Extraktionen und Bewertungen der eingeschlossenen Studien zu den Fragen #1 bis #13

Tabellenverzeichnis

Tab. 1 Systemische Pharmakologie: Paracetamol, Metamizol, NSAR, COX-2-Inhibitoren: *systematische Reviews zu NSAR (Fragen #1 bis #5)*

Review / reference	**Inclusion, exclusion criteria, search period, number of included studies**	**Intervention group(s) (IG)/ control group (CG)**	**Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)**	**Level of evidence: CEbM 2009 (CEbM 2011)** **critical appraisal/ conclusion**
Bainbridge, D., et al. (2006), NSAID-analgesia, pain control and morbidity in cardiothoracic surgery. Can J Anesth, 2006. 53(1): p. 46-59.	**Inclusion criteria** - randomized allocation to a NSAID-containing analgesic regimen vs non-NSAID-containing narcotic or regional analgesic regimen given pre-, intra- or postoperatively to pre-empt pain - adult patients undergoing cardiac or thoracic surgery - reporting at least one pertinent clinical or economic outcome - blinded and unblended studies **Exclusion criteria** - Patients receiving COX-2 selective NSAIDs were excluded from this analysis - Pediatric surgical studies - studies focused primarily on the management of pericardial effusions or postoperative atrial fibrillation rather than analgesia - Studies involving regional anesthesia techniques when the regional block was not offered to both the NSAID and control groups **Search period** MEDLINE, Cochrane CENTRAL, EMBASE, Current Contents, DARE, NEED, and INAHTA from date of their inception to September 2005 **Number of included studies (n participants)** 20 (1065)	**Intervention:** different NSAIDs plus narcotics (7 studies: diclofenac, 6 studies: ketorolac, six studies: indomethacin) **Control:** Narcotics without NSAIDs	**Clinical outcomes at 24h or during hospitalization** **Intervention vs. control** **VAS, 24h** (7 studies) WMD -0.91 (95% CI: -1.48, -0.34), p=0.002 I^2=66% **Morphine equivalents, cumulative, 24h** (13 studies) WMD -7.67 (95% CI: -8.97, -6.38), p <0.00001 I^2=70% ***Rescue Analgesics*** (3 studies) OR 0.46 (CI 95%: 0.20, 1.07), p=0.07 I^2=79% ***Death, all cause*** (2 studies) OR 0.19 (CI 95%: 0.01, 4.22), p=0.29 ***Acute myocardial infarction*** (3 studies) OR 0.71 (CI 95%: 0.09, 5.71), p=0.75 I^2=0% ***Arterial fibrillation*** (3 studies) OR 0.62 (CI 95%: 0.24, 1.56), p=0.3 I^2=12% ***Bleeding, all-causes*** (3 studies) OR 0.72 (CI 95%: 0.09, 5.66), p=0.75 I^2=0% ***Postoperative nausea & vomiting*** (9 studies) OR 1.24 (CI 95%: 0.79, 1.95), p=0.34 I^2=0%	**Level of evidence** 1a (1) **Author conclusion** "In conclusion, patients undergoing cardiothoracic surgery who received NSAIDs adjunctive to narcotics experienced improved analgesia." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: ? Publication bias: + Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			GI disturbance (3 studies) OR 0.52 (CI 95%: 0.13, 2.1), p=0.36 I^2=0% ***GI bleeding*** (4 studies) OR 0.96 (CI 95%: 0.13, 7.09), p=0.97 I^2=NA ***Renal dysfunction*** (7 studies) OR 0.95 (CI 95%: 0.37, 2.46), p=0.92 I^2=0% ***Pneumonia*** (2 studies) OR 3.15 (CI 95%: 0.12, 82.16), p=0.49 I^2=N/A ***Excess sedation*** (4 studies) OR 1.96 (CI 95%: 0.53, 7.19), p=0.31 I^2=0%	
Barden, J., et al. (2009) Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD007355.pub2.	**Inclusion criteria** - full publications of double blind trial of a single dose single dose oral ketoprofen or dexketoprofen against placebo for the treatment of moderate to severe postoperative pain -age > 15years - at least 10 participants randomly allocated to each treatment group - studies using a visual scale (VAS) **Exclusion criteria** - posters or abstracts not followed up by full publication - review articles, case reports, and clinical observations - reports of trials concerned with pain other than postoperative pain (including experimental pain) - studies using healthy volunteers	**Intervention** Single dose oral ketoprofen or dexketoprofen **Control** Placebo	**[all analyses with fixed effects models]** **<u>Number of patients achieving at least 50% pain relief over 4 to 6 hours</u>** ***Ketoprofen 12.5 mg versus placebo*** (3 studies, 274 participants) RR 4.21 (95% CI: 2.68, 6.63), p < 0.00001 I^2=0% NNT 2.4 (95% CI: 1.9, 3.1) ***Ketoprofen 25 mg versus placebo*** (8 studies, 535 participants) RR 4.88 (95% CI: 3.48, 6.85), p < 0.00001 I^2=0% NNT 2.0 (95% CI: 1.8, 2.3)	**Level of evidence** 1a (1) **Author conclusion** "Ketoprofen at doses of 25 mg to 100 mg is an effective analgesic in moderate to severe acute postoperative pain with an NNT for at least 50% pain relief of 3.3 with a 50 mg dose. This is similar to that of commonly used NSAIDs such as ibuprofen (NNT 2.5 for 400mg dose) and diclofenac (NNT 2.7 at 50 mg dose). Duration of action is about 5 hours. Dexketoprofen is also effective with NNTs of 3.2 to 3.6 in the dose range 10 mg to 25 mg. Both

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	- studies where pain relief is assessed only by clinicians. nurses or carers (i.e., not patient-reported) - studies of less than 4 hours duration or studies that fail to present data over 4 to 6 hours post-dose - studies investigating pain due to uterine cramps alone **Search period** Cochrane CENTRAL (Issue 3, 2009). MEDLINE via Ovid (August 2009). EMBASE via Ovid (August 2009). Oxford Pain Relief Database **Number of included studies (n participants)** Ketoprofen: 14 (1488) Dexketoprofen: 7 (970)		*Subgroup-Analysis:* Dental surgery (6 studies, 452 participants) RR 5.07 (95% CI: 3.50, 7.36), p < 0.00001 I^2=0% NNT 2.0 (95% CI: 1.7, 2.3) Other surgery (2 studies, 83 participants) RR 3.96 (95% CI: 1.77, 8.86), p=0.00079 I^2=0% ***Ketoprofen 50 mg versus placebo*** (8 studies, 624 participants) RR 2.67 (95% CI: 2.06, 3.46), p=0.00 I^2=76% NNT 3.3 (95% CI: 2.7, 4.3) *Subgroup-Analysis:* Dental surgery (3 studies, 190 participants) RR 9.04 (95% CI: 4.23, 19.30), p < 0.00001 I^2=0% NNT 1.8 (95% CI: 1.5, 2.2) Other surgery (5 studies, 434 participants) RR 1.82 (95% CI: 1.38, 2.41), p=0.000024 I^2=59% NNT 5.3 (95% CI: 3.7, 9.9) ***Ketoprofen 100 mg versus placebo*** (5 studies, 321 participants) RR3.72 (95% CI: 2.62, 5.28), p < 0.00001 I^2=79% NNT 2.1 (95% CI: 1.7, 2.6) *Subgroup-Analysis:* Dental surgery (3 studies, 195 participants) RR 6.93 (95% CI: 3.85, 12.48), p < 0.00001 I^2=0%	drugs were well tolerated in single doses." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: - List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			NNT 1.6 (95% CI: 1.4, 2.0) Other surgery (2 studies, 126 participants) RR 1.94 (95% CI: 1.26, 3.00), p=0.0027 I^2=61% ***Dexketoprofen 10 mg/12.5 mg versus placebo*** (5 studies, 452 participants) RR 2.68 (95% CI: 1.95, 3.68), p < 0.00001 I^2=66% NNT 3.6 (95% CI: 2.8, 5.0) *Subgroup-Analysis:* Dental surgery (3 studies, 251 participants) RR 3.29 (95% CI: 2.05, 5.31), p < 0.00001 I^2=15% NNT 3.1 (95% CI: 2.3, 4.6) Other surgery (2 studies, 201 participants) RR 2.14 (95% CI: 1.40, 3.27), p=0.00041 I^2=83% NNT 4.4 (95% CI: 2.8, 9.7) ***Dexketoprofen 20 mg/25 mg versus placebo*** (6 studies, 523 participants) RR 3.27 (95% CI: 2.40, 4.46), p < 0.00001 I^2=66% NNT 3.2 (95% CI: 2.6, 4.1) *Subgroup-Analysis:* Dental surgery (4 studies, 322 participants) RR4.32 (95% CI: 2.72, 6.88), p < 0.00001 I^2=11% NNT 2.9 (95% CI: 2.3, 3.9) Other surgery (2 studies, 201 participants) RR 2.34 (95% CI: 1.56, 3.53), p=0.000045	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			I^2=81% NNT 3.7 (95% CI: 2.5, 7.0) **<u>Patients using rescue medication over 6 h/ 6 to 8h</u>** ***Ketoprofen 12.5 mg versus placebo*** (2 studies, 198 participants) RR 0.81 (95% CI: 0.74, 0.90), p=0.000095 I^2=0% ***Ketoprofen 25 mg versus placebo*** (6 studies, 402 participants) RR 0.60 (95% CI: 0.52, 0.69), p < 0.00001 I^2=80% ***Ketoprofen 50 mg versus placebo*** (7 studies, 554 participants) RR 0.65 (95% CI: 0.57, 0.73), p < 0.00001 I^2=97% ***Ketoprofen 100 mg versus placebo*** (4 studies, 259 participants) RR 0.54 (95% CI: 0.44, 0.67), p < 0.00001 I^2=0% ***Dexketoprofen 10 mg/12.5 mg versus placebo*** (5 studies, 446 participants) RR 0.69 (95% CI: 0.59, 0.80), p < 0.00001 I^2=88% ***Dexketoprofen 20 mg/25 mg versus placebo*** (7 studies, 597 participants) RR 0.69 (95% CI: 0.62, 0.78), p < 0.00001 I^2=91% **<u>Patients with any adverse event</u>** ***Ketoprofen 12.5 mg versus placebo*** (3 studies, 274 participants) RR 1.33 (95% CI: 0.48, 3.64), p=0.58 I^2=0%	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Ketoprofen 25 mg versus placebo (7 studies, 490 participants) RR 1.15 (95% CI: 0.68, 1.96), p=0.60 I^2=0% ***Ketoprofen 50 mg versus placebo*** (4 studies, 278 participants) RR 1.55 (95% CI: 0.91, 2.62), p=0.11 I^2=67% ***Ketoprofen 100 mg versus placebo*** (3 studies, 175 participants) RR 1.19 (95% CI: 0.65, 2.16), p=0.58 I^2=0% ***Dexketoprofen 10 mg/12.5 mg versus placebo*** (3 studies, 258 participants) RR 0.63 (95% CI: 0.32, 1.26), p=0.19 I^2=0% ***Dexketoprofen 20 mg/25 mg versus placebo*** (5 studies, 413 participants) RR 0.1.30 (95% CI: 0.82, 2.08), p=0.27 I^2=31%	
Derry, C. J., et al. (2009) Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD001548.pub2.	**Inclusion criteria** - RCTs - full publications - adults > 15y - patients with moderate to severe acute postoperative pain - at least 10 participants randomly allocated to each treatment group - single dose orally administered ibuprofen (any formulation) - Multiple dose studies were included if appropriate data from the first dose were available - cross-over studies were included if data from the first arm were presented separately **Exclusion criteria** - posters or abstracts not followed up by full publication	**Intervention:** single dose oral ibuprofen **Control:** placebo	**[all analyses with fixed-effect models]** **<u>Comparison 1: Ibuprofen 50mg vs. placebo</u>** **Participants with at least 50% pain relief over 4 to 6 hours** (3 studies, 316 participants) RR 3.15 (1.94, 5.12), p<0.00001 I^2=75% **Participants using rescue medication over 6 hours** (2 studies, 208 participants) RR 0.61 (0.44, 0.84), p=0.0023 I^2=89% **Participants with any adverse event** (2 studies, 225 participants) RR 1.31 (0.57, 3.00), p=0.52	**Level of evidence** 1a (1) **Author conclusion** "This updated review does not change the overall primary estimate of efficacy, the NNT for at least 50% pain relief over 4 to 6 hours compared with placebo, but does demonstrate differences in efficacy with different formulations, and provides additional estimates of efficacy in terms of use of rescue medication." ***Methodological quality***

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	- reports of trials concerned with pain other than postoperative pain (including experimental pain) - studies using healthy volunteers - studies where pain relief was assessed by clinicians, nurses or carers (i.e. not patient-reported) - studies of less than 4 hours' duration or which failed to present data over 4 to 6 hours post-dose - studies investigating participants with pain due to uterine cramps **Search period** The Cochrane Library (August 1996); The Specialised Register of the Cochrane Pain, Palliative and Supportive Care group (December 1996); MEDLINE (1966 to December 1996); EMBASE (1980 to January 1997); Biological Abstracts (Jan 1985 to December 1996; Cochrane CENTRAL (Issue 2, 2009); MEDLINE via Ovid (1996 to May 2009); EMBASE via Ovid (1996 to May 2009) **Number of included studies (n participants)** 66 (9186)		I^2=0.0% **Comparison 2: Ibuprofen 100mg vs. placebo** **Participants with at least 50% pain relief over 4 to 6 hours** (4 studies, 396 participants) RR 3.68 (2.29, 5.92), p<0.00001 I^2=77% **Participants using rescue medication over 6 hours** (3 studies, 296 participants) RR 0.69 (0.57, 0.84), p=0.00024 I^2=45% **Participants with any adverse event** (3 studies, 310 participants) RR 1.21 (0.71, 2.07), p=0.48 I^2=42% **<u>Comparison 3: Ibuprofen 200mg vs. placebo</u>** **Participants with at least 50% pain relief over 4 to 6 hours** (20 studies, 2690 participants) RR 4.62 (3.85, 5.56), p<0.00001 I^2=59% **Participants using rescue medication over 6 hours** (8 studies, 794 participants) RR 0.63 (0.57, 0.70), p<0.00001 I^2=89% **Participants with any adverse event** (14 studies, 1808 participants) RR 0.85 (0.71, 1.02), p=0.086 I^2=0.0% ***<u>Subgroup-analysis</u>***	A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Ibuprofen 200 mg vs. placebo 1. Type of surgery **Participants with at least 50% pain relief over 4 to 6 hours** Dental surgery (18 studies, 2470 participants) RR 4.48 (3.71, 5.41), p<0.00001 I^2=56% Other surgery (2 studies, 220 participants) RR 7.73 (3.24, 18.41), p<0.00001 I^2=90% **Participants using rescue medication over 6 hours** Dental surgery (7 studies, 694 participants) RR 0.67 (0.60, 0.73), p<0.00001 I^2=87% 2. Formulation **Participants with at least 50% pain relief over 4 to 6 hours, all surgery** Standard ibuprofen (1 study, 2103 participants) RR 6.11 (4.84, 7.73), p<0.00001 I^2=64% ibuprofen lysine, arginine, or soluble (7 studies, 828 participants) RR 5.73 (4.15, 7.90), p<0.00001 I^2=44% **Participants with at least 50% pain relief over 4 to 6 hours, dental surgery** Standard ibuprofen (15 studies, 1883 participants) RR 5.98 (4.69, 7.62), p<0.00001 I^2=60% ibuprofen lysine, arginine, or soluble (7 studies, 828 participants) RR 5.73 (4.15, 7.90), p<0.00001 I^2=44% **Participants using rescue medication over 6 hours,**	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			dental surgery Standard ibuprofen (4 studies, 345 participants) RR 0.74 (0.66, 0.84), p<0.00001 I^2=85% Ibuprofen lysine, arginine, or soluble (4 studies, 349 participants) RR 0.57 (0.48, 0.68), p<0.00001 I^2=84% 3. <u>study size</u> **Participants with at least 50% pain relief over 4 to 6 hours, dental surgery** 40 or more participants (11 studies, 1953 participants) RR 4.56 (3.71, 5.61), p<0.00001 I^2=75% Fewer than 40 participants (4 studies, 229 participants) RR 5.15 (2.41, 11.00), p= 0.000023 I^2=0.0% **<u>Comparison 4: Ibuprofen 400mg vs. placebo</u>** **Participants with at least 50% pain relief over 4 to 6 hours** (57 studies, 6475 participants) RR 3.94 (3.58, 4.35), p<0.00001 I^2=72% **Participants using rescue medication over 6 hours** (28 studies, 2983 participants) RR 0.54 (0.51, 0.57), p<0.00001 I^2=75% **Participants with any adverse event** (36 studies, 4865 participants) RR 0.92 (0.82, 1.04), p=0.18 I^2=0.0%	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Subgroup-analysis **Ibuprofen 400 mg vs. placebo** 1. Type of surgery **Participants with at least 50% pain relief over 4 to 6 hours** Dental surgery (45 studies, 5428 participants) RR 4.63 (4.13, 5.20), p<0.00001 I^2=65% Other surgery (12 studies, 1047 participants) RR 2.18 (1.81, 2.62), p<0.00001 I^2=65% **Participants using rescue medication over 6 hours** Dental surgery (22 studies, 2554 participants) RR 0.52 (0.48, 0.55), p<0.00001 I^2=72% 2. Formulation **Participants with at least 50% pain relief over 4 to 6 hours, all surgery** Standard ibuprofen (51 studies, 5604 participants) RR 4.64 (4.14, 5.18), p<0.00001 I^2=69% ibuprofen lysine, arginine, or soluble (12 studies, 1124 participants) RR 3.70 (3.00, 4.56), p<0.00001 I^2=85% **Participants with at least 50% pain relief over 4 to 6 hours, dental surgery** Standard ibuprofen (42 studies, 4772 participants) RR 5.17 (4.56, 5.87), p<0.00001 I^2=69% Ibuprofen lysine, arginine, or soluble (9 studies, 959 participants) RR 6.55 (4.85, 8.85), p<0.00001 I^2=24%	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Participants using rescue medication over 6 hours, dental surgery Standard ibuprofen (18 studies, 1857participants) RR 0.55 (0.51, 0.59), p<0.00001 I^2=49% Ibuprofen lysine, arginine, or soluble (6 studies, 449 participants) RR 0.42 (0.35, 0.50), p<0.00001 I^2=91% 3. <u>study size</u> **Participants with at least 50% pain relief over 4 to 6 hours, dental surgery** 40 or more participants (15 studies, 3086 participants) RR 4.44 (3.80, 5.19), p<0.00001 I^2=74% Fewer than 40 participants (14 studies, 856 participants) RR 4.06 (3.21, 5.14), p<0.00001 I^2=52% **<u>Comparison 5: Ibuprofen 600mg vs. placebo</u>** **Participants with at least 50% pain relief over 4 to 6 hours** (3 studies, 203 participants) RR 1.98 (1.52, 2.58), p<0.00001 I^2=75% **<u>Comparison 6: Ibuprofen 800mg vs. placebo</u>** **Participants with at least 50% pain relief over 4 to 6 hours** (1 study, 76 participants) RR 2.59 (1.72, 3,89), p<0.00001 I^2=N/A	
Derry CJ, et al. (2009) Single dose	**Inclusion criteria**	**Intervention:** Orally administered naproxen (4	**[all analyses with fixed-effect models]**	**Level of evidence** 1a

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
oral naproxen and naproxen sodium for acute postoperative pain in adults. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD004234. DOI: 10.1002/14651858.CD004234.pub3.	- double blind RCTs - cross-over studies (if data from the first arm were presented separately) - full publications - adults > 15y - patients with moderate to severe acute postoperative pain - participants with postpartum pain - Multiple dose studies were included if appropriate data from the first dose were available **Exclusion criteria** - posters or abstracts not followed up by full publication - reports of trials concerned with pain other than postoperative pain - studies using healthy volunteers - studies where pain relief was assessed by clinicians, nurses or carers (i.e. not patient-reported) - studies of less than 4 hours' duration or which failed to present data over 4 to 6 hours post-dose - Studies investigating participants with pain due to uterine cramps alone **Search period** Cochrane CENTRAL (to December 2002 for original search and January 2003 to October 2008 for the update); MEDLINE via Ovid (1966 to December 2002 for the original search and 2002 to October 2008 for the update); EMBASE via Ovid (1980 to December 2002 for the original search and 2002 to October 2008 for the update); Oxford Pain Database (Jadad 1996). **Number of included studies (n participants)** 15 (1509)	studies) or naproxen sodium (11 studies) **Control:** Placebo	**<u>Comparison 1: Naproxen 200 mg or naproxen sodium 220 mg vs. placebo</u>** **Participants with at least 50% pain relief over 4 to 6 hours** (2 studies, 202 participants) RR 2.87 (1.60, 5.15), p=0.00039 I^2=83% **<u>Comparison 2: Naproxen 400 mg or naproxen sodium 440 mg vs. placebo</u>** **Participants with at least 50% pain relief over 4 to 6 hours** (3 studies, 334 participants) RR 4.80 (2.75, 8.38), p<0.00001 I^2=75% **Participants with any adverse event** (2 studies, 257 participants) RR 1.32 (0.78, 2.24), p=0.30 I^2=0.0% **<u>Comparison 3: Naproxen 500 mg or naproxen sodium 550 mg vs. placebo</u>** **Participants with at least 50% pain relief over 4 to 6 hours** (9 studies, 783 participants) RR 3.39 (2.64, 4.36), p<0.00001 I^2=86% **Participants with any adverse event** (7 studies, 581 participants) RR 0.96 (0.74, 1.24), p=0.77 I^2=0.0% **Participants using rescue medication within 12 hours** (5 studies, 480 participants) RR 0.82 (0.74, 0.91), p=0.00024 I^2=21%	(1) **Author conclusion** "Naproxen and naproxen sodium at the most commonly used dose of 500 mg/550 mg is an effective analgesic, providing at least 50% pain relief to about half of treated patients with acute, moderate to severe, postoperative pain. The NNT of 2.7 for at least 50% pain relief, and nine hour average duration of action, compare favourably with other analgesics commonly used for postoperative pain. In single dose, it is associated with a low rate of adverse events, similar to that with placebo. Lower doses (400 mg/440 mg and 200 mg/220 mg) may provide equivalent levels of analgesia. This review suggests that there may be differences in efficacy following different types of surgery." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: - List of studies: + Study characteristics: + Critical appraisal: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Subgroup-analysis **(Naproxen 500 mg or naproxen sodium 550 mg vs. placebo)** 1. Type of surgery **Participants with at least 50% pain relief over 4 to 6 hours** Dental surgery (5 studies, 402 participants) RR 8.67 (5.22, 14.41), p<0.00001 I^2=22% Other surgery (4 studies, 382 participants) RR 1.76 (1.31, 2.35), p=0.00016 I^2=47% 2. Study size **Participants with at least 50% pain relief over 4 to 6 hours** ≥ 40 participants per group (5 studies, 513 participants) RR 3.67 (2.60, 5.19), p<0.00001 I^2=63% < 40 participants per group (4 studies, 271 participants) RR 3.05 (2.13, 4.36), p<0.00001 I^2=93% **Comparison 4: Naproxen or naproxen sodium (all doses) vs. placebo** **Participants with at least 50% pain relief over 4 to 6 hours** (14 studies, 1345 participants) RR 3.21 (2.59, 3.96), p<0.00001 I^2=80% **Participants with any adverse event** (10 studies, 991 participants) RR 1.06 (0.85, 1.33), p=0.59 I^2=22%	Conclusion: - Combining findings: + Publication bias: - Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Participants using rescue medication within 12 hours (6 studies, 602 participants) RR 0.77 (0.70, 0.85), p<0.00001 I^2=64% **Participants using rescue medication within 24 hours** (3 studies, 298 participants) RR 0.67 (0.60, 0.76), p<0.00001 I^2=65% *Subgroup-analysis* **Naproxen or naproxen sodium (all doses) vs. placebo** 1. Type of surgery **Participants with at least 50% pain relief over 4 to 6 hours** Dental surgery (8 studies, 781 participants) RR 7.96 (5.34, 11.87), p<0.00001 I^2=0.0% Other surgery (6 studies, 647 participants) RR 1.89 (1.48, 2.42), p<0.00001 I^2=59%	
Derry S and Moore RA (2012) Single dose oral aspirin for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD002067. DOI: 10.1002/14651858.CD002067.pub2.	**Inclusion criteria** - double-blind trials - single dose oral aspirin compared with placebo for the treatment - moderate to severe postoperative pain - age: > 15 years) - established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery - at least 10 participants randomly allocated to each treatment group. - multiple dose studies if appropriate data from the first dose were available and cross-over studies provided that data from the first arm were presented separately **Exclusion criteria**	**Intervention:** Single dose oral aspirin **Control:** Placebo	**[all analyses with fixed-effects models]** **Comparison 1** **Aspirin 500 mg versus placebo** **Participants with at least 50% pain relief** (2 studies, 213 participants) RR 1.28 (95% CI: 0.82, 2.00), p=0.27 I^2=0% **Comparison 2** **Aspirin 600 or 650 mg versus placebo** **participants with at least 50% pain relief** (60 studies, 4644 participants) RR 2.46 (95% CI: 2.22, 2.72), p < 0.00001	**Level of evidence** 1a (1) **Authors' conclusion** "This updated review confirms that aspirin is an effective analgesic for acute postoperative pain of moderate to severe intensity. The 600/650 mg dose has comparable efficacy to the same dose of paracetamol, and a 1200mg gives a better response. However, even in these single dose studies, adverse events such as gastric irritation and nausea were more common with aspirin than placebo at higher does."

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	- review articles, case reports, and clinical observations; - studies of experimental pain; - studies where pain relief is assessed only by clinicians, nurses, or careers (i.e. not patient-reported); - studies of less than four hours duration - studies that fail to present data over four to six hours post dose - studies investigating pain due to uterine cramps alone **Search period** the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*) (1998, Issue 1); MEDLINE (1966 to March 1998); EMBASE (1980 to January 1998); Oxford Pain Relief Database (1950 to 1994; Jadad 1996). updated searches using the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*) (issue 1, 2012) MEDLINE via Ovid (25 January 2012) EMBASE via Ovid (25 January 2012) **Number of included studies (n participants)** 68 (5743)		I^2=37% NNT 4.2 (95% CI: 3.9, 4.8) *Subgroup-Analysis* <u>Dental surgery</u> (43 studies, 3433 participants) RR 2.53 (95%CI: 2.23, 2.88), p < 0.00001 I^2=29% <u>Non-dental surgery</u> (17 studies, 1211 participants) RR 2.31 (95%CI: 1.93, 2.75), p < 0.00001 I^2=51% **Participants using rescue medication at 4 to 5h** (11 studies, 982 participants) RR 0.58 (95% CI: 0.50, 0.67), p < 0.00001 I^2=64% NNTp 4.9 (95% CI: 3.9, 6.8) **Participants using rescue medication at 6h** (20 studies, 1923 participants) RR 0.77 (95% CI: 0.73, 0.82), p < 0.00001 I^2=85% NNTp 5.1 (95% CI: 4.2, 6.5), **Participants using rescue medication at 12h** (4 studies, 291 participants) RR 0.95 (95% CI: 0.86, 1.05), p=0.31 I^2=68% **Any adverse event** (46 studies, 3633 participants) RR 1.20 (95% CI: 1.00, 1.44), p=0.051 I^2=0% **<u>Comparison 3</u>** **Aspirin 900 or 1000 mg versus placebo** **Participants with at least 50% pain relief** (6 studies, 618 participants)	**Methodological quality** A-priori design: + Two reviewers: + Literature search: + Status of publication: - List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: ? Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			RR 2.70 (95% CI: 2.00, 3.64), p < 0.00001 I^2=74%NNT 3.8 (95% CI: 3.0, 5.1) **Participants using rescue medication at 4 to 5 h** (5 studies, 501 participants) RR 0.64 (95% CI: 0.56, 0.74), p < 0.00001 I^2=92% NNTp 4.8 (95% CI: 3.4, 8.1) **Participants using rescue medication at 6 h** (2 studies, 233 participants) RR 0.82 (95% CI: 0.71, 0.95), p=0.0069 I^2=0% NNTp 6.4 (95% CI: 3.8, 21) **Any adverse event** (4 studies, 404 participants) RR 1.55 (95% CI: 1.05, 2.30), p=0.029 I^2=0% NNH 7.5 (95% CI: 4.8, 17) **<u>Comparison 4</u>** **Aspirin 1200 mg versus placebo** **participants with at least 50% pain relief** (3 studies, 249 participants) RR 2.86 (95% CI: 1.95, 4.20), p < 0.00001 I^2=68% NNT 2.7 (95% CI: 2.0, 3.8)	
Derry S. et al. (2013) Single dose oral dexibuprofen [S(+)-ibuprofen] for acute postoperative pain in adults. Cochrane Database of Systematic Reviews, Issue 10. Art. No.: CD007550. DOI: 10.1002/14651858.CD007550.pub3**.**	**Inclusion criteria** - double blind RCTs - multiple dose studies if appropriate data from the first dose were available - cross-over studies provided that data from the first phase were presented separately - adults > 15y - patients with postoperative pain of moderate to severe intensity following day surgery or in-patient surgery **Exclusion criteria** - review articles, case reports, and clinical	**Intervention:** Dexibuprofen administered as a single oral dose **Control:** Matched placebo or racemic ibuprofen	"Included studies involved 313 participants of whom 97 received dexibuprofen 200 mg, 50 received dexibuprofen 400 mg, 101 received racemic ibuprofen 400 mg, and 76 received placebo. Dexibuprofen at 200 mg and 400 mg single doses produced more participants with good pain relief than did placebo, and roughly the same proportion as with the same or double doses (in mg) of racemic ibuprofen. No analyses of the available data were sensible given the small numbers, and the high likelihood of false conclusions being arrived at by chance"	**Level of evidence** 1a (1) **Author conclusion** "There are no implications for practice because there is insufficient information at present to draw conclusions about efficacy or harm of dexibuprofen, or to make any sensible comparisons with racemic ibuprofen or other analgesics."

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	observations - studies of experimental pain - studies where pain relief is assessed only by clinicians, nurses or carers - studies of less than four hours duration or studies that fail to present data over four to six hours post-dose - studies investigating pain due to uterine cramps alone **Search period** The Cochrane Central Register of Controlled Trials CENTRAL) on The Cochrane Library, (Issue 2, 2009 for the original review and Issue 7, 2013 for this update); MEDLINE via Ovid (to May 2009 for the original review and from 2008 to 19 August 2013 for this update); EMBASE via Ovid (to May 2009 for the original review and from 2008 to 19 August 2013 for this update). **Number of included studies (n participants)** 2 (318)			***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: N/A Publication bias: N/A Conflict of interest: -
Derry S et al. (2013) Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010289. DOI: 10.1002/14651858.CD010289.pub2.	**Inclusion criteria** - double-blind trials of single dose oral ibuprofen plus oxycodone compared with placebo for the treatment - moderate to severe postoperative pain following day surgery or in-patient surgery - age >15years - at least 10 participants randomly allocated to each treatment group **Exclusion criteria** - Review articles, case reports, and clinical observations - Studies of experimental pain. - Studies where pain relief is assessed only by clinicians, nurses, or caregivers (i.e. not patient-reported). - Studies of less than four hours duration - Studies that fail to present data over four to six	**Intervention:** Single dose oral ibuprofen plus oxycodone **Control:** Placebo / ibuprofen alone / oxycodone alone	**[all analyses with fixed-effect models]** **<u>Comparison 1</u>** **Ibuprofen 400 mg + oxycodone 5 mg vs placebo** (3 studies, 603 participants) **participants with at least 50% pain relief at 6h** RR 3.63 (95% CI: 2.6, 5.07), p < 0.00001 I^2=63% NNT 2.3 (95% CI: 2.0, 2.8) **participants using rescue medication within 6h** RR 0.45 (95% CI: 0.39, 0.52), p < 0.00001 I^2=86% NNTp 2.4 (95% CI: 2.0, 2.90) **participants with any adverse event over 6h** RR 0.87 (95% CI: 0.66, 1.15), p=0.33 I^2=22%	**Level of evidence** 1a (1) **Authors' conclusion** "The combinations of ibuprofen 400 mg + oxycodone 5 mg is better than either drug alone. There were sufficient studies and participants, together with consistent large effects for pain, remedication, and adverse events, to consider that this is an important finding, as good analgesia was provided by relatively low doses of ibuprofen and oxycodone. In appropriate circumstances this combination might be useful."

