al., *Systemic antibiotics for treating malignant wounds.* Cochrane Database Syst Rev, 2017. **8**: p. CD011609.
331. Vermeulen, H., S.J. Westerbos, and D.T. Ubbink, *Benefit and harm of iodine in wound care: a systematic review.* J Hosp Infect, 2010. **76**(3): p. 191-9.
332. Ashford, R.F., et al., *Metronidazole in smelly tumours.* Lancet, 1980. **1**(8173): p. 874-5.
333. Ashford, R., et al., *Double-blind trial of metronidazole in malodorous ulcerating tumours.* Lancet, 1984. **1**(8388): p. 1232-3.
334. Brusis, T. and H. Luckhaupt, *[Anaerobic infections in ulcerating tumors of the head and neck. A contribution to the problem of odors].* Laryngologie, Rhinologie, Otologie, 1986. **65**(2): p. 65-8.
335. Dankert, J., et al., *Metronidazole in smelly gynaecological tumours.* Lancet, 1981. **2**(8258): p. 1295.
336. Sparrow, G., et al., *Metronidazole in smelly tumours.* Lancet, 1980. **1**(8179): p. 1185.
337. Luckett, T., et al., *Evidence for interventions to improve psychological outcomes in people with head and neck cancer: a systematic review of the literature.* Supportive Care in Cancer, 2011. **19**(7): p. 871-881.
338. Plummer, F., et al., *Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis.* Gen Hosp Psychiatry, 2016. **39**: p. 24-31.
339. Vodermaier, A., W. Linden, and C. Siu, *Screening for emotional distress in cancer patients: a systematic review of assessment instruments.* J Natl Cancer Inst, 2009. **101**(21): p. 1464-88.
340. Ziegler, L., et al., *Identifying psychological distress at key stages of the cancer illness trajectory: a systematic review of validated self-report measures.* J Pain Symptom Manage, 2011. **41**(3): p. 619-36.
341. Fulton, J.J., et al., *Psychotherapy Targeting Depression and Anxiety for Use in Palliative Care: A Meta-Analysis.* J Palliat Med, 2018. **21**(7): p. 1024-1037.
342. Grossman, C.H., et al., *Death anxiety interventions in patients with advanced cancer: A systematic review.* Palliative Medicine, 2018. **32**(1): p. 172-184.
343. Wang, C.W., A.Y. Chow, and C.L. Chan, *The effects of life review interventions on spiritual well-being, psychological distress, and quality of life in patients with terminal or advanced cancer: A systematic review and meta-analysis of randomized controlled trials.* Palliative Medicine, 2017. **31**(10): p. 883-894.
344. Salt, S., C.A. Mulvaney, and N.J. Preston, *Drug therapy for symptoms associated with anxiety in adult palliative care patients.* Cochrane Database Syst Rev, 2017. **5**: p. CD004596.
345. Nubling, G., S. Allmendinger, and S. Lorenzl, *[Drug therapy of anxiety and fear in palliative care patients with cancer or other illnesses : a systematic review].* Der Schmerz, 2012. **26**(5): p. 537-49.
346. Majumdar, M., B. Wilks, and D. Charlesworth, *Safe and Efficacious Use of Dexmedetomidine over a Prolonged Duration for Anxiolysis and as an Adjunct to Analgesia during End-of-Life Care.* Journal of Palliative Care, 2015. **31**(4): p. 265-7.
347. Razavi, D., et al. *Comparative study of the efficacy and safety of trazodone versus clorazepate in the treatment of adjustment disorders in cancer patients: a pilot study*. Journal of international medical research, 1999. 264-272 DOI: 10.1177/030006059902700602.
348. Stockler, M.R., et al., *Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial.* Lancet Oncol, 2007. **8**(7): p. 603-12.
349. Suzuki, N., et al., *Clinical study on the efficacy of fluvoxamine for psychological distress in gynecologic cancer patients.* International Journal of Gynecological Cancer, 2011. **21**(6): p. 1143-9.

350. Meijer, A., et al., *Depression screening and patient outcomes in cancer: a systematic review.* PLoS One, 2011. **6**(11): p. e27181.
351. Mitchell, A.J., *Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders.* J Clin Oncol, 2007. **25**(29): p. 4670-81.