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	hours postdose - Studies investigating pain due to uterine cramps alone **Search period** The Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, (Issue 4, 2013). MEDLINE (via OVID) (1950 to 21 May 2013). EMBASE (via OVID) (1974 to 21 May 2013). Oxford Pain Relief Database (Jadad 1996). www.clinicaltrials.gov **Number of included studies (n participants)** 3 (1202)		**Comparison 2** **Ibuprofen 400 mg + oxycodone 5 mg versus ibuprofen 400mg alone** (2 studies, 717 participants) **participants with at least 50% pain relief at 6h** RR 1.15 (95% CI: 1.00, 1.31), p=0.048 I^2=0% **participants using rescue medication within 6h** RR 0.83 (95% CI: 0.72, 0.97), p=0.016 I^2=58% NNTp 11 (95%CI: 6.1, 56) **participants with any adverse event over 6h** RR 1.07 (95% CI: 0.85, 1.34), p=0.57 I^2=46% **Comparison 3** **Ibuprofen 400 mg + oxycodone 5 mg versus oxycodone 5 mg alone** (2 studies, 471 participants) **participants with at least 50% pain relief at 6h** RR 2.46 (95% CI: 1.75, 3.46), p < 0.00001 I^2=91% NNT 2.9 (95% CI: 2.3, 4.0) **participants using rescue medication within 6h** RR 0.53 (95% CI: 0.46, 0.62), p < 0.00001 I^2=85% NNTp 2.6 (95%CI 2.1, 3.4) **participants with any adverse event over 6h** RR 0.78 (95% CI: 0.58, 1.04), p=0.093 I^2=54%	**Methodological quality** A-priori design: + Two reviewers: + Literature search: + Status of publication: ? List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: ? Conflict of interest: ?
Derry S. et al. (2015) Single dose oral diclofenac for acute postoperative pain in adults. Cochrane Database of Systematic Reviews, Issue 7. Art. No.: CD004768.	**Inclusion criteria** - double blind RCTs - multiple dose studies if appropriate data from the first dose were available - cross-over studies provided that data from the first phase were presented separately - adults > 15y - patients with postoperative pain of moderate to severe intensity following day surgery or in-patient	**Intervention:** Orally administered diclofenac sodium or potassium **Control:** Potassium with matched placebo administered as a single oral dose	**[all analyses with fixed-effect models]** **Comparison 1: Diclofenac fast-acting vs. placebo** **At least 50% of maximum pain relief over 6 hours** **- 25mg** (2 studies, 325 participants) RR 8.73 (3.18, 23.97), p=0.000026	**Level of evidence** 1a (1) **Author conclusion** "Diclofenac potassium provides good pain relief at 25 mg, 50 mg, and 100 mg doses. Choice of dose may depend on the situation. Diclofenac

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
DOI: 10.1002/14651858.CD004768.pub3.	surgery **Exclusion criteria** - review articles, case reports, and clinical observations - studies of experimental pain - studies where pain relief is assessed only by clinicians, nurses or carers - studies of less than four hours duration or studies that fail to present data over four to six hours post-dose - studies investigating pain due to uterine cramps alone **Search period** Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library Issue 4, 2008 for the earlier version, and via Cochrane Register of Studies Online (CRSO) to 9 March 2015 for this update. MEDLINE (via Ovid) from inception to December 2008 for the earlier versions, and 2008 to 9 March 2015 for this update. EMBASE (via Ovid) from inception to December 2008 for the earlier versions, and 2008 to 9 March 2015 for this update **Number of included studies (n participants)** 18 (3714)		I^2=0.0% **- 50 mg** (4 studies, 486 participants) RR 2.90 (2.23, 3.76), p<0.00001 I^2=79% - **100 mg** (2 studies, 168 participants) RR 18.09 (3.60, 90.75), p=0.00043 I^2=0.0% **Remedication within 6 or 8 hours** **- 50 mg** (4 studies, 486 participants) RR 0.46 (0.38, 0.56), p<0.00001 I^2=0.0% - **100 mg** (2 studies, 168 participants) RR 0.61 (0.48, 0.77), p=000047 I^2=65% **Adverse events within 24 hours** (5 studies, 636 participants) RR 1.04 (0.60, 1.83), p=0.88 I^2=0.0% **<u>Comparison 2: Diclofenac potassium vs. placebo</u>** **At least 50% of maximum pain relief over 6 hours** **- 25mg** (4 studies, 502 participants) RR 3.88 (2.84, 5.32), p<0.00001 I^2=63% **- 50 mg** (7 studies, 757 participants) RR 3.68 (2.90, 4.68), p<0.00001 I^2=39%	sodium has limited efficacy and should probably not be used in acute pain." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			- 100 mg (6 studies, 589 participants) RR 5.05 (3.74, 6.82), p<0.00001 I^2=58% **Remedication within 6 or 8 hours** **- 25mg** (4 studies, 502 participants) RR 0.72 (0.63, 0.82), p<0.00001 I^2=81% **- 50 mg** (7 studies, 757 participants) RR 0.52 (0.45, 0.60), p<0.00001 I^2=0.0% **- 100 mg** (6 studies, 589 participants) RR 0.45 (0.38, 0.54), p<0.00001 I^2=82% **Adverse events within 24 hours** (7 studies, 1090 participants) RR 1.03 (0.66, 1.62), p=0.88 I^2=0.0% **<u>Comparison 3: Diclofenac sodium vs. placebo</u>** **At least 50% of maximum pain relief over 6 hours** **- 50 mg** (3 studies, 313 participants) RR 2.04 (1.26, 3.31), p=0.0038 I^2=36% **- 100 mg** (1 study, 169 participants) RR 3.14 (1.07, 9.22), p=0.038 I^2=N/A	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Remedication within 6 or 8 hours **- 50 mg** (2 studies, 284 participants) RR 0.82 (0.69, 0.98), p=0.028 I^2=15%	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
Fischer, H.B. and C.J. Simanski. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement. Anaesthesia, 2005. 60(12): p. 1189-202.	**Inclusion criteria** - RCTs, double-blinded - pre-operative, intra-operative or postoperative analgesic regimens or anaesthetic or operative interventions - study population underwent total hip replacement - use of a visual analogue scale (VAS), other linear analogue scales or a verbal rating scale to assess pain **Exclusion criteria** - Non-English language reports **Search period** MEDLINE (1966 to May 2004) EMBASE (1988 to February 2004) **Number of included studies (n participants)** 8 studies comparing NSAIDs with placebo (ibuprofen: 2 studies, ketorolac: 2 studies, dexketoprofen: 1 study, diclofenac: 1 study, indomethacin: 1 study, piroxicam: 1 study) [1 COX-2-inhibitors-study and 2 paracetamol-studies]	**Intervention** NSAIDs **Control** Placebo	**NSAIDS vs. Placebo** **<u>Pain scores (VAS)</u>** • ***0-8h after surgery*** (3 studies, 163 participants) WMD (random) -9.48 (95% CI: -18.06, -0.90), p=0.03 • ***8-16h after surgery*** (2 studies, 90 participants) WMD (fixed) -4.12 (95% CI: -7.56, -0.68), p=0.02 • ***16-32h after surgery*** (2 studies, 90 participants) WMD (fixed) -8.46 (95% CI: -14.88, -2.05), p=0.010 ***<u>Postoperative morphine consumption</u>*** (3 studies, 126 participants) WMD (random) -8.34 (95% CI: -13.92, -2.75), p=0.003 [Cox2 inhibitors: "One COX-2 inhibitor study was included, which assessed valdecoxib 20 mg vs. 40 mg vs. placebo, each administered before and after surgery. The study demonstrated that valdecoxib was superior to placebo for decreasing pain scores and supplementary analgesic consumption, but that there was no significant difference between the two different valdecoxib doses." Paracetamol: "Two paracetamol studies were included. One demonstrated that propacetamol (an intravenous form of paracetamol) was superior to placebo for decreasing supplementary analgesic consumption, while the pain scores were not significantly different between the groups. The second study showed that paracetamol plus codeine was superior to placebo for decreasing pain scores, decreasing supplementary analgesic use and increasing the time to first analgesic request."]	**Level of evidence** 1a (1) **Author conclusion** "Non-steroidal anti-inflammatory drugs or selective COX-2 inhibitors are recommended because they decrease pain and supplementary analgesic consumption" ***Methodological quality*** A-priori design: + Two reviewers: ? Literature search: + Status of publication: - List of studies: + Study characteristics: - Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: ?
Gobble, R.M., et al.	**Inclusion criteria**	**Intervention**	**[all analyses with random-effects models]**	**Level of evidence**

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. Plast Reconstr Surg, 2014. 133(3): p. 741-55.	- RCTs - double-blinded studies - surgical patients - reported perioperative adverse effects, including bleeding **Exclusion criteria** - healthy volunteers no surgical intervention - bone cancer patients **Search period** Medline EMBASE Cochrane Library databases **Number of included studies (n participants)** 27 (2314)	Keterolac Dose range from 7.5 to 60mg Intraoperatively and postoperatively 24h to 4 days postoperatively 16 studies using dose > 30mg 11 studies using dose ≤ 30mg **Control** Placebo	**<u>Postoperative Bleeding</u>** (Intervention vs control) (27 studies) OR 1.12 (95% CI: 0.61, 2.06), p= 0.72 I^2=0% *<u>Subgroup-Analyses</u>* Keterolac dose ≤ 30mg OR 0.76 (95% CI: 0.17, 3.34), p=0.71 I^2=27% Keterolac dose > 30mg OR 1.24 (95% CI: 0.61, 2.06), p=0.55 I^2=0% **<u>Adverse Events</u>** **(including nausea, vomiting, respiratory depression and bleeding; i**ntervention vs control) (19 studies) OR 0.64 (95% CI: 0.41, 1.01), p=0.06 I^2=64% *<u>Subgroup-Analyses</u>* Keterolac dose ≤ 30mg OR 0.49 (95% CI: 0.27, 0.91), p=0.02 I^2=46% Keterolac dose > 30mg OR 0.75 (95% CI: 0.40, 1.40), p=0.37 I^2=69%	1a (1) **Author conclusion** "This is the first meta-analysis of randomized controlled trials examining whether there is increased postoperative bleeding with ketorolac. Postoperative bleeding was not significantly increased with ketorolac compared with controls, and adverse effects were not statistically different between the groups." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: - Status of publication: - List of studies: - Study characteristics: + Critical appraisal: ? Conclusion: + Combining findings: + Publication bias: + Conflict of interest: -
Mason, L., et al., Single dose oral indometacin for the treatment of acute	**Inclusion criteria** - randomised, double blind, placebo-controlled clinical trials using a single oral dose of indometacin in adults with acute postoperative pain	**Intervention:** Single dose oral Indometacin **Control:**	Insufficient data to conduct a meta-analysis, and it was not possible to assess the mean time to remedication, or the adverse effects of single dose oral indometacin	**Level of evidence** 1a **Authors conclusion**

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
postoperative pain. Cochrane Database Syst Rev, 2004(4): p. CD004308.	- study contained extractable, patient- reported, single dose pain intensity or pain relief information - study provided pain intensity or pain relief data, or both, recorded over four to six hours using standard pain assessment scales - study recruited a minimum of ten participants randomly assigned to a treatment or placebo group **Exclusion criteria** - no placebo arm in the study - Participants not randomised to treatment/placebo arms - rectal administration of indomethacin - non- standard pain scales - Baseline pain not assessed - no single dose data - no extractable pain data **Search period** Cochrane CENTRAL (Issue 2, 2004 for original review and Issue 4, 2007 for the update) MEDLINE and Pre-MEDLINE (from 1966 to December 2002 for the original review, and MEDLINE, January 2002 to December 2007 for the update) EMBASE (1980 to December 2002 for the original review and January 2002 to December 2007 for the update) Oxford Pain Relief database (handsearch records for the years 1954 to 1995) **Number of included studies (n participants)** 1 (94)	Placebo	**Indometacin 50 mg versus placebo** Patients with at least 50% pain relief at 6 hours: 20 out of 29 (69%) for indometacin vs 16 out of 30 (53%) for placebo therefore no significant difference between treatment and placebo (Relative Risk 1.3, 95% CI 0.85 to 1.96)	„The update of this review has not identified any further information to provide evidence for or against the use of Single dose oral indometacin for the treatment of acute postoperative pain. Until more information becomes available, it is not possible to make recommendations about the use of single dose oral indometacin for the relief of postoperative pain.“ ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: NA Conflict of interest: -
Mason, L., et al., Single dose oral naproxen and naproxen sodium for acute postoperative pain. Cochrane Database Syst Rev,	**Inclusion criteria** - randomised, double blind clinical trials - minimum of 10 patients assigned to each treatment group received either naproxen/naproxen sodium or a matched placebo - studies had to provide extractable, single dose data for the first treatment given, with pain intensity	**Intervention:** single dose of naproxen or naproxen sodium **Control:** placebo	**[all analyses with fixed-effect models]** **Patients with at least 50% pain relief** ***Naproxen sodium 550 mg versus placebo*** (6 studies, 500 patients)	**Level of evidence** 1a (1) **Authors conclusion** “Naproxen sodium 550 mg (equivalent to naproxen 500 mg) and

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
2004(4): p. CD004234.	recorded at 4 to 6 hours following initial administration of study treatment, using standard pain measurement scales - Age 12 or older with moderate to severe pain following any surgical procedure, carried out in either a day surgery or inpatient setting - all languages, publication types/status **Exclusion criteria** Abstracts, review articles, case reports and clinical observations **Search period** The Cochrane Library (Issue 4 2002) MEDLINE and PreMEDLINE (1966 - 2002) EMBASE (1980 - 2002) PubMed (1966 - 2002) **Number of included studies (n participants)** 10 (996) 6 (500) for quantitative analysis		*percentage of patients with at least 50% pain relief* Mean response rate (MRR) for naproxen sodium was 50% (127 patients out of 252), ranging from 30% to 72% in individual trials vs MRR for placebo:12% (30 patients out of 248), ranging from 6% to 19%. RR 4.18 (95% CI 2.93 to 5.97) NNT was 2.6 (95% CI 2.2 to 3.2). I^2=9,8% ***Naproxen 400 mg / naproxen sodium 440 mg versus placebo*** (3 studies, 334 patients) MRR for naproxen 400 mg and naproxen sodium 440 mg was 49% (103 out of 210 patients), ranging from 46% to 53% in individual trials MRR for placebo was 11% (14 out of 124 patients), ranging from 5% to 23% RR 4.8 (95% CI 2.75 to 8.4) NNT 2.7 (2.2 to 3.5) I^2=74,6% ***Naproxen 200 mg / naproxen sodium 220 mg versus placebo*** (2 studies, 202 patients) MRR for naproxen 200 mg and naproxen sodium 220 mg was 45% (54 out of 120 patients), ranging from 30% to 53% MRR for placebo was 16% (13 out of 82 patients), ranging from 10% to 23% RR 2.9 (95% CI 1.6 to 5.2) NNT was 3.4 (95% CI 2.4 to 5.8) P=0.00004, I^2=83.0% **<u>Adverse events</u>** ***Naproxen sodium 550mg***	naproxen sodium 440 mg (equivalent to naproxen 400 mg) are effective analgesics in adults with acute (moderate to severe) postoperative pain. The NNT for naproxen sodium 550 mg compares favourably with other analgesics for postoperative pain relief. A low incidence of adverse events was found but these were poorly reported." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: - Publication bias: - Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(5 studies, 392 patients) For naproxen 550mg 47/197 (25%) reported at least 1 adverse event vs placebo 52/195 (27%) RR 0.89 (0.63, 1.25) I^2=5.3% ***Naproxen sodium 400/440mg*** (2 studies, 257 patients patients) RR 1.32 (0.78, 2.24) I^2=0.2% ***Naproxen sodium 200/220mg*** (1 study, 122 patients) RR 2.21 (0.90, 5.43)	
Moore RA. et al. (2000) Single dose oral piroxicam for acute postoperative pain. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD002762. DOI: 10.1002/14651858.CD002762.	**Inclusion criteria** - double-blind RCTs - adults - full journal publication - trials of piroxicam over four to six hours in postoperative pain - Multiple dose studies were included if they provided single-dose efficacy and adverse effect data - Study drugs administered by injection or orally postoperatively to adult participants with moderate or severe pain **Exclusion criteria** - pre and perioperative dosing - Other formulations of piroxicam with different pharmacokinetic properties **Search period** Cochrane CENTRAL (Issue 3, 1999 for original review and Issue 4, 2007 for the update); MEDLINE from 1966 to October 1999 for the original review, and MEDLINE from January 1999 to December 2007 for the update; EMBASE from 1980 to October 1999 for the original review and January 1999 to December 2007 for the update; the Oxford Pain Relief database (handsearch records for the years 1954 to 1995 (Jadad 1996a).	**Intervention:** Oral piroxicam **Control:** Placebo	**[all analyses with fixed-effect models]** **<u>Comparison 1: Piroxicam 20 mg vs. placebo</u>** **Patients with at least 50% pain relief** (3 studies, 280 participants) RR 2.45 (1.82, 3.30), p<0.00001 I^2=0.0% **<u>Comparison 2: Piroxicam 40 mg vs. placebo</u>** **Patients with at least 50% pain relief** (1 study, 30 participants) RR 3.0 (1.25, 7.21), p=0.014 I^2=N/A	**Level of evidence** 1a (1) **Author conclusion** "There remains insufficient high quality information available on which to make purchasing or policy decisions. However, the NNTs suggest that single doses of piroxicam (20 mg and 40 mg) are reasonably effective for treating moderate to severe postoperative pain, and compare favourably with opioid analgesics such as dextropropoxyphene and tramadol, and other NSAIDs. Few adverse effects were reported and piroxicam appears to be fairly well tolerated in this clinical context." ***Methodological quality*** A-priori design: + Two reviewers: - Literature search: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	Number of included studies (n participants) 3 (548)			Status of publication: - List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: -
Moll, R., et al. (2011) Single dose oral mefenamic acid for acute postoperative pain in adults. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD007553.pub2.	**Inclusion criteria** - Randomised, double blind trials of single dose oral mefenamic acid - Treatment of moderate to severe pain in adults - At least 10 participants in each treatment group - Patients >15 years with established postoperative pain - Multiple dose studies if data from first dose available Cross-over studies if data from first arm presented separately - All languages **Exclusion criteria** - Review articles, case reports, and clinical observations - Studies of experimental pain - Pain relief only assessed by clinician, nurse of carers (i.e, not patient-reported) - Studies of less than 4h duration or failure to present data over 4-6h post-dose **Search period** Cochrane CENTRAL (December 2010); MEDLINE via Ovid (December 2010); EMBASE via Ovid (December 2010); Oxford Pain Relief Database (Jadad 1996a)	**Intervention:** Single dose oral mefenamic acid **Control:** Placebo	**[all analyses with fixed-effect models]** **Mefenamic acid 500mg versus placebo** ***At least 50% pain relief over 4-6h*** (2 studies. 256 participants) Mean proportion (%): 48/22 RR 2.14 (95% CI: 1.48, 3.08) NNT 4.0 (95% CI: 2.7, 7.1) p= 0.90, I^2=0% ***Use of rescue medication over 6h*** (2 studies, 256 participants) Mean proportion (%): 47/62 RR 0.75 (95% CI: 0.61, 0.93) NNT 6.5 (95% CI: 3.6, 29) **Adverse effects** (2 studies, 105 participants) Mefenamic acid (250mg or 500mg): 7/52 (13%) Placebo: 3:53 (5.7%) Too few data for statistical analysis	**Level of evidence** 1a (1) **Authors' conclusion** "Mefenamic acid 500 mg is likely to be an effective analgesic, but there is insufficient evidence from this limited data set to give a reliable estimate of the size of its effect. No serious adverse events were reported in any of the studies, though numbers were too small to exclude rare but serious harm." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	Number of included studies (n participants) 4 studies (842)			List of studies: + Study characteristics: + Critical appraisal: ? Conclusion: + Combining findings: ? Publication bias: + Conflict of interest: -
Moore OA, McIntyre M, Moore RA, Derry S, McQuay HJ. (2010) Single dose oral tenoxicam for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD007591. DOI: 10.1002/14651858.CD007591.pub2.	**Inclusion criteria** - RCT's - double-blinded trials - at least 10 participants randomly allocated to each treatment group - adults >15 years with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery **Exclusion criteria** - review articles, case reports and clinical observations - studies of experimental pain - studies where pain relief is assessed only y clinicians, nurse or carers - studies of less than four hours duration or studies that fail to present data over 4-6h post-dose **Search period** • Cochrane CENTRAL (Issue 1, 2009), • MEDLINE via Ovid (March 2009), • EMBASE via Ovid (March 2009), • Oxford Pain Relief Database (Jadad 1996a) **Number of included studies (n participants)** No studies matching the inclusion criteria	**Intervention:** Oral tenoxicam for relief of acute postoperative pain in adults **Control:** Matched placebo	***No results available***	**Level of evidence** 1a (1) **Authors' conclusion** "In the absence of evidence of efficacy for oral tenoxicam in acute postoperative pain, its use in this indication is not justified. Because trials clearly demonstrating analgesic efficacy in the most basic of acute pain studies is lacking, use in other indications should be evaluated carefully." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: - List of studies: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
				Study characteristics: + Critical appraisal: NA Conclusion: + Combining findings: NA
Moore, R.A. et al. Single dose oral meloxicam for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, DOI: 10.1002/14651858.CD007552.pub2.	**Inclusion criteria** - double blind trials of single dose oral meloxicam - compared with placebo - for treatment of moderate to severe postoperative pain in adults - groups at least 10 participants randomly allocated to each treatment group - multiple dose studies included if appropriate data from the first dose available - cross over studies included if data from the first arm were presented separately - all languages - adult participants (<15 yrs) - with established postoperative pain of moderate to severe intensity - following day surgery or in-patient surgery **Exclusion criteria** - review articles - case reports - clinical observations - studies of experimental pain - studies where pain relief is only assessed by clinicians, nurse or carers - studies of less than 4 hours of duration - studies that fail to present data over 4 to 6 hours post dose **Search period** Cochrane Central (Issue 2, 2009) MEDLINE (June 2009) EMBASE via Ovid (June 2009) Oxford Pain Relief Database (Jadad 1996a)	**Intervention:** Meloxicam administered as a single oral dose **Control:** Matched placebo administered as a single oral dose	***No results available***	**Level of evidence** 1a (1) **Authors' conclusion** "In the absence of evidence of efficacy for oral meloxicam in acute postoperative pain, its use in this indication is not justified. Because trials clearly demonstrating analgesic efficacy in the most basic of acute pain studies is lacking, use in other indications should be evaluated carefully." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: - Study characteristics: + Critical appraisal: ? Conclusion: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	Number of included studies (n participants) No studies were included			Combining findings: - Publication bias: NA Conflict of interest: -
Moore, R.A., et al. Single dose oral indometacin for the treatment of acute postoperative pain. Cochrane Database of Systematic Reviews 2004, DOI: 10.1002/14651858.CD004308.pub2.	**Inclusion criteria** - randomised double blind trial - participants received either oral indometacin or matched placebo - contained extractable, patient- reported, single dose pain intensity or pain relief information - provided pain intensity or pain relief data - recorded over four to six hours using standard pain assessment scales - minimum of 10 participants randomly assigned to treatment or placebo group - abstracts, review articles, case reports and clinical observations were considered acceptable only if they contained evaluable data - all languages **Exclusion criteria** - Studies without baseline assessment - No placebo arm - Other than oral administration of indometacin **Search period** - Cochrane CENTRAL (Issue 4, 2007 for update) - MEDLINE and Pre – MEDLINE (January 2002 to December 2007 for the update) - EMBASE (January 2002 to December 2007 for update) - Oxford Pain Relief database (hand search records for the year 1945 to 1995, Jadad 1996) **Number of included studies (n participants)** 1 study (94 participants) was included	**Intervention:** Postoperative, oral administration of single dose of indometacin **Control:** Postoperative, oral administration of matched placebo	**Indometacin 50 mg versus placebo** at least 50% pain relief at six hours (%): 69/53 RR: 1.3 (95% CI: 0.85 to 1.96)	**Level of evidence** 1a (1) **Authors' conclusion** "The update of this review has not identified any further information to provide evidence for or against the use of Single dose oral indometacin for the treatment of acute postoperative pain. Until more information becomes available, it is not possible to make recommendations about the use of single dose oral indometacin for the relief of postoperative pain." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: - List of studies: + Study characteristics: + Critical appraisal: ? Conclusion: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
				Combining findings: + Publication bias: - Conflict of interest: -
Smith, L.A., et al., Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis. Br J Anaesth, 2000. 84(1): p. 48-58.	**Inclusion criteria** - RCTs of ketorolac (or pethidine) versus placebo in postoperative pain - full journal publications - single dose treatment groups - double-blind design - baseline postoperative pain of moderate to severe intensity or visual analogue pain intensity of at least 30mm - patients >15years - standard pain scale **Exclusion criteria** - studies of epidural, intrathecal or i.v. routes using PCA **Search period** MEDLINE (1966 to July 1998) EMBASE (1980-1998) The Cochrane Library (1998, issue 2) The Oxford pain relief database (1950-1994) **Number of included studies (n participants)** Keterolac: 14 studies	**Intervention** Keterolac, single dose (i.m., i.v., or oral) **Control** Placebo	**[analyses with fixed effects models]** **Proportion of patients who achieved at least 50% pain relief of max. possible total pain relief (maxTOTPAR)** **Keterolac i.m. versus Placebo** • ***Dose 10mg*** (2 studies) RB 1.6 (95% CI: 1.1, 2.4) NNT 5.7 (95% CI: 3.0, 5.3) • ***Dose 30mg*** (5 studies) RB 2.3 (95% CI: 1.8, 3.1) NNT 3.4 (95% CI: 2.5, 4.9) • ***Dose 60mg*** (1 study) RB 40 (95% CI: 2.5, 626) NNT 1.8 (95% CI: 1.5, 2.3) **Keterolac oral versus Placebo** • ***Dose 5mg*** (1 study) RB 1.2 (95% CI:) 0.8, 1.8) • ***Dose 10mg*** (8 studies) RB 4.3 (95% CI: 3.2, 5.8) NNT 2.6 (95% CI: 2.3, 3.1) • **D*ose 20mg*** (1 study) RB 39 (95% CI:) 2.5, 632) NNT 1.8 (95% CI: 1.4, 2.5) **Keterolac i.v. 10 mg versus Placebo** (1 study) RB 6.5 (95% CI: 2.6, 27) NNT 3.4 (95% CI: 2.1, 7.9)	**Level of evidence** 1a (1) **Authors' conclusion** "The clinical conclusion is that opioids carry a small but finite risk of serious adverse effects such as respiratory depression, and a greater risk of minor adverse effects than single-dose injected or oral NSAID […]. Our information suggests that in patients who can swallow, and in whom NSAID are not contra-indicated, oral NSAID are as effective as injected NSAID, and provide analgesia equivalent to that from conventional doses of injected opioid." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: - List of studies: ? Study characteristics: + Critical appraisal: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			<u>Adverse effects</u> • **Keterolac 10mg** ***Any adverse effects*** (2 studies) RR 2.1 (95% CI: 0.9, 5.0) ***Drowsiness/somnolence*** (1 study) RR 1.3 (95% CI: 0.4, 3.9) ***Nausea/vomiting*** (2 studies) RR 3.7 (95% CI: 0.8, 17) • **Keterolac 30mg** ***Any adverse effects*** (3 studies) RR 1.2 (95% CI: 0.6, 2.2) ***Drowsiness/somnolence*** (2 studies) RR 0.9 (95% CI: 0.4, 2.1) ***Dizziness/light-headedness*** (1 study) RR 0.1 (95% CI: 0.01, 1.6) ***Nausea/vomiting*** (3 studies) RR 1.3 (95% CI: 0.7, 2.4)	Conclusion: ? Combining findings: ? Publication bias: - Conflict of interest: ?

+: low risk; -: high risk; ?: unclear risk; N/A: not applicable; CI: confidence interval; NR: not reported; NS: not significant; NNT: Number needed to treat; RR: relative risk; RB: Relative Benefit; OR: odds ratio; MD mean difference; WMD: weighted mean difference; SMD: standardized mean difference; I^2 und Q: Heterogenitätsmaße

Tab. 2 Systemische Pharmakologie: Paracetamol, Metamizol, NSAR, COX-2-Inhibitoren: *systematische Reviews zu Paracetamol (Fragen #1 bis #5)*

Review / reference	**Inclusion, exclusion criteria, search period, number of included studies**	**Intervention group(s) (IG)/ control group (CG)**	**Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)**	**Level of evidence: CEbM 2009 (CEbM 2011)** **critical appraisal/ conclusion**
Apfel, C.C., et al. (2013) Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis. Pain, 2013. 154(5): p. 677-89.	**Inclusion criteria** - RCTs (human and clinical) - placebo controlled - general anesthesia - report PON (postoperative nausea), PONV or postoperative vomiting outcomes **Exclusion criteria** - not randomized for i.v. acetaminophen - no inactive control - no surgery under general anesthesia - PONV data missing, not obtainable **Search period** Medline (March 4, 2012) Cochrane database Contacting Cadence Pharmaceuticals, Inc **Number of included studies (n participants)** 30 (2364)	**Intervention:** Intravenous acetaminophen **Control:** Placebo	**[all analyses with random-effects models]** **<u>Intravenous acetaminophen versus placebo</u>** **Nausea** RR 0.73 (95% CI: 0.60, 0.88), p=0.001 I^2 =38% NNT 12.3 (95% CI: 7.6, 32.3) **Vomiting** RR 0.63 (95% CI: 0.45, 0.88), p=0.008 I^2 =47% NNT 14.2 (95% CI: 8.3, 50.8) ***Subgroup-Analysis*** **Nausea** *Industry-sponsored trials* RR 1.12 (95% CI: 0.85, 1.48), p=0.42 *Investigator-initiated trials* RR 0.63 (95% CI: 0.54, 0.75), p < 0.001 *Before surgery* RR 0.54 (95% CI: 0.40, 0.74), p < 0.0001 I^2 =0% *Intraoperatively* RR 0.70 (95% CI: 0.57, 0.86), p=0.0008 I^2 =0% Immediately after surgery RR 0.31 (95% CI: 0.11, 0.89), p=0.03 I^2 =33% *Prophylactic single dose* RR 0.50 (95% CI: 0.38, 0.66), p < 0.00001 I^2 =0% *Prophylactic repeated doses*	**Level of evidence** 1a (1) **Author conclusion** "In summary, this systematic review and meta-analysis demonstrated that prophylactic i.v. acetaminophen reduces postoperative nausea and vomiting with an effect size that compares well with data known from other antiemetics." ***Methodological quality*** A-priori design: + Two reviewers: ? Literature search: + Status of publication: - List of studies: - Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: + Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			RR 0.72 (95% CI: 0.58, 0.89), p=0.002 I^2 =3% **Vomiting** *Industry-sponsored trials* RR 1.41 (95% CI: 1.02, 1.96), p=0.04 *Investigator-initiated trials* RR 0.42 (95% CI: 0.31, 0.56), p < 0.001*Before surgery* RR 0.29 (95% CI: 0.14, 0.57) heterogeneity p=0.87 *During or immediately after surgery* RR 0.46 (95% CI: 0.33, 0.63) heterogeneity p=0.84 *Prophylactic single dose* RR 0.31 (95% CI: 0.19, 0.51) heterogeneity p=0.96 *Prophylactic repeated doses* RR 0.49 (95% CI: 0.35, 0.70) heterogeneity p=0.77	
Barden, J., et al. (2004), Single dose oral paracetamol (acetaminophen) for postoperative pain. Cochrane Database Syst Rev, 2004(1): p. CD004602.	**Inclusion criteria** - RCTs, double-blind,of paracetamol for acute postoperative pain in adults **Exclusion criteria** Not stated **Search period** - the Cochrane Library (Issue 3, 2002) - the trials register of the Cochrane Pain, Palliative and Supportive Care group (November 2002) - MEDLINE (1966 to May 1996) - PubMed (1996 to August 2001) - EMBASE (1980 to 1996) - the Oxford Pain Relief Database (1950 to 1994) - reference lists of articles in order to update an existing version of the review. **Number of included studies (n participants)** 47 (4186)	**Intervention** Single oral dose paracetamol (325 mg in 1 trial 500 mg in 6 trials 600/650 mg in 19 trials 975/1000 mg in 23 trials 1500 mg in 1 trial) **Control** Placebo	**Comparison 1** **Paracetamol 325 mg versus placebo** NNT for at least 50% pain relief over 4-6 hours (1 study, 100 patients): 3.8 (95% CI: 2.2, 13.3) **Comparison 2** **Paracetamol 500 mg versus placebo** (6 study, 561 patients) NNT for at least 50% pain relief over 4-6 hours: 3.5 (95% CI: 2.7, 4.8) Efficacy RR 1.91 (95% CI: 1.57, 2.32) **Comparison 3** **Paracetamol 600/650 mg versus placebo** (19 study, 1886 patients) NNT for at least 50% pain relief over 4-6 hours: 4.6 (95% CI: 3.9, 5.5) Efficacy RR 2.42 (95% CI: 2.05, 2.84) *Subgroup-Analysis* <u>Postoperative pain following dental surgery</u> (10 studies, 1265 patients) NNT for at least 50% pain relief over 4-6 hours: 4.2 (95%	**Level of evidence** 1a (1) **Author conclusion** "Single doses of paracetamol are effective analgesics for acute postoperative pain and give rise to few adverse effects." ***Methodological quality*** A-priori design: ? Two reviewers: + Literature search: + Status of publication: - List of studies: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			CI: 3.6, 5.2) Efficacy RR 2.93 (95% CI: 2.34, 3.66) <u>Postoperative pain following other surgery</u> (9 studies, 621 patients) NNT for at least 50% pain relief over 4-6 hours: 5.5 (95% CI: 33.9, 9.1) Efficacy RR 1.86 (95% CI: 1.46, 2.36) **Comparison 4** **Paracetamol 975/1000 mg versus placebo** (23 study, 2759 patients) NNT for at least 50% pain relief over 4-6 hours: 3.8 (95% CI: 3.4, 4.4) Efficacy RR 2.47 (95% CI: 2.18, 2.81) *Subgroup-Analysis* <u>Postoperative pain following dental surgery</u> (9 studies, 916 patients) NNT for at least 50% pain relief over 4-6 hours: 3.7 (95% CI: 3.1, 4.7) Efficacy RR 3.50 (95% CI: 2.57, 4.77) <u>Postoperative pain following other surgery</u> (14 studies, 1721 patients) NNT for at least 50% pain relief over 4-6 hours: 3.9 (95% CI: 3.3, 4.7) Efficacy RR 2.16 (95% CI: 1.88, 2.48) **Comparison 5** **Paracetamol 1500 mg versus placebo** NNT for at least 50% pain relief over 4-6 hours: 3.7 (95% CI: 2.3, 9.5) **Adverse Events for Paracetamol 975/1000 mg versus placebo** ***Drowsiness/sleepiness/somnolence*** (6 studies) RR 0.93 (95% CI: 0.53, 1.64) ***Dizziness***	Study characteristics: - Critical appraisal: ? Conclusion: ? Combining findings: ? Publication bias: - Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(7 studies) RR 0.73 (95% CI: 0.31, 1.75) ***Nausea*** (6 studies) RR 0.99 (95% CI: 0.54, 1.80) ***Vomiting*** (4 studies) RR 1.34 (95% CI: 0.57, 3.17) ***Headache*** (9 studies) RR 0.90 (95% CI: 0.59, 1.37)	
McNicol, E.D., et al., Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. Br J Anaesth, 2011. 106(6): p. 764-75.	**Inclusion criteria** - blinded or unblinded, placebo- or active controlled, single-dose RCTs - children or adults with postoperative pain after any kind of surgery - able to self-report pain intensity or pain relief - period of interest was 4–6 h post-intervention - - Multiple-dose studies that provided separate data for the first dose - Interventions had to be given within the last 30 min of surgery, in the immediate postoperative period or at any time within the first three postoperative days **Exclusion criteria** - crossover studies - studies with less than 4 h of follow-up post-intervention **Search period** Cochrane Central Register of Controlled Trials (CENTRAL, 2nd Quarter 2010) MEDLINE using OVID platform (1950 to May 2010) EMBASE (1980–2010, Week 18) LILACS (1992 to May 2010) **Number of included studies (n participants)** 36 studies were included (3896 participants)	**Intervention:** Propacetamol or Paracetamol i.v. **Control:** Placebo	**At least 50% pain relief over 4 h (n/N) (OR)** *Propacetamol* Number of studies: 8, total patients enrolled: 807 Overall estimate (95% CI): 4.6 (3.1, 6.8), $p < 0.000001$ I^2= 32% *Paracetamol* Number of studies: 3, total patients enrolled: 367 Overall estimate (95% CI): 17.2 (5.6, 53.2), $p< 0.000001$ I^2= 0% *Combined data* Number of studies: 9, total patients enrolled: 1072 Overall estimate (95% CI): 5.8 (4.1, 8.4), $p<0.000001$ I^2= 42% **At least 50% pain relief over 6 h (n/N) (OR)** *Propacetamol* Number of studies: 6, total patients enrolled: 662 Overall estimate (95% CI): 4.2 (2.6, 7.0) *Paracetamol* Number of studies: 3, total patients enrolled: 367 Overall estimate (95% CI): 22.0 (5.3, 91.2)	**Level of evidence** 1a (1) **Authors' conclusion** "In conclusion, our analyses suggest that propacetamol or i.v. paracetamol are effective analgesics with a safety profile similar to placebo. Given alone, they are unlikely to provide sufficient analgesia in surgery which produces moderate to- severe pain. If used in combination with opioids, they reduce opioid consumption, but this reduction does not appear sufficient to reduce opioid-induced AEs. Larger trials are required." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	33 studies included in a meta-analysis		*Combined data* Number of studies: 7, total patients enrolled: 927 Overall estimate (95% CI): 6.0 (3.8, 9.6) **Requirement for additional analgesia (n/N) (OR)** *Propacetamol* Number of studies: 3, total patients enrolled: 204 Overall estimate (95% CI): 0.28 (0.16, 0.50) *Paracetamol* Number of studies: 3, total patients enrolled: 340 Overall estimate (95% CI): 0.12 (0.05, 0.30) *Combined data* Number of studies: 6, total patients enrolled: 544 Overall estimate (95% CI): 0.21 (0.13, 0.33) **Time to additional analgesia (min) (MD)** *Propacetamol* Number of studies: 3, total patients enrolled: 316 Overall estimate (95% CI): 23.7 (13.8, 33.6) *Paracetamol* Number of studies: 1, total patients enrolled:74 Overall estimate (95% CI): 56.0 (30.2, 81.8) *Combined data* Number of studies: 4, total patients enrolled: 390 Overall estimate (95% CI): 27.9 (18.6, 37.2) **Opioid consumption over 4h (i.v. morphine equivalents, mg) (MD)** *Propacetamol* Number of studies: 2, total patients enrolled: 114 Overall estimate (95% CI): -2.0 (-3.2, -1.0)	Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: + Conflict of interest: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Paracetamol Number of studies, total patients enrolled: 1.40 Overall estimate (95% CI): -1.2 (-1.6, -0.8) *Combined data* Number of studies: 3, total patients enrolled: 154 Overall estimate (95% CI): -1.3 (-1.7, -0.9) **Opioid consumption over 6h (i.v. morphine equivalents, mg) (MD)** *Propacetamol* Number of studies: 6, total patients enrolled: 399 Overall estimate (95% CI): -2.9 (-4.4, -1.4) *Paracetamol* Number of studies: 2, total patients enrolled: 141 Overall estimate (95% CI): - 2.0 (-2.6, -1.4) *Combined data* Number of studies: 7, total patients enrolled: 488 Overall estimate (95% CI): -2.1 (-2.6, -1.6) **Global evaluation: (good/satisfied or better, n/N) (OR)** *Propacetamol* Number of studies: 8, total patients enrolled: 1114 Overall estimate (95% CI): 2.4 (1.8, 3.1) *Paracetamol* Number of studies: 4, total patients enrolled: 392 Overall estimate (95% CI): 3.7 (2.1, 6.7) *Combined data* Number of studies: 10, total patients enrolled:1404 Overall estimate (95% CI): 2.6 (2.0, 3.3) **Global evaluation: VAS (0-10) (MD)** *Propacetamol*	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Number of studies: 2, total patients enrolled:82 Overall estimate (95% CI): 1.6 (1.0, 2.2) *Paracetamol vs. placebo,* *Subtotal (95% CI)* Active Events: 232 Placebo Events: 135 Weight: 9.8% OR M-H, Fixed (95% CI): 17.22 (5.58, 53.17) *Total (95% CI)* Active Events: 647 Placebo Events: 527 Weight: 100% OR M-H, Fixed (95% CI): 5.84 (4.06, 8.40) ***Number of patients reporting pain on infusion: propacetamol vs. i.v. paracetamol. CI, confidence interval:*** Propacetamol Events: 182 Paracetamol Events: 180 Weight: 100% OR M- H, Fixed (95% CI): 12.31 (5.88, 25.78), p< 0.000001 I^2= 52%	
Moore, A., et al., Single dose paracetamol (acetaminophen), with and without codeine, for postoperative pain. Cochrane Database Syst Rev, 2000(2): p. CD001547.	**Inclusion criteria** - full journal publication of single dose, double blind, randomised controlled trials in postoperative pain - placebo control - same dose of paracetamol alone - multiple dose included if appropriate data from the first dose was available - adult patients with established postoperative pain of moderate to severe intensity **Exclusion criteria** - no randomization - studying other pain conditions - experimental pain - paracetamol used in combination with drugs other than codeine - trials investigating pain due to uterine cramps alone were excluded	**Intervention:** Treatment of paracetamol alone or combination of paracetamol plus codeine all orally administered **Control:** Placebo orally administered	**[analyses with fixed-effect models]** ***Paracetamol vs. placebo, combining data across conditions, the pooled relative benefits (RB) for each dose of paracetamol vs. placebo for at least 50% pain relief*** • 325 mg, 100 patients, (95% CI): RB 1.6 (1.1, 2.3), NNT 3.9 (2.2, 13) • 500 mg, 567 patients, (95% CI): RB 1.5 (1.2, 1.8), NNT 5.6 (3.9, 9.5) • 600/650 mg, 1167 patients, (95% CI): RB 1.9 (1.6, 2.3), NNT 5.3 (4.1, 7.2) • 1000 mg, 2283 patients, (95% CI): RB 2.2 (1.9, 2.5), NNT 4.6 (3.8, 5.4) • 1500 mg, 348 patients, (95% CI): RB 1.4 (1.2, 2.8), NNT 5.0 (3.3, 11)	**Level of evidence** 1a (1) **Authors' conclusion** "Paracetamol is an effective analgesic in postoperative pain with a low incidence of adverse effects. The addition of codeine 60 mg to paracetamol produces additional pain relief even in single oral doses, but this appears to be accompanied by an increase in drowsiness and dizziness. Evidence produced by the same method (Collins 1998a) suggests that ibuprofen provides better analgesia for postoperative pain than either paracetamol plus codeine or

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	- abstracts, review articles, case reports, clinical observations, unpublished data **Search period** - Medline (1966- May 1966) - Embase (1980- 1996) - Cochrane Library (March 1996) - Oxford Pain Relief Database (1950- 1994) (Jadad 1996a) **Number of included studies (n participants)** 38 studies (4224) paracetamol vs. placebo 21 studies (1407) paracetamol + codeine vs. placebo		***Paracetamol plus Codeine vs. Paracetamol alone, combining data across conditions,*** RB for addition of codeine 60mg to all doses for paracetamol (95%CI): 1.3 (1.1, 1.5)	paracetamol alone.“ ***Methodological quality*** A-priori design: + Two reviewers: ? Literature search: + Status of publication: - List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: - Conflict of interest: -
Weil et al. (2007) Paracetamol for pain relief after surgical removal of lower wisdom teeth Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD004487. DOI: 10.1002/14651858.CD004487.pub2.	**Inclusion criteria** - RCT’s double blinded - patients of all health states who required the surgical removal of a lower wisdom tooth and who had a baseline pain intensity of moderate to severe pain - single and multiple dose studies **Exclusion criteria** - patients taking concurrent analgesia **Search period** TheCochraneOralHealthGroup’sTrialsRegister (to 24th August 2006)	**Intervention:** Paracetamol given up to 7 days by mouth in any dose and in any formulation **Control:** Placebo	**[all analysis with random-effects models]** **<u>Paracetamol versus placebo</u>** **Comparison 1** **50% pain relief using pain relief measures at 4h** (16 studies, 1498 participants) RR 2.85 (95% CI: 1.89, 4.29), p < 0.00001 I^2=76% *Subgroup up to 1000 mg of paracetamol* (10 studies, 710 participants) RR 1.96 (95% CI: 1.34, 2.86), p=0.00048	**Level of evidence** 1a (1) **Authors’ conclusion** “Paracetamol is a safe, effective drug for the treatment of postoperative pain following the surgical removal of lower wisdom teeth.” ***Methodological quality*** A-priori design: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2006, Issue 3) The Cochrane Pain, Palliative and Supportive Care Group's Trials Register (to 24th August 2006) MEDLINE (1966 to 24th August 2006) EMBASE (1980 to 25th August 2006) Current Controlled Trials Register (www.controlled-trials.com) (to 24th August 2006) **Number of included studies (n participants)** 21(2048)		I^2=66% *Subgroup 1000 mg paracetamol or more* (6 studies, 788 participants) RR 4.56 (95% CI: 2.86, 7.27), p < 0.00001 I^2=8% **50% pain relief using pain relief measures at 6h** (13 studies, 1155 participants) RR 3.32 (95% CI: 1.88, 5.87), p=0.000038 I^2=81% *Subgroup up to 1000 mg of paracetamol* (6 studies, 378 participants) RR 1.89 (95% CI: 0.98, 3.67), p=0.058 I^2=65% *Subgroup 1000 mg paracetamol or more* (7 studies, 777 participants) RR 4.21 (95% CI: 2.97, 5.98), p < 0.00001 I^2=0% **Comparison 2** **50% pain relief using pain intensity measures at 4h** (17 studies, 1658 participants) RR 4.87 (95% CI: 2.83, 8.37), p < 0.00001 I^2=66% *Subgroup up to 1000 mg of paracetamol* (10 studies, 737 participants) RR 4.33 (95% CI: 2.19, 8.58), p=0.000026 I^2=66% *Subgroup 1000 mg paracetamol or more* (8 studies, 921 participants) RR 6.46 (95% CI: 2.34, 17.85), p=0.00032 I^2=70% **50% pain relief using pain relief at 6h** (13 studies, 1184 participants) RR 3.41 (95% CI: 2.34, 4.97), p < 0.00001	Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			I^2=29% *Subgroup up* to 1000 mg of paracetamol (6 studies, 403 participants) RR 2.67 (95% CI: 1.46, 4.90), p=0.0015 I^2=29% *Subgroup* 1000 mg paracetamol or more (8 studies, 781 participants) RR 3.96 (95% CI: 2.52, 6.23), p < 0.000001 I^2=19% **Comparison 3** **Number of people with adverse events** (17 studies, 1645 participants) RR 1.19 (95% CI: 0.90, 1.57), p=0.23 I^2=28% *Subgroup up to 1000 mg of paracetamol* (9 studies, 672 participants) RR 1.25 (95% CI: 0.69, 2.25), p=0.46 I^2=23% *Subgroup 1000 mg paracetamol or more* (8 studies, 973 participants) RR 1.16 (95% CI: 0.84, 1.60), p=0.37 I^2=36%	

+: low risk; -: high risk; ?: unclear risk; N/A: not applicable; CI: confidence interval; NR: not reported; NS: not significant; NNT: Number needed to treat; RR: relative risk; RB: Relative Benefit; OR: odds ratio; MD mean difference; WMD: weighted mean difference; SMD: standardized mean difference; I^2 und Q: Heterogenitätsmaße

Tab. 3 Systemische Pharmakologie: Paracetamol, Metamizol, NSAR, COX-2-Inhibitoren: *systematische Reviews zu COX-2-Inhibitoren (Fragen #1 bis #5)*

Review / reference	**Inclusion, exclusion criteria, search period, number of included studies**	**Intervention group(s) (IG)/ control group (CG)**	**Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)**	**Level of evidence: CEbM 2009 (CEbM 2011)** **critical appraisal/ conclusion**
Barden, J., et al., Single dose oral celecoxib for postoperative pain. Cochrane Database Syst Rev, 2003(2): p. CD004233.	**Inclusion criteria** - RCTs of a single dose oral celecoxib compared withplacebo for acute postoperative pain - studies undertaken in either day surgery or in-patient settings - patients ≥15 years with moderate to severe pain **Exclusion criteria** - study did not clearly state that the interventions had been randomly allocated and double blind - pain conditions other than postoperative pain - were conducted with volunteer participants and/or with laboratory induced pain - study did not use standard pain assessment scales. - patients did not have at least moderate pain (> 30 mm VAS) at baseline- abstracts, review articles, case reports and clinical observations - trials investigating pain due to uterine cramps alone - trials of active controls **Search period** - Cochrane Library Issue 4, 2001 and Issue 2 2002 - MEDLINE (1966-May 2002) - PubMed (May 2002) - Biological Abstracts (1985-December 2001) - Oxford Pain database (Jadad 1996a) (1950-1994) **Number of included studies (n participants)** 2 (418) (232 celecoxib 200mg/186 placebo)	**Intervention** Single dose of oral celecoxib **Control** Placebo	**[analyses with fixed-effect models]** **<u>Celecoxib 200 mg versus placebo</u>** **Number of patients with at least 50% pain relief over 4-6 hours** (2 studies, 418 participants; 1 study dental, 1 study orthopaedic) RR 2.32 (95% CI: 1.62, 3.34), p < 0.00001 I^2=71.1% NNT 4.5 (95% CI: 3.3, 7.2) **Minor adverse events over 24h period** (1 study, 136 participants, dental) ***Nausea*** Mean proportion (%): 12.2 vs. 20, p-value NR ***Vomiting*** Mean proportion (%): 6.6 vs. 13.3, p-value NR ***Headache*** Mean proportion (%): 13.2 vs. 13.3, p-value NR **Median time to remedication over 24h** Time (h): 5.1 vs.1.5, p-value NR	**Level of evidence** 1a (1) **Author conclusion** "Single dose oral celecoxib is an effective means of postoperative pain relief, similar in efficacy to aspirin 600/650 mg, and paracetamol 1000 mg. The two trials included used celecoxib 200 mg, a dose 50% less than is recommended for acute pain. More trials are needed to estimate efficacy for recommended dose of 400 mg, and to reinforce current findings for 200 mg, and provide data for pooled quantitative estimates of adverse effects." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: - List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
				Publication bias: + Conflict of interest: ?
Chen, L.C., R.A. Elliott, and D.M. Ashcroft, Systematic review of the analgesic efficacy and tolerability of COX-2 inhibitors in post-operative pain control. J Clin Pharm Ther, 2004. 29(3): p. 215-29.	**Inclusion criteria** - RCTs, double-blinded - postoperative single-dose treatment group of a COX-2 inhibitor - full journal publication - age: > 15 years - baseline postoperative pain of moderate to severe intensity (VAS) - outcomes: reported with standardized pain intensity measures, or the proportion of patients who experienced adverse events **Exclusion criteria** - preoperative drug administration - postoperative analgesic combined regime - no extractable data **Search period** - MEDLINE (1966 to March 2003) - EMBASE (1980-2003) - the Cochrane Library Database **Number of included studies (n participants)** 18 (2783)	**Intervention** Single dose COX-2 inhibitors **Control** Placebo or active comparator	**[analyses with random effects models]** **<u>Rate ratio for patients receiving 50% pain relief of COX-2 inhibitors compared with placebo</u>** ***Celecoxib 200mg vs placebo (dental)*** (1 study, 136 participants)) RR 6.43 (95% CI: 2.19, 19.68) ***Rofecoxib 50mg vs placebo (dental)*** (6 studies, 786 participants) RR 5.37 (95% CI: 3.65, 7.90), p < 0.00001 I^2=0% ***Rofecoxib 500mg vs placebo (dental)*** (1 study, 62 participants) RR 12.27 (95% CI: 3.16, 47.62) ***Valdecoxib 20mg vs placebo (dental)*** (2 studies, 203 participants) RR 8.34 (95% CI: 4.01, 17.35), p < 0.00001 I^2=12.5 % ***Valdecoxib 40mg vs placebo (dental)*** (4 studies, 473 participants) RR 7.17 (95% CI: 4.42, 11.62), P < 0.00001 I^2=16.3 % ***Parecoxib 20mg IM vs placebo (dental)*** (1 study, 102 participants) RR 16.00 (95% CI: 4.05, 63.27) ***Parecoxib 20mg IV vs placebo (dental)*** (1 study, 101 participants) RR 15.30 (95% CI: 3.86, 60.64) ***Parecoxib 40mg IM vs placebo (dental)*** (1 study, 101 participants) RR 19.89 (95% CI: 5.07, 77.99)	**Level of evidence** 1a (1) **Author conclusion** "The analgesic efficacy and tolerability of single-dose COX-2 inhibitors were more effective than opioid-containing analgesics and similar to non-selective NSAIDs in post-operative pain management. Further studies are needed to examine the efficacy and tolerability of COX-2 inhibitors compared against active comparators over a longer duration to assess whether these short-term effects are mirrored by longer-term outcomes and to determine their ultimate risk -benefit profile." ***Methodological quality*** A-priori design: + Two reviewers: ?Literature search: + Status of publication: + List of studies: - Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Parecoxib 40mg IV vs placebo (dental) (1 study, 102 participants) RR 18.00 (95% CI: 4.57, 70.83) ***Rofecoxib 50mg vs placebo (orthopaedic)*** (1 study, 163 participants) RR 2.38 (95% CI: 1.30, 3.99) ***Parecoxib 20mg IV vs placebo (orthopaedic)*** (1 study, 82 participants) RR 1.81 (95% CI: 0.82, 4.03) ***Parecoxib 40mg IV vs placebo (orthopaedic)*** (1 study, 81 participants) RR 2.79 (95% CI: 1.33, 5.82) ***Parecoxib 20mg IV vs placebo (gyn)*** (2 studies, 161 participants) RR 2.40 (95% CI: 0.95, 6.09), p=0.07 I^2=71.3% ***Parecoxib 40mg IV vs placebo (gyn)*** (2 studies, 164 participants) RR 2.79 (95% CI: 1.36, 5.72), p=164 I^2=56.4% **<u>Rate ratio for patients receiving 50% pain relief of COX-2 inhibitors compared with active comparators</u>** ***Rofecoxib 50mg vs codeine/paracetamol 60/600mg (dental)*** (1 study, 362 participants) RR 2.10 (95% CI: 1.60, 2.75) ***Valdecoxib 20mg vs oxycodone/paracetamol 10/1000mg*** (2 studies, 203 participants) RR 1.16 (95% CI: 0.79, 1.71), p=0.45 I^2=70.4% ***Valdecoxib 40mg vs oxycodone/paracetamol 10/1000mg*** (2 studies, 202 participants) RR 1.34 (95% CI: 1.11, 1.62), p=0.002I^2=0%	Publication bias: - Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Celecoxib 200mg vs ibuprofen 400mg (dental) (1 study, 137 participants) RR 0.66 (95% CI: 0.48, 0.90) ***Rofecoxib 50mg vs ibuprofen 400mg (dental)*** (3 studies, 289 participants) RR 1.01 (95% CI: 0.83, 1.22), p=0.95 I^2=0% ***Parecoxib 20mg IM vs ketorolac 60mg IM (dental)*** (1 study, 102 participants) RR 0.82 (95% CI: 0.63, 1.06) ***Parecoxib 20mg IV vs ketorolac 60mg IM (dental)*** (1 study, 101 participants) RR 0.78 (95% CI: 0.60, 1.03) ***Parecoxib 40mg IM vs ketorolac 60mg IM (dental)*** (1 study, 101 participants) RR 1.02 (95% CI: 0.83, 1.26) ***Parecoxib 40mg IV vs ketorolac 60mg IM(dental)*** (1 study, 102 participants) RR 0.92 (95% CI: 0.73, 1.17) ***Parecoxib 20mg IV vs morphine 4 mg IV (orthopaedic)*** (1 study, 85 participants) RR 1.24 (95% CI: 0.64, 2.42) ***Parecoxib 40mg IV vs morphine 4 mg IV (orthopaedic)*** (1 study, 84 participants) RR 1.91 (95% CI: 1.06, 3.45) ***Parecoxib 20mg IV vs keterolac 30mg IV (orthopaedic)*** (1 study, 85 participants) RR 0.68 (95% CI: 0.40, 1.17) ***Parecoxib 40mg IV vs ketorolac 30mg IV (orthopaedic)*** (1 study, 84 participants) RR 1.05 (95% CI: 0.68, 1.63) ***Rofecoxib 50mg vs naproxen sodium 550mg (orthopaedic)***	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(1 study, 165 participants) RR 1.04 (95% CI: 0.73, 1.48) ***Parecoxib 20mg IV vs morphine 4mg IV (gyn)*** (1 study, 81 participants) RR 1.71 (95% CI: 0.96, 3.03) ***Parecoxib 40mg IV vs morphine 4mg IV (gyn)*** (1 study, 80 participants) RR 1.84 (95% CI: 1.05, 3.24) ***Parecoxib 20mg vs ketorolac 30mg IV (gyn)*** (1 study, 80 participants) RR 0.83 (95% CI: 0.55, 1.26) ***Parecoxib 40mg vs ketorolac 30mg IV (gyn)*** (1 study, 79 participants) RR 0.90 (95% CI: 0.60, 1.34) **Risk ratio for patients receiving 50% pain relief of COX-2 inhibitors compared with COX-2 inhibitors** ***Celecoxib 200mg vs rofecoxib 50mg (dental)*** (1 study, 181 participants) RR 0.65 (95% CI: 0.49, 0.87) ***Rofecoxib 50mg vs valdecoxib 40mg (dental)*** (2 studies, 362 participants) RR 0.76 (95% CI: 0.49, 1.20), p=0.24 I^2=80.3% ***Valdecoxib 20mg vs valdecoxib 40mg (dental)*** (2 studies, 201 participants) RR 0.87 (95% CI: 0.59, 1.27), p=0.47 I^2=80.7% ***Parecoxib 20mg IM vs parecoxib 20mg IV (dental)*** (1 study, 101 participants) RR 1.05 (95% CI: 0.77, 1.43) ***Parecoxib 20mg IM vs parecoxib 40mg IM (dental)*** (1 study, 101 participants)	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			RR 0.80 (95% CI: 0.62, 1.04) ***Parecoxib 20mg IM vs parecoxib 40mg IV (dental)*** (1 study, 102 participants) RR 0.89 (95% CI: 0.67, 1.17) ***Parecoxib 20mg IV vs parecoxib 40mg IM (dental)*** (1 study, 100 participants) RR 0.77 (95% CI: 0.59, 1.01) ***Parecoxib 20mg IV vs parecoxib 40mg IV (dental)*** (1 study, 101 participants) RR 0.85 (95% CI: 0.64, 1.13) ***Parecoxib 40mg IM vs parecoxib 40mg IV (dental)*** (1 study, 101 participants) RR 1.11 (95% CI: 0.88, 1.39) ***Parecoxib 20mg IV vs parecoxib 40mg IV (orthopaedic)*** (1 study, 85 participants) RR 0.65 (95% CI: 0.38, 1.10) ***Parecoxib 20mg vs parecoxib 40mg (gyn)*** (2 studies, 157 participants) RR 0.81 (95% CI: 0.63, 1.05), p=0.12 I^2=0% **Adverse Events** **Comparison COX-2 inhibitors against placebo (pooled results for all COX-2 inhibitors)** ***Headache*** RR 0.65 (95% CI: 0.51, 0.82) ***Nausea*** RR 0.63 (95% CI: 0.48, 0.82) ***Vomiting*** RR 0.57 (95% CI: 0.38, 0.83) **Comparison of different COX-2 inhibitors** No significant differences in overall adverse events **Comparison of COX-2 inhibitors vs. other active**	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			<u>comparator</u> **Rofecoxib 50mg vs codeine/paracetamol 60/600mg (dental)** ***Any adverse events*** RR 0.73 (95% CI: 0.56, 0.94), p<0.05 ***Nausea*** RR 0.24 (95% CI: 0.13, 0.45), p<0.05 ***Vomiting*** RR 0.21 (95% CI: 0.10, 0.46), p<0.05 **Rofecoxib 50mg vs oxycodone/paracetamol 5/325mg (dental)** ***Nausea*** RR 0.48 (95% CI: 0.29, 0.79), p<0.05 ***Vomiting*** RR 0.29 (95% CI: 0.12, 0.68), p<0.05 **Valdecoxib 20mg vs oxycodone/paracetamol 10/1000mg (dental)** ***Any adverse events*** RR 0.51 (95% CI: 0.38, 0.69), p<0.05 ***Dizziness*** RR 0.19 (95% CI: 0.10, 0.39), p<0.05 ***Nausea*** RR 0.21 (95% CI: 0.10, 0.46), p<0.05 ***Vomiting*** RR 0.18 (95% CI: 0.06, 0.49), p<0.05 **Valdecoxib 40mg vs oxycodone/paracetamol 10/1000mg (dental)** ***Any adverse events*** RR 0.39 (95% CI: 0.27, 0.55), p<0.05 ***Headache*** RR 0.43 (95% CI: 0.20, 0.94), p<0.05 ***Dizziness*** RR 0.07 (95% CI: 0.02, 0.23), p<0.05 ***Nausea*** RR 0.22 (95% CI: 0.10, 0.47), p<0.05 ***Vomiting*** RR 0.18 (95% CI: 0.06, 0.49), p<0.05 **Celecoxib 400mg vs ibuprofen 400mg**	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Vomiting RR 0.22 (95% CI: 0.05, 0.96), p<0.05 All other comparisons no significant differences *No study reported minor or major bleeding rates, renal or cardiac outcomes.*	
Clarke, R., S. Derry, and R.A. Moore (2014) Single dose oral etoricoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD004309.pub4.	**Inclusion criteria** - RCTs - full publications - double-blind - placebo-controlled clinical trials of single-dose oral etoricoxib for acute postoperative pain - established postoperative moderate to severe pain following day surgery or in-patient surgery - age: ≥15 years - at least 10 participants **Exclusion criteria** - posters or abstracts not followed up by full publication - reports of studies concerned with pain other than postoperative pain (including experimental pain) - studies using volunteer participants - studies where pain relief was assessed by clinicians , nurses, or carers (i.e. not patient-reported) - studies of less than four hours' duration or that failed to present data over four to six hours post dose - studies investigating participants with pain due to uterine cramps alone **Search period** Cochrane Central Register of Controlled Trials (CENTRAL) (2014) MEDLINE (1996 to 31 January 2014) EMBASE (1980 to 31 January 2014) The Oxford Pain Database www.clinicaltrials.gov **Number of included studies (n participants)**	**Intervention:** Single-dose oral etoricoxib **Control:** Placebo	**[analyses of calculated risk and benefit estimates with fixed-effect models]** **Effects of Intervention** **Participants achieving at least 50% pain relief over 4 to 6 hours (primary outcome)** **Etoricoxib 60mg versus placebo** (1 study, 124 participants, dental) 50% pain relief over 6h: 59% versus 12%, p-value NR RR and NNT not calculated **Etoricoxib 90mg versus placebo** (1 study, 237 participants, dental) 50% pain relief over 4 to 6h: 77% versus 17% RR 4.5 (95% CI: 2.4, 8.4) NNT 1.7 (95% CI: 1.4, 2.1) **Etoricoxib 120mg versus placebo** (6 studies, 798 participants) 50% pain relief over 4 to 6h: 66% versus 12% RR 5.6 (95% CI: 4.0, 7.8), p < 0.0001 NNT 1.8 (95% CI: 1.7, 2.0) I^2 =50% Dental studies only (5 studies, 643 participants) RR 6.7 (95% CI: 4.6, 9.8) NNT 1.6 (1.5, 1.8) **Etoricoxib 180mg versus placebo** (1 study, 123 participants) 50% pain relief over 6h: 85% versus 12%, p-value NR RR and NNT not calculated	**Level of evidence** 1a (1) **Author's conclusion** "Single-dose oral etoricoxib produces high levels of good quality pain relief after surgery, and adverse events did not differ from placebo in these studies. The 120 mg dose is as effective as, or better than, other commonly used analgesics." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	6 (1214)		**Etoricoxib 240mg versus placebo** (1 study 125 participants) 50% pain relief over 6h: 72% versus 12%, p-value NR RR and NNT not calculated ***Sensitivity analyses of primary outcome*** **<u>Use of rescue medication over 6h</u>** **Etoricoxib 90mg versus placebo** (2 studies, 237 participants) 8.4% versus 65%, p-value NR **Etoricoxib 120mg versus placebo** (2 studies, 268 participants) 17% versus 68%, p-value NR RR 0.24 (95% CI: 0.17, 0.34) NNTp: 2.0 (95% CI: 1.6, 2.6) **Use of rescue medication over 24h** **Etoricoxib 60mg versus placebo** (4 studies, 124 participants) 52% versus 82%, p-value NR **Etoricoxib 120mg versus placebo** (4 studies, 505 participants) 50% versus 89% RR 0.60 (95% CI: 0.53, 0.67), p < 0.00001 I^2 =94% NNTp: 2.6 (95% CI: 2.2, 3.1) <u>Dental studies only (350 participants)</u> 39% versus 84% RR 0.46 (95% CI: 0.38, 0.56) NNTp 2.2 (95%CI: 1.9, 2.8) **Etoricoxib 180mg versus placebo** (123 participants) 26% versus 82%, p-value NR	Publication bias: + Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Etoricoxib 240mg versus placebo (125 participants) 33% versus 82%, p-value NR **Time to use of rescue medication** **Any adverse Events** **Etoricoxib (all doses) versus placebo** (6 studies, 1059 participants) RR 0.91 (95% CI: 0.74, 1.2), p=0.37 I^2 =0% **Etoricoxib 120mg versus placebo** (643 participants) RR 0.93 (95% CI. 0.74, 1.2)	
Derry S,Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD004233. DOI: 10.1002/14651858.CD004233.pub4.	**Inclusion criteria** - double-blind RCTs - oral celecoxib against placebo for the treatment of moderate to severe postoperative pain - age: ≥ 15years - at least 10 participants randomly allocated to each treatment group. - multiple dose studies if appropriate data from the first dose were available - cross-over studies provided that data from the first arm were presented separately - orally administred celecoxib **Exclusion criteria** - posters or abstracts not followed up by full publication - reports of trials concerned with pain other thanpostoperative pain (including experimental pain) - trials using healthy volunteers; - trials where pain relief was assessed by clinicians, nurses or careers (i.e. not patient-reported) - trials of less than four hours' duration or which failed to present data over four to six hours post dose **Search period** We searched the following electronic databases: the Cochrane Central Register of Controlled Trials	**Intervention:** Single dose oral celecoxib **Control:** Placebo	**[analyses of calculated risk and benefit estimates with fixed-effect models]** **<u>Comparison 1</u>** **Celecoxib 200mg versus placebo, participants with at least 50% pain relief over 4-6h (primary outcome)** **dental and orthopaedic /postsurgical pain** (4 studies, 705 participants) RR 3.49 (95% CI: 2.40, 5.06), p < 0.00001 I^2=83% NNT 4.2 (95% CI: 3.40, 5.60) **Dental pain** (3 studies, 423 participants) RR 15.86 (95% CI: 5.14, 48.99), p < 0.00001 I^2=83% NNT 3.2 (95% CI: 2.7, 3.9) **Postsurgical pain** (1 study, 85 participants) RR 1.83 (95% CI: 1.26, 2.68), p=0.002 **Use of rescue medication over 24h** (2 studies, 271 participants) RR 0.78 (95% CI: 0.70, 0.86), p< 0.00001 I^2=72%	**Level of evidence** 1a (1) **Authors' conclusion** "Single-dose oral celecoxib is an effective analgesic for postoperative pain relief. Indirect comparison suggests that the 400 mg dose has similar efficacy to ibuprofen 400 mg." **Methodological quality** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	(CENTRAL) (The Cochrane Library 2013, Issue 5 of 12) MEDLINE via Ovid (1966 to 31 May 2013) EMBASE via Ovid (1980 to 31 May 2013) Oxford Pain Database (Jadad 1996a) ClinicalTrials.gov (on 31 May 2013) for update only **Number of included studies (n participants)** 10 studies (1785)		NNTp: 4.8 (95% CI: 3.5, 7.7) **Any adverse event** (4 studies, 669 participants) RR 0.90 (95% CI: 0.63, 1.29), p=0.78 I^2=0% **<u>Comparison 2</u>** **Celecoxib 400mg versus placebo, participants with at least 50% pain relief over 4-6h** **dental pain** (5 studies, 722 participants) RR 10.26 (95% CI: 5.70, 18.47), p < 0.00001 I^2=6% NNT 2.6 (95% CI: 2.3, 3.0) **Use of rescue medication over 24h** (3 studies, 518 participants) RR 0.68 (95% CI: 0.62, 0.74), p < 0.00001 I^2=44% NNTp: 3.5 (95% CI: 2.9, 4.6) **Any adverse Events** (6 studies, 725 participants) RR 1.00 (95% CI: 0.84, 1.17), p=0.96 I^2=81%NNH: 12 (6.3, 78)	Critical appraisal: + Conclusion: + Combining findings: + Publication bias: + Conflict of interest: ?
Kranke, P., et al., Patients' global evaluation of analgesia and safety of injected parecoxib for postoperative pain: a quantitative systematic review. Anesth Analg, 2004. 99(3): p. 797-806, table of contents**.**	**Inclusion criteria** - RCTs, double-blinded - full reports - comparisons of i.v or i.m. injected parecoxib compared with placebo or any other analgesic regimen for acute postoperative pain **Exclusion criteria** - **Search period** MEDLINE EMBASE CENTRAL The Cochrane Library The Science Citation Index	**Intervention** Parecoxib i.v. or i.m. **Control** Placebo (*active controls (morohine / ketorolac) not extracted)*	**[all analyses with random effects models]** **<u>Injected parecoxib versus placebo</u>** **RR of a "good / excellent" evaluation with intervention versus placebo** ***Prophylaxis 20mg*** (4 studies, 403 participants) RR 1.42 (95% CI: 0.91, 2.24) ***Prophylaxis 40mg*** (5 studies, 859 participants) RR 1.40 (95% CI: 1.10, 1.79) NNT 4.0 (95% CI: 2.3, 17) Assuming a "best case" scenario of the data presented in one trial:	**Level of evidence** 1a (1) **Author conclusion** "In conclusion, in the perioperative setting, injected parecoxib significantly improves patients' global evaluation of the analgesic regimen compared with placebo. Parecoxib was judged better by means of dichotomous patients' global assessment of the study drug if it was administered the first time as treatment instead of as prophylaxis. Parecoxib 40 mg seems to be more

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	Up to June 2003 Contact – German manufacturer of parecoxib **Number of included studies (n participants)** 9 (1738)		RR 1.46 (95% CI: 1.11, 1.92) NNT 3.7 (95% CI: 2.3, 17) ***Treatment 20mg*** (3 studies, 313 participants) RR 3.44 (95% CI: 1.49, 7.96) NNT 2.5 (95% CI: 2.0, 4.8) ***Treatment 40mg*** (3 studies, 305 participants) RR 4.65 (95% CI: 2.04, 10.61) NNT 1.7 (95% CI: 1.3, 2.4) **Adverse Effect – injected parecoxib versus placebo** ***Any adverse effects all dose*** (7 studies, 1106 patients treated with parecoxib) RR 1.00 (95% CI: 0.95, 1.05) ***Any adverse effects 20mg*** (6 studies, 427 patients treated with parecoxib) RR 1.01 (95% CI: 0.91, 1.12) ***Any adverse effects 40mg*** (7 studies, 679 patients treated with parecoxib) RR 1.00 (95% CI: 0.95, 1.06) ***Fever*** (6 studies, 773 patients treated with parecoxib) RR 0.31 (95% CI: 0.21, 0.46) NNT 7.7 (95% CI: 5.9, 11.1) ***Nausea*** (9 studies, 1162 patients treated with parecoxib) RR 0.96 (95% CI: 0.84, 1.10) ***Vomiting*** (9 studies, 1160 patients treated with parecoxib) RR 1.08 (95% CI: 0.82, 1.42) ***Dizziness*** (4 studies, 889 patients treated with parecoxib) RR 0.81 (95% CI: 0.61, 1.08) ***Headache*** (4 studies, 532 patients treated with parecoxib) RR 0.68 (95% CI: 0.48, 0.97) NNT 20 (95% CI: 11.1, 50) ***Tachycardia***	effective than 20 mg without being associated with additional side effects. Both doses were equally well tolerated compared with placebo and in head-to-head comparisons versus morphine or ketorolac." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: ? List of studies: - Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(4 studies, 604 patients treated with parecoxib) RR 0.69 (95% CI: 0.35, 1.33) ***Somnolence*** (3 studies, 473 patients treated with parecoxib) RR 0.76 (95% CI: 0.49, 1.20) ***Abnormal breath sounds*** (2 studies, 388 patients treated with parecoxib) RR 0.95 (95% CI: 0.64, 1.14) ***Pruritus*** (5 studies, 532 patients treated with parecoxib) RR 0.98 (95% CI: 0.64, 1.49) ***Hypotension*** (3 studies, 443 patients treated with parecoxib) RR 1.28 (95% CI: 0.58, 2.80) ***Postoperative anemia*** (2 studies, 263 patients treated with parecoxib) RR 1.02 (95% CI: 0.55, 1.88) ***Death*** (2 studies, 443 patients treated with parecoxib) RR 0.85 (95% CI: 0.14, 5.04) ***Constipation*** (2 studies, 396 patients treated with parecoxib) RR 0.91 (95% CI: 0.51, 1.61)	
Lloyd, R., et al. (2009) Intravenous or intramuscular parecoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD004771.pub4.	**Inclusion criteria** - double blind trials of single dose parecoxib - adult participants at least 15 years old - established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery - all languages **Exclusion criteria** - review articles - case reports - clinical observations - studies of experimental pain - studies where pain relief is assessed only by clinicians, nurses or carers (i.e. not patient-reported) - studies of less than four hours duration or studies that fail to present data over 4 to 6 hours post-dose. **Search period**	**Intervention:** Parecoxib administered as a single parenteral dose for postoperative pain **Control:** Matched placebo administered as a single parenteral dose for acute postoperative pain	**participants with at least 50% pain relief(PR) over 6 hours** *Dose 1mg* *(2 studies, 202 participants)* 50% PR: parecoxib 12% 50% PR: placebo 3% RB (95% CI): 4.9 (1.3 to 18) Number needed to treat to benefit (NNT) (95% CI): 10 (5.9 to 37) *Dose 2mg* *(2 studies, 201 participants)* 50% PR: parecoxib 16% 50% PR: placebo 3% RB (95% CI): 6.6 (1.8 to 24) NNT (95% CI): 7.2 (4.6 to 17) *Dose 5mg* *(2 studies, 202 participants)*	**Level of evidence** 1a (1) **Authors' conclusion** **"**Parecoxib is an effective analgesic in postoperative pain with a low incidence of adverse events when given as a single dose. At a dose of 20 mg to 40 mg it provided effective analgesia for 50 to 60% of patients with moderate to severe postoperative pain following various types of surgery. For every two participants treated with parecoxib 20 mg or 40 mg, one would experience at least 50% pain relief who would not have done so with placebo. Associated adverse events were generally mild to

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	Cochrane CENTRAL (searched in November 2008) MEDLINE via Ovid (searched in November 2008) EMBASE via Ovid (searched in November 2008) Oxford Pain Relief Database (searched in November 2008) (Update searches in August 2011) **Number of included studies (n participants)** 7 studies (1446 participants) were included		50% PR: parecoxib 30% 50% PR: placebo 3% RB (95% CI): 12.0 (3.4 to 42) NNT (95% CI): 3.7 (2.7 to 5.6) *Dose 10mg* *(2 studies, 200 participants)* 50% PR: parecoxib 35% 50% PR: placebo 3% RB (95% CI): 14.0 (3.9 to 49) NNT (95% CI): 3.1 (2.4 to 4.5) *Dose 20mg* *(7 studies, 591 participants)* 50% PR: parecoxib 53% 50% PR: placebo 11% RB (95% CI): 5.1 (3.5 to 7.4) NNT (95% CI): 2.4 (2.1 to 2.8) I^2=79% *Dose 40mg* *(6 studies, 509 participants)* 50% PR: parecoxib 63% 50% PR: placebo 17% RB (95% CI): 3.9 (2.9 to 5.3) NNT (95% CI): 2.2 (1.9 to 2.6) I^2=53% **Sensitivity analyses of the primary outcome** *Pain model, Intervention group (IG)/control group (CG)* Dental (20 to 50mg)(%): 61/3 NNT (95% CI): 1.7 (1.6 to 1.9) Other surgery (20 to 40mg)(%): 54/21 NNT (95% CI): 3.0 (2.4 to 4.0) *Route of administration, IG/CG* Intramuscular route (20mg)(%): 58/4 NNT (95% CI): 1.8 (1.5 to 2.3)	moderate in intensity." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: - List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Intravenous route (20mg)(%): 50/13 NNT (95% CI): 2.7 (2.2 to 3.5) Intramuscular route (40mg)(%): 67/16 NNT (95% CI): 2.0 (1.6 to 2.5) Intravenous route (40mg)(%): 60/18 NNT (95% CI): 2.4 (1.9 to 3.1) **number of participants using rescue medication over 24 hours** *Dose 10mg* NNTp: not calculated *Dose 20mg* NNTp: 7.5 (5.3 to 12.8) *Dose 40mg* NNTp: 3.3 (2.6 to 4.5) **weighted mean of median time (h) to use of rescue medication (IG/CG)** Dose 10mg (h): 3.1/1.0 Dose 20mg (h): 6.9/1.6 Dose 40mg (h): 10.6/2.0 **participants with one or more adverse events (IG/CG)** Dose All (%): 53/55 NNH (95% CI) any AE: not calculated Dose 20mg (%): 53/54 NNH (95% CI) any AE: not calculated Dose 40mg (%): 53/56 NNH (95% CI) any AE: not calculated **Forest plot of comparison: 4 Parecoxib (20 to 40 mg) vs. Placebo, outcome: 4.1 Number of participants using rescue medication in 24 h (IG/CG)**	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Parecoxib 20mg *(6 studies, 491 participants)* Subtotal (95% CI): 209/282 RR M-H, Fixed, 95% CI: 0.85 (0.80, 0.91) *Parecoxib 40mg* *(4 studies, 283 participants)* Subtotal (95% CI): 108/175 RR M-H, Fixed, 95% CI: 0.71 (0.64, 0.79) **Forest plot of comparison: 2 Parecoxib 20 mg vs. Placebo, outcome: 2.3 Number or participants with any adverse event (IG/CG)** (5 studies, 516 participants) Total (95% CI): 284/232 RR M-H, Fixed, 95% CI: 1.04 (0.89, 1.22) **Forest plot of comparison: 3 Parecoxib 40 mg vs. Placebo, outcome: 3.3 Number of participants with any adverse event (IG/CG)** (5 studies, 445 participants) Total (95% CI): 243/202 RR M-H, Fixed, 95% CI: 1.03 (0.88, 1.21)	
Romsing et al. Reduction of opioid-related adverse events using opioid-sparing analgesia with COX-2 inhibitors lacks documentation: A systematic review Acta Anaesthesiologica Scandinavica 2005. 49: 133-142.	**Inclusion criteria** - double-blinded RCTs of a COX-2 inhibitor versus placebo - administered systemically (i.e orally, intravenously or intramuscularly) - adults or children undergoing surgery - reported data on significant reduction in consumption of supplementary opioids and opioid-related adverse events - pain evaluation 0-24h postoperatively **Exclusion criteria** - sample sizes less than 10 patients **Search period** Medline (from 1966) Embase (from 1989) Cochrane Controlled Trials Register (2004) Last electronic search June 2004	**Intervention:** COX-2 inhibitors (single dose or repeatedly) **Control:** Placebo	**[all analyses with fixed-effect models]** **<u>Opioid-related adverse events</u>** **Nausea** (14 studies, 2226 participants) RR 1.04 (95% CI: 0.92, 1.18) **Vomiting** (18 studies, 2464 participants) RR 0.91 (95% CI: 0.74, 1.12) **Constipation** (6 studies, 1163 participants) RR 0.86 (95% CI: 0.69, 1.07) **Dizziness** (7 studies, 1472 participants) RR 0.70 (95% CI: 0.50, 0.96) NNT 33 (95% CI: 17, 125)	**Level of evidence** 1a (1) **Authors' conclusion** "The limitation of this review is the lack of quality of data of adverse events from the original trials. Although supplementary opioid consumption in all trials was significantly reduced by on average 35% with the COX-2 inhibitors, it was only sporadically possible to demonstrate a clinically important reduction in opioid-related adverse events. Data did not support the common opinion that opioid-sparing with COX-2 inhibitors provides much clinical beneficial effect with respect to opioid-related adverse events.