352. Mitchell, A.J., *Are one or two simple questions sufficient to detect depression in cancer and palliative care? A Bayesian meta-analysis.* Br J Cancer, 2008. **98**(12): p. 1934-43.
353. Mitchell, A.J., N. Meader, and P. Symonds, *Diagnostic validity of the Hospital Anxiety and Depression Scale (HADS) in cancer and palliative settings: a meta-analysis.* J Affect Disord, 2010. **126**(3): p. 335-48.
354. Mitchell, A.J., K. Lord, and P. Symonds, *Which symptoms are indicative of DSMIV depression in cancer settings? An analysis of the diagnostic significance of somatic and non-somatic symptoms.* J Affect Disord, 2012. **138**(1-2): p. 137-48.
355. Nelson, C.J., et al., *Are gold standard depression measures appropriate for use in geriatric cancer patients? A systematic evaluation of self-report depression instruments used with geriatric, cancer, and geriatric cancer samples.* J Clin Oncol, 2010. **28**(2): p. 348-56.
356. Vodermaier, A. and R.D. Millman, *Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis.* Support Care Cancer, 2011. **19**(12): p. 1899-908.
357. Wasteson, E., et al., *Depression assessment and classification in palliative cancer patients: a systematic literature review.* Palliat Med, 2009. **23**(8): p. 739-53.
358. Fulton, J.J., et al., *Psychotherapy Targeting Depression and Anxiety for Use in Palliative Care: A Meta-Analysis.* J Palliat Med, 2018: p. 1-14.
359. Rayner, L., et al., *Antidepressants for depression in physically ill people.* Cochrane Database Syst Rev, 2010(3): p. CD007503.
360. Rayner, L., et al., *Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis.* Palliat Med, 2011. **25**(1): p. 36-51.
361. Ujeyl, M. and B. Muller-Oerlinghausen, *[Antidepressants for treatment of depression in palliative patients : a systematic literature review].* Schmerz, 2012. **26**(5): p. 523-36.
362. Ostuzzi, G., et al., *Antidepressants for the treatment of depression in people with cancer.* Cochrane Database of Systematic Reviews, 2018(4 Art. No.: CD011006).
363. Abbasowa, L., L.V. Kessing, and M. Vinberg, *Psychostimulants in moderate to severe affective disorder: A systematic review of randomized controlled trials.* Nord J Psychiatry, 2013.
364. Candy, M., et al., *Psychostimulants for depression.* Cochrane Database Syst Rev, 2008(2): p. CD006722.
365. Kerr, C.W., et al., *Effects of methylphenidate on fatigue and depression: a randomized, double-blind, placebo-controlled trial.* J Pain Symptom Manage, 2012. **43**(1): p. 68-77.
366. Rodriguez-Prat, A., et al., *Understanding patients' experiences of the wish to hasten death: an updated and expanded systematic review and meta-ethnography.* BMJ Open, 2017. **7**(9): p. e016659.
367. Bellido-Perez, M., et al., *Assessment of the wish to hasten death in patients with advanced disease: A systematic review of measurement instruments.* Palliat Med, 2017. **31**(6): p. 510-525.
368. Blades, C.A., et al., *The benefits and risks of asking research participants about suicide: A meta-analysis of the impact of exposure to suicide-related content.* Clin Psychol Rev, 2018. **64**: p. 1-12.
369. DeCou, C.R. and M.E. Schumann, *On the Iatrogenic Risk of Assessing Suicidality: A Meta-Analysis.* Suicide Life Threat Behav, 2018. **48**(5): p. 531-543.
370. Crawford, M.J., et al., *Impact of screening for risk of suicide: randomised controlled trial.* British Journal of Psychiatry, 2011. **198**(5): p. 379-84.
371. de Beurs, D.P., et al., *Psychological Distress Because of Asking about Suicidal Thoughts: A Randomized Controlled Trial among Students.* Arch Suicide Res, 2016. **20**(2): p. 153-9.
372. Harris, K.M. and M.T. Goh, *Is suicide assessment harmful to participants? Findings from a randomized controlled trial.* Int J Ment Health Nurs, 2016. **26**(2): p. 181-190.
373. Breitbart, W., et al., *Meaning-centered group psychotherapy for patients with advanced cancer: a pilot randomized controlled trial.* Psycho-Oncology, 2010. **19**(1): p. 21-8.