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	Number of included studies (n participants) 19 studies (1606 patients received a COX-2-inhibitor)		**Sedation** (4 studies, 945 participants) RR 0.94 (95% CI: 0.63, 1.41) **Pruritus** (8 studies, 1002 participants) RR 0.84 (95% CI: 0.57, 1.24) **Urinary retention** (3 studies, 549 participants) RR 1.20 (95% CI: 0.50, 2.91)	Future studies have to increase the awareness and proper reporting of adverse events in the postoperative period." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: - List of studies: + Study characteristics: + - Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: -
Wei Wei et al. Efficacy and safety of parecoxib sodium for acute postoperative pain: A meta-analysis. Experimental and Therapeutic Medicine 2013; 6: 525-531.	**Inclusion criteria** - RCTs - patients with no statistically significant differences in baseline characteristics - outcome variables according to patients' global evaluation of study medication (PGESM), pain relief 24, 48 and 72h after the initial intravenous dose 40 mg parecoxib, adverse reactions of opioids **Exclusion criteria** - a single injection of parecoxib sodium before PCA - PCA not combined with parecoxib sodium following surgery	**Intervention:** PCA combined with parecoxib sodium (successively injected for < 3 days) intravenously at 40+20/40 mg bid **Control:** Same volume of saline (Placebo)	**[all analyses with fixed-effect models]** **<u>PCA combined with parecoxib sodium versus PCA alone</u>** **<u>Patients' global evaluation of study medication</u>** **- after 24h after surgery** (2 studies, 165*) participants) RR 0.99 (95% CI: 0.80, 1.21), p=0.91 I^2=85% *Subgroup "effective results"*(2 studies, 114 participants) RR 1.41 (95% CI: 1.13, 1.75), p=0.002	**Level of evidence** 1a (1) **Authors' conclusion** "In conclusion, although certain limitations exist in this meta-analysis, based on the results of our meta-analysis, we identified that parecoxib is an effective and relatively safe option for acute postoperative pain. However, further high quality RCTs are required to determine the long-

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	Search period PubMed, Cochrane Central Register of Controlled Trials, EBSCO, Springer, Ovid and Chinese National Knowledge Infrastructure (CNKI) databases from January 1999 to January 2013, **Number of included studies (n participants)** 7 (1939)		I^2=0% *Subgroup "ineffective results"* (2 studies, 51 participants) RR 0.43 (95% CI: 0.26, 0.72), p=0.001 I^2=0% **- after 48h after surgery** (3 studies, 842*) participants) RR 0.98 (95% CI: 0.90, 1.07), p=0.67 I^2=93% *Subgroup "effective results"* (3 studies, 643 participants) RR 1.25 (95% CI: 1.15, 1.35), p < 0.00001 I^2=0% *Subgroup "ineffective results"* (3 studies, 201 participants) RR 0.44 (95% CI: 0.34, 0.57), p < 0.00001 I^2=0% **- after 72h after surgery** (2 studies, 715*) participants) RR 1.03 (95% CI: 0.95, 1.12), p=0.51 I^2=96% *Subgroup "effective results"* (2 studies, 585 participants) RR 1.30 (95% CI: 1.21, 1.40), p < 0.00001 I^2=41% *Subgroup "ineffective results"* (2 studies, 130 participants) RR 0.33 (95% CI: 0.23, 0.48), p < 0.00001 I^2=44% **<u>Adverse drug reactions</u>** **(intervention vs. control)** ***Respiratory depression*** (2 studies, 440*) participants) RR 0.84 (95% CI: 0.38, 1.83), p=0.66I^2=0%	term effects of parecoxib for postoperative pain." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: ? List of studies: - Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Pruritus (2 studies, 437 participants) RR 0.91 (95% CI: 0.54, 1.52), p=0.71I^2=0% ***Fever*** (5 studies, 1032*) participants) RR 0.34 (95% CI: 0.22, 0.53), p < 0.00001I^2=26% ***Headache*** (4 studies, 1155*) participants) RR 0.77 (95% CI: 0.47, 1.28), p=0.32I^2=0% ***Nausea and vomiting*** (3 studies, 567 participants) RR 0.69 (95% CI: 0.57, 0.83), p < 0.0001I^2=0% **Total events** RR 0.64 (95% CI: 0.54, 0.75), p < 0.00001 I^2=13% *) *note: inconsistent reporting of number of participants*	

+: low risk; -: high risk; ?: unclear risk; N/A: not applicable; CI: confidence interval; NR: not reported; NS: not significant; NNT: Number needed to treat; RR: relative risk; RB: Relative Benefit; OR: odds ratio; MD mean difference; WMD: weighted mean difference; SMD: standardized mean difference; I^2 und Q: Heterogenitätsmaße

Tab. 4 Systemische Pharmakologie: Paracetamol, Metamizol, NSAR, COX-2-Inhibitoren: *systematische Reviews zu verschiedenen Nichtopioid-Analgetika / Kombinationen von Nichtopioiden (Fragen #1 bis #5)*

Review / reference	**Inclusion, exclusion criteria, search period, number of included studies**	**Intervention group(s) (IG)/ control group (CG)**	**Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)**	**Level of evidence: CEbM 2009 (CEbM 2011)** **critical appraisal/ conclusion**
Bailey, E., et al. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth. Cochrane Database of Systematic Reviews, 2013 DOI: 10.1002/14651858.CD004624.pub2.	**Inclusion criteria** - RCTs, double-blinded - direct comparison of ibuprofen to paracetamol or the combination of both agents in the same drug given as a single dose postop. by mouth in any dose and in any formulation - patients who required the surgical removal of a lower wisdom tooth or teeth that required bone removal or at least having a baseline pain intensity of moderate to severe pain - patients who required removal of an additional tooth or teeth - age: 16-40 years **Exclusion criteria** - taking concurrent analgesia **Search period** The Cochrane Oral Health Group's Trials Register (to 20 May 2013) The Cochrane Central Register of Controlled Trials MEDLINE (1946 to 20 May 2013) EMBASE (1980 to 20 May 2013) MetaRegister of Controlled Trials (www.controlledtrials.com) (to 20 May 2013) **Number of included studies (n participants)** 7 (2241)	**Comparison 1** **Intervention:** Single dose oral Ibuprofen postop. **Control:** Single dose oral Paracetamol postop. **Comparison 2** **Intervention:** Single dose oral Ibuprofen and paracetamol combined postop. **Control:** Single dose of single drug (paracetamol or ibuprofen) postop.	**Comparison 1: Ibuprofen *versus* Paracetamol** **[analyses with random-effects models except for the outcome "number of patients using rescue medication at 8h"]** **Proportion of patients with >50% pain relief (TOTPAR) over 6h** (6 studies, 926participants) RR 1.45 (95% CI: 1.31, 1.61) p<0.00001 I^2=3% *Subgroup-Analysis* Ibuprofen 200 mg vs. paracetamol 1000 mg (1 study, 92 participants) RR 1.29 (95% CI: 0.90, 1.84), p=0.17 Ibuprofen 400 mg vs. paracetamol 1000 mg (5 studies, 646 participants) RR 1.47 (95% CI: 1.28, 1.69), p < 0.00001 I^2=19% Ibuprofen 400 mg vs. paracetamol 600 mg (1 study, 68 participants) RR 2.41 (95% CI: 1.13, 5.16), p=0.023 Ibuprofen 512 mg vs. paracetamol 1000 mg (1 study, 120 participants) RR 1.43 (95% CI: 1.15, 1.78), p=0.0015 **Proportion of patients with >50% pain relief (TOTPAR) over 2h** (6 studies, 926 participants) RR 1.29 (95% CI: 1.13, 1.46) p=0.00012 I^2=38% *Subgroup-Analysis* Ibuprofen 512 mg vs. paracetamol 1000 mg	**Level of evidence** 1a (1) **Author conclusion** "This review proves ibuprofen to be superior to paracetamol in terms of analgesic efficacy when used postoperatively for pain management following the surgical removal of lower wisdom teeth." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: ? Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(1 study, 120 participants) RR 1.28 (95% CI: 0.98, 1.67), p=0.067 Ibuprofen 400 mg vs. paracetamol 1000 mg (5 studies, 645 participants) RR 1.30 (95% CI: 1.09, 1.55), p=0.0034 I^2=52% Ibuprofen 200 mg vs. paracetamol 1000 mg (1 study, 93 participants) RR 1.09 (95% CI: 0.85, 1.41), p=0.48 Ibuprofen 400 mg vs. paracetamol 600 mg (1 study, 68 participants) RR 1.74 (95% CI: 0.96, 3.14), p=0.066 **Number of patients using rescue medication at 6h** (5 studies, 823 participants) RR 1.44 (95%CI: 1.26, 1.64), p < 0.00001 I^2=16% *Subgroup-Analysis* Ibuprofen 200 mg vs. paracetamol 1000 mg (1 study, 93 participants) RR 1.38 (95% CI: 0.94, 2.02), p=0.10 Ibuprofen 400 mg vs. paracetamol 1000 mg (4 studies, 542 participants) RR 1.50 (95% CI: 1.25, 1.79), p < 0.00001 I^2=37% Ibuprofen 512 mg vs. paracetamol 1000 mg (1 study, 120 participants) RR 1.17 (95% CI: 0.86, 1.60), p=0.31 Ibuprofen 400 mg vs. paracetamol 600 mg (1 study, 68 participants) RR 1.93 (95% CI: 0.87, 4.30), p=0.11 **Number of patients using rescue medication at 8h**	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(2 studies, 402 participants) RR 2.02 (95% CI: 1.57, 2.60), p < 0.00001 I^2=30% *Subgroup-Analysis* Ibuprofen 200 mg vs. paracetamol 500 mg (1 study, 75 participants) RR 2.63 (95% CI: 1.31, 4.25), p=0.0042 Ibuprofen 400 mg vs. paracetamol 500 mg (1 study, 75 participants) RR 2.77 (95% CI: 1.57, 4.89), p=0.00042 Ibuprofen 200 mg vs. paracetamol 1000 mg (1 study, 75 participants) RR 1.87 (95% CI: 1.10, 3.17), p=0.021 Ibuprofen 400 mg vs. paracetamol 1000 mg (2 studies, 177 participants) RR 1.66 (95% CI: 1.11, 2.48), p=0.013 I^2=71% **Comparison 2: Combined (ibuprofen and paracetamol) *versus* single drugs** **[analyses with fixed effects models]** **Proportion of patients with >50% pain relief (TOTPAR) over 6h** Paracetamol 1000 mg / ibuprofen 400 mg vs paracetamol 1000 mg or ibuprofen 400 mg (1 study, 170 participants) RR 1.77 (95% CI: 1.32, 2.39), p=0.0002 **Proportion of patients with >50% pain relief (TOTPAR) over 2h** Paracetamol 1000 mg / ibuprofen 400 mg vs paracetamol 1000 mg or ibuprofen 400 mg (1 study, 170 participants) RR 1.29 (95% CI: 0.91, 1.85), p=0.15 **Number of patients using rescue medication at 8h**	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Paracetamol 1000 mg / ibuprofen 400 mg vs paracetamol 1000 mg or ibuprofen 400 mg (2 studies, 467 participants) RR 1.60 (95% CI 1.36, 1.88), p < 0.00001 I^2=82%	
Barden, J., et al., Relative efficacy of oral analgesics after third molar extraction. Br Dent J, 2004. 197(7): p. 407-11; discussion 397.	**Inclusion criteria** - study in third molar extraction (postoperative dental pain) - full journal publication (except valdecoxib which included information from a poster) - RCTs which included single dose treatment groups of oral analgesic and placebo -double blind design - baseline postoperative pain of moderate to severe intensity - age >15years - at least 10 patients per group -pain outcome measures TOTPAR or SPID over 4-6h **Exclusion criteria** Not stated **Search period** the Cochrane Library Biological Abstracts, MEDLINE PubMed the Oxford Pain Relief database search dates in 2002 **Number of included studies (n participants)** 155 (14150) without 1 dihydrocodeine-study: 154 (14051)	**Intervention:** Single dose oral analgesic **Control:** Placebo	**Number (%) of patients achieving at least 50% pain relief, intervention vs. control** ***Valdecoxib 40mg*** (4 studies, 473 patients) Mean proportion (%): 73/10 Relative Benefit 7.3 (95% CI: 4.8, 11.2) NNT 1.6 (95% CI: 1.4, 1.7) ***Diclofenac 100 mg*** (2 studies, 204 patients) Mean proportion (%): 70/8 Relative Benefit 8.9 (95% CI: 4.5, 17.5) NNT 1.6 (95% CI: 1.4, 1.9) ***Valdecoxib 20 mg*** (2 studies, 204 patients) Mean proportion (%): 68/8 Relative Benefit 8.8 (95% CI: 4.5, 17.3) NNT 1.7 (95% CI: 1.4, 2.0) ***Diclofenac 50 mg*** (5 studies, 367 patients) Mean proportion (%): 59/12 Relative Benefit 4.9 (95% CI: 3.3, 7.5) NNT 2.1 (95% CI: 1.8, 2.6) ***Rofecoxib 50 mg*** (6 studies, 819 patients) Mean proportion (%): 57/9 Relative Benefit 6.6 (95% CI: 4.4, 9.9) NNT 2.1 (95% CI: 1.9, 2.3) ***Ibuprofen 400 mg*** (37 studies, 3402 patients) Mean proportion (%): 56/12 Relative Benefit 4.7 (95% CI: 4.0, 5.4) NNT 2.2 (95% CI: 2.1, 2.4)	**Level of evidence** 1a (1) **Author conclusion** "NSAIDs and COX-2 inhibitors have the lowest (best) NNTs. They may also have fewer adverse effects after third molar surgery, though conclusive evidence is lacking. At least 80% of analgesic prescribing by UK dentists is in line with the best available evidence on efficacy and safety." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: ? List of studies: - Study characteristics: - Critical appraisal: - Conclusion: + Combining findings: ? Publication bias: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Ibuprofen 200 mg (14 studies, 1194 patients) Mean proportion (%): 46/9 Relative Benefit 4.6 (95% CI: 3.5, 6.1) NNT 2.7 (95% CI: 2.4, 3.1) ***Ibuprofen 600 mg*** (3 studies, 203 patients) Mean proportion (%): 479/43 Relative Benefit 1.9 (95% CI: 1.5, 2.5) NNT 2.8 (95% CI: 2.0, 4.3) ***Celecoxib 200 mg*** (1 studies, 136 patients) Mean proportion (%): 43/9 Relative Benefit 4.8 (95% CI: 1.8, 12.7) NNT 2.9 (95% CI: 2.1, 4.8) ***Paracetamol 975/1000 mg*** (10 studies, 1038 patients) Mean proportion (%): 37/9 Relative Benefit 3.8 (95% CI: 2.8, 5.2) NNT 3.7 (95% CI: 3.1, 4.7) ***Paracetamol 600/650 + codeine 60 mg*** (12 studies, 911 patients) Mean proportion (%): 48/19 Relative Benefit 2.5 (95% CI: 1.9, 3.1) NNT 4.2 (95% CI: 3.4, 5.5) ***Paracetamol 600/650 mg*** (10 studies, 1265 patients) Mean proportion (%): 36/12 Relative Benefit 2.9 (95% CI: 2.3, 3.7) NNT 4.2 (95% CI: 3.6, 5.2) ***Aspirin 600/650 mg*** (46 studies, 3635 patients) Mean proportion (%): 36/15 Relative Benefit 2.5 (95% CI: 2.2, 2.9) NNT 4.7 (95% CI: 4.2, 5.4)	Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Paracetamol 300 + codeine 30 mg (3 studies, 299 patients) Mean proportion (%): 29/9 Relative Benefit 3.3 (95% CI: 1.8, 6.2) NNT 5.4 (95% CI: 3.7, 9.7) **Adverse Events: number (%) of patients harmed with, intervention vs. control** ***Valdecoxib 40mg*** (3 studies, 324 patients) Mean proportion (%): 35/53 RR 0.6 (95% CI: 0.5, 0.8) ***Diclofenac 100 mg*** (1 studies, 104 patients) Mean proportion (%): 4/4 RR 1.0 (95% CI: 1.2, 6.8) ***Valdecoxib 20 mg*** (2 studies, 203 patients) Mean proportion (%): 36/53 RR 0.7 (95% CI: 0.5, 0.9) ***Diclofenac 50 mg*** (4 studies, 432 patients) Mean proportion (%): 7/6 RR 1.2 (95% CI: 0.6, 2.4) ***Rofecoxib 50 mg*** (6 studies, 819 patients) Mean proportion (%): 33/39 RR 0.9 (95% CI: 0.7, 1.1) ***Ibuprofen 400 mg*** (19 studies, 1777 patients) Mean proportion (%): 13/12 RR 1.1 (95% CI: 0.8, 1.4) ***Ibuprofen 200 mg*** (10 studies, 926 patients) Mean proportion (%): 15/19	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			RR 0.8 (95% CI: 0.6, 1.0) ***Paracetamol 975/1000 mg*** (9 studies, 1300 patients) Mean proportion (%): 24/20 RR 1.1 (95% CI: 0.9, 1.3) ***Paracetamol 600/650 + codeine 60 mg*** (10 studies, 824 patients) Mean proportion (%): 25/14 RR 1.8 (95% CI: 1.3, 2.5) NNH 5.3 (95% CI: 4.1, 7.4) ***Paracetamol 600/650 mg*** (7 studies, 457 patients) Mean proportion (%): 14/9 RR 1.6 (95% CI: 0.9, 2.7) ***Aspirin 600/650 mg*** (36 studies, 3031 patients) Mean proportion (%): 12/12 RR 1.0 (95% CI: 0.8, 1.2) ***Paracetamol 300 + codeine 30 mg*** (3 studies, 299 patients) Mean proportion (%): 15/16 RR 0.9 (95% CI: 0.6, 1.6)	
Burton P. et al. Nonsteroidal Anti-inflammatory Drugs and Anastomotic Dehiscence in Bowel Surgery: Systematic Review and Meta-Analysis of Randomized, Controlled Trials. Disease of the Colon & Rectum, 2013, 56(1), p. 126-134.	**Inclusion criteria** - RCTs - adults >16 y - surgery with formation of at least 1 anastomosis of the small bowl, colon, or rectum - trials reported in 1999 or later - incidence of anastomotic dehiscence within 30 days of surgery - unpublished trials - NSAID given during or within 48 hours of surgery **Exclusion criteria** - studies which are not directly comparing NSAID with control	**Intervention:** NSAIDs **Control:** other analgesics or placebo	**[all analyses with fixed-effect models]** **Anastomotic dehiscence** (6 studies, 480 participants) Peto OR 2.16 (0.85, 5.53), p=0.11 I^2=0.0% **Movement-evoked pain** (4 studies, 260 participants) I^2=0.0% **On postoperative day 0** MD -0.06 (-0.27, -0.05) **On postoperative day 1** MD -0.10 (-0.26, -0.05)	**Level of evidence** 1a (1) **Author conclusion** "This systematic review and meta-analysis of RCTs did not demonstrate a statistically significant increase in risk of bowel anastomotic dehiscence with perioperative NSAID therapy." ***Methodological quality*** A-priori design: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	Search period Databases (Medline, the Cochrane Library, Scopus, and the World Health Organization International Clinical Trials Registry Platform) Available abstracts from recent (5 years or later) major conferences (including the American Society of Colon and Rectal Surgeons annual meeting, the American College of Surgeons Clinical Congress, Association of Coloproctology of Great Britain and Ireland annual meeting, the annual meeting of the European Society of Coloproctology, and the American Society of Anesthesiologists annual meeting) were hand searched. All sources were last searched in May 2011 **Number of included studies (n participants)** 6 (562)		**On postoperative day 2** MD -0.28 (-0.43, -0.13), p=0.0002 I^2=0.0% **Pain score at rest** (4 studies, 260 participants) **Postoperative day = 0** MD -0.16 (-0.27, -0.05), p=0.004 **Postoperative day = 1** MD -0.23 (-0.42, -0.04), p=0.02 **Postoperative day = 2** MD -0.11 (-0.19, -0.02), p=0.001 **Opioid usage during the first 48 hours after surgery** (5 studies, 439 participants) MD -21.86 (-28.07, -15.66), p<0.00001 I^2=49% **Return to bowel motions** (5 studies, 505 participants) MD -0.43 (-0.66, -0.21), p<0.0002 I^2=10% ***Subgroup-analysis*** 1. non selective NSAID **Anastomotic dehiscence** (6 studies, 351 participants): Peto OR 2.14 (0.78, 5.84), p=0.14 2. COX- inhibitors **Anastomotic dehiscence** (6 studies, 186 participants): Peto OR 1.46 (0.25, 8.60), p=0.67	Two reviewers: + Literature search: + Status of publication: + List of studies: - Study characteristics: - Critical appraisal: + Conclusion: + Combining findings: + Publication bias: + Conflict of interest: -
Derry, CJ. et al. Single dose oral ibuprofen plus	**Inclusion criteria** - double-blind trials of single dose oral ibuprofen plus paracetamol compared with placebo or the same	**Intervention:** Combination of ibuprofen and paracetamol	**[all analyses with fixed effect models]** **Comparison 1: Ibuprofen 200 mg + paracetamol 500 mg**	**Level of evidence** 1a (1)

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
paracetamol (acetaminophen) for acute postoperative pain. Cochrane Database of Systematic Reviews 2013, DOI: 10.1002/14651858.CD010210.pub2.	dose of ibuprofen alone - at least 10 participants randomly allocated to each treatment group - multiple dose studies if appropriate data from the first dose were available, and cross-over studies provided that data from the first arm were presented separately - age > 15 years - established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery - For postpartum pain, we included studies if the pain investigated was due to episiotomy or Caesarean section irrespective of the presence of uterine cramps **Exclusion criteria** - review articles, case reports, and clinical observations - studies of experimental pain - studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported); - studies of less than four hours duration or studies that fail to present data over four to six hours post dose - studies investigating pain due to uterine cramps alone **Search period** The Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library, (Issue 4 of 12, 2013); MEDLINE (via OVID) (1950 to 21 May 2013); EMBASE (via OVID) (1974 to 21 May 2013); Oxford Pain Relief Database (Jadad 1996). www.clinictrials.gov **Number of included studies (n participants)** 3 (1647)	**Control:** Placebo or the same dose of ibuprofen alone	**versus placebo** **Participants achieving at least 50% of maximum pain relief over six hours** (3 studies, 508 participants) RR 10.29 (95%CI: 5.70, 18.58), p < 0.00001 I^2=33% NNT 1.6 (95%CI: 1.5, 1.8) **Participants using rescue medication within 8 h** (2 studies, 280 participants) RR 0.46 (95%CI: 0.37, 0.58), p < 0.00001 I^2=85% **Participants with any adverse event** (3 studies, 508 participants) RR 0.69 (95%CI: 0.55, 085), p=0.000075 I^2=63% **Comparison 2: Ibuprofen 400 mg + paracetamol 1000 mg versus placebo** **Participants achieving at least 50% of maximum pain relief over six hours** (3 studies, 543 participants) RR 11.21 (95%CI: 6.18, 20.35), p < 0.00001 I^2=51% NNT: 1.5 (95%CI: 1.4, 1.7) **Participants using rescue medication within 8 h** (2 studies, 320 participants) RR 0.31 (95%CI: 0.24, 0.40), p < 0.00001 I^2=0% **Participants with any adverse event** (3 studies, 543 participants) RR 0.62 (95%CI: 0.50, 077), p=0.000013 I^2=86% **Comparison 3: Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg**	**Author conclusion** "Ibuprofen plus paracetamol combinations provided better analgesia than either drug alone (at the same dose), with a smaller chance of needing additional analgesia over about eight hours, and with a smaller chance of experiencing an adverse event." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: ? Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Participants achieving at least 50% of maximum pain relief over six hours (2 studies, 359 participants) RR 1.30 (95%CI: 1.10, 1.55), p=0.0028 I^2=63% NNT: 5.4 (95%CI: 3.5, 12) **Participants using rescue medication within 8 h** (2 studies, 359 participants) RR 0.57 (95%CI: 0.42, 0.77), p=0.00026 I^2=61% **Participants with any adverse event** (2 studies, 359 participants) RR 0.81 (95%CI: 0.66, 0.99), p=0.038 I^2=56%	
Elia, N., C. Lysakowski, and M.R. Tramer. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology, 2005. 103(6): p. 1296-304.	**Inclusion criteria** - RCTs testing acetaminophen, NSAIDs or COX-2 inhibitors for pain management after surgery - trials in adults that reported the 24h cumulative dose of morphine **Exclusion criteria** - use of intrathecal opioids or peripheral nerve blocks - less than 10 patients per group **Search period** MEDLINE EMBASE CINHAL Biosis Indmed Cochrane Controlled Trials Register Last electronic search on July 21, 2004 **Number of included studies (n participants)** 52 (4893)	**Intervention:** Acetaminophen NSAIDs COX-2 inhibitors **Control:** Placebo or no treatment	**[all analyses with random effects models]** **<u>24h morphine consumption</u>** **(IG / CG)** **Acetaminophen** ***Multiple dose*** (713 participants) WMD -8.31 (95% CI: -10.9, -5.72) **NSAIDS** ***Single dose*** (1029 participants) WMD -10.3 (95% CI: -18.3, -2.34) ***Multiple dose*** (893 participants) WMD -19.7 (95% CI: -26.3, -13.0) ***Continuous*** (529 participants) WMD -18.3 (95% CI: -26.8, -9.74) **COX-2 inhibitors** ***Single dose – 200mg celocoxib*** (139 participants) WMD -7.22 (95% CI: -10.6, -3.82) ***Single dose – 50mg rofecoxib***	**Level of evidence** 1a (1) **Author conclusion** "A decrease in morphine consumption is not a good indicator of the usefulness of a supplemental analgesic. There is evidence that the combination of nonsteroidal anti-inflammatory drugs with patient-controlled analgesia morphine offers some advantages over morphine alone." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(182 participants) WMD -27.8 (95% CI: -44.3, -11.4) ***Multiple low dose – valdecoxib and parecoxib 20mg/12h*** (545 participants) WMD -9.99 (95% CI: -13.4, -6.58) ***Multiple high dose – valdecoxib and parecoxib 40mg/12h and parecoxib 40mg/6h*** (946 participants) WMD -13.3 (95% CI: -17.8, -8.8.1) **<u>VAS score for pain intensity at rest at 24h</u>** **(IG/CG)** **Acetaminophen** ***Multiple dose*** (355 participants) WMD -0.29 (95% CI: -0.71, 0.14) **NSAIDS** ***Single dose*** (759 participants) WMD -0.75 (95% CI: -1.61, 0.11) ***Multiple dose*** (553 participants) WMD -1.00 (95% CI: -1.25, -0.75) ***Continuous*** (426 participants) WMD -0.97 (95% CI: -1.37, -0.57) **<u>Morphine-related adverse events</u>** **(intervention vs. control)** **Acetaminophen** ***Resp. depression*** (337 participants) Mean proportion (%): 3/5.9 RR 0.48 (95% CI: 0.17, 1.32) ***PONV*** (432 participants) Mean proportion (%): 22/27 RR 0.78 (95% CI: 0.56, 1.07) ***Urinary retention***	List of studies: - Study characteristics: - Critical appraisal: ? Conclusion: + Combining findings: + Publication bias: - Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(260 participants) Mean proportion (%): 7.2/8.9 RR 0.76 (95% CI: 0.34, 1.68) ***Sedation*** (366 participants) Mean proportion (%): 12/14 RR 0.86 (95% CI: 0.53, 1.38) **NSAIDS** ***Resp. depression*** (911 participants) Mean proportion (%): 3.9/6.5 RR 0.65 (95% CI: 0.39, 1.11) ***Nausea*** (934 participants) Mean proportion (%): 51/53 RR 0.92 (95% CI: 0.82, 1.04) ***Vomiting*** (955 participants) Mean proportion (%): 21/27 RR 0.84 (95% CI: 0.67, 1.04) ***PONV*** (1387 participants) Mean proportion (%): 22/29 RR 0.72 (95% CI: 0.61, 0.86) ***Urinary retention*** (624 participants) Mean proportion (%): 13/15 RR 1.00 (95% CI: 0.68, 1.48) ***Pruritus*** (1369 participants) Mean proportion (%): 11/13 RR 0.78 (95% CI: 0.59, 1.04) ***Dizziness*** (1187 participants) Mean proportion (%): 7.3/8.1 RR 0.88 (95% CI: 0.60, 1.28) ***Sedation*** (1304 participants) Mean proportion (%): 13/15 RR 0.69 (95% CI: 0.54, 0.88) ***Bowel dysfunction*** (793 participants)	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Mean proportion (%): 0.5/0.8 RR 0.66 (95% CI: 0.11, 3.96) **COX-2 inhibitors** ***Nausea*** (1339 participants) Mean proportion (%): 43/39 RR 1.09 (95% CI: 0.95, 1.25) ***Vomiting*** (1375 participants) Mean proportion (%): 18/15 RR 1.14 (95% CI: 0.89, 1.47) ***PONV*** (178 participants) Mean proportion (%): 18/24 RR 0.70 (95% CI: 0.39, 1.26) ***Urinary retention*** (681 participants) Mean proportion (%): 3.9/3.1 RR 1.26 (95% CI: 0.53, 2.97) ***Pruritus*** (595 participants) Mean proportion (%): 13/13 RR 0.92 (95% CI: 0.58, 1.46) ***Dizziness*** (872 participants) Mean proportion (%): 11/14 RR 0.74 (95% CI: 0.52, 1.07) ***Sedation*** (671 participants) Mean proportion (%): 8.9/12 RR 0.75 (95% CI: 0.47, 1.20) ***Bowel dysfunction*** (726 participants) Mean proportion (%): 27/27 RR 1.01 (95% CI: 0.80, 1.29) **Adverse effects related to nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors** **Intervention vs. control** **NSAIDs**	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			GI bleeding (282 participants) Mean proportion (%): 2.3/0.0 OR 5.12 (95% CI: 0.65, 40.6) ***Oliguria*** (969 participants) Mean proportion (%): 4.3/2.2 OR 1.69 (95% CI: 0.82, 3.47) ***Renal failure*** (216 participants) Mean proportion (%): 0.9/0.0 OR 7.03 (95% CI: 0.14, 355) ***Any bleeding*** (1364 participants) Mean proportion (%): 1.7/0.2 OR 4.54 (95% CI: 1.54, 13.4) ***Severe bleeding*** (669 participants) Mean proportion (%): 1.7/0.0 OR 6.08 (95% CI: 1.33, 27.9) **COX-2 inhibitors** ***GI bleeding*** (663 participants) Mean proportion (%): 0.7/0.0 OR 4.45 (95% CI: 0.40, 50.0) ***Oliguria*** (671 participants) Mean proportion (%): 12/8.1 OR 1.47 (95% CI: 0.87, 2.48) ***Renal failure*** (803 participants) Mean proportion (%): 1.4/0.0 OR 4.86 (95% CI: 1.01, 23.4)	
Gurusamy KS. et al. Pharmacological interventions for prevention or treatment of postoperative pain in people undergoing laparoscopic cholecystectomy.	**Inclusion criteria** - RCTs - adults - people undergoing laparoscopic cholecystectomy irrespective of age, elective or emergency surgery **Exclusion criteria** - quasi-randomized trials	**Intervention:** NSAIDs (administered orally, sublingually, intravenously, and rectally) **Control:** Inactive controls (no intervention or placebo)	**[all analyses with fixed-effect models]** **Morbidity** (3 studies, 543 participants) RR 0.75 (0.37, 1.53), p=0.43 I^2=11% **Pain (4 to 8h)** (11 studies, 999 participants)	**Level of evidence** 1a (1) **Author conclusion** "There is evidence of very low quality that different pharmacological agents including non-steroidal anti-inflammatory drugs (NSAIDs),

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
Cochrane Database of Systematic Reviews, 2014 Issue 3. Art. No.: CD008261. DOI: 10.1002/14651858.CD008261.pub2.	**Search period** Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Science Citation Index Expanded (Royle 2003), The World Health Organization International Clinical Trials Registry Platform portal (WHO ICTRP) (apps.who.int/trialsearch/) to March 2013 **Number of included studies (n participants)** (25 (2505) for quantitative analysis) 18 studies comparing NSAIDs with inactive control		RR -0.88 (-1.07, -0.70), p<0.00001 I^2=85% **Pain (9 to 24h)** (9 studies, 707 participants) RR -0.50 (-0.67, -0.33), p<0.00001 I^2=88% <u>*Sensitivity analysis*</u> **Morbidity (sensitivity analysis: with imputed data** (5 studies, 2268 participants) RR 0.80 (0.59, 1.07), p=0.13 I^2=36% Best-best (5 studies, 567 participants) RR 0.75 (0.36, 1.53), p=0.42 I^2=9% Best-worst (5 studies, 567 participants) RR 0.43 (0.23, 0.82), p=0.0097 I^2=0.0% Worst-best (5 studies, 567 participants) RR 1.46 (0.79, 2.67), p=0.22 I^2=80% Worst-worst (5 studies, 567 participants) RR 0.83 (0.50, 1.36), p=0.45 I^2=0.0% **Pain (4 to 8h) (sensitivity analysis, studies without trials with imputed data)** (8 studies, 433 participants) RR -0.91 (-1.10,-0.71), p<0.00001 I^2=93% **Pain (9 to 24h) (sensitivity analysis, studies without trials with imputed data)** (4 studies, 433 participants)	opioid analgesics, and anticonvulsant analgesics reduce pain scores in people at low anaesthetic risk undergoing elective laparoscopic cholecystectomy. However, the decision to use these drugs has to weigh the clinically small reduction in pain against uncertain evidence of serious adverse events associated with many of these agents." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			RR -0.50 (-0.67, -0.33), p<0.00001 I^2=94% **<u>Pain (4 to 8h) stratified by drug</u>** Celecoxib (1 study, 38 participants) RR -1.03 (-7.01, 4.95), p=0.74 I^2=n.a. Diclofenac (1 study, 49 participants) RR -2.50 (-7.56, 2.56), p=0.33 I^2=n.a. Etofenomate (1 study, 118 participants) RR -0.34 (-0.60, -0.08), p=0.0093 I^2=n.a. Flurbiprofen (1 study, 23 participants) RR -2.26 (-3.26, -1.26), p<0.00001 I^2=n.a. Lornoxicam (1 study, 150 participants) RR -2.70 (-3.13, -2.26), p<0.00001 I^2=0.0% Metamizol (1 study, 40 participants) RR 0.20 (-0.74, 1.14), p=0.68 I^2=n.a. Paracetamol (3 studies, 146 participants) RR -0.10 (-1.02, 0.82), p=0.83 I^2=0.0% Parecoxib (4 studies, 355 participants) RR -0.76 (-1.21, -0.31), p=0.0010 I^2=0.0% Tenoxicam (2 studies, 80 participants) RR -0.46 (-4.42, 3.51), p=0.82 I^2=0.0% **<u>Pain (9 to 24h) stratified by drug</u>**	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Celecoxib (1 study, 38 participants) RR -0.37 (-5.52, 4.78), p=0.89 I^2=n.a. Diclofenac (1 study, 49 participants) RR 0.50 (-3.94, 4.94), p=0.83 I^2=n.a. Etofenomate (1 study, 118 participants) RR 0.01 (-0.22, 0.24), p=0.93 I^2=n.a. Flurbiprofen (1 study, 23 participants) RR -0.98 (-2.08, 0.12), p=0.080 I^2=n.a. Lornoxicam (1 study, 150 participants) RR -2.07 (-2.42, -1.72), p<0.00001 I^2=79% Metamizol (1 study, 40 participants) RR 0.40 (-0.35, 1.15), p=0.30 I^2=n.a. Paracetamol (2 studies, 77 participants) RR 0.21 (-0.48, 0.90), p=0.55 I^2=0.0% Parecoxib (3 studies, 132 participants) RR -0.50 (-1.08, 0.08), p=0.088 I^2=0.0% Tenoxicam (2 studies, 80 participants) RR -0.60 (-4.10, 2.89), p=0.73 I^2=0.0% **<u>Pain (4 to 8h) stratified by time</u>** (Before (4 studies, 285 participants) RR -0.35 (-0.60, -0.09), p=0.0078 I^2=0.0%) (During (1 study, 150 participants)	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			RR -2.70 (-3.13, -2.26), p<0.00001 I^2=0.0%) After (4 studies, 271 participants) RR -0.73 (-1.17, -0.29), p=0.0010 I^2=64% Before and after (2 studies, 293 participants) RR -0.69 (-1.28, -0.11), p=0.019 I^2=0.0% **<u>Pain (9 to 24h) stratified by time</u>** (Before (4 studies, 285 participants) RR 0.01 (-0.22, 0.24), p=0.92 I^2=0.0%) (During (1 study, 150 participants) RR -2.07 (-2.42, -1.72), p<0.00001 I^2=79%) After (3 studies, 202 participants) RR -0.16 (-0.53, 0.20), p=0.37 I^2=32% Before and after (1 study, 70 participants) RR 0.09 (-3.62, 3.80), p=0.96 I^2=n.a.	
Jirarattanaphochai, K. and S. Jung. Nonsteroidal antiinflammatory drugs for postoperative pain management after lumbar spine surgery: a meta-analysis of randomized controlled trials. J Neurosurg Spine, 2008. 9(1): p. 22-31.	**Inclusion criteria** - RCTs, double-blinded - reported pain scores and opioid consumption - any types, doses and administrations of NSAIDs combined with opioid analgesics alone **Exclusion criteria** studies incorporating a local steroid, local anesthetic technique, or nerve block as part of the anesthetic regimen **Search period** Electronic databases: PubMed, MEDLINE, EMBASE, Cochrane CENTRAL, CINAHL, PsycINFO, AMED Science Citation Index Expanded, Google and Yahoo	**Intervention** NSAIDs in addition to opioid analgesics in lumbar spine surgery (nonselective NSAIDs: ketorolac, ketoprofen, indomethacin, flurbiprofen, lornoxicam, piroxicam; selective COX-2 inhibitors: celecoxib, rofecoxib, parecoxib) administration in part preop. or postop. or both **Control** opioid analgesics alone	**[all analyses with random effects models]** ***<u>VAS pain score</u>*** ***At 0-2h (in PACU)*** (8 studies, 385 participants) WMD -8.98 (95% CI: -14.80, -3.17), p=0.002 I^2=68.1% *Subgroup nonselective NSAIDs* (3 studies, 130 participants) WMD -15.23 (95% CI: -31.87, -1.40), p=0.07 I^2=84.3% *Subgroup COX-2 inhibitors* (5 studies, 255 participants)	**Level of evidence** 1a (1) **Author conclusion** "Our meta-analysis offers evidence that NSAIDs provide superior analgesia (reduced VAS pain scores and reduced narcotic consumption) in comparison with conventional analgesia in patients undergoing lumbar spine surgery for discectomy or laminectomy and spinal fusion. Despite sig-nificantly lower opioid consumption in patients using NSAIDs, there is no decrease in

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	Number of included studies (n participants) 17 (789)		WMD -5.80 (95% CI: -10.36, -1.24), p=0.01 I^2=34.3% ***At 4-6h*** (11 studies, 477 participants) WMD -10.35 (95% CI: -12.99, -7.71), p < 0.00001 I^2=10% *Subgroup nonselective NSAIDs* (6 studies, 243 participants) WMD -9.83 (95% CI: -13.52, -6.14), p < 0.00001 I^2=0% *Subgroup COX-2 inhibitors* (5 studies, 255 participants) WMD -10.36 (95% CI: -15.16, -5.57), p < 0.0001 I^2=47.6% ***At 24h*** (14 studies, 652 participants) WMD -10.45 (95% CI: -14.02, -6.88), p < 0.00001 I^2=67.4% *Subgroup nonselective NSAIDs* (9 studies, 418 participants) WMD -14.47 (95% CI: -19.03, -9.90), p < 0.00001 I^2=65.7% *Subgroup COX-2 inhibitors* (5 studies, 234 participants) WMD -3.79 (95% CI: -6.89, -0.69), p=0.02 I^2=67.4% *Subgroup non-PCA morphine trials excluded* (9 studies, 374 patients) WMD -7.14 (95% CI: -9.75 to -4.52) I^2=35% *Subgroup low-quality trials excluded* (9 studies, 449 patients) WMD -11.30 (95% CI: -16.70 to -5.89) I^2=57%	adverse effects. Further well-designed, large, randomized trials are needed to con-firm these findings." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: - Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			At 48h (5 studies, 255 participants) WMD -9.06 (95% CI: -20.65, 2.53), p=0.006 I^2=79.9% *Subgroup nonselective NSAIDs* (4 studies, 221 participants) WMD -15.66 (95% CI: -20.87, -10.45), p < 0.00001 I^2=0% *Subgroup COX-2 inhibitors* (1 study, 34 participants) WMD 24.70 (95% CI: 6.93, 42.47), p=0.006 Test for heterogeneity n.a. ***At 72h*** (2 studies, 133 participants) WMD -8.92 (95% CI: -15.67, -2.18), p=0.01 I^2=0% **<u>Cumulative morphine consumption</u>** ***At 0-2h (in PACU)*** (8 studies, 385 patients) WMD -2.22 (95% CI: -3.63, -0.82), p=0.002 I^2=58% *Subgroup nonselective NSAIDs* (3 studies, 130 participants) WMD -1.55 (95% CI: -2.83, -0.28), p=0.02 I^2=0% *Subgroup COX-2 inhibitors* (5 studies, 255 participants) WMD -2.80 (95% CI: -5.01, -0.59), p=0.01 I^2=68.2% ***At 4-6h*** (6 studies, 204 patients) WMD -6.90 (95% CI: -8.28, -5.52), p < 0.00001I^2=0% *Subgroup nonselective NSAIDs*	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(3 studies, 90 participants) WMD -5.38 (95% CI: -7.53, -3.23), p < 0.00001 I^2=0% *Subgroup COX-2 inhibitors* (3 studies, 114 participants) WMD -7.97 (95% CI: -9.77, -6.17), p < 0.00001 I^2=0% ***At 0-24h*** (13 studies, 582 patients) WMD -20.66 (95% CI: -32.32, -9.00), p=0.0005I^2=96.4% *Subgroup nonselective NSAIDs* (8 studies, 348 participants) WMD -14.76 (95% CI: -24.74, -4.79), p=0.004 I^2=89.4% *Subgroup COX-2 inhibitors* (5 studies, 234 participants) WMD -30.18 (95% CI: -46.17, -14.19), p=0.0002 I^2=95% *Subgroup non-PCA morphine trials excluded* (9 studies, 360 patients) WMD -25.46 (95% CI: -36.68 to -14.23) I^2=92% *Subgroup low-quality trials excluded* (7 studies, 301 patients) WMD -17.21 (95% CI: -35.06 to -0.63) I^2=97% ***At 0-48h*** (3 studies, 117 patients) WMD -8.40 (95% CI: -22.15, 5.36), p=0.23I^2=71.2% *Subgroup nonselective NSAIDs* (2 studies, 83 participants) WMD -14.80 (95% CI: -25.99, -3.61), p=0.01 I^2=0% *Subgroup COX-2 inhibitors* (1 study, 34 participants)	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			WMD 1.20 (95% CI: -4.53, 6.93), p=0.68 Test for heterogeneity n.a.***At 25-48h*** (2 studies, 135 patients) WMD -8.23 (95% CI: -22.23, 5.77), p=0.25I^2=93% ***At 49-72h*** (2 studies, 135 patients) WMD -5.00 (95% CI: -9.11, -0.89), p=0.02I^2=0% **<u>Effect of NSAIDs on opioid adverse events</u>** ***Postop nausea and/or vomiting*** (10 studies, 472 patients) RR 0.79 (95% CI: 0.62, 1.01) I^2=0% ***Sedation*** (6 studies, 263 patients) RR 0.79 (95% CI: 0.41, 1.53) I^2=47% ***Pruritus*** (3 studies, 113 patients) RR 0.40 (95% CI: 0.13, 1.20) I^2=0% ***Urinary retention*** (5 studies, 203 patients) RR 1.11 (95% CI: 0.64, 1.91) I^2=3.8% ***Respiratory depression*** (2 studies, 70 patients) RR 0.21 (95% CI: 0.03, 1.77) I^2=0% **Adverse events of NSAIDs** ***Periop bleeding*** (5 studies, 305 patients) WMD -22.19 (95% CI: -46.38, 2.44) I^2=38% ***Dyspepsia*** (2 studies, 138 patients)	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			RR 0.59 (95% CI: 0.12, 2.87) I^2=46% ***Headache*** (1 studies, 40 patients) RR 0.20 (95% CI: 0.03, 1.56) ***Nonunion*** (1 studies, 80 patients) RR 1.33 (95% CI: 0.32, 5.58)	
Lee A. et al. Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD002765. DOI: 10.1002/14651858.CD002765.pub3.	**Inclusion criteria** - RCTs - quasi-randomized controlled trials - adults with normal preoperative renal function - renal outcome measures - outcome within the first 48h of surgery **Exclusion criteria** - no immediate NSAID treatment - patients with history of renal insufficiency **Search period** The Cochrane Central Register of Controlled Trials (CENTRAL, in The Cochrane Library, Issue 2, 2006) Electronic databases: MEDLINE 1966-May 2006, EMBASE 1980-May 2006 **Number of included studies (n participants)** 23 (1459)	**Intervention:** NSAID or NSAID multiple (ketorolac, ibuprofen, diclofenac, indomethacin, tenoxicam, ketoprofen, etodolac, parecoxib) **Control:** Placebo	**[all analyses with fixed-effect models]** **NSAID vs. placebo** **Change in creatinine clearance (mL/min)** Day 1 (6 studies, 141 participants) MD -16.48 (-28.03, -4.94), p=0.0051 I^2=0.0% Day 2 (4 studies, 114 participants) MD -5.02 (-20.95, 10.91), p=0.54 I^2=15% **Change in serum creatinine (µmol/L)** Day 1 (7 studies, 242 participants) MD 0.19 (-3.31, -3.69) p=0.92 I^2=4% Day 2 (5 studies, 140 participants) MD 3.79 (-4.52, 12.10), p=0.37 I^2=65% **Change in urine output (mL/h)** Day 1 (3 studies, 72 participants) MD -15.25 (-31.63, 1.13) p=0.068 I^2=49% Day 2 (2 studies, 51 participants) MD -2.90 (-19.40, 13.60), p=0.73 I^2=4% **Change in sodium output (mmol/d)** Day 1 (3 studies, 67 participants) MD -37.07 (-79.43, 5.28) p=0.086	**Level of evidence** 1a (1) **Author conclusion** "While the use of NSAIDs as sole analgesics has not been justified, the efficacy of NSAIDs as components of multimodal analgesia has been confirmed (ANZCA 2005). In considering the adverse renal effects of NSAIDs, this review has shown that there was a clinically unimportant transient reduction in renal function in the early postoperative period in a wide variety of surgical settings in patients with normal preoperative renal function." ***Methodological quality*** A-priori design: + Two reviewers: - Literature search: + Status of publication: + List of studies: - Study characteristics: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			I^2=36% Day 2 (2 studies, 45 participants) MD -11.34 (-48.82, 26.14), p=0.55 I^2=0.0% **Change in potassium output (mmol/d)** Day 1 (3 studies, 67 participants) MD -37.50 (-55.91, -19.09) p=0.000065 I^2=0.0% Day 2 (2 studies, 45 participants) MD -14.79 (-38.62, 9.04), p=0.22 I^2=30% **Change in fractional excretion of electrolyte (%)** Change in sodium on day 1 (3 studies, 77 participants) MD -0.20 (-0.75, 0.34) p=0.47 I^2=30% Change in sodium on day 2 (1 study, 30 participants) MD -0.6 (-1.35, 0.15), p=0.12 I^2=n.a. Change in potassium on day 1 1 (2 studies, 51 participants) MD -0.02 (-0.06, 0.02) p=0.27 I^2=0.0% Change in potassium on day 2 (1 study, 30 participants) MD 0.01 (-0.03, 0.05) p=0.63 I^2=n.a. ***Subgroup-analysis:* Multiple vs. single NSAID dose regimen** **Change in creatinine clearance (mL/min) on Day 1** Multiple NSAID vs. placebo (3 studies, 66 participants) MD -24.63 (-42.29, -6.98), p=0.0062 I^2=0.0% Single NSAID vs. placebo (3 studies, 75 participants) MD -10.40 (-25.65, 4.86), p=0.18 I^2=0.0%	Critical appraisal: + Conclusion: - Combining findings: + Publication bias: - Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Change in creatinine clearance (mL/min) on Day 2 Multiple NSAID vs. placebo (2 studies, 44 participants) MD -7.59 (-30.66, 15.47), p=0.52 I^2=0.0% Single NSAID vs. placebo (2 studies, 70 participants) MD 1.22 (-33.27, 35.72), p=0.94 I^2=62%	
Marret, E., et al., Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. Anesthesiology, 2005. 102(6): p. 1249-60.	**Inclusion criteria** - randomized, double-blind design - quality assessment score of 3 or greater14 - inclusion of adolescents (aged >12 yr) or - adults who underwent major surgery that necessitated morphine administrated by a patient-controlled-analgesia device - NSAID therapy compared to a placebo - report of data on morphine adverse effects such as nausea, vomiting, sedation urinary retention and respiratory depression - report of patient satisfaction - studies regarding nonselective NSAIDs and selective cyclooxygenase- 2 inhibitors - English language studies **Exclusion criteria** - score of 2 or lower on the three-item Oxford quality five-point scale14 - inclusion of children (aged < 12 years) - use of a continuous morphine infusion in addition to PCA - use of a continuous regional analgesia in addition to PCA or other regional techniques exclusively - need for postoperative ventilation during the first 24 h (*i.e.*, cardiac surgery) - duration of the study less than 24 h - PCA with an opioid other than morphine (*e.g.*, meperidine, alfentanil, fentanyl, • hydromorphone, oxycodone) - control group with an NSAID - administration of another nonopioid analgesic in both groups (*i.e.*, acetaminophen, nefopam)	**Intervention:** NSAIDs in postoperative patients treated with PCA morphine on opioid adverse effects **Control:** Placebo	**Overall incidences of postoperative nausea, vomiting and PONV (IG/CG)** nausea (%): 50 (extremes, 8-66) / 55 (extremes, 16-78) (7 studies, 909 participants) vomiting (%): 14 (extremes, 0-26) / 21 (extremes, 0-27) (7 studies, 909 participants) PONV (%): 22 (extremes, 0-40) / 30 (extremes, 10- 70) (14 studies, 1343 participants) **NSAIDs risk of nausea, vomiting and PONV** postoperative nausea: (7 studies, 909 participants) RR: 0.879 95% CI: 0.785–0.983 p= 0.024 NNT value was 16 (95% CI, 9–108) postoperative vomiting: (7 studies, 909 participants) RR: 0.678 95% CI: 0.508 – 0.906 p=0.0086 NNT value was 15 (95% CI, 10–51) PONV: (14 studies, 1343 participants) RR: 0.704 95% CI: 0.590–0.841; p < 0.001 **linear relation between the incidence of postoperative nausea and vomiting and morphine consumption in the**	**Level of evidence** 1a (1) **Authors' conclusion** **"**In conclusion, the current meta-analysis highlights the benefits of combining NSAIDs and morphine to decrease opioid-related side effects such as PONV and sedation but not pruritus, urinary retention, or respiratory depression." ***Methodological quality*** A-priori design: + Two reviewers: - Literature search: + Status of publication: - List of studies: + Study characteristics: - Critical appraisal: + Conclusion: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	- NSAID intrarectal administration **Search period** PubMed (MEDLINE): January 1966 - December 2003 Cochrane Controlled Trials Register: January 1966 - December 2003 **Number of included studies (n participants)** 22 studies (1316 participants)		**postoperative period** postoperative nausea: *r* = 0.61, p=0.007; 0.9% decrease/mg morphine vomiting: r = 0.51, p=0.02; 0.3% decrease/mg morphine **subgroup analysis of NSAIDs on PONV: orthopedic surgery or abdominal surgery** *orthopedic subgroup* NSAIDs decreased PONV: RR 0.655 95% CI: 0.467–0.920*; p* = 0.01 *Pelvic or abdominal subgroup* NSAIDs decreased PONV: RR 0.684 95% CI: 0.459 –1.020 *P* = 0.06 **Overall incidence of sedation** (10 studies, 1333 participants) RR: 0.714, 95% CI: 0.537–0.950, *p* = 0.02 NNT to prevent sedation in one patient was 27 (95% CI: 17–154) **subgroup analysis sedation: orthopedic, abdominal surgery** NSAIDs in the orthopedic subgroup: RR 0.167, 95% CI: 0.031 – 0.941, p = 0.04 NSAIDs in the pelvic or abdominal subgroup: RR 0.334, 95% CI: 0.175 – 0.637, p < 0.001	Combining findings: + Publication bias: + Conflict of interest: -
Maund, E., et al., Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review.	**Inclusion criteria** - RCTs - at least 10 participants per trial arm of adult patients requiring pain relief immediately - after major surgery, which compared patient-controlled analgesia (PCA) morphine plus paracetamol (including propacetamol), NSAIDs, or COX-2 inhibitors (licensed for use in the UK) with PCA morphine plus placebo or PCA morphine plus a different non-opioid class - No language restrictions	**Intervention:** paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase 2 (COX-2) inhibitors **Control:** Placebo	**Comparisons for primary morphine related outcomes (IG/CG)** *Paracetamol vs. placebo* Morphine consumption, unadjusted, mean difference, mg (95% CrI): -6.34 (-9.02, -3.65) Morphine consumption, adjusted, mean differences, mg (95% CrI): -8.68 (-11.43, -5.94)	**Level of evidence** 1a (1) **Authors' conclusion** "In conclusion, when paracetamol, NSAIDs, and COX-2 inhibitors are compared with each other, the differences in morphine consumption were small and unlikely to be of clinical

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
Br J Anaesth, 2011. 106(3): p. 292-7.	**Exclusion criteria** - Studies of PCA morphine with a background infusion - PCA opioids other than morphine - intrathecal opioids - peripheral nerve blocks - studies with a 'no treatment' comparisongroup - Studies of rofecoxib and valdecoxib and those conducted by Reuben **Search period** MEDLINE (January 2003 to February 2009) EMBASE (January 2003 to February 2009) Cochrane Central Register of Controlled Trials (January 2003 to February 2009) Trials before 2003 were identified from the references of a previous good-quality systematic review (search end date July 2004), **Number of included studies (n participants)** 60 studies were included		Nausea and PONV, pairwise OR (95% CrI): 1.0 (0.60, 1.53) Sedation, pairwise OR (95% CrI): 1.62 (0.32, 5.02) *NSAID vs. placebo* Morphine consumption, unadjusted, mean difference, mg (95% CrI): -10.18 (-11.65, -8.72) Morphine consumption, adjusted, mean differences, mg (95% CrI): -9.45 (-10.90, -8.01) Nausea and PONV, pairwise OR (95% CrI): 0.70 (0.53, 0.88) Sedation, pairwise OR (95% CrI): 0.53 (0.20, 1.01) *COX-2 vs. placebo* Morphine consumption, unadjusted, mean difference, mg (95% CrI): -10.92 (-12.77, -9.08) Morphine consumption, adjusted, mean differences, mg (95% CrI): -10.67 (-12.42 , -8.94) Nausea and PONV, pairwise OR (95% CrI): 0.88 (0.61, 1.25) Sedation, pairwise OR (95% CrI): 0.63 (0.18, 1.49) *NSAID vs. paracetamol* Morphine consumption, unadjusted, mean difference, mg (95% CrI): -3.85 (-6.80, -0.89) Morphine consumption, adjusted, mean differences, mg (95% CrI): -0.77 (-3.75, 2.21) Nausea and PONV, pairwise OR (95% CrI):	significance. In addition, the benefits in terms of a reduction in morphine-related adverse effects do not strongly favour one of the three non-opioid classes." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: - Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			0.74 (0.44, 1.17) Sedation, pairwise OR (95% CrI): 0.51 (0.08, 1.63) *COX – 2 vs. paracetamol* Morphine consumption, unadjusted, mean difference, mg (95% CrI): -4.58 (-7.83, -1.35) Morphine consumption, adjusted, mean differences, mg (95% CrI): -1.99 (-5.24, 1.24) Nausea and PONV, pairwise OR (95% CrI): 0.93 (0.51, 1.63) Sedation, pairwise OR (95% CrI): 0.63 (0.07, 2.33) *Cox – 2 vs. NSAID* Morphine consumption, unadjusted, mean difference, mg (95% CrI): -0.74 (-3.03, 1.56) Morphine consumption, adjusted, mean differences, mg (95% CrI): -1.22 (-3.43, 1.00) Nausea and PONV, pairwise OR (95% CrI): 1.28 (0.81, 1.97) Sedation, pairwise OR (95% CrI): 1.40 (0.30, 4.31) *Number of arms; residual deviance* Morphine consumption, unadjusted, mean difference, mg (95% CrI): 116; 186 Morphine consumption, adjusted, mean differences, mg (95% CrI): 116 ; 114 Nausea and PONV, pairwise OR (95% CrI): 86; 97	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Sedation, pairwise OR (95% CrI): 31; 41	
Mkontwana, N. and N. Novikova, Oral analgesia for relieving post-caesarean pain. Cochrane Database Syst Rev, 2015. 3: p. CD010450.	**Inclusion criteria** - RCT's - All women requiring pain relief in the early postpartum period following caesarean section **Exclusion criteria** - Quasi-randomised and cross-over trials **Search period** 1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); 2. Weekly searches of MEDLINE (Ovid); 3. weekly searches of Embase (Ovid); 4. Handsearches of 30 journals and the proceedings of major conferences; 5. Weekly current awareness alerts for a further 44 journals **Number of included studies (n participants)** 8 studies (962) included in meta-analysis *Note: here only studies regarding non-opioid-analgesics were considered*	**Intervention:** Oral analgesia **Control:** Placebo/no drug treatment/non-opioid analgesics/combination analgesics	**Non-opioid analgesics versus placebo** ***Need for additional pain relief*** (6 studies, 584 participants) RR (random) 0.70 (95% CI: 0.48, 1.01), p=0.053 I^2=85% *Subgroup analysis* • ***Celecoxcib versus placebo*** (1 study, 60 participants) RR 0.89 (95% CI: 0.59, 1.35) • ***(Gabapentin versus placebo*** (1 study, 126 participants) RR 0.34 (95% CI: 0.23, 0.51)) • ***Ibuprofen versus placebo*** (1 study, 62 participants) RR 0.66 (95% CI: 0.41, 1.07) • ***Ketoprofen versus placebo*** (1 study,120 participants) RR 1.05 (95% CI: 0.01, 2.00) • ***Naproxen versus placebo*** (1 study, 80 participants) RR 0.11 (95% CI: 0.01, 2.00) • ***Paracetamol versus placebo*** (2 study, 136 participants) RR 0.77 (95% CI: 0.43, 1.40) ***Maternal adverse effects*** (2 studies, 267 participants) RR (fixed)11.12 (95% CI: 2.13, 58.22), p=0.0043 I^2=0% **Non-opioid analgesics versus combination analgesics.** ***Need for additional pain relief with a different drug*** (1 study, 192 participants) RR (fixed) 0.87 (95% CI: 0.81, 0.93) **Non-opioid analgesics versus placebo (*subgroup analysis***	**Level of evidence** 1a (1) **Authors' conclusion** "Mefenamic acid 500 mg is likely to be an effective analgesic, but there is insufficient evidence from this limited data set to give a reliable estimate of the size of its effect. No serious adverse events were reported in any of the studies, though numbers were too small to exclude rare but serious harm." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: ? Conclusion: + Combining findings: ? Publication bias: ? Conflict of interest: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			by high and low doses of the same drug*)** • ***Ketoprofen 50mg (1 study, 72 participants) RR (fixed) 0.83 (95% CI: 0.64, 1.07) • ***Ketoprofen 100mg*** (1 study, 72 participants) RR (fixed) 0.55 (95% CI: 0.39, 0.79)	
Ong, C.K., et al., Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg, 2010. 110(4): p. 1170-**9.**	**Inclusion criteria** - RCT's in English - comparison paracetamol/NSAID combinations with 1 or both of their constituent drugs for pain relief **Exclusion criteria** - comparison paracetamol/NSAID combination with analgesics other than paracetamol or NSAIDs - other pain models, e.g. chronic pain - retrospective, nonrandomized, or nonblinded trials **Search period** MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, PubMed January 1988 to June 1999 **Number of included studies (n participants)** 21 studies (1909)	**Intervention:** Combination of paracetamol and NSAID NSAIDs used: ibuprofen (6 studies), diclofenac (8 studies), ketoprofen (3 studies), ketorolac (1 study), aspirin (1 study), tenoxicam (1 study), rofecoxib (1 study) **Control:** Paracetamol/NSAID alone	**[no quantitative analysis due to heterogeneity of studies]** **Combination versus paracetamol alone** (17/20 studies with positive results for IG) Overall mean reduction in pain intensity (SD), %: 35 (10.9) Reduction in analgesic supplementation (SD), %: 38.8 (13.1) **Combination versus NSAIDs alone** (9/14 with positive results for IG) Overall mean reduction in pain intensity (SD), %: 37.7 (26.6) Reduction in analgesic supplementation (SD), %: 31.3 (13.4) **Adverse effects** "There were no serious adverse effects reported for any of the combination analgesics tested in combination or alone."	**Level of evidence** 1a (1) **Authors' conclusion** "Current evidence suggests that a combination of paracetamol and an NSAID may offer superior analgesia compared with either drug alone." ***Methodological quality*** A-priori design: + Two reviewers: ? Literature search: + Status of publication: - List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: ? Conflict of interest: ?

+: low risk; -: high risk; ?: unclear risk; N/A: not applicable; CI: confidence interval; NR: not reported; NS: not significant; NNT: Number needed to treat; RR: relative risk; RB: Relative Benefit; OR: odds ratio; MD mean difference; WMD: weighted mean difference; SMD: standardized mean difference; I^2 und Q: Heterogenitätsmaße

Tab. 5 Systemische Pharmakologie: Paracetamol, Metamizol, NSAR, COX-2-Inhibitoren: *Overviews zu oralen Analgetika (extrahiert: nur relevante Nichtopioide) (Fragen #1 bis #5)*

Overview / reference	**Inclusion, exclusion criteria, search period, number of included studies**	**Intervention group(s) (IG)/ control group (CG)**	**Outcomes (IG vs. CG: RR [CI], NNT [CI]; N studies, n participants)**
Moore, R.A., et al. (2015) Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD008659.pub3.	**Inclusion criteria** - Cochrane review of randomized controlled trials - single dose oral analgesics for acute postoperative pain compared with Placebo - Age > 15 years **Exclusion criteria** NR **Search** Cochrane Database of Systematic Reviews (Issue 5 of 12, 2015)	**Intervention:** Single dose oral analgesics (here: relevant non-opioid analgesics) **Control:** Placebo	**At least 50% maximum pain relief over 4 to 6 hours, RR (95%CI), NNT (95%CI)** [*only "results judged to be reliable" were extracted]* **Aspirin, 600/650 mg** (65 studies, 4965 participants) RR 2.5 (2.3, 2.8), NNT 4.2 (3.8, 4.6) **Aspirin, 1000 mg** (6 studies, 618 participants) RR 2.7 (2.0, 3.7), NNT 4.2 (3.8, 4.6) **Aspirin, 1200 mg** (3 studies, 249 participants) RR 3.3 (1.8, 6.3), NNT 2.4 (1.9, 3.2) **Celecoxib, 200 mg** (4 studies, 705 participants) RR 3.5 (2.4, 5.1), NNT 4.2 (3.4, 5.6) **Celecoxib, 400 mg** (5 studies, 722 participants) RR 10 (5.7, 18), NNT 2.6 (2.3, 3.0) **Dexketoprofen, 10/12.5 mg** (5 studies, 452 participants) RR 2.7 (2.0, 3.7), NNT 3.6 (2.8, 5.0) **Dexketoprofen, 20/25 mg** (6 studies, 523 participants) RR 3.3 (2.4, 4.5), NNT 3.2 (2.6, 4.1) **Diclofenac fast acting, 50 mg** (4 studies, 486 participants) RR 2.9 (3.2, 3.8), NNT 2.4 (2.0, 3.0) **Diclofenac potasium, 25 mg** (4 studies, 502 participants) RR 3.9 (2.8, 5.3), NNT 2.4 (2.0, 2.9) **Diclofenac potasium, 50 mg**

Overview / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (IG vs. CG: RR [CI], NNT [CI]; N studies, n participants)
			(7 studies, 757 participants) RR 3.7 (2.9, 4.7), NNT 2.1 (1.9, 2.5) **Diclofenac potasium, 100 mg** (6 studies, 589 participants) RR 4.8 (3.6, 6.5), NNT 1.9 (1.7, 2.3) **Dipyrone, 500 mg** (5 studies, 288 participants) RR 2.4 (1.8, 3.1), NNT 2.3 (1.9, 3.1) **Etoricoxib, 120 mg** (6 studies, 798 participants) RR 5.6 (4.0, 7.8), NNT 1.8 (1.7, 2.0) **Etoricoxib, 180/240 mg** (2 studies, 199 participants) RR 6.4 (3.1, 14), NNT 1.5 (1.3, 1.7) **Ibuprofen acid, 100 mg** (4 studies, 396 participants) RR 3.7 (2.3, 5.9), NNT 4.3 (3.2, 6.4) **Ibuprofen acid, 200 mg** (18 studies, 2103 participants) RR 6.5 (5.1, 8.2), NNT 2.9 (2.7, 3.2) **Ibuprofen acid, 400 mg** (51 studies, 5604 participants) RR 4.6 (4.0, 5.1), NNT 2.5 (2.4, 2.6) **Ibuprofen acid, 600 mg** (3 studies, 203 participants) RR 2.0 (1.5, 2.6), NNT 2.7 (2.0, 4.2) **Ibuprofen fast acting, 200 mg** (7 studies, 828 participants) RR 5.7 (4.2, 7.9), NNT 2.1 (1.9, 2.4) **Ibuprofen fast acting, 400 mg** (13 studies, 1364 participants) RR 3.9 (3.2, 4.7), NNT 2.1 (1.9, 2.3) **Ibuprofen + caffeine, 100 +100 mg**

Overview / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (IG vs. CG: RR [CI], NNT [CI]; N studies, n participants)
			(2 studies, 200 participants) RR 45 (36.3, 320), NNT 2.4 (1.9, 3.1) **Ibuprofen + caffeine, 200 +100 mg** (4 studies, 334 participants) RR 5.5 (3.5, 8.7), NNT 2.1 (1.9, 3.1) **Ibuprofen + paracetamol, 200 +500 mg** (3 studies, 508 participants) RR 10 (5.7, 19), NNT 1.6 (1.5, 1.8) **Ibuprofen + paracetamol, 400 +1000 mg** (3 studies, 543 participants) RR 11 (6.2, 20), NNT 1.5 (1.4, 1.7) **Ketoprofen, 12.5 mg** (3 studies, 274 participants) RR 4.2 (2.7, 6.6), NNT 2.4 (1.9, 3.1) **Ketoprofen, 25 mg** (8 studies, 535 participants) RR 4.9 (3.5, 6.9), NNT 2.0 (1.8, 2.3) **Ketoprofen, 50 mg** (8 studies, 624 participants) RR 2.7 (2.0, 3.5), NNT 3.3 (2.7, 4.3) **Ketoprofen, 100 mg** (5 studies, 321 participants) RR 3.6 (2.5, 5.1), NNT 2.1 (1.7, 2.6) **Naproxen, 400/440 mg** (3 studies, 334 participants) RR 4.8 (2.8, 8.4), NNT 2.7 (2.2, 3.5) **Naproxen, 500/550 mg** (9 studies, 784 participants) RR 3.4 (2.6, 4.4), NNT 2.7 (2.3, 3.3) **Paracetamol, 500 mg** (6 studies, 561 participants) RR 1.9 (1.6, 2.3), NNT 3.5 (2.7, 4.8) **Paracetamol, 600/650 mg**

Overview / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (IG vs. CG: RR [CI], NNT [CI]; N studies, n participants)
			(19 studies, 1886 participants) RR 2.4 (2.0, 2.8), NNT 4.6 (3.9, 5.5) **Paracetamol, 975/1000 mg** (28 studies, 3232 participants) RR 2.7 (2.4, 3.0), NNT 3.6 (3.2, 4.1) **Piroxicam, 20 mg** (3 studies, 280 participants) RR 2.5 (1.8, 3.3), NNT 2.7 (2.1, 3.8)
Moore, R.A., et al. (2015) Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD011407.pub2.	**Inclusion criteria** - Cochrane review of randomized controlled trials - single dose oral analgesics for acute postoperative pain compared with Placebo - Age > 15 years **Exclusion criteria** NR **Search** Cochrane Database of Systematic Reviews (Issue 5 of 12, 2015)	**Intervention:** Single dose oral analgesics (here: relevant non-opioid analgesics) **Control:** Placebo	**Participants with at least one adverse advent with non-opioid analgesics vs. placebo, RR (95%CI)** **Aspirin, 600/650 mg** (46 studies, 3633 participants) RR 1.2 (1,0, 1.4) **Aspirin, 1000 mg** (4 studies, 404 participants) RR **1.6 (1.1, 2.3)** **Celecoxib, 200 mg** (4 studies, 669 participants) RR 0.9 (0.6, 1.3) **Celecoxib, 400 mg** (6 studies, 725 participants) RR 1.0 (0.8, 1.2) **Dexketoprofen, 10/12.5 mg** (3 studies, 258 participants) RR 0.6 (0.3, 1.3) **Dexketoprofen, 20/25 mg** (5 studies, 413 participants) RR 1.3 (0.8, 2.1) **Diclofenac fast acting, all doses** (5 studies, 636 participants) RR 1.0 (0.6, 1.8) **Diclofenac potasium, all doses** (7 studies, 1090 participants) RR 1.0 (0.7, 1.6)

Overview / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (IG vs. CG: RR [CI], NNT [CI]; N studies, n participants)
			Etoricoxib, 120 / 180 / 240 mg (5 studies, 1029 participants) RR 0.9 (0.7, 1.1) **Ibuprofen, 50 mg** (2 studies, 225 participants) RR 1.3 (0.6, 3.0) **Ibuprofen, 100 mg** (3 studies, 310 participants) RR 1.2 (0.7, 2.1) **Ibuprofen, 200 mg** (14 studies, 1808 participants) RR 0.9 (0.7, 1.02) **Ibuprofen, 400 mg** (40 studies, 4867 participants) RR 0.9 (0.8, 1.04) **Ibuprofen + caffeine, 100 +100 mg** (2 studies, 201 participants) RR 1.9 (0.8, 4.1) **Ibuprofen + caffeine, 200 +100 mg** (4 studies, 336 participants) RR **2.2 (1.03, 4.9**) **Ibuprofen + paracetamol, 200 +500 mg** (3 studies, 508 participants) RR **0.7 (0.6, 0.9)** **Ibuprofen + paracetamol, 400 +1000 mg** (3 studies, 543 participants) RR **0.6 (0.5, 0.8)** **Ketoprofen, 12.5 mg** (3 studies, 274 participants) RR 1.3 (0.5, 3.6) **Ketoprofen, 25 mg** (7 studies, 490 participants) RR 1.2 (0.7, 2.0)

Overview / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (IG vs. CG: RR [CI], NNT [CI]; N studies, n participants)
			Ketoprofen, 50 mg (4 studies, 278 participants) RR 1.6 (0.9, 2.6) **Ketoprofen, 100 mg** (3 studies, 175 participants) RR 1.2 (0.7, 2.2) **Mefenamic acid, 500 mg** (2 studies, 104 participants) RR 2.2 (0.7, 7.2) **Naproxen, 400/440 mg** (3 studies, 334 participants) RR 1.3 (0.8, 2.2) **Naproxen, 500/550 mg** (9 studies, 784 participants) RR 1.0 (0.7, 1.2) **Paracetamol, 500 mg** (3 studies, 319 participants) RR 0.9 (0.4, 1.9), NNT 3.5 (2.7, 4.8) **Paracetamol, 600/650 mg** (13 studies, 1522 participants) RR 1.2 (0.9, 1.5) **Paracetamol, 975/1000 mg** (19 studies, 2342 participants) RR 1.1 (0.9, 1.3)

N/A: not applicable; CI: confidence interval; NR: not reported; NS: not significant; NNT: Number needed to treat; RR: relative risk; RB: Relative Benefit; OR: odds ratio; MD mean difference; WMD: weighted mean difference; SMD: standardized mean difference

Tab. 6 Spezielle Patientengruppen: Patienten mit vorbestehender Schmerzchronifizierung: *randomisierte kontrollierte Studien (Fragen #6 und #7)*

Study / reference	**Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)**	**Intervention group(s) (IG) / control group (CG)**	**Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)**	**Level of evidence: CEbM 2009 (CEbM 2011)** **Critical appraisal / conclusion**

Archer, K.R., et al., Cognitive-behavioral based physical therapy for patients with chronic pain undergoing lumbar spine surgery: a randomized controlled trial. J Pain, 2015.
 	
Randomized controlled trial
	Region/setting
	USA, single academic medical center
	
	Inclusion criteria
	- 21 years of age or older
	- English speaking
	- back and/or lower extremity pain for greater than 6 months- no history of neurological movement disorder
	- no presence of psychotic disease
	- participants report high fear of movement, based on a score of 39 or greater on the Tampa Scale for Kinesiophopia (TSK)
	
	Exclusion criteria
	- spinal deformity as the primary indication for surgery
	- surgery for pseudarthrosis, trauma, infection, or tumor
	- having microsurgical techniques as the primary procedure
	
	Baseline characteristics (IG/CG)
	<u>*Demographic*</u>
	- Age [y], mean(SD): 56.9 (11.1) / 58.4 (13.3)
	- Female Sex (%): 25 (58.1) / 23 (53.5)
	- More than High School Education, N (%): 30 (69.8) / 32 (74.4)
	- Obese BMI Category, N (%): 23 (53.5) / 21 (48.8)
	- Employed prior to Surgery, N (%):
	  - Not Working: 14 (32.6) / 15 (34.9)
	  - Working: 21 (48.8) / 18 (41.9)
	  - Retired: 8 (18.6) / 10 (23.3)
	- Current Smoker, N (%): 10 (23.3) / 7 (16.3)
	- Co morbid conditions, N (%):
	  - 0: 4 (9.3) / 2 (4.7)
	  - 1-2: 32 (74.4) / 34 (79.1)
	  - >2: 7 (16.3) / 7 (16.3)
	<u>*Clinical*</u>
	- Fusion Surgery, N (%): 29 (67.4) / 31 (72.1)
	- Prior Spine Surgery, N (%): 17 (39.5) / 17 (39.5)
		(6 weeks to 3 months after surgery)
		
		Intervention:
		Cognitive-behavioral-based physical therapy (CBPT)
		
		Control:
		Educational program
			***<u>Primary Outcomes</u>*, <u>MD (95% CI)</u>**
			
			Brief Pain Inventory (BPI): Back Pain
			Post–Treatment: 0.22 (-0.46, 0.9), p=0.52
			3 Month: -0.88 (-1.5, -0.25), p=0.007
			
			BPI: Leg Pain
			Post – Treatment: -0.53 (-1.1, 0.04), p=0.07
			
			3 Month: -1.2 (-2.1, -0.34), p=0.0007
			
			BPI: Interference
			Post–Treatment: -0.35 (-1.1, 0.38), p=0.34
			3 Month: -1.5 (-2.4, -0.57), p=0.002
			
			Oswestry Disability Index (ODI) Score
			Post–Treatment: -3.7 (-8.6, 1.2), p=0.143 Month: -9.8 (-15.3, -4.4), p<0.001
			
			***<u>Secondary Outcomes</u>*, <u>MD (95% CI)</u>**
			
			SF-12: PCS (Physical Component Scale)
			Post–Treatment: 1.7 (-1.9, 5.3), p=0.34
			3 Month: 7.1 (2.9, 11.3), p=0.001
			
			SF-12: MCS (Mental Health Component Scale)
			Post–Treatment: 7.6 (4.2, 11.1), p<0.001
			3 Month, Mean (SD): 13.0 (8.7, 17.2), p<0.001
			
			5-Chair Stand, seconds
			Post–Treatment: -3.1 (-7.5, 1.4), p=0.17
			3 Month: -7 (-13.7, -0.37), p=0.04
			
			TUG, seconds
			Post–Treatment: -2.0 (-3.9, -0.11), p=0.04
			3 Month: -1.6 (-3.3, 0.19), p=0.08
			
			10-Meter Walk, m/s
			Post–Treatment: 0.09 (-0.01, 0.19), p=0.07
				Level of evidence
				1b
				(2)
				
				Author conclusion
				„This randomized trial demonstrates that screening patients for fear of movement and using a targeted CBPT program results in significant and clinically meaningful improvement in pain, disability, general health, and physical performance after spine surgery for degenerative conditions. The CBPT program delivered by physical therapists over the telephone, has the potential to be an evidence-based program that clinicians can recommend for patients at risk for poor postoperative outcomes.“
				
				Risk of bias
				
				Random sequence generation:
				+
				
				Allocation concealment:
				+
				
				Blinding:
				?
				