374. Breitbart, W., et al., *Meaning-centered group psychotherapy: an effective intervention for improving psychological well-being in patients with advanced cancer.* Journal of Clinical Oncology, 2015. **33**(7): p. 749-54.
375. Breitbart, W., et al., *Individual meaning-centered psychotherapy for the treatment of psychological and existential distress: A randomized controlled trial in patients with advanced cancer.* Cancer, 2018. **124**(15): p. 3231-3239.

376. Chochinov, H.M., et al., *Effect of dignity therapy on distress and end-of-life experience in terminally ill patients: a randomised controlled trial.* Lancet Oncol, 2011. **12**(8): p. 753-62.
377. Juliao, M., et al., *Effect of dignity therapy on end-of-life psychological distress in terminally ill Portuguese patients: A randomized controlled trial.* Palliative & Supportive Care, 2017. **15**(6): p. 628-637.
378. Eychmüller, S., et al., *"Diagnosing dying" in cancer patients - a systematic literature review.* European Journal of Palliative Care, 2013. **20**(6): p. 292-296.
379. Kehl, K.A. and J.A. Kowalkowski, *A systematic review of the prevalence of signs of impending death and symptoms in the last 2 weeks of life.* Am J Hosp Palliat Care, 2013. **30**(6): p. 601-16.
380. Kennedy, C., et al., *Diagnosing dying: an integrative literature review.* BMJ Support Palliat Care, 2014. **4**(3): p. 263-270.
381. Domeisen Benedetti, F., et al., *International palliative care experts' view on phenomena indicating the last hours and days of life.* Support Care Cancer, 2013. **21**(6): p. 1509-17.
382. Hui, D., et al., *Clinical signs of impending death in cancer patients.* Oncologist, 2014. **19**(6): p. 681-7.
383. Boettger, S., et al., *Aripiprazole and haloperidol in the treatment of delirium.* Aust N Z J Psychiatry, 2011. **45**(6): p. 477-82.
384. Breitbart, W., et al., *A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients.* Am J Psychiatry, 1996. **153**(2): p. 231-7.
385. Breitbart, W., A. Tremblay, and C. Gibson, *An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients.* Psychosomatics, 2002. **43**(3): p. 175-82.
386. Lin, C.J., et al., *An open trial comparing haloperidol with olanzapine for the treatment of delirium in palliative and hospice center cancer patients.* Journal of Internal Medicine of Taiwan, 2008. **19**(4): p. 346-354.
387. Burry, L., et al., *Antipsychotics for treatment of delirium in hospitalised non-ICU patients.* Cochrane Database Syst Rev, 2018. **6**: p. CD005594.
388. Agar, M.R., et al., *Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial.* JAMA Intern Med, 2017. **177**(1): p. 34-42.
389. Hui, D., et al., *Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer Receiving Palliative Care: A Randomized Clinical Trial.* JAMA, 2017. **318**(11): p. 1047-56.
390. Pastrana, T., H. Reineke-Bracke, and F. Elsner, *Empfehlung bei Rasselatmung.* Der Schmerz, 2012. **26**(5): p. 600-608.
391. Wee, B. and R. Hillier, *Interventions for noisy breathing in patients near to death.* Cochrane Database Syst Rev, 2008(1): p. CD005177.
392. Likar, R., et al., *Efficacy of glycopyrronium bromide and scopolamine hydrobromide in patients with death rattle: a randomized controlled study.* Wien Klin Wochenschr, 2008. **120**(21-22): p. 679-83.
393. Davies, A.N., *A comparison of artificial saliva and chewing gum in the management of xerostomia in patients with advanced cancer.* Palliat Med, 2000. **14**(3): p. 197-203.
394. Raijmakers, N.J.H., et al., *Artificial nutrition and hydration in the last week of life in cancer patients. A systematic literature review of practices and effects.* Annals of Oncology, 2011. **22**(7): p. 1478-86.
395. Bruera, E., et al., *Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial.* J Clin Oncol, 2013. **31**(1): p. 111-8.
396. Nakajima, N., Y. Hata, and K. Kusumuto, *A clinical study on the influence of hydration volume on the signs of terminally ill cancer patients with abdominal malignancies.* J Palliat Med, 2013. **16**(2): p. 185-9.