				Incomplete outcome data:
				+
				
				Selective reporting:
				+
				
				Other bias:
				+

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	- Duration of Preoperative Pain, Mean (SD): 25.1 (30.2) / 23.1 (24.5) - Taking Narcotics Prior to Surgery, N (%): 23 (53.5) / 24 (55.8) - Expectations of successful surgery, mean (SD): 8.7 (2.1) / 9.2 (1.1) - Preoperative depression, PHQ-9, mean (SD): 11 (5.6) / 9.6 (6) - Preoperative fear of movement, TSK, mean (SD): 43.5 (5) / 43.2 (5.6) - Preoperative pain self-efficacy, PSEQ, mean(SD): 25.5 (10.6) / 27.7 (12.1) - Preoperative back pain, BPI mean (SD): 6.8 (1.9) / 6.5 (2.3) - Preoperative leg pain, BPI, mean (SD): 7.0 (2.6) / 7.1 (2.2) - Preoperative disability, ODI (Oswestry Disability Index) mean (SD): 49.2 (13.7) / 49 (13.1) - Preoperative physical health, SF-12, mean (SD): 25.4 (5.7) / 26.2 (6.1) - Preoperative mental health, SF-12, mean (SD): 46 (11) / 47.7 (12.4) - 5-Chair Stand score, mean seconds (SD): 38 (21.7) / 40.6 (21.5) - TUG (Timed Up and Go) score, mean seconds (SD): 18.7 (9.8) / 21.3 (11.2) - 10-Meter Walk score, mean m/s, (SD): 0.79 (0.29) / 0.81 (0.35) **Patient flow and follow up (IG/CG)** 86 randomized postoperatively (43/43) Intention to treat analysis: Analysed patient reported outcomes: 38 / 42 Analysed performance outcomes: 37 / 37 Follow –up 6 months after surgery **Excluded from analysis (reason)** n=5 excluded because didn't finish all 6 sessions		3 Month, 0.10 (-0.14, 0.21), p=0.08	
Barreveld, A.M., et al., Ketamine	**Region/setting** USA, 1 hospital	**Intervention** Ketamine i.v. (0.2mg/kg/hour) postop.	***Postoperative pain scores (primary outcome)***	**Level of evidence** 1b

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
decreases postoperative pain scores in patients taking opioids for chronic pain: results of a prospective, randomized, double-blind study. Pain Med, 2013. 14(6): p. 925-34. Randomized controlled trial	**Inclusion criteria** - patients taking opioids for chronic pain - undergoing nononcologic surgery - patients having moderate to severe pain in the absence of acute tissue damage for at least 3 months prior to enrollment **Exclusion criteria** - chronic pain due to metastatic or locally invasive cancer - primary cancer diagnosis - evidence of psychosis - pregnant women - patients with an altered mental status - regional anesthesia intraoperatively or postoperatively - patients who were taking methadone **Baseline characteristics (IG/CG)** - *Age* [y],mean (SD): 48.5 (11.9) / 55 (11.2) - *Sex: n (%)* Male: 13 (22.0) / 13 (22.0) Female: 16 (27.1) / 17(28.8) - *Height* [Inches], mean (SD): 66.6 (3.8) / 66.9 (5.1) - *Weight* [kg]: mean (SD): 77.5 (22.8) / 80.5 (17.0) - *Morphine category: n* <200 mg/day: 20 / 20 >200 mg/day: 9 / 10 - *HADS (depression)*, median score (interquartile range): 8.5 (5–13) / 8 (5–11) - *HADS (anxiety)*, median score (interquartile range): 9 (5.5–13.5) / 8.5 (5–11) - *Pre-op worst pain*, score, mean (SD): 9.3 (1.5) / 9.5 (0.8) - *Pre-op least pain*,score, mean (SD): 4.2 (2.2) / 4.3 (2.4) - *Pre-op average pain*, score, mean (SD): 6.7 (2.0) / 6.5 (1.7) **Patient flow and follow up** - randomized: 64 (32/32)	**Control** Placebo	***Postoperative pain scores(NRS 0-10)*** pain worst, mean (SD): 8.7 (2.0) / 9.0 (1.9), p=0.4102 pain least, mean (SD): 4.4 (3.1) / 5.6 (3.0), p=0.1085 pain average, mean (SD): 6.0 (2.2) / 7.3 (2.2), p=0.0241 ***Change in postoperative vs preoperative pain scores*** ☐ pain worst (SD):- 0.6 (1.9) / -0.6 (1.7), p=0.93 ☐ pain least (SD): 0.2 (2.7) / 1.3 (2.9), p=0.15 ☐ pain average (SD):- 0.6 (1.9) / 0.8 (2.2), p=0.0135 ***Percent (%) change in postoperative vs preoperative pain scores*** ☐☐☐ pain worst (SD): 8.2 (2.7%) / - 6.1 (19%), p=0.95 ☐☐☐ pain least (SD): 2.3 (64%) / 26.1 (64%), p=0.19 ☐☐☐ pain average (SD): 13.5 (37%) / 15.5 (42%), p=0.0057 ***<u>Secondary outcomes</u>*** ***24-h postop. opioid use (oral morphine equivalents),* mean (SD):** 726 (489) / 770 (560), p=0.7480 ***24-h prior to discharge opioid use (oral morphine equivalents),* mean (SD):** 344 (238) / 392 (380), p= 0.5584	(2) **Author conclusion** **"**Our study demonstrates that a ketamine infusion at 0.2 mg/kg/hour in addition to IV PCA results in a statistically significant improvement in postoperative "average" pain scores in this population. We did not find differences in "least" or "worst" pain scores in patients receiving ketamine or placebo." **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: + Incomplete outcome data: + Selective reporting: + Other bias: +

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	- analysed: 59 **Excluded from analysis (reasons)** 3 patients excluded: discharged postop. day 1 2 patients excluded: morphine PCA			
Burke, S. M., et al., Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. Anesth Analg, 2010. 110(4): p: 1180-5. Randomized controlled trial	**Region/setting** Ireland, university hospital **Inclusion criteria** - aged 18 to 60 years - chronic lumbar sacral radiculopathy undergoing elective lumbar discectomy **Exclusion criteria** - Low back pain of < 3-month or >12-month duration - previous lumbar surgery - previous treatment with or allergy to pregabalin or gabapentin - perioperative use of benzodiazepines, - neurological or psychiatric disorders - patients with known spinal structural abnormalities - obesity (body mass index >30 kg m^{-2}) **Baseline characteristics** <u>*Demographics (IG/CG)*</u> - *Age* [y]:mean (SD): 37 (7.8) / 41 (12.4) - *Sex (M/F):* 13/5 / 11/9 - *ASA physical status* (I/II): 14/4 / 13/7 - *BMI* [kg/m^2]: mean (SD): 23.4 (2.8) / 24.8 (2.5) - *Smoker* (%): 28 / 25 - *Manual labour* (%): 22 / 25 - *Workers compensation*: 0 / 1 - *Other litigation*: 0 / 2 - *Professional qualification* (s): 8 / 8 <u>*Clinical features (IG/CG)*</u> - *Site of pain* (back and leg/leg): 16/2 / 18/2 - *Duration of pain* [mo]: mean (SD): 6.3 (3.1) / 6.3 (3.7) - *Level of surgery* (L4-5/L5-S1): 7/11 / 5/15 - *MRI grade (2/3):* 5/13 / 5/15 - *VAS pain rest* (mm), mean (SD), time 0: 58.7 (24.7) / 47.1 (26.8)	**Intervention** Perioperative Pregabalin (600 mg over 24 h) **Control** Placebo	***Acute pain*** VAS pain rest 24 h, mean (SD): 17.3 (20.2) / 23.8 (17.7), p=0.16 VAS pain movement 24 h, mean (SD): 35.2 (31.3) / 37 (23.1), p=0.51 ***Analgesia*** Intraoperative opioid (morphine mg), mean (SD): 6.4 (2.7) / 6.1 (2.4), p=0.70 Opioid in PACU (morphine mg): mean (SD): 1.55 (2.1) / 3.3 (3.8), p=0.10 Number of patients who received supplementary analgesia within 24 h of discharge from PACU: 2/18 (11%) / 9/20 (45%), p=0.03 ***Outcomes at 3 month*** Decrease in MGPQ (short form McGill pain questionnaire, PPI-VAS (present pain intensity visual analogue scale) time 0–3/ 12 (mm), mean (SD): 37.6 (19.6) / 25.3 (21.9), p=0.08 VAS pain movement 3/12 (mm), mean (SD): 9.6 (11.0) / 21.3 (21.7), p=0.09 VAS pain rest 3/12(mm), mean (SD): 10.7 (15.6) / 15.4 (19.5), p=0.249 RMDQ (Roland Morris disability questionnaire) 3/12, mean (SD): 2.7 (2.4) / 5.6 (4.8), p=0.032 SF-36 physical function 3/12, mean (SD): 84.7 (9.6) / 69.2 (20.2), p=0.005	**Level of evidence** 1b (2) **Author conclusion** "The results of this study indicate that perioperative pregabalin administration may benefit patients undergoing lumbar discectomy in terms of pain and functional outcomes. Further clinical investigations are merited to define the optimal dose and duration of the pregabalin regimen and the duration of the resultant benefits." **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: ? Incomplete outcome data: ? Selective reporting: ? Other bias: ?

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	- *VAS pain movement* (mm): mean (SD), time 0: 69.0 (22.2) / 65.4 (22.7) - *Present pain intensity* PPI-VAS (mm), mean (SD), time 0: 43.6 (17.5) / 36.4 (18.0) - *Roland Morris disability score*: mean (SD), time 0: 14.7 (4.8) / 16.2 (4.0) - *Pain tolerance threshold* in *the symptomatic leg* (mA): mean (SD),time 0: 41.2 (27.9) / 53.5 (32.8) - *Pain tolerance threshold in the asymptomatic leg* (mA)(SD), time 0: 46.9(32.0) / 51.3 (31.4) - *SF-36 MOS physical function*, mean (SD),time 0: 34.17 (23.2) / 30.7 (18.5) - *SF-36 MOS total physical component score*, mean (SD), time 0: 158.6 (63.6) / 141.2 (56.5) - *SF-36 MOS total mental component score*, mean (SD), time 0: 215.2 (90.9) / 191.9 (77.8) - *SF-36 total score*, mean (SD), time 0: 373.9 (138.3) / 333.2 (112.5) - *Hospital anxiety and depression score*, mean (SD), time 0: 13.9 (6.7) / 15.3 (5.9) **Patient flow and follow up** Randomized: 40 Analysed: 38 Follow-up: 3 mo **Excluded from analysis (reasons)** 1 patient: commenced on the study drug by his general practitioner postoperatively 1 patient: surgery postponed because of somnolence after receiving pregabalin		SF-36 total physical component score 3/12, mean (SD): 170.8 (17.8) / 138.7 (32.7), p=0.01 SF-36 total mental component score 3/12, mean (SD): 345.3 (86.3) / 296.4 (37.9), p=0.054 SF-36 total score, mean (SD): 516.2 (45.1) / 435.1 (110), p=0.006 SF-36 health transition, mean (SD): 72.2 (29.6) / 53.7 (29.5), p=0.06 Prolo score 3/12, mean (SD): 8.3 (1.2) / 7.2 (1.4), p=0.01 Number of patients achieving a good outcome at 3/12 (RMDQ ≤4): 16 (89%) / 11 (55%), p=0.03 Number of patients returned to work at 3/12: 18 (100%) / 15 (75%), p=0.048 Number of patients reporting a “good” or “excellent” outcome at 3/12: 16 (89%) / 16 (80%), p=0.66	
Karst, M., et al., Effect of celecoxib and dexamethasone on postoperative pain after lumbar disc surgery. Neurosurgery, 2003. 53(2): p: 331-6.	**Region/setting** Germany **Inclusion criteria** - diagnosis of herniated lumbar disc (confirmed by magnetic resonance imaging or, in selected patients by myelography and postmyelography computed tomography) - American Society of Anesthesiologists Class I or II - age between 18 and 70 years	**Intervention:** Perioperative Celecoxib (200 mg doses, 2 before surgery, 4 after surgery) **Control:** Placebo	**PCA opiod consumption (piritramid doses, mg), mean (SD),** no significant differences (p-value NR) at ***PACU*** 2.69 (3.34) / 2.65 (4.49) ***24h*** 22.63 (23.72) / 26.14 (22.57) ***24 to 48h*** 6.82 (14.14) / 5.76 (9.74) ***Cumulative piritramide doses***	**Level of evidence** 1b (2) **Author conclusion** “In summary, our results demonstrate that perioperative administration of celecoxib has no significant opioid-sparing effect or benefits with regard to pain levels and von Frey thresholds

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
Randomized controlled trial	- body mass index less than 35 - no renal, hepatic, gastrointestinal, or hematological abnormality **Exclusion criteria** - recurrent disease - multilevel disease - lateral recess stenosis - inability to speak German - history of narcotics addiction, and previous adverse reaction to any NSAID **Baseline characteristics (IG/CG)** - *Age* [yr], mean (SD): 44.82 (12.74) / 43.71 (13.80) - *Sex (F/M*): 7/10 / 6/11 - *BMI* (kg/m2), mean (SD): 27.04 (3.66) / 25.90 (3.60) - *VAS (at rest/on movement),* mean (SD): IG: 4.51 (3.41) / 6.31 (3.14) CG: 5.63 (3.08) / 7.41 (2.61) - *Duration of pain (mo),* mean (SD): 6.09 (7.23) / 9.90 (13.73) - *Preoperative anxiety* (range, 0–10), mean (SD): 4.33 (3.85) / 6.65 (3.06) - *BDI* (range, 0–63), mean (SD): 10.56 (10.09) / 7.81 (6.37) - *Operative time* (min), mean (SD):75.88 (36.07) / 67.94 (21.29) - *Fentanyl* (mg), mean (SD): 0.32 (0.11) / 0.31 (0.09) **Patient flow and follow up** Randomized and analysed: 34 **Excluded from analysis (reason)** 0		32.14 (32.34) / 34.55 (27.98) **<u>Postoperative pain scores</u>** **<u>VAS at rest / on movement, mean (SD) (IG vs. CG),</u>** no significant differences (p-value NR) at ***1h*** 3.82 (2.82) / 4.36 (3.22) vs. 4.04 (2.07) / 5.30 (2.67) ***4h*** 2.92 (2.60) / 4.18 (2.98) vs. 2.74 (1.99) / 3.37 (2.59) ***6h*** 2.22 (2.12) / 3.18 (2.72) vs. 2.35 (1.76) / 3.35 (2.59) ***day 1***1.76 (2.40) / 3.47 (2.43) vs. 1.45 (1.08) / 4.35 (2.77) ***day 2*** 0.84 (0.87) / 3.29 (2.91) vs. 0.78 (0.87) / 2.19 (1.59) ***discharge day*** 0.80 (1.35) / 2.09 (2.40) vs. 0.82 (0.97) / 1.61 (1.72) **<u>Von Freyshold thresholds in the wound area (g), mean (SD),</u>** no significant differences (p-value NR) at ***day 1*** 4.65 (0.38) / 4.53 (0.40) ***day 2*** 5.05 (0.64) / 4.91 (0.43) ***discharge day*** 5.39 (0.79) / 5.54 (0.74)	in the wound area after lumbar disc surgery. However, intraoperative dexamethasone at a mean dose of 40 mg is able to significantly decrease PCA opioid consumption and pain levels in the first 24 hours after lumbar disc surgery." **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: ? Incomplete outcome data: ? Selective reporting: ? Other bias: +
Loftus, R.W., et al., Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent	**Region/setting** USA, Dartmouth-Hitchcock Medical Center **Inclusion criteria** - adult patients - history of daily opiate use for at least 6 weeks	**Intervention:** IV Ketamine intraoperative (0.5 mg/kg on induction of anesthesia, and a continuous infusion at 10 $\mu kg^{-1}min^{-1}$)	**48-h morphine consumption (ME, morphine equivalent total [mg], primary outcome),** mean (SD): 195 (111) vs. 309 (341), p=0.029 Adjusted (analysis of patients who did not receive intraop. nonsteroidal medications): 203 (109) / 323 (347), p=0.045	**Level of evidence** 1b (2) **Author conclusion** **"**Intraoperative ketamine reduces

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
patients with chronic back pain undergoing back surgery. Anesthesiology, 2010. 113(3): p. 639-46. Randomized controlled trial	- chronic back pain for at least 3 months - scheduled to undergo elective lumbar back surgery requiring in-patient admission to the hospital **Exclusion criteria** - intolerance or known allergy to ketamine increased - intraocular pressure - uncontrolled hypertension - increased intracranial pressure - history of psychosis - pregnancy **Baseline characteristics (IG/CG)** (no significant differences) - *Age* [y], mean (SD): 51.7 (14.2) / 51.4 (14.4) - *Weight* [kg], mean (SD): 95.4 / 89.3 - *BMI* (kg/m2), mean (SD): 32.5 / 30.7 - *Female, %*: 36.5 / 44.0 - *ASA Status* (%): • I–II: 69.2 / 70.0 • III–IV: 30.8 / 30.0 -*PreoperativeMedications, %* • Synthetic Opioid: 0.0 / 4.0 • Acetaminophen or NonsteroidalDrug: 88.5 / 76.0 • Muscle Relaxant: 11.5 / 8.0 • Anticonvulsant: 26.9 / 32.0 • Antidepressant: 32.7 / 40.0 • Lidoderm Patch: 7.7 / 8.0 • Antihypertension • Other: 36.5 / 38.0 • Beta-Adrenergic Receptor Blocker: 23.1 / 20.0 - *Prior Back Surgery (%)*: 36.5 / 34.0 - *MCS (Mental component summary)* [%], mean (SD): 44.8 (14) 42.7 (14) - *VAS, cm, mean (SD)*: 7.0 (1.8) / 6.9 (1.6) - *Duration of Chronic Pain* [mo], mean (SD): 70 (73)/ 95 (108) - *Functional Capacity* (Working), disabled, working, mean (SD): 1.9 (0.8)/ 1.9 (0.7) - *Morphine Equivalents*, median (interquartile range): 0.4 (0.3-0.9)/ 0.5 (0.3-0.9)	**Control:** Placebo	**24-h morphine consumption (ME, total [mg]),** mean (SD): 142 (82) vs. 202 (176), p=0.032 **PACU VAS, cm,** mean (SD): 4.1 (3.1) vs. 5.6 (3.0), p=0.033 **PACU ME, mg total,** mean (SD): 18 (14) vs. 22 (20), p=0.218 **Ward VAS 24-h, cm**, mean (SD): 4.7 (2.7) vs. 4.8 (2.4), p=0.902 **Ward VAS 48-h, cm,** mean (SD): 5.4 (2.1) vs. 5.3 (2.2), p=0.838 **6- week ME, mg/h intravenous morphine,** mean (SD): 0.8 (1.1) vs. 2.8 (6.9), p=0.041 **6- week VAS, cm,** mean (SD): 3.1 (2.4) vs. 4.2 (2.4), p=0.026	opiate consumption in the 48-h postoperative period in opiate-dependent patients with chronic pain. Ketamine may also reduce opioid consumption and pain intensity throughout the post- operative period in this patient population. This benefit is without an increase in side effects." **Risk of bias** Random sequence generation: + Allocation concealment: ? Blinding: ? Incomplete outcome data: + Selective reporting: + Other bias: +

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	- *Heart Rate* [beats/min], mean (SD):73 (14) / 77 (13) - *Systolic Blood Pressure* [mmHg], mean (SD): 131 (15) / 135 (20) - *Diastolic Blood Pressure* [mmHg], mean (SD): 78 (11) / 82 (13) 4.65 (0.38) / 4.53 (0.40) **Patient flow and follow up (IG/CG)** - Randomized and analysed: 102 (52/50) - follow up: 6 weeks **Excluded from analysis (reason)** No exclusion from primary analysis			
Reichart et al., Short Psychological Intervention as a Perioperative Pain Reduction Treatment in Spinal Neurosurgery. Cen Eur Neurosurg, 2011. 72:1-9. Randomized controlled trial	**Region/setting** University hospital, Germany **Inclusion criteria** - minimum age of 18 years - back pain requiring surgery - had severe degenerative spinal disease with spinal canal stenosis and instability - patients had undergone conservative treatment prior to surgery, without success - surgery was clearly indicated for all patients - posterior lumbar interbody fusion (PLIF) - speaking German **Exclusion criteria** - severe psychiatric co-morbidities **Baseline characteristics (IG/CG)** *Male*, n: 8 / 9 *Female*, n: 11 / 11 *Age*, mean: 59.36 / 58.8 *First surgery*, n: 10/13 **Patient flow and follow up (IG/CG)** - Randomized: 40 (20/20) - Analysed: 19/20 - follow up: 6 weeks **Excluded from analysis (reason)** 1 person refused to participate because of private	**Intervention:** Short psychological intervention (SPI) (2 sessions, one preop. and one 2-4 days postop.) **Control:** No intervention	**Mean pain intensity (German pain questionnaire DSF)** - Analysis of the Group-Time interaction: F(1;37)=2.830, p=0.051 in favour of IG - 6 weeks postop.: mean pain intensity (SD): 3.17 (4.02) / 5.00 (2.16) (t= 1.491, df= 37), p= 0.072 ***Highest pain intensity*** **(German pain questionnaire DSF)** - Analysis of the Group-Time interaction: F(1;37)=3.741, p=0.031 in favour of IG - 6 weeks postop.: Lower pain intensity in IG (t=1.990, df=37, p=0.027) ***Fear avoidance beliefs questionnaire*** - Analysis of the Group-Time interaction: F(1; 37)=2.214, p=0.073 (trend towards an increase in fear-avoidance beliefs in the CG and a decrease in the IG) - 6 weeks postop.: t=1.240, df=37, p=0.112 ***Physical fitness*** **(Hanover Back Function questionnaire)** - Analysis of the Group-Time interaction: F(1;37)=4.191, p=0.0024 in favour of IG - 6 weeks postop.: t=-1.688, df=37, p=0.05 in favour of IG	**Level of evidence** 1b (2) **Author conclusion** "Our preliminary study demonstrated that use of a SPI resulted in a significant reduction of pain (highest pain intensity) and a higher physical fi tness compared to patients in the control group. Unexpectedly, fear-avoidance beliefs were not found to be decreased by any statistically significant level. Our study showed promising results after the application of a SPI, which should be demonstrated in a randomized, placebo-controlled study with a larger sample size." **Risk of bias** Random sequence generation: + Allocation concealment: ? Blinding: ?

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	reasons (death in family)			Incomplete outcome data: ? Selective reporting: ? Other bias: ?

+: low risk; -: high risk ?: unclear risk; N/A not applicable; IG: intervention group(s); CG: control group; CI: confidence interval; NR: not reported: NS: not significant; RR: Relative Risk, OR Odds ratio, MD: mean difference; SMD: standardised mean difference; IQR: interquartile range

Tab. 7 Patienteninformation und -aufklärung: *systematisches Review (Fragen #8 und #9)*

Review / reference	**Inclusion, exclusion criteria, search period, number of included studies**	**Intervention group(s) (IG)/ control group (CG)**	**Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)**	**Level of evidence: CEbM 2009 (CEbM 2011)** **critical appraisal/ conclusion**
McDonald, S., et al., Preoperative education for hip or knee replacement. Cochrane Database Syst Rev, 2014. 5: p. CD003526. Systematic review	**Inclusion criteria** - RCT or quasi-randomized trial - planned total hip or total knee replacement surgery - preoperative education regarding the surgery and its postoperative course delivered by a health professional within six weeks of surgery - Education could be given verbally or in any written or audiovisual form, and could include preoperative instruction of postoperative exercise routines - all comparators **Exclusion criteria** - trials comparing various methods of delivery of preoperative education in the absence of a control group receiving standard or routine care - trials that incorporated some form of postoperative intervention (e.g. use of reminder systems to perform exercises) **Search period** Electronic databases, unrestricted by date or language, up to 31 May 2013: • Cochrane Central Register of Controlled Trials (Issue 5, 2013); • MEDLINE (Ovid); • EMBASE (Ovid); • CINAHL (EBSCO); • PsycINFO (Ovid). Physiotherapy Evidence Database (PEDro) in July 2010 **Number of included studies (n participants)** 18 (1453) (13 studies hip replacement, 3 studies knee replacement, 2 studies both; 17 RCTs, 1 quasi-randomized) 10 studies included in a quantitative synthesis	**Intervention** Preoperative education (verbal, written or audiovisual) **Control** Usual care	**1. <u>Hip replacement, IG vs. CG</u>** **Pain up to 3 months, SMD (random, 95%CI)** (3 studies, 227 participants) -0.17 (-0.47, 0.13), p=0.26 I^2 =20% *Sensitivity analysis (removing the trials that reported inadequate or unclear allocation concealment)* **Pain up to 6 weeks [VAS 0-10, lower scores indicate less pain], MD (95%CI)** (1 study, 100 participants) -7.0 (-14.85, 0.85), p=0.081 **Function 3 to 24 months, SMD (random, 95%CI)** (4 studies, 177 participants) -0.44 (-0.93, 0.06), p=0.082 I^2 =61% *Sensitivity analysis (removing the trials that reported inadequate or unclear allocation concealment)* **Function 6 months postop. [0-68, lower scores indicate better function], MD (95%CI)** (1 study, 47 participants) -7.0 (-10.55, -3.45), p=0.00011 **Postoperative anxiety up to 6 weeks [20-80, lower scores indicate less anxiety] , MD (random, 95%CI)** (3 studies, 264 participants) -2.28 (-5.68, 1.12), p=0.19 I^2 =22% **Any serious postop. complications, RR (random, 95% CI)** (2 studies, 150 participants) 0.79 (0.19, 3.21), p=0.74 I^2 =78% **Preoperative anxiety [20-80, lower scores indicate less anxiety], MD (random, 95%CI)**	**Level of evidence** 1a (1) **Author conclusion** "Although preoperative education is embedded in the consent process, we are unsure if it offers benefits over usual care in terms of reducing anxiety, or in surgical outcomes, such as pain, function and adverse events. Preoperative education may represent a useful adjunct, with low risk of undesirable effects, particularly in certain patients, for example people with depression, anxiety or unrealistic expectations, who may respond well to preoperative education that is stratified according to their physical, psychological and social need." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(4 studies, 333 participants) -5.10 (-7.17, -3.03), p < 0.00001 I^2 =4% **Mobility (days to standing or walking), MD (random, 95%CI)** (6 studies, 417 participants) -0.12 (-0.30, 0.07), p=0.22 I^2 =47% **Range of motion (degrees)** • **Hip abduction up to 6 weeks postop., MD (fixed, 95%CI)** (2 studies, 95 participants) -1.09 (-5.35, 3.17), p=0.62 I^2 =0% • **Flexion of the hip with flexed knee up to 6 weeks postop., MD (95%CI)** (1 study, 36 participants) 0.75 (-7.67, 9.17), p=0.86 • **Flexion of the hip with extended knee up to 6 weeks postop., MD (95%CI)** (1 study, 36 participants) -0.25 (-9.17, 8.67), p=0.96 **2. Knee replacement, IG vs. CG** **Pain [VAS 0-10, lower scores indicate less pain], MD (95%CI)** • **2 days postop.** (1 study, 26 participants) -12.20 (-29.77, 5.37), p=0.17 • **12 months postop.** (1 study, 109 participants) 2.0 (-3.45, 7.45), p=0.47 **Function 12 months postop. [0-68, lower scores indicate better function], MD (95%CI)** (1 study, 109 participants) 0.0 (-5.63, 5.63), p=1.0 **Health related quality of life, MD (95%CI)**	Critical appraisal: + Conclusion: + Combining findings: + Publication bias: + Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			• **SF-36 physical component score 12 months postop.** (1 study, 109 participants) -3.0 (-6.38, 0.38), p=0.082 • **SF-36 mental component score 12 months postop.** (1 study, 109 participants) -2.0 (-5.06, 1.06), p=0.20 **Total number of serious events, RR (95%CI)** • **Deep vein thrombosis** (1 study, 115 participants) 0.55 (0.14, 2.08), p=0.37 • **Pulmonary emboli** (1 study, 115 participants) 1.09 (0.16, 7.48), p=0.93 • **Infection** (1 study, 115 participants) 0.73 (0.13, 4.19), p=0.72 • **Any serious postop. complications** (1 study, 115 participants) 0.69 (0.29, 1.66), p=0.41 **Preoperative anxiety [20-80, lower scores indicate less anxiety], MD (95%CI)** (1 study, 68 participants) -5.52 (-8.34, -2.70), p=0.00012 **Mobility (days to standing or walking), MD (95%CI)** (1 study, 68 participants) -1.13 (-2.82, 0.56), p=0.19 **Range of motion (degrees)** **Flexion and extension 12 months postop., MD (95% CI)** (1 study, 109 participants) -4.0 (-10.02, 2.02), p=0.19	

+: low risk; -: high risk; ?: unclear risk; N/A: not applicable; CI: confidence interval; NR: not reported; NS: not significant; NNT: Number needed to treat; RR: relative risk; RB: Relative Benefit; OR: odds ratio; MD mean difference; WMD: weighted mean difference; SMD: standardized mean difference; I^2 und Q: Heterogenitätsmaße

Tab. 8 Patienteninformation und -aufklärung: *randomisierte kontrollierte Studien (Fragen #8 und #9)*

Study / reference	**Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)**	**Intervention group(s) (IG) / control group (CG)**	**Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)**	**Level of evidence: CEbM 2009 (CEbM 2011)** **Critical appraisal / conclusion**
Angioli, R., et al., The effects of giving patients verbal or written pre-operative information in gynecologic oncology surgery: a randomized study and the medical-legal point of view. Eur J Obstet Gynecol Reprod Biol, 2014. 177: p. 67-71. Randomized controlled trial	**Region/setting** University hospital (Department of Obstetrics and Gynaecology), Italy **Inclusion criteria** - histologically confirmed endometrial cancer diagnosis - age: between 18 and 70 years - Eastern Cooperative Oncology Group performance status 0–2 according to World Health Organization (WHO) criteria - normal cardiac, hematological and respiratory functions - absence of malignancy - informed consent obtained from the patient - current hospital stay of at least one day **Exclusion criteria** - any systemic disease or mental illness - postoperative major complications (wound infection, fever, bowel obstruction - presence of diabetes or neurologic dysfunctions - postoperative major complications - previous cancer - Body mass index (BMI) > 30 **Baseline characteristics (IG/CG)** (no significant differences) - *Number of patients:* 98 / 92 - *Age* [y], median (range): 64.2 (38-79) / 64.7 (42-78) - *Highest level of education*, % Less than compulsory: 24 / 30 Compulsory: 51 / 46 Post-compulsory school: 17 / 12 University level: 8 / 12 - *Employment status*, % Full time: 85 / 87 Part time: 15 / 13 - *Employment type*, % Homemaker: 66 % 62 Student: 4 / 4	**Intervention:** Verbal preoperative information **Control:** Written preoperative information Information were given about type of surgery, hospitalization stay, pain and postoperative management	**Postoperative pain experienced (VAS 0-10), mean (SD)** 6.8 (1.21) / 5.7 (1.05), p=0.0023 **Pain medication / day, mean (SD)** 2.89 (0.87) / 2.26 (0.56), p=0.0120 *(Note: measurement time-points NR)*	**Level of evidence** 2b↓ (3↓) **Author conclusion** "We support the use of preoperative information leaflet to better prepare patients for a surgical procedure, showing a faster recovery, low medications use and a better quality of life outcome." **Risk of bias** Random sequence generation: + Allocation concealment: ? Blinding: ? Incomplete outcome data: - Selective reporting: ? Other bias: ?

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	Unemployed: 13 / 17 Retired: 17 / 17 - *Surgery*, % Laparoscopic surgery: 32 / 33 Laparotomic surgery: 68 / 67 Lymphoadenectomy: 52 / 50 **Patient flow and follow up (IG/CG)** - Randomized: 240 - Analysed: 190 (98 / 92) - follow-up: hospital stay for outcomes "postop pain" and "pain medication/day" **Excluded from analysis (reason)** - n=12: major postoperative complications - n=38: did not complete questionnaires (concerning satisfaction about preoperative received information)			
Biau, D.J., et al., Neither pre-operative education or a minimally invasive procedure have any influence on the recovery time after total hip replacement. Int Orthop, 2015. 39(8): p. 1475-81. Randomized controlled trial	**Region/setting** Teaching hospital, France **Inclusion criteria** Patients with symptomatic osteoarthritis of the hip, primitive or secondary to avascular necrosis undergoing a primary total hip replacement **Exclusion criteria** - history of previous hip operation (bone) - age > 90 or < 40 years - inflammatory arthritis - important proximal femur or acetabular deformity - BMI > 30 **Baseline characteristics (IG/CG)** (no significant differences) - *Age* [y], median (IQR): 67 (60-75) / 66 (59-72) - *Women*, %: 63 / 53 - *Primary arthritis*, %: 91 / 91 - *Working*, %: 22 / 24 - *Hip flexion < 90 degrees*, %: 57 / 59 - *Symptomatic joint*, % • Contralateral hip: 28 / 27 • Homolateral knee: 7 / 4	**Intervention:** Preoperative education (individual or small group session; a physiotherapist showed and had patients practice exercises they were expected to perform after the operation; a nurse explained the pain management) (**IG1:** education +mini-invasive surgery **IG2:** education + standard surgery) **Control:** No education (usual care: patients were offered to attend an information session in a large group where general information regarding the operation and postop. period was given) (**CG1:** no education (usual care program) + mini-invasive surgery **CG2:** no education (usual care program) + standard surgery)	**Time to reach complete functional independence (primary outcome)** Median time: 5 days in all groups, p=NS HR: 1.1 (95%CI: 0.76-1.5), p=0.77 **Secondary outcomes** **<u>Pain level (0= no pain to 10=worst pain), median (IQR)</u>** • **Recovery** 2 (1-5) / 2 (0-6), p=0.95 • **Postop. day 1** 2 (1-4) / 2 (1-4), p=0.43 • **Postop. day 3** 1 (0-3) / 2 (0-3), p=0.26 **<u>Morphine dose [mg], median (IQR)</u>** • **Titration in recovery** 7 (2-10) / 10 (4-11), p=0.074 • **PCA total** 12 (5-24) / 15 (6-28), p=0.31 • **Total over hospital stay** 17 (8-34) / 20 (13-38), p=0.3 **Complication (yes), %** 4 / 4, p=1	**Level of evidence** 1b (2) **Author conclusion** "Neither pre-operative education nor miniinvasive surgery reduces the time to reach complete functional independence." **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: + Incomplete outcome data: ? Selective reporting: ?

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	• Contralateral knee: 4 / 7 • Spine: 10 / 11 - *Physical activity > 2h/week*, %: 64 / 52 - *ASA score*, % • 1: 27 / 26 • 2: 62 / 55 • 3: 11 / 19 - *Weight [kg]*, median (IQR): 70 (60-80) / 74 (63-82) - *BMI [kg/m^2]*, median (IQR): 25 (23-28) / 25 (22-28) **Patient flow and follow up (IG/CG)** - **1.** randomized to education / no education: 106 / 103 **2.** randomized to mini-invasive surgery / standard surgery (IG1/IG2 and CG1/CG2): 54/52 and 52/51 - Analysed for primary outcome: 101/94 - Analysed for secondary outcomes: 103 / 96 - Follow-up: until discharge **Excluded from analysis (reason)** n=2 withdrew their consent during the trial n=10 did not undergo surgery (IG: 3 and CG: 7)			Other bias: +
Glindvad, J. and M. Jorgensen, Postoperative education and pain in patients with inguinal hernia. J Adv Nurs, 2007. 57(6): p. 649-57. Randomized controlled trial	**Region/setting** 1 hospital (department of gastrointestinal surgery), Denmark **Inclusion criteria** - elective, unilateral inguinal hernia operation - age: > 18 years **Exclusion criteria** - patients who could not communicate in Danish - laparoscopic and bilateral operation was planned **Baseline characteristics (IG/CG)** (no significant differences) - *age* [y], mean (SD): 54.2 (17.7) / 54.0 (15.0) - *male*, %: 92 /94 - *career status*, % Working: 61.5 / 60.8	**Intervention:** Education at the time of discharge (30-60 min) and a follow-up telephone call on the second postoperative day **Control:** Usual routine information (5-10 min) All patients received preoperative oral information covered postop. pain, postop. stomach and bowel function and recommendations about lifting and sick leave and 5 pamphlets containing information about anaesthesia, hospital stay and pre- and postop. care.	**Postoperative pain, VAS (0-100 mm) (primary outcome) (1st, 3rd, 7th postop. day, measurements 3 times daily)** <u>Pain at rest (change from baseline):</u> MD: p=NS *Number of patients with pain while resting (> 29 mm) on the morning, noon and night of the 7th postop. day*, n (%): IG: 7 (7.5), 12 (13.0) and 7 (7.9) CG: 6 (5.0), 18 (15.0) and 15 (13.2) IG vs. CG: p=NS <u>Pain at movement (change from baseline):</u> - MD IG vs. CG p < 0.001 in favour of IG - 7th postop. day: MD [mm] (95% CI): 7 (0.7, 13.1), p=0.0028 in favour of IG *Number of patients with pain while moving (> 39 mm) on*	**Level of evidence** 1b (2) **Author conclusion** "…it seems that a costly and time-consuming intervention such as that used in our study is not justified, given the present state of knowledge." **Risk of bias** Random sequence generation: + Allocation concealment: +

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	Unemployed: 3.1 / 4.2 Student: 2.1 / 0.8 Pensioner: 28.1 / 27.5 Other: 5.2 / 6.7 - *Working conditions*, % Sitting: 36.5 / 30.8 Walking some of the time: 15.9 / 25.6 Mostly walking: 27.0 / 30.8 Hard labour: 20.6 / 12.8 - *BMI* [kg/m^2], mean (SD): 24.4 (2.9) / 24.2 (3.0) - *pain while resting, the day prior to operation* [mm], median (IQR): 3.0 (0.0-6.0) / 2.0 (0.0-7.8) - *pain while moving, the day prior to operation* [mm], median (IQR): 11.0 (2.8-26.5) / 7.0 (1.0-20.8) - *Morphine before operation*, %: 1 / 1 - *Peripheral acting analgesics before operation (NSAID or paracetamol)*, %: 10.5 / 11.0 **Patient flow and follow up (IG/CG)** - Randomized: 234 (103 / 131) - Analysed: 216 (96 / 120) - n=1 in IG was not given the planned intervention, but was included in the analyses of the IG (intention to treat) Follow- up: 7 days postop. **Excluded from analysis (reason)** - n=9: surgical complications - n=9: did not return the diary		*the 7th postop. day*, n (%): IG: 11 (12.0) CG: 14 (11.9) IG vs. CG: p=NS **Daily use of analgesics** IG vs. CG: p=NS **Return to work before the 7th postop. day** IG: 25/52 (48.1%) CG: 22/62 (35.5%) IG vs. CG: p=0.19	Blinding: + Incomplete outcome data: - Selective reporting: ? Other bias: ?
Gräwe, J.S., et al., Impact of preoperative patient education on postoperative pain in consideration of the individual coping style. Schmerz, 2010. 24(6): p. 575-86. Randomized	**Region/setting** Universitätsklinik (Klinik für Chirurgie), Deutschland **Inclusion criteria** Elektive viszeral- oder gefäßchirurgische Operationen (Alter: 19-71 Jahre) **Exclusion criteria** Nicht berichtet **Baseline characteristics (IG1 / CG1/ IG2 / CG2)** Keine signifikanten Unterschiede für folgende	**Intervention:** Präoperative Patienteninformation (Einzelgespräch, Dauer ca. 25 min., Informationen zu postop. Schmerzen und Informationen, wie Schmerzerleben aktiv beeinflussbar ist, Zusammenfassung der Edukationsinhalte) **IG1**: Patienten mit niedriger negativer Schmerzverarbeitung **IG2**: Patienten mit hoher negativer Schmerzverarbeitung	**Varianzanalyse für die Schmerzindikatoren Schmerzstärke (NRS, 0=kein Schmerz bis 10=stärkste vorstellbare Schmerzen) und Schmerzqualität (Schmerzempfindungskala, SES)** **Schmerzstärke (IG1 / IG2 / CG1 / CG2), mean (SD)** • *Ruheschmerzstärke:* Postop. Tag 1: 2.58 (2.59) / 2.83 (2.62) / 2.25 (2.05) / 2.62 (1.97) Postop. Tag 2: 1.92 (1.79) / 2.00 (1.78) / 1.92 (2.39) / 2.29 (2.26) Postop. Tag 3: 1.08 (1.06) / 1.30 (1.19) / 2.08 (2.17) / 1.79 (1.79)	**Level of evidence** 1b (2) **Author conclusion** „Die Ergebnisse unserer Studie zeigen, dass eine Schulung unabhängig vom Ausmaß negativer Stressverarbeitung effektiv ist. Um jedoch abschließend beurteilen zu können, ob bzw. in welchem Ausmaß die Ausprägung negativer Stressverarbeitung die Effektivität

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
controlled trial	Variablen: - *Alter* [y], mean (SD): 57.1 (11.1) / 58.4 (12.4) / 55.0 (11.6) / 56.4 (14.2) - *BMI [kg/m²],* mean (SD): 27.5 (4.4) / 26.4 (5.1) / 25.7 (4.9) / 26.2 (5.7) - *Präoperative Zustandsangst*, mean (SD): 42.2 (10.6) / 43.0 (10.0) / 45.6 (13.2) / 46.9 (12.3) - *Präoperative Schmerzstärke [NRS],* mean (SD): 0.87 (1.3) / 0.42 (1.3) / 0.88 (1.7) / 0.46 (1.3) - *Operationsdauer [min]*, mean (SD): 163.2 (69.3) / 169.6 (91.7) / 123.2 (69.7) / 153.3 (80.1) Signifikante Unterschiede (p < 0.001) IG1 / CG1 vs. IG2 / CG2 für *Habituelle Ängstlichkeit*, mean (SD): 33.1 (6.5) / 32.5 (8.4) vs. 38.2 (9.0) / 40.9 (8.2) **Patient flow and follow up** - Randomisiert und analysiert: 96 (4 Gruppen mit je n=24) - Follow-up: 3. Tag postop. **Excluded from analysis (reason)** NR	**Control:** 5-minütiges Einzelgespräch (Informationen zu Hintergrund und Zielsetzung der Studie **CG1:** Patienten mit niedriger negativer Schmerzverarbeitung **CG2**: Patienten mit hoher negativer Schmerzverarbeitung Alle Patienten erhielten die gleichen Informationen zur Schmerzmessung.	Treatment (IG, CG): p=0.54, Interaktion von Treatment und zeitlichem Verlauf: p=0.07 • *Durchschnittliche Schmerzstärke:* Postop. Tag 1: 3.50 (2.00) / 3.61 (2.43) / 3.08 (2.24) / 3.29 (1.94) Postop. Tag 2: 2.62 (2.10) / 2.52 (1.88) / 2.71 (2.24) / 3.08 (2.23) Postop. Tag 3: 2.08 (1.67) / 1.96 (1.43) / 2.62 (1.88) / 2.67 (1.97) Treatment (IG, CG): p=0.58, Interaktion von Treatment und zeitlichem Verlauf: p=0.045 • *Max. Schmerzstärke:* Postop. Tag 1: 5.00 (2.90) / 4.78 (2.78) / 4.08 (3.12) / 4.54 (2.69) Postop. Tag 2: 3.96 (3.09) / 3.70 (2.48) / / 3.88 (2.56) / 4.29 (2.53) Postop. Tag 3: 3.17 (2.37) / 3.13 (2.18) / 3.33 (2.37) / 3.67 (2.76) Treatment (IG, CG): p=0.98, Interaktion von Treatment und zeitlichem Verlauf: p=0.12 **Schmerzqualität (IG1 / IG2 / CG1 / CG2), mean (SD)** • *Affektives Schmerzempfinden:* Postop. Tag 1: 21.71 (9.21) / 21.23 (10.13) / 19.46 (9.24) / 20.13 (6.36) Postop. Tag 2: 18.54 (6.25) / 19.20 (8.73) / 20.79 (10.95) / 19.25 (7.98) Postop. Tag 3: 16.75 (7.46) / 18.27 (9.11) / 19.46 (9.24) / 20.13 (6.36) Treatment (IG, CG): p=0.90, Interaktion von Treatment und zeitlichem Verlauf: p=0.12 • *Sensorisches Schmerzempfinden:* Postop. Tag 1: 16.17 (7.56) / 14.14 (4.76) / 12.83 (5.21) / 15.05 (4.89) Postop. Tag 2: 13.06 (5.47) / 14.00 (6.00) / 12.67 (4.75) / 13.00 (4.24) Postop. Tag 3: 12.21 (4.17) / 13.09 (5.50) / 12.54 (4.46) / 12.67 (3.81) Treatment (IG, CG): p=0.47, Interaktion von Treatment und zeitlichem Verlauf: p=0.48	einer psychologischen schmerzbezogenen Edukationseinheit beeinflusst, sind weitere Untersuchungen nötig.“ **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: + Incomplete outcome data: ? Selective reporting: ? Other bias: +
Guo, P., L. East, and A. Arthur. A	**Region/setting** 2 public hospitals, China	**Intervention:** Preoperative education 2-3 days before	**[outcome measures were assessed on the 7th day after surgery]**	**Level of evidence** 1b

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
preoperative education intervention to reduce anxiety and improve recovery among Chinese cardiac patients: a randomized controlled trial. Int J Nurs Stud, 2012. 49(2): p. 129-37. Randomized controlled trial	**Inclusion criteria** - age ≥ 18 years - able to speak, read and write Chinese - cardiac surgery (coronary artery bypass Grafting, valve surgery, congenital and other open heart surgery) **Exclusion criteria** - emergency cases - patients who undergone cardiac surgery on a previous occasion **Baseline characteristics (IG/CG)** - *Number of patients:* 76 / 77 - *Age* [y], mean (SD): 52.0 (16.12) / 52.3 (15.99) - *male*, %: 57.9 / 51.9 - *Education*, %:≤ 9 years: 73.7 / 72.7 - *Employment status*, % Employed: 21.1 / 24.7 Unemployed: 53.9 / 49.4 Retired: 25.0 / 26.0 - *Type of surgery*,% Coronary artery bypass grafting: 48.7 / 42.9 Valve surgery: 31.6 / 36.4 Congenital and others: 19.8 / 20.8 - *Comorbidities*, %, yes: 36.8 / 29.9 - *Previous hospitalization*, %: 11.8 / 7.8 - *Previous operations*, %: 11.8 / 7.8 - *Anxiety and depression*, mean (SD) HADS (Hospital Anxiety and Depression Scale) anxiety subscale: 6.0 (3.59) / 7.3 (4.33) HADS depression subscale: 4.8 (3.17) / 5.9 (4.35) - *Pain measures*, mean (SD) BPI-sf pain severity items • Average pain: 0.8 (1.33) / 1.1 (1.65) • Current pain: 0.2 (0.66) BPI-sf pain interference items • General activity: 1.3 (2.28) / 1.6 (2.59) • Mood: 1.6 (2.29) / 1.8 (2.60) • Walking ability: 2.1 (2.74) / 2.3 (3.20) • Sleep: 1.2 (2.38) / 1.5 (2.72)	surgery: information leaflet about preoperative tests and preparation, stay in the ICU after surgery, returning to the cardiac surgical ward, and recovery at home; 15-20 min verbal advice **Control:** No intervention (usual care alone)	**Anxiety, measured by the anxiety subscale of the HADS (primary outcome)** Mean change (SD) from baseline -3.5 (4.50) / -0.7 (4.95) MD (adjusted): -3.6 (95% CI: -4.62, -2.57), p<0.001 ***Secondary outcomes*** **Pain severity items (visual analog scale 0 = no pain to 10 = worst imaginable pain)** Mean change (SD) from baseline *Average pain*: 0.7 (1.94) / 1.1 (2.23); MD (adjusted): -0.4 (95% CI: -0.96, 0.13), p=0.13 *Current pain:* 0.6 (1.28) / 0.8 (1.63); MD (adjusted): -0.3 (95% CI: -0.72, 0.11), p=0.14 **Pain interference items (visual analog scale 0 = does not interfere to 10 = completely interferes)** Mean change (SD) from baseline *General activity*: 1.4 (2.74) / 1.6 (3.21); MD (adjusted): -0.2 (95% CI: -0.95, 0.62), p=0.67 *Mood*: -0.0 (2.86) / 0.7 (3.25); MD (adjusted): -0.8 (95% CI: -1.60, 0.02), p=0.06 *Walking ability*: 0.4 (3.03) / 1.1 (3.77); MD (adjusted): -0.6 (95% CI: -1.43, 0.14), p=0.10 *Sleep*: -0.1 (2.77) / 0.9 (3.10); MD (adjusted): -0.9 (95% CI: -1.63, -0.16), p=0.02 **Depression subscale (depression score on HADS 0 to 21: higher score indicating a greater degree of depression)** Mean change (SD) from baseline -2.3 (4.41) / -0.6 (4.94); MD (adjusted): -2.1 (95% CI: -3.19, -0.92), p<0.001	(2) **Author conclusion** "This form of preoperative education is effective in reducing anxiety and depression among Chinese cardiac surgery patients. Based upon existing evidence and international practice, preoperative education should be incorporated into routine practice to prepare Chinese cardiac patients for surgery." **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: + Incomplete outcome data: + Selective reporting: ? Other bias: +

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	- *Heart Rate* [beats/min], mean (SD): 78.9 (8.85) / 76.3 (7.67) - *Systolic Blood Pressure* [mmHg], mean (SD): 113.8 (11.78) / 116.8 (14.15) - *Diastolic Blood Pressure* [mmHg], mean (SD): 71.0 (8.76) / 72.1 (9.58) *[p-values: NR]* **Patient flow and follow up (IG/CG)** - Randomized: 153 (76/77) - Analysed: 68/67 - Follow-up: 7 days postop. **Excluded from analysis (reason)** - n=14 discharged without surgery - n=2 care transferred - n=2 died after surgery			
Ihedioha, U., et al., Patient education videos for elective colorectal surgery: results of a randomized controlled trial. Colorectal Dis, 2013. 15(11): p. 1436-41. Randomized controlled trial	**Region/setting** University hospital, UK **Inclusion criteria** - elective colorectal surgery **Exclusion criteria** - severe physical disability - patients who could not speak or understand English **Baseline characteristics (IG/CG)** (no significant differences) - *Number of patients:* 31 / 29 - *Age* [y], median: 65 / 64 - *Male*, %: 71 / 67 - *BMI*, median 27 / 27 - *Operation technique*, % Laparoscopic: 45 / 40 Open: 55 / 60 **Patient flow and follow up (IG/CG)** - Randomized: 61 - Analysed: 60 (31 / 29) - follow- up: 30-day: 31 / 28 (1 death)	**Intervention:** Video education (15-min clip that explained patients‘ preoperative assessment and recovery after surgery including postop. advice in discharge) **Control:** No intervention All patients received information leaflets and verbal information	**Hospital stay (primary outcome), median (IQR)** 5 (4-6) / 5 (4-7), p=0.239 **Epidural analgesics use 48h, median** 207 mg / 245 mg, p=0.984 **Other analgesics (paracetamol / voltarol)** IG vs. CG p=0.44 / p=0.506 **Pain scores at rest (postop. day 1-4) (VAS)** IG vs. CG p=0.989 **Pain scores at movement (postop. day 1-4) (VAS)** IG vs. CG p=0.338 **Nausea scores (postop. day 1-3)** IG vs. CG p=0.74 **SF-36 (after 3 months)** IG vs. CG: NS (all components)	**Level of evidence** 1b (2) **Author conclusion** “Use of video education in the psychological preparation of patients undergoing elective colorectal surgery does not improve short-term outcomes” **Risk of bias** Random sequence generation: + Allocation concealment: ? Blinding: ? Incomplete outcome data: +

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	3-month: 28 / 26 completed questionnaire **Excluded from analysis (reason)** n=1 dropout			Selective reporting: ? Other bias: ?
Louw, A., et al., Preoperative pain neuroscience education for lumbar radiculopathy: a multicenter randomized controlled trial with 1-year follow-up. Spine (Phila Pa 1976), 2014. 39(18): p. 1449-57. Randomized controlled trial	**Region/setting** 7 clinical sites, US **Inclusion criteria** - scheduled for lumbar surgery (LS) for radiculopathy - willingness to comply with the predetermined follow-ups - willingness to complete postoperative questionnaires at designated time intervals **Exclusion criteria** - age < 18 years or > 65 years - not being proficient in reading or comprehending the English language - scheduled for LS involving instrumentation (e.g, spinal fusion, arthroplasty); - participation in a formal back school or multidisciplinary pain management program - undergoing LS for a condition other than lumbar radiculopathy - presence of chronic pain-related conditions (e.g, fibromyalgia, chronic fatigue syndrome) - symptoms of cord compression **Baseline characteristics (IG/CG)** (no significant differences) - *Number of patients:* 32 / 35 - *Age* [y], mean: 49.59 / 49.65 - - *Duration of symptoms [d]*, mean: 91.41 / 92.29 - *Low back pain* (numeric pain rating scale 0-10, NPRS), mean: 4.57 / 5.12 - *Leg pain* (NPRS 0-10), mean: 5.25 / 6.06 - *Pain catastrophization scale* (0-52), mean: 24.54 / 27.24 - *Fear avoidance – work subscale* (0-42), mean: 17.79 / 17.08	**Intervention:** Preoperative neuroscience education (NE) (1 session delivered by a physical therapist and a NE booklet) **Control:** No intervention All patients received preoperative usual care (education by staff).	**Low back pain (LBP) and leg pain (NPRS score), and function (ODI score) (primary outcomes)** <u>NPRS for LBP, mean</u> No significant differences at 1 mo: 4.44 / 5.12 3 mo: 2.09 / 3.39 6 mo: 2.56 / 3.03 12 mo: 3.07 / 2.64 <u>NPRS for leg pain, mean</u> No significant differences at 1 mo: 1.43 / 2.91 3 mo: 1.96 / 2.82 6 mo: 2.44 / 2.79 12 mo: 1.63 / 2.73 <u>ODI scores, mean</u> No significant differences at 1 mo: 31.78 / 35.58 3 mo: 20.81 / 29.15 6 mo: 23.33 / 24.48 12 mo: 24.15 / 23.58	**Level of evidence** 1b (2) **Author conclusion** "The addition of NE to usual care after LS for lumbar radiculopathy did not result in significant differences in pain and disability, and indeed, some residual pain and disability after surgery is normal and expected. Patients who received NE did report a more favorable view of their surgical experience and also used fewer postoperative health care resources. Educating patients about the normal responses to LS in a neuroscience framework may result in significant behavior changes after surgery, and decrease the ongoing health care utilization of a large percentage of patients with LS." **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: + Incomplete outcome data: ? Selective reporting:

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	- *Fear avoidance – physical activity subscale* (0-24), mean: 17.54 / 17.70 - *Oswestry Disability Index* (*ODI*) (0-100), mean: 44.21 / 46.67 **Patient flow and follow up (IG/CG)** - Randomized: 67 - Analysed: 61 (28 / 33) - follow-up: 12 mo **Excluded from analysis (reason)** - n=2 no surgery - n=1 patient undergoing litigation and lawyer directed patient withdrawal from the study - n=3 lost to follow-up			? Other bias: ?
Makki, D., et al., The efficacy of patient information sheets in wrist arthroscopy: a randomised controlled trial. J Orthop Surg (Hong Kong), 2011. 19(1): p. 85-8. Randomized controlled trial	**Region/setting** Hospital, UK **Inclusion criteria** Diagnostic wrist arthroscopy **Exclusion criteria** Advanced osteoarthritis or rheumatoid arthritis **Baseline characteristics (IG/CG)** (no significant differences) - *Number of patients:* 28 / 27 - *Age* [y], mean (SD): 30 (11) / 26 (9) - *No. of men / women*: 18/10 / 12/15 - *Preop. VAS scores*, mean (SD): 42 (14) / 39 (10) - *Quick Dash score*, mean (SD): 34(11) / 36(12) **Patient flow and follow up (IG/CG)** - Randomized: 64 - Analysed: 55 (28 / 27) - Follow-up: 7 days postop. **Excluded from analysis (reason)** n=9 underwent trimming for complex tears of the triangular fibrocartilage and other forms of debridement during arthroscopy	**Intervention:** Specific preoperative information on the procedure (pictures of the wrist joint anatomy, portal entry sites, and the arthroscope) and written instructions on postop. care **Control:** Standard preoperative information and verbal instructions on postop. care	**Postoperative Pain (VAS 0-100 mm), mean (SD)** *Day 1*: 67 (9) / 72 (10), p=0.06 *Day 2:* 60 (8) / 67 (10), p=0.005 *Day 3:* 55 (6) / 62 (7), p=0.0003 *Day 4:* 48 (9) / 56 (11), p=0.004 *Day 5:* 42 (8) / 49 (9), p=0.004 *Day 6:* 41 (8) / 46 (10), p=0.04 *Day 7*: 39 (8) / 42 (9), p=0.19 **Analgesic intake (tablets of codydramol, each tablet contained 500 mg paracetamol and 8 mg codeine phosphate), mean (SD)** *Day 1*: 4.4 (1.6) / 5.5 (1.8), p=0.02 *Day 2:* 3.9 (1.7) / 4.9 (1.6), p=0.02 *Day 3:* 3.6 (1.6) / 4.5 (1.6), p=0.04 *Day 4:* 3.5 (1.7) / 4.4 (1.4), p=0.03	**Level of evidence** 2b↓ (3↓) **Author conclusion** "Patients who received specific preoperative information on the procedure and written instructions on postoperative care experienced less pain, consumed less analgesics, and had an earlier return to daily activities." **Risk of bias** Random sequence generation: ? Allocation concealment: ? Blinding: ? Incomplete outcome data: ? Selective reporting:

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
			Day 5: 3.2 (1.4) / 4.2 (1.5), p=0.01 *Day 6:* 1.7 (1.5) / 2.1 (1.2), p=0.2 *Day 7:* 1.4 (1.3) / 1.5 (1.1), p=0.8 **Quick Dash score for return to daily activities, mean (SD)** *Day 7:* 40 (11) / 47 (11), p=0.02	? Other bias: ?
Neary, P.M., et al., The benefits of an interactive, individualized online patient pathway for patients undergoing minimally invasive radio guided parathyroidectomy: a prospective, double-blinded, randomized clinical trial. Surg Innov, 2010. 17(3): p. 236-41. Randomized controlled trial	**Region/setting** University hospital, Ireland **Inclusion criteria** - elective minimally invasive radioguided parathyroidectomy (MIRP) for primary hyperparathyroidism - age > 18 years - full capacity to consent to both the study and the operation **Exclusion criteria** - cognitive or visual impairment - lack of access to Internet facilities **Baseline characteristics (IG/CG)** (no significant differences) - *Number of patients:* 30 / 21 - *Age* [y], mean (SD): 61.4 (11.9) / 61.5 (16.0) - *Male: Female:* 4:17 / 11:40 **Patient flow and follow up (IG/CG)** - Randomized: 64 - Analysed: 51 (30 / 21) - follow-up: NR **Excluded from analysis (reason)** - n=13 did not access their Website post-randomization	**Intervention:** Preoperative interactive, individualized online patient pathway **Control:** Access to standard website	**Postop. Pain Score (VAS, max=10) at 24 h, mean (SD)** 3.45 (2.7) / 3.38 (2.7), p=0.929 **Postop. analgesic requirements (tramadol / codeine, max=3) after 24 h , median (IQR)** 1 (1-2) / 1 (1-2), p=0.769 **Preop. hospital Anxiety and depression Scale (HADS) anxiety score (max=21), mean (SD)** 6.7 (4.4) / 7.5 (5.2), p=0.558 **Preop. HADS depression score (max=21), median (IQR)** 3.5 (1-6) / 4.0 (2-7), p=0.969 **Preop. combined HADS score (max=42), mean (SD)** 10.8 (6.4) / 12.2 (9.4), p=0.530 **Consent score (max=30), median (IQR)** 28 (25.3-30) / 28 (26-30), p=0.976	**Level of evidence** 1b (2) **Author conclusion** "Although it did not influence patient anxiety or analgesic requirements, the novel online, interactive patient pathway makes a positive impression on our patients' journey through the health care system and so would seem to provide added value to the overall experience." **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: + Incomplete outcome data: + Selective reporting: ?

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
				Other bias: +
O'Connor, G., V. et al. Randomised controlled trial of a tailored information pack for patients undergoing surgery and treatment for rectal cancer. Eur J Oncol Nurs, 2014. 18(2): p. 183-91. Randomized controlled trial	**Region/setting** Six sites in four health care trusts, Northern Ireland **Inclusion criteria** - Diagnosis of rectal cancer (RC) **Exclusion criteria** - Prognosis of less than 6 months **Baseline characteristics (IG/CG)** - *Number of patients:* 43 / 33 - *Age [y]*, mean (SD): 63.12 (10.69) / 68.29 (9.34), p=0.017 All other variables (gender, education level, type of operation, pathology, adjuvant therapies) no stat. significant differences. **Patient flow and follow up (IG/CG)** - Randomized: 85 - Analysed: 76 (43 / 33) (4 patients didn't complete secondary outcome measures) - Follow-up: 6 months after hospital stay **Excluded from analysis (reason)** n=9 did not receive allocated intervention (n=4: withdrew before pre-intervention data collection, n=5: randomized to soon) Lost to follow-up after 6 months: n=3	**Intervention:** Preop. tailored information pack (series of 14 leaflets on various aspects of disease and treatment of RC), a Stoma Care Nurse Specialist (SCNS) went to "guided tour" of the pack, record of leaflets was offered) **Control:** Generic colorectal cancer and stoma information leaflets All patients received "usual care" whereby the condition, treatment options and concerns were discussed by SCNS. Patients in both groups were assured of the continuing support of the SCNS with a contact number to access further information and support.	**Satisfaction with information (primary outcome), mean (SD)** *time 2* (after surgery prior to discharge): 58.30 (7.38) / 51.42 (6.52), stat. significant difference *time 3* (6 months after hospital stay): 60.21 (6.76) / 51.68 (6.84), stat. significant difference **Reintegration to Normal Living Index (RNLI)** p=NS at *time 2* and *time 3* (IG > CG) **Anxiety score** *Time 2:* p=NS *Time 3:* p=0.04 in favour of IG **Depression score** Very similar (according authors); p=NS at *time 2* and *time 3*	**Level of evidence** 1b (2) **Author conclusion** "Patients who received the tailored information pack were significantly more satisfied than those in the control group at Times 2 and 3 showed significantly lower anxiety scores at Time 3. Clearly, there are benefits to patients in receiving information that is tailored to their individual treatment plan. These results will undoubtedly enhance the knowledge base surrounding the provision of tailored information to specific patient groups." **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: + Incomplete outcome data: + Selective reporting: ? Other bias: -
Stergiopoulou, A., et al., The effect of a	**Region/setting** University hospital, Greece	**Intervention:** **IG1:** preop. information about the	**Postoperative pain during the first 16h (NRS)** IG (IG1 / IG2 / IG3) vs. CG: p=0.021 in favour of IG	**Level of evidence** 2b ↓

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
multimedia health educational program on the postoperative recovery of patients undergoing laparoscopic cholecystectomy. Stud Health Technol Inform, 2006. 124: p. 920-5. Randomized controlled trial	**Inclusion criteria** Elective laparoscopic cholecystectomy (LC) for cholelithiasis **Exclusion criteria** - age > 75 and < 18 years - ASA-score > 2 - patients unable to understand Greek - patients with serious sight and deaf impairment - patients undergoing LC combined with another laparoscopic or open procedure, simultaneously **Baseline characteristics (all participants)** Characteristics for each group and differences: NR **Patient flow and follow up (IG1 / IG2 / IG3 / CG)** - Randomized and analysed: 60 (15 / 15 / 15 / 15) - follow-up: NR **Excluded from analysis (reason)** NR	scheduled operation through a Multimedia Health Educational Program (MHEP) presented by a Registered Nurse (RN) (20-30 min) **IG2:** preop. information through a leaflet (designed and developed using the exact contents of the MHEP) **IG3:** preop. verbal information by a RN **Control:** No intervention All patients received conventional preop. information about the operation and postoperative course by the attending surgeon and anesthesiologist.	**Postoperative nausea during the first 16h (NRS)** IG (IG1 / IG2 / IG3) vs. CG: p=0.039 in favour of IG	(3 ↓) **Author conclusion** "Use of MHEP in structured preoperative informative sessions, in patients undergoing LC has been proven effective as far as the learning transfer in concerned. However, the impact of MHEP on preoperative anxiety and postoperative pain and nausea is less obvious. Further double blind control studies with broader sample is necessary to establish definitive conclusions." **Risk of bias** Random sequence generation: ? Allocation concealment: ? Blinding: ? Incomplete outcome data: ? Selective reporting: + Other bias: ?

+: low risk; -: high risk ?: unclear risk; N/A not applicable; IG: intervention group(s); CG: control group; CI: confidence interval; NR: not reported: NS: not significant; RR: Relative Risk, OR Odds ratio, MD: mean difference; SMD: standardised mean difference; IQR: interquartile range

Tab. 9 Patienteninformation und -aufklärung: *randomisierte kontrollierte Studien (Frage #10)*

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
Varelmann, D., et al. Nocebo-induced hyperalgesia during local anesthetic injection. Anesth Analg 2010. 110(3): 868-870. Randomized controlled trial	**Region/setting** 1 hospital, USA **Inclusion criteria** Healthy parturients at term requesting epidural analgesia or nonlaboring parturients presenting for elective delivery under spinal anesthesia **Exclusion criteria** - administration of opioids in the 4 hours before study enrollment - i.v. magnesium sulfate within the last 24 hours - diabetes mellitus (type I and II) - > 1 attempt at i.v. cannulation during the current admission - neurocardiogenic signs or symptoms (e.g., dizziness, lightheadedness, bradycardia, and syncope) during i.v. cannulation, and cervical dilation 2 or 6 cm (if in labor) **Baseline characteristics (IG/CG)** (no significant differences) - *Age* [y], mean (SD): 33 (1) / 32 (1) - *BMI [kg/m^2]*, mean (SD): 30 (1) / 29 (1) - *Gestational age [wk]*, median (IQR): 39 (38-40) / 39 (38-40) - *Gravidity*, median (IQR): 2 (1-3) / 2 (1-2) - *Parity*, median (IQR): 1 (0-1) / 1 (0-1) - *Cervical dilation (only labor group) [cm]*, median (range): 4 (2-6) / 4 (2-6) **Patient flow and follow up (IG/CG)** - Randomized and analysed: 140 (70/70) - Follow-up: 1 measurement immediately after the local anesthetic injection	**Intervention:** Placebo-group (words used during the administration of the local anesthesic: "We are going to inject the local anesthetic that will numb the area where we are going to do the epidural/spinal anesthesia and you will be comfortable during the procedure.") **Control:** Nocebo-group (words used during the administration of the local anesthesic: "You are going to feel a big sting and burn in your back now, like a big bee sting; this is the worst part of the procedure.")	**Pain score (verbal analog scale 0 = no pain to 10 = worst imaginable pain; primary endpoint)** CG significantly higher scores compared with IG ($p<0.01$) **Subgroup analysis** CG significantly higher scores compared with IG in the labor analgesia and caesarean delivery groups ($p<0.01$ and $p<0.05$)	**Level of evidence** 1b (2) **Author conclusion** "Our data suggest that using gentler, more reassuring words improves the subjective experience during invasive procedures." **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: + Incomplete outcome data: + Selective reporting: ? Other bias: +
Wang, F., et al. Negative words on surgical wards result in	**Region/setting** 1 hospital, China **Inclusion criteria**	**Intervention:** **IG1:** postop. positive words ("The PCA pump was great in treating pain, especially for people	**Pain score at rest (visual analog scale 0 = no pain to 10 = worst imaginable pain; primary endpoint)*** • IG1 vs. CG: Single words, mean (SD): 1.7 (0.4) vs. 1.5 (0.2),	**Level of evidence** 1b (2)

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
therapeutic failure of patient-controlled analgesia and further release of cortisol after abdominal surgeries. Minerva Anestesiol 2008. 74(7-8): 353-365. Randomized controlled trial	- elective abdominal hysterectomy - ASA-status I-II - post-anesthesia care unit score > 6/10 and arterial oxygen saturation measured by pulse oximetry > 92% **Exclusion criteria** - age: < 18 and > 65 years - pregnancy - patients with diagnosed endocrinopathies - allergic to opioids - those who were not willing to or could not finish the whole study at any time or an incoherent state of PCA - history of the use of centrally-acting drugs of any sort, chronic pain and psychiatric diseases records **Baseline characteristics (IG1/IG2/IG3/CG)** (no significant differences) - *number of patients:* 248 / 241 / 247 / 35 - *age* [y], mean (SD): 45 (8) / 44 (6) / 45 (9) / 43 (7) - *weight* [kg], mean (SD): 55 (6) / 59 (9) / 56 (6) / 56 (8) - *education* [y], mean (SD): 6 (2) / 8 (3) / 7 (2) / 7 (3) - *ASA status I/II*, %: 85/15 / 84/16 / 87/13 / 86/14 - *intraoperative propofol* [mg], mean (SD): 363 (54) / 358 (48) / 361 (53) / 354 (59) - *intraoperative fentanyl* (µg), mean (SD): 255 (70) / 276 (66) / 259 (64) / 260 (50) - *intraoperative midazolam* [mg], mean (SD): 6 (2) / 6 (3) / 5 (1) / 5 (2) - *intraoperative vecuronium* [mg], mean (SD): 11 (4) / 13 (5) / 12 (3) / 12 (5) - *intraoperative fluid therapy* [ml], mean (SD) ☐ Crystalloids: 2190 (230) / 1955(315) / 2030 (355) / 1920 (250) ☐ Colloids: 453 (72) / 433 (68) / 440 (90) / 465 (80) - *surgical duration* [min], mean (SD): 128 (55) /	who like you underwent abdominal surgeries." "You took a correct decision on using a PCA pump for your postoperative pain." "The PCA pump was very effective in removing the postoperative pain affliction.") **IG2:** postop. partially negative words ("The effect of the PCA pump was limited, believe it or not." "Sometimes, the pain-treating pump played a small role in treating postoperative pain." "It might not be good for you to select the so-called PCA pump, as its role was limited.") **IG3:** postop. totally negative words ("Oh, dear, the use of the PCA pump was so bad for you, it was cheating." "The PCA pump was absolutely a waste of money, why did you use it?" "Please, it was useless, do not trust the PCA pump.") Each group was divided into 6 subgroups: • Single words at 3h • Single words at 6h • Single words at 12h • Single words at 18h • Repeated words at 3h (words 3 times at the 3rd h) • Repeated words at 6 h (words 3 times at the 6th h) Words were delivered after PCA (morphine) by a nurse.	p=NS Repeated words: p=NS • IG2 and IG3 vs. IG1 and CG Single words at 3 h: higher pain scores in IG2 and IG3, p<0.01 Repeated words at 3h and 6h: higher pain scores in IG2 and IG3, p<0.001 • IG2 and IG3 vs. IG1 Single words at 6h: higher pain scores in IG2 and IG3, p<0.05 • IG2 vs. IG3 Single words at 3h and 6h: higher pain scores in IG3, p<0.05 Repeated words at 3h and 6h: higher pain scores in IG3, p<0.05 ** VAS scores were recorded hourly from 1h until 12h after the first bolus of morphine and four-hourly during the period of 13-48h* ***Secondary outcomes*** **Total morphine consumption [mg], median (95%CI)** IG1: 47.6 (28.1, 69.2) IG2: 63.5 (36.7, 88.9) IG3: 72.1 (44.3, 89.3) CG: 45.4 (23.5, 67.7) IG2 vs. IG1 and CG p<0.05 IG3 vs. IG1, IG2 and CG p<0.05	**Author conclusion** "In conclusion, negative words from surgical wards strongly influenced the postoperative pain management with PCA during earlier period of time after total abdominal hysterectomy, and such influence was significantly associated with the further elevation of plasma cortisol concentrations. Positive words and relatively later negative words produced little influence on postoperative pain therapy, but not on side effects. Summarily, negative environmental influence on surgical wards should be avoided during the earlier period after lower abdominal surgeries." **Risk of bias** Random sequence generation: + Allocation concealment: + Blinding: + Incomplete outcome data: ? Selective reporting: ?

Study / reference	Region/setting, inclusion criteria, exclusion criteria, baseline characteristics (IG/CG) of study population and patient flow (IG/CG)	Intervention group(s) (IG) / control group (CG)	Outcomes (IG/CG; relative effect measure (RR, OR) or MD; 95% CI or p; primary outcome marked)	Level of evidence: CEbM 2009 (CEbM 2011) Critical appraisal / conclusion
	113 (65) / 134 (61) / 124 (51) - *estimated blood loss* [ml], mean (SD): 364 (64) / 387 (66) / 358 (71) / 380 (74) - *preop. systolic blood pressure* [mmHg], mean (SD): 116 (8) / 117 (11) / 128 (13) / 124 (10) - *preop. diastolic blood pressure* [mmHg], mean (SD): 75 (9) / 77 (10) / 76 7) / 73 (8) - *preop. heart rate* [beats/min], mean (SD): 71 (8) / 65 (5) / 74 (8) / 68 (6) - *preop. respiratory rate* [tpm], mean (SD): 19 (2) / 21 (2) / 23 (3) / 22 (3) **Patient flow and follow up (IG1/IG2/IG3/CG)** - Randomized: 771 (248/241/247/35) - Analysed: 614 (209/197/208/32) - Follow-up: 48h postop. **Excluded from analysis (reason)** - n=63 lost to follow-up - n=40 retreated from study - n=22 incoherent analgesia	**Control:** • No words		

+: low risk; -: high risk ?: unclear risk; N/A not applicable; IG: intervention group(s); CG: control group; CI: confidence interval; NR: not reported: NS: not significant; RR: Relative Risk, OR Odds ratio, MD: mean difference; SMD: standardised mean difference; IQR: interquartile range

Tab. 10 Systemische Pharmakotherapie: Adjuvantien (Lidocain): *systematische Reviews (Fragen #11 und #12)*

Review / reference	**Inclusion, exclusion criteria, search period, number of included studies**	**Intervention group(s) (IG)/ control group (CG)**	**Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)**	**Level of evidence: CEbM 2009 (CEbM 2011)** **critical appraisal/ conclusion**
Joshi et al. Evidence-based postoperative pain management after laparoscopic colorectal surgery. Colorectal Dis, 2013. 15(2): p. 146-55.	Keine Extraktion, da die eingeschlossene relevante Studie (Kaba et al. 2007) in Metaanalyse (Kranke et al. 2015) berücksichtigt ist.			
Kranke P. et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery (Review). Cochrane Database Syst Rev, 2015. 7: p. CD003591.	**Inclusion criteria** - only RCTs - adults > 18 y - only of procedure required general anesthesia - studies comparing the effect of perioperative lidocaine infusions with no treatment/placebo or with epidural analgesia **Exclusion criteria** - participants undergoing any kind of emergency procedure - participants undergoing minor surgical procedures - administration of lidocaine after surgery - receiving lidocaine as repeated bolus - stopping infusion before the end of the surgical procedure -administration of lidocaine before skin closure -giving lidocaine as part of a multimodal drug **Search period** Cochrane Library, CENTRAL(Issue 5 2014), MEDLINE (January 1966 to May 2014), EMBASE (1980 to May 2014), CINAHL (1982 to May 2014) **Number of included studies (n participants)** 45 (2802)	**Intervention:** Perioperative intravenous lidocaine infusion **Control:** Placebo/no treatment or epidural analgesia	**[all analyses with random-effect models]** **<u>Comparison 1: Lidocaine IV vs. placebo</u>** **Postoperative Pain Score (VAS to 10), rest, "early time points" (1 to 4h, PACU)** (23 studies, 1286 participants) MD -0.84 (-1.10, -0.59), p<0.00001 I^2=86% **Postoperative Pain Score (VAS to 10), rest, "intermediate time points" (24h)** (25 studies, 1393 participants) MD -0.34 (-0.57, -0.11), p=0.0044 I^2=91% **Postoperative Pain Score (VAS to 10), rest, "late time points" (48h)** (19 studies, 1077 participants) MD -0.22 (-0.47, 0.03), p=0.086 I^2=92% **Postoperative ileus (dichotomous)** (3 studies, 205 participants) RR 0.38 (0.15, 0.99), p=0.047 I^2=0.0% **Time to first defaecation (h)** (4 studies, 214 participants) MD -9.52 (-23.24, 4.19), p=0.17 I^2=85%	**Level of evidence** 1a (1) **Author conclusion** "In this systematic review we found low to moderate evidence for an effect of intravenous lidocaine on pain at rest as one of the major predefined outcomes." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Time to first flatus (h) (11 studies, 566 participants) MD -5.49 (-7.97, -3.00), p=0.000015) I^2=88% **Time to bowel movements/sounds (h)** (6 studies, 288 participants) MD -6.12 (-7.36, -4.89), p<0.00001 I^2=0.0% **Surgical complication – postoperative infection** (4 studies, 278 participants) RR 1.19 (0.25, 5.67), p=0.82 I^2=0.0% **Postoperative nausea (PONV), early PACU** (7studies, 440 participants) RR 0.72 (0.53, 0.99), p=0.044 I^2=0.0% **Postoperative nausea (PONV), late (0 to 24h, to 48h, to 72h)** (21 studies, 1084 participants) RR 0.82 (0.70, 0.97), p=0.020 I^2=0.0% **Postoperative vomiting, early PACU** (4 studies , 305 participants) RR 0.49 (0.16, 1.48), p=0.21 I^2=0.0% **Postoperative vomiting, late (0 to 24h, to 48h, to 72h)** (13 studies, 731 participants) RR 0.92 (0.68, 1.24), p=0.58 I^2=0.0% **Intraoperative opioid consumption (MEQ, mg)** (12 studies, 667 participants) MD -3.30 (-6.59, -0.02), p=0.048 I^2=86% **Postoperative opioid consumption PACU (MEQ, mg)**	Combining findings: + Publication bias: ? Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(18 studies, 1001 participants) MD -4.17 (-6.40, -1.94), p=0.00025 I^2=94% **Postoperative opioid consumption (MEQ, mg)** (29 studies, 1553 participants) MD -5.36 (-7.12, -3.59), p<0.00001 I^2=77% **<u>Comparison 2: Lidocaine IV vs. TEA</u>** **Pain Score (VAS to 10), rest, "intermediate time points" (24h)** (2 studies, 102 participants) MD 1..51 (-0.29, 3.32), p=0.10 I^2=85% **Pain Score (VAS to 10), rest, "late time points" (48h)** (2 studies, 102 participants) MD 0.98 (-1.19, 3.16), p=0.38 I^2=88% **Time to bowel movements/sounds (h)** (2 studies, 102 participants) MD -1.66 (-10.88, 7.56), p=0.72 I^2=0.0% **Intraoperative opioid consumption (MEQ, mg)** (2 studies, 100 participants) MD 7.27 (-13.92, 28.47),p=0.50 I^2=91% ***<u>Subgroup-analysis</u>*** 1. <u>Surgery technic:</u> **Pain Score (VAS to 10), rest, "early time points" (1 to 4h, PACU)** Open abdominal surgery (6 studies, 332 participants): MD -0.72 (-0.96, -0.47), p<0.00001 I^2=0.0%	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Laparoscopic abdominal surgery (9 studies, 470 participants): MD -1.14 (-1.51, -0.78), p<0.00001 I^2=93% Other surgery (8 studies, 484 participants): MD -0.30 (-0.89, 0.28), p=0.31 I^2=62% **Pain Score (VAS to 10), rest, "intermediate time points" (24h)** Open abdominal surgery (7 studies, 372 participants): MD -0.14 (-0.54, 0.25), p=0.47 I^2=56% Laparoscopic abdominal surgery (9 studies, 470 participants): MD -0.56 (-0.93, -0.20), p=0.0024 I^2=96% Other surgery (9 studies, 551 participants): MD -0.16 (-0.41, -0.08), p=0.19 I^2=0.0% **Pain Score (VAS to 10), rest, "late time points" (48h)** Open abdominal surgery (6 studies, 352 participants): MD -0.17 (-0.57, 0.24), p=0.42 I^2=70% Laparoscopic abdominal surgery (6 studies, 281 participants): MD -0.36 (-0.78, 0.06), p=0.091 I^2=97% Other surgery (7 studies, 444 participants): MD -0.07 (-0.44, 0.31), p=0.73 I^2=38% **Time to first flatus (h)** Open abdominal surgery (3 studies, 130 participants): MD -8.84 (-12.91, -4.76), p=0.000022 I^2=62%	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Laparoscopic abdominal surgery (5 studies, 274 participants): MD -3.95 (-7.62, -0.28), p=0.035 I^2=89% Other surgery (3 studies, 162 participants): MD -5.26 (-10.81, 0.28), p=0.063 I^2=69% **Intraoperative opioid consumption (MEQ, mg)** Open abdominal surgery (4 studies, 218 participants): MD -2.35 (-5.80, 1.11), p=0.18 I^2=0.0% Laparoscopic abdominal surgery (4 studies, 233 participants): MD -3.52 (-9.16, 2.11), p=0.22 I^2=94% Other surgery (4 studies, 216 participants): MD -3.92 (-8.63, 0.79), p=0.10 I^2=50% **Postoperative opioid consumption PACU (MEQ, mg)** Open abdominal surgery (3 studies, 192 participants): MD -3.11 (-7.05, 0.84), p=0.12 I^2=0.0% Laparoscopic abdominal surgery (7 studies, 366 participants): MD -4.87 (-8.17, -1.58), p=0.0037 I^2=96% Other surgery (8 studies, 443 participants): MD -3.32 (-4.99, -1.66), p=0.000092 I^2=58% **Postoperative opioid consumption (MEQ, mg)** Open abdominal surgery (9 studies, 440 participants): MD -3.26 (-4.80, -1.71), p=0.000035 I^2=18%3 Laparoscopic abdominal surgery (9 studies, 470	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			participants): MD -7.40 (-11.41, -3.38), p=0.00030 I^2=75% Other surgery (11 studies, 643 participants): MD -7.28 (-12.91, -1.65), p=0.011 I^2=80% 2. Lidocaine infusion dose **Pain Score (VAS to 10), rest, "early time points" (1 to 4h, PACU)** < 2mg/kg/h (6 studies, 313 participants) MD -0.59 (-1.20, 0.03), p=0.063 I^2=70% ≥ 2mg/kg/h (17 studies, 973 participants) MD -0.94 (-1.22, -0.65), p<0.00001 I^2=88% **Pain Score (VAS to 10), rest, "intermediate time points" (24h)** < 2mg/kg/h, Lidocaine infusion until end of surgery or until PACU (1 to 8h) (5 studies, 274 participants) MD -0.12 (-0.45, 0.21), p=0.47 I^2=0.0% ≥ 2mg/kg/h, Lidocaine infusion until end of surgery or until PACU (1 to 8h) (13 studies, 744 participants) MD -0.28 (-0.50, -0.07), p=0.0086 I^2=81% < 2mg/kg/h, Lidocaine infusion ≥ 24h postoperatively (6 studies, 313 participants) MD -0.72 (-1.30, -0.15), p=0.014 I^2=82% ≥ 2mg/kg/h, Lidocaine infusion ≥ 24h postoperatively (1 studies, 62 participants) MD -0.70 (-0.30, 1.70), p=0.17 Heterogeneity not applicable **Pain Score (VAS to 10), rest, "late time points" (48h)**	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			< 2mg/kg/h, Lidocaine infusion until end of surgery or until PACU (1 to 8h) (5 studies, 269 participants) MD -0.14 (-0.42, 0.14), p=0.32 I^2=0.0% ≥ 2mg/kg/h, Lidocaine infusion until end of surgery or until PACU (1 to 8h) (10 studies, 553 participants) MD -0.25 (-0.53, -0.03), p=0.079 I^2=90% < 2mg/kg/h, Lidocaine infusion ≥ 24h postoperatively (3 studies, 193 participants) MD -0.15 (-1.12, 0.81), p=0.75 I^2=94% ≥ 2mg/kg/h, Lidocaine infusion ≥ 24h postoperatively (1 studies, 62 participants) MD 0.20 (-0.70, 1.10), p=0.66 Heterogeneity not applicable **Intraoperative opioid consumption (MEQ, mg)** < 2mg/kg/h (3 studies, 134 participants) MD -1.16 (--2.79, 0.46), p=0.16 I^2=0.0% ≥ 2mg/kg/h (9 studies, 533 participants) MD -4.05 (-8.01, -0.09), p=0.045 I^2=84% **Postoperative opioid consumption PACU (MEQ, mg)** < 2mg/kg/h (4 studies, 172 participants) MD -4.03 (--7.37, -0.68), p=0.018 I^2=75% ≥ 2mg/kg/h (14 studies, 829 participants) MD -4.15 (-6.65, -1.66), p=0.0011 I^2=95% **Postoperative opioid consumption (MEQ, mg)** < 2mg/kg/h, Lidocaine infusion until end of surgery or until PACU (1 to 8h) (6 studies, 292 participants) MD -3.59 (-6.29, -0.89), p=0.0091 I^2=5%	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			≥ 2mg/kg/h, Lidocaine infusion until end of surgery or until PACU (1 to 8h) (15 studies, 878 participants) MD -8.28 (-11.52, -5.05), p<0.00001 I^2=79% < 2mg/kg/h, Lidocaine infusion ≥ 24h postoperatively (6 studies, 291 participants) MD -4.04 (-8.37, 0.30), p=0.068 I^2=78% ≥ 2mg/kg/h, Lidocaine infusion ≥ 24h postoperatively (2 studies, 92 participants) MD -3.31 (-7.56, 0.94), p=0.13 I^2=0.0%	
Marret E. et al. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. British Journal of Surgery.2008; 95 (11):1331-1338.	**Inclusion criteria** - a randomized double-blind design - adults > 18 y - abdominal surgery -Oxford Quality Score of at least 3 **Exclusion criteria** - inclusion of children - Oxford Score of below 3 - no control group - comparison of intravenous lidocaine infusion with epidural analgesia only - lidocaine administered by bolus with no continuous infusion - no perioperative lidocaine administration **Search period** Pubmed, the Cochrane Controlled Trials Register, Embase (studies published up to December 2007) **Number of included studies (n participants)** 8 (328)	**Intervention:** Intravenous lidocaine infusion **Control:** Placebo	**Duration of postoperative ileus (time to first flatus, faeces or bowel movement)** (7 studies, 300 participants) WMD (random) -8.36 (-13.24, -3.47), p<0.001 I^2=90.6% **Postoperative pain at 24h after surgery** (5 studies, 170 participants) WMD (random) -5.93 (-9.63, -2.23), p=0.002 I^2=63.6% **Postoperative nausea and vomiting** (13 studies, 1021 participants) OR (fixed) 0.39 (0.20, 0.76), p=0.006 I^2=0%	**Level of evidence** 1a (1) **Author conclusion** "Continuous intravenous administration of lidocaine during and after abdominal surgery improves patient rehabilitation and shortens hospital stay." ***Methodological quality*** A-priori design: + Two reviewers: - Literature search: + Status of publication: - List of studies: - Study characteristics: - Critical appraisal: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
				Conclusion: - Combining findings: + Publication bias: - Conflict of interest: -
McCarthy, G.C., S.A. Megalla, and A.S. Habib, Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs, 2010. 70(9): p. 1149-63.	**Inclusion criteria** - RCTs only - human studies - abdominal surgery (open, laparoscopic, orthopaedic, cardiac, tonsillectomy, variety of ambulatory surgeries) **Exclusion criteria** - literature reviews - studies on intravenous regional anaesthesia - involving neuraxial lidocaine - studies on topical, local and peripheral nerve blocks - using lidocaine as a rescue analgesic - animal studies - no relevance to the study criteria **Search period** MEDLINE, CINAHL and Cochrane Library 1966 – December 2009 **Number of included studies (n participants)** 16 (764, lidocaine n=395, control n=369)	**Intervention:** Lidocaine infusion perioperative **Control:** Placebo	**Meta-Analysis of studies in Abdominal Surgery** **Pain score patients receiving lidocaine 24h** (6 studies, 250 participants) WMD -5.93 (95% CI) (-9.63. -2.23) **Duration of postoperative ileus after intravenous lidocaine infusion (h)** (7 studies, 300 participants) WMD -8.36 (95% CI) (-13.24, -3.47) **Adverse Effects (PONV)** (5 studies, 170 participants) OR 0.39 (95% CI) (0.20, 0.76) <u>*SUBGROUP ANALYSIS*</u> regarding the effects of intravenous lidocaine on postoperative gut dysfunction in different surgical populations: **Duration of postoperative ileus (hours)** • **in cholecystectomy (h)** WMD -1.23 (95% CI) (-2.12, -0.34) • **colonic resection (h)** WMD -12.00 (95% CI) (-14.86, -9.13) • **laparoscopy (h)** WMD (-1.06 (95% CI) (-2.00, -0.13) **Orthopaedic Surgery** (initial IC bolus dose of 1.5mg/kg after introduction of anaesthesia and 1.5mg/kg/hour up to 1 hour postoperatively) (1 study, 58 participants)	**Level of evidence** 1a (1) **Author conclusion** "This review shows that a perioperative intravenous infusion of lidocaine had a useful analgesic effect in patients undergoing abdominal surgery. Its administration facilitated early recovery and resulted in faster return of bowel function and a shorter duration of hospital stay. However, these benefits were not seen in patients undergoing orthopaedic surgery, cardiac surgery or tonsillectomy." ***Methodological quality*** A-priori design: ? Two reviewers: ? Literature search: + Status of publication: - List of studies: - Study characteristics: - Critical appraisal: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			no significant reduction in pain scores at rest or during movement at 24, 28 hours and 3 months; no reduction in postoperative analgesic requirements or duration of hospital stay **Cardiac Surgery** (initial bolus dose 1.5mg/kg at introduction of anaesthesia and 30microgram/kg/minute for up to 48 hours postoperatively. (1 study, 89 participants) no significant reduction in VAS pain scores, postoperative fentanyl requirements, time to discharge from ICU or length of hospital stay **Tonsillectomy** (initial bolus dose OF 1.5MG/KG 30 minutes before beginning of surgery and infusion 3 mg//kg/hour for 6 hours and then 0.5 mg/kg/hour for an additional 18 hours) /1 study, 40 participants) no significant reduction in VAS scores or postoperative analgesic requirements **Ambulatory Surgery (**variety of ambulatory procedures, initial intravenous bolus dose of 1.5 mg/kg after induction of anaesthesia followed by infusion of 2mg/kg/hour until 1 hour after arrival in PACU. • Significantly lower VAS scores at rest • No significant CAS scores at 24 hours • 50% reduction in morphine • no difference in PACU stay	Conclusion: + Combining findings: - Publication bias: - Conflict of interest: +
Sun, Y., et al., Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. Dis Colon Rectum, 2012. 55(11): p. 1183-94.	**Inclusion criteria** - RCTs of systematic administration of lidocaine for postoperative analgesia and recovery after abdominal surgery - adults ≥ 18 years - no language restrictions - relevant postoperative pain or recovery outcomes **Exclusion criteria** - abstract, case reports, letters, reviews - animal studies - human volunteer studies - inclusion of other types of surgery	**Intervention:** Lidocaine **Control:** Blank or placebo	**[all analyses with random-effects models]** **Postoperative Pain Intensity:** **At Rest** after 6h (11 trials, 335 (L), 345 (control) patients) WMD -8.07mm (95% CI: -14.69, -1.49) I^2 =90.6% After 24h (13 trials, 390(L), 400 (C) patients) WMD -4.41mm (95% CI: -7.70, -1.13) I^2 =67.8%	**Level of evidence** 1a (1) **Author conclusion** "This systematic review suggests that perioperative systemic lidocaine is a useful adjunct for pain management after abdominal surgery." ***Methodological quality*** A-priori design: -

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	- other methods to administer lidocaine - intravenous regional anesthesia - local infiltration - no postoperative pain or recovery-related outcomes reported - other types of pain **Search period** Medline (1966-2010) CINAHL The Cochrane Central Register of Controlled Trials Scopus **Number of included studies (n participants)** 21 (1108; Lidocaine n=548)		After 72 h (8 trials, 206 (L), 206 (C) patients) WMD -3.21 (95% CI: -11.30, 4.73) **During activity** (7 trials, 210 (L), 210 (C) patients) WMD –10.56mm (95% CI: -16.89, -4.23) I^2=82% After 24h (9 trials, 254 (L) and 254 (C) patients) WMD -4.04mm (95% CI: -8.00, -0.09) I^2=55.6% After 72 h (8 trials, 206 patients in each group) WMD -1.83 (95% CI: -5.00, 1.35) **Cumulative Opioid Consumption** **end of surgery to 48h after surgery** (14 trials) WMD -7.04mg (95% CI: -10.40, -3.68) I^2=46.1% **GI Function** Time to first flatus (8 trials) WMD -6.92h (95% CI: -9.21, -4.63) I^2=62.8% **Time to First Bowel Movement** (5 trials) WMD -11.74h (95% CI: -16.97, -6.51) I^2=0% **Length of hospital stay** (5 studies, 91 (L) and 91 (C) patients) WMD -0.48 (-1.03, 0.07) I^2=43.63% **Opioid-Related Side Effects** Nausea occurred in 19% of patients in lidocaine group and	Two reviewers: + Literature search: + Status of publication: - List of studies: - Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			in 24% of patients in control group RR 0.76 (95% CI: 0.58, 0.99) I^2 =0 **Plasma Levels of Cytokines at 24h** **(3 trials)** WMD -3.62 pg/mL (95% CI: -5.84, -1.40) I^2 =0% **Lidocaine-related side effects** ““Eighteen of the 21 included trials reported no significant lidocaine-related adverse events. One trial reported cardiac arrhythmia with stable vital signs in 1 patient receiving lidocaine intervention. One study reported mild headache in 10% of patients in the lidocaine group. Another study reported that the incidence of light headedness and dry mouth was significantly higher in the lidocaine group in comparison with the placebo control group on day 1 and day 2 after surgery. However, these side effects were mild and did not require therapeutic intervention.“ *Subgroup Analysis (type of procedure)* **1. Open abdominal surgery** (15 trials) **Postoperative Pain Scores at rest** **6h** WMD -4.53mm (95% CI: -8.57, -0.50) I^2 =59.6% **24h** WMD -4.87mm (95% CI: -8.61, -1.13) I^2 =69.0% **Pain scores during activity** **6h** WMD -6.39mm (95% CI: -9.06, -3.71) I^2 =0% **Postoperative Opioid consumption** WMD -6.54mg (95% CI: -11.61, -1.47) I^2 =45.4%	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Time to first flatus WMD -11.11h (95% CI: -13.99, -8.23) I^2 =0% **Time to bowel movement** WMD -15.11h (95% CI: -22.27, -7.95) I^2 =0% **2. Laparoscopic surgery** (6 trials) **Pain scores during activity** **6h** WMD -17.58 (95% CI: -31.05, -4.11) I^2 =81.2% **24h** WMD -7.92mm (95% CI: -15.77, -0.08) I^2 =59.7% **72h** WMD -7.53mm (95% CI: -14.92, -0.13) I^2 =0% **Postoperative Opioid consumption** WMD -8.27mg (95% CI: -11.82, -4.71) I^2 =35.7% **Time to first flatus** WMD -4.90h (95% CI: -5.75, -4.05) I^2 =0% **3. Colonic surgery** (3 trials) **Pain scores at rest** **6h** WMD -6.52mm (95% CI: -9.84, -3.21) I^2 =0% **24h** WMD -6.93mm (95% CI: -9.60, -4.26) I^2 =0% **Pain scores during activity**	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			6h WMD -7.84mm (95% CI: -15.27, -0.41) I^2 =59.85 **Time to first flatus** WMD -11.58 (95% CI: -14.45, -8.11) I^2 =0% **4. Cholecystectomy** (6 studies) **Postoperative Opioid consumption** WMD -9.65mg (95% CI: -13.10, -6.21) I^2 =0% **Time to first flatus** WMD -4.89h (95% CI: -5.74, -4.05) I^2 =0% **Time to first bowel movement** WMD -8.76h (95% CI: -16.11, -1.41) I^2 =0%	
Ventham, N.T., et al., Efficacy of Intravenous Lidocaine for Postoperative Analgesia Following Laparoscopic Surgery: A Meta-Analysis. World J Surg, 2015. 39(9): p. 2220-34.	**Inclusion criteria** - RCTs - abdominal laparoscopic surgery - adults >16 years - human studies in English Language **Exclusion criteria** - open surgery - neuraxial techniques - non-general anaesthetic - pharmacokinetic studies - irrelevant techniques - children **Search period** PubMed/Ovid Medline, Embase, Cochrane Library, clinicaltrails.org search: 18th June 2014 **Number of included studies (n participants)**	**Intervention:** IV lidocaine administered perioperatively **Control:** Placebo/routine care	**Primary Outcomes:** **[analyses with random-effects models]** **Opiate consumption at 24 hours postoperatively** (6 studies, 355 patients) WMD -7.62 mg (-12.37, -2.86), p=0.002 I^2 =78.70% <u>*Subgroups per laparoscopic surgery type:*</u> Laparascopic urology (2 studies, 104 patients) WMD –5.16 mg (-9.66, -0.67), p=0.02 I^2 =0% Laparoscopic cholecystectomy (1 study, ? participants) WMD -11.40 (-15.68,-7.12) Laparoscopic colectomy	**Level of evidence** 1a (1) **Author conclusion** "IV lidocaine has a multidimensional effect on the quality of recovery. IV lidocaine was associated with lower opiate requirements, reduced nausea and vomiting and a shorter time until resumption of diet." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: +

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	14 (742)		(2 studies, 108 participants) WMD -6.24 mg (-20.31, 7.83) p=0.4 Laparoscopic gynaec. (1 study, ? participants) WMD -10.00 (-17.31, -2.69) **Secondary Outcomes:** **Cumulative opiate consumption postoperatively** (8 studies, 430 patients) WMD -5.93 mg (-11.07, -0.79), p=0.02 I^2 =86.67% *Subgroups (surgery type):* **Cumulative opiate use in** laparoscopic chlolecystectomy (3 studies, 179 patients) WMD -6.08 (-7.96, -4.21), p<0.0001 I^2 =0% Laparoscopic colectomy (1 study) WMD 7.60 mg (1.36. 13.84) Laparoscopic gynae (1 study) WMD -2.10 mg (-6.70, 2.50) Laparoscopic urology (2 studies) WMD -6.48 (-16.71, 3.72) Other laparoscopic procedures (1 study) WMD -32.30 (-50.38, -14.22) **Pain Score at rest** (Continuous 0–10 scale)	Status of publication: + List of studies: - Study characteristics: Critical appraisal: + Conclusion: + Combining findings: Publication bias: ? Conflict of interest: ?-

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			• **(2h)** (8 studies, 430 patients) WMD -1.14 (-1.87, -0.41), p=0.002 I^2=98.18% • **(12h)** (6 studies, 317 patients) WMD -1.09 (-1.67, -0.51), p=0.0002 I^2=97.46% • **(24h)** (10 studies, 538 patients) WMD -0.42 (-0.76, -0.08), p=0.02 I^2=92.81% • **(48 h)** (7 studies, 349 patients) WMD 0.15, CI -0.28 to 0.58, p=0.5 I^2 = 93.02 % **Pain Score on movement** (Continuous 0–10 scale) • **(2h)** (4 studies, 254 patients) WMD -0.81, CI -2.05 to 0.42, p = 0.2) I^2 = 93.40 %, • **(12h)** (3 studies, 190 participants) WMD -1.15 (-1.97, -0-32), p=0.006 I^2 = 92.42 % • **(24h)** (6 studies, 343 patients) WMD -0.69, CI -1.39 to 0.01, p = 0.05) I^2 = 89.44 % • **(48h)** h (3 studies, 154 patients), WMD -0.04, (CI -0.46 to 0.54, p = 0.88) I^2 = 0% **Recovery Indices** **1. Nausea and Vomiting** (in pooled analysis) (12 studies, 647 participants) OR=0.52 (0.35, 0.75), p=0.003 I^2=0%	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			2. Diet resumption in IV lidocaine group quicker (6 studies, 295 patients) WMD -6.20 (-12.37, -0.03), p=0.049 I^2=93.79% Subgroup (laparoscopic surgery type): Diet resumption in colorectal surgery group (2 studies, 128 patients) WMD -6.01 (-6.92, -5.10), p<0.001 I^2=0.00% **3. Time until first bowel movement (h)** (7 studies, 360 patients) WMD -3.06 (-9.81, 3.68), p=0.37 I^2=84,48% **4. Time until flatus (h)** (8 studies, 437 patients)) WMD -2.24 (-6.71, 1.69), p=0.26 I^2=89.00% **5. IV lidocaine associated side effects** Arrhythmia (8 studies, 486 patients) N=1 Neurological side effects N=0	
Vigneault, L., et al., Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anaesth, 2011. 58(1): p. 22-37.	**Inclusion criteria** - no restrictions in language - RCTs - evaluation of efficacy on postoperative outcomes of administering IVLI during general anesthesia - adults ≥ 18 y **Exclusion criteria** None mentioned **Search period** Ovid Medline (1950-July 2010, week 1) Embase (1974-July 2010, week 1) the Cochrane Central Register of CTs Scopus database	**Intervention:** Intravenous Lidocain during general anesthesia for any type of surgery **Control:** All comparator groups, including placebo and usual care	**[all analyses with random effects model]** **<u>Primary outcomes</u>** **Postoperative pain and opioid requirement** **1. Postoperative pain at rest** statistically significant at: **6h** (9 studies, Lidocaine n=289, Control n=290) WMD -8.70 (-16,19, -1.21) I^2=89% **12h** (6 studies, Lidocaine n=195, Control n=195)	**Level of evidence** 1a (1) **Author conclusion** "Perioperative IVLI reduced postoperative pain opioid requirement, as well as ileus recovery time, hospital length of stay, and nausea/vomiting. Intravenous lidocaine infusion was effective mainly in abdominal surgery populations."

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
	OpenSIGLE for grey literature Three public search engines: i.G. Google Scholar, Intute, Trip databases **Number of included studies (n participants)** 29 (1754)		WMD -6.52 (-12.12, -0.91) I^2=79% No statistically significant differences after 12 h: **24 h** (10 studies, Lidocaine n=317, Control n=320) WMD -2.04 (-4.4, 0.32) **48h** (8 studies, Lidocaine n=267, Control n=270) 0.28 (-1.35, 1.91) **72h** (3 studies, Lidocaine n=81, Control n=79) WMD -3.11 (-8.73, 2.51) <u>*Sensitivity analyses (abdominal / non abdominal surgery):*</u> **Postoperative pain at rest** **6h** *Abdominal surgery* (7 studies, Lidocaine n=215, Control n=215) WMD -11.21 (-21.10, 1.31) *Non abdominal surgery* (1 study, Lidocaine n=44, Control n=45) WMD 3.50 (-3.83, 10.83) **12h** *Abdominal surgery* (5 studies, Lidocaine n=150, Control n=150) WMD -7.75 (-14.68, -0.83) *Non abdominal surgery* (1 study, Lidocaine n=44, Control n=45) WMD -2.00 (-8.30, 4.30) **24 h** *Abdominal surgery* (8 studies, Lidocaine n=245, Control n=245) WMD -4.44 (-9.22, 0.33) *Non abdominal surgery* (2 studies, Lidocaine n=72, Control n=75) WMD 0.81 (-4.20, 5.83) **48h** *Abdominal surgery*	***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: + Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			(6 studies, Lidocaine n=195, Control n=195) WMD -0.02 (-1.78, 1.74) *Non abdominal surgery* (2 studies, Lidocaine n=72, Control n=75) WMD 2.12 (-2.25, 6.48) **2. Pain during cough** statistically significant at: **6h** (7 studies, Lidocaine n=211, Control n=209) WMD -11.19 (-17.73, -4.65) I^2=84% **12h** (4 studies, Lidocaine n=140, Control n=140) WMD -7.44 (-14.24, -0.63) I^2=84% **24h** (6 studies, Lidocaine n=191, Control n=189) WMD -6.94 (-12.87, -1.01) I^2=78% No statistically significant differences at **48h** (5 studies, Lidocaine n=151, Control n=149) WMD -1.85 (-4.05, 0.35) **72h** (3 studies, Lidocaine n=81, Control n=79) WMD -1.48 (-7.02, 4.06) *Sensitivity analyses (abdominal / non abdominal surgery):* **Postoperative pain during cough at 6h** *Abdominal surgery* (6 studies, Lidocaine n=191, Control n=189) WMD -11.25 (-18.62, -3.87) *Non abdominal surgery* (1 study, Lidocaine n=20, Control n=20) WMD 3.50 (-20.73, -1.47)	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			3. Pain during movement decreased significantly with iv. Lidocain at: **6h** (2 studies, Lidocaine n=64, Control n=66) WMD -9.56 (-17.31, -1.80) I^2=45% No statistically significant differences at **24h** (3 studies, Lidocaine n=92, Control n=96) WMD -5.23 (-16.73, 6.28) **48h** (3 studies, Lidocaine n=92, Control n=96) WMD -4.76 (-18.51, 8.99) *Sensitivity analyses (abdominal / non abdominal surgery):* **Pain during movement** **24h** *Abdominal surgery* (2 studies, Lidocaine n=64, Control n=66) WMD -9.69 (-26.27, 6.90) *Non abdominal surgery* (1 study, Lidocaine n=28, Control n=30) WMD 3.00 (-8.32, 14.32) **48h** *Abdominal surgery* (2 studies, Lidocaine n=64, Control n=66) WMD -9.40 (-32.90, 14.09) *Non abdominal surgery* (1 study, Lidocaine n=28, Control n=39) WMD 3.00 (-7.04, -13.04) **4. Postoperative morphine administration** (12 studies, Lidocaine n=344, Control n=346) WMD -8.44 (-11.32, -5-56) *Sensitivity analyses (abdominal / non abdominal surgery):* **Postoperative morphine consumption** *Abdominal surgery* (10 studies, Lidocaine n=271, Control n=274)	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			WMD -8.72 (-12.22, -5.23) *Non abdominal surgery* (1 study, Lidocaine n=44, Control n=45) WMD -6.90 (-37.29, -23.49) **Secondary outcomes** **Mortality** IG vs. CG (6 studies, n=611) RR: 0.87 (0.42, 1.80) I^2=0% **Nausea or vomiting** (12 studies, n=617) RR: 0.71 (0.57, 0.90) I^2=0% **Length of stay (days)** (9 studies, n=539) WMD -0.17day (-0.41, 0.07) I^2 =8% **Bowel function** **Time to first flatus (abdominal surgery)** significant reduction in favour of iv Lidocain (7 studies, n=288) WMD – 7.62 hr (-10,87, -4-45) I^2=59% *Subgroup analysis:* **Time to first flatus** **Open surgery** (4 studies, n=168) WMD -11.41 (-14,36, -8-45) I^2=0% **Laparoscopic surgery** (3 studies, n=220) WMD -5.21 (-6.65, -3.59) I^2=0%	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Time to first feces significant reduction in favour of iv Lidocain (4 studies, n=168) WMD -10.71 (-16.16, -5.28) I^2=0% **Adverse Events:** "Overall, the incidence of adverse events between the iv Lidocain-groups and the control groups was comparable"	

+: low risk; -: high risk; ?: unclear risk; N/A: not applicable; CI: confidence interval; NR: not reported; RR: relative risk; OR: odds ratio; MD mean difference; WMD: weighted mean difference; SDM: standardized mean difference; I^2 und Q: Heterogenitätsmaße

Tab. 11 Prozedurenspezifisches Schmerzmanagement: Eingriffe an Kopf und Hals: *systematisches Review (Frage #13)*

Review / reference	**Inclusion, exclusion criteria, search period, number of included studies**	**Intervention group(s) (IG)/ control group (CG)**	**Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)**	**Level of evidence: CEbM 2009 (CEbM 2011)** **critical appraisal/ conclusion**
Lewis et al. Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy (Review). Cochrane Database Syst Rev, 2013. 7: p. CD003591.	**Inclusion criteria** - RCTs - reported results for bleeding outcomes - children ≤ 16 y - tonsillectomy or adenotonsillectomy (all indications, all surgical techniques) - studies comparing NSAIDs vs. other analgesics or placebo - NSAIDs pre-, intra- or postoperatively by any route **Exclusion criteria** - studies only for adenoidectomy - patients with a bleeding tendency - patients with contraindications to the use of NSAIDs (asthma, renal disease) - studies that included aspirin or COX-2 inhibitors -studies for lozenges and local (intratonsillar) injections **Search period** Cochrane Library, CENTRAL, MEDLINE, EMBASE: last search 2012; Current Problems, MedWatch and Australian Adverse Drug Reactions Bulletins: to May 2010 **Number of included studies (n participants)** 15 (1101)	**Intervention:** NSAIDs **Control:** other analgesics or placebo *(2 studies: Ibuprofen vs. Paracetamol, 1 study: Ketorolac vs. Paracetamol)*	**[all analyses with fixed-effect models]** **Perioperative bleeding requiring surgical intervention** (14 studies, 1044 participants) OR 1.69 (0.71-4.01), p=0.24 I^2=0.0% **Perioperative bleeding requiring non-surgical intervention** (10 studies, 745 participants) OR 0.99 (0.41-2.40), p=0.98 I^2=61% **Vomiting** (13 studies, 1021 participants) RR 0.72 (0.61-0.85), p=0.00011 I^2=26% ***Subgroup-analysis*** 1. <u>NSAID type (Ketorolac, NSAID other than Ketorolac)</u> **Perioperative bleeding requiring surgical intervention** Ketorolac (5 studies, 359 participants): OR 3.82 (1.03-14.10), p=0.044 I^2=0.0% NSAID other than Ketorolac (9 studies, 685 participants): OR 0.89 (0.28-2.83), p=0.84 I^2=0.0% **Perioperative bleeding requiring non-surgical intervention** Ketorolac (5 studies, 365 participants): OR 1.19 (0.45-3.14), p=0.72 I^2=71% NSAID other than Ketorolac (5 studies, 380 participants): OR 0.39 (0.04-3.46), p=0.40 I^2: N/A	**Level of evidence** 1a (1) **Author conclusion** "From the data available to date, there is no evidence that using NSAIDs caused any statistically significant increase in bleeding that required further clinical intervention." ***Methodological quality*** A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias:+ Conflict of interest: ?

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			Vomiting Ketorolac (5 studies, 364 participants): OR 0.58 (0.35-0.94), p=0.028 I^2=26% NSAID other than Ketorolac (8 studies, 657 participants): OR 0.56 (0.40-0.80), p=0.0014 I^2=44% 2. <u>timing of administration</u> **Perioperative bleeding requiring surgical intervention** Preop admin. (7 studies, 497 participants): OR 1.16 (0.26-5.20), p=0.85 I^2=14% Postop. Admin. (4 studies, 255 participants): OR 3.18 (0.65-15.58), p=0.15 I^2=0.0% Both (1 study, 45 participants): OR 0.22 (0.01-4.22), p=0.31 I^2: N/A **Perioperative bleeding requiring non-surgical intervention** Preop admin. (6 studies, 311 participants): OR 1.43 (0.42-4.82), p=0.56 I^2=66% Postop. Admin. (3 studies, 214 participants): OR 0.90 (0.22-3.59), p=0.88 I^2=0.0% **Vomiting** Preop admin. (8 studies, 543 participants): OR 0.70 (0.54-0.90), p=0.0066 I^2=43% Postop. Admin. (3 studies, 213 participants): OR 0.72 (0.56-0.92), p=0.0090 I^2=0.0% Both (1 study, 45 participants):	

Review / reference	Inclusion, exclusion criteria, search period, number of included studies	Intervention group(s) (IG)/ control group (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SMD [CI]; p-value; I^2/ Q; N; n)	Level of evidence: CEbM 2009 (CEbM 2011) critical appraisal/ conclusion
			OR 1.0 (0.52-1.94), p=1.0 I^2: N/A 3. Control group (placebo or other treatment) **Perioperative bleeding requiring surgical intervention** Other treatment (9 studies, 672 participants): OR 1.46 (0.49-4.38), p=0.50 I^2=5% Placebo (6 studies, 387 participants): OR 1.77 (0.44-7.05), p=0.42 I^2=21% **Perioperative bleeding requiring non-surgical intervention** Other treatment (5 studies, 389 participants): OR 3.16 (0.88-11.33), p=0.077 I^2=32% Placebo (4 studies, 298 participants): OR 0.31 (0.07-1.40), p=0.13 I^2: N/A **Vomiting** Other treatment (8 studies, 651 participants): OR 0.73 (0.61-0.88), p=0.0012 I^2=36% Placebo (6 studies, 385 participants): OR 0.71 (0.51-0.99), p=0.044 I^2=12%	

+: low risk; -: high risk; ?: unclear risk; N/A: not applicable; CI: confidence interval; NR: not reported; RR: relative risk; OR: odds ratio; MD mean difference; WMD: weighted mean difference; SMD: standardized mean difference; I^2 und Q: Heterogenitätsmaße