not updated for > 5 years, Guideline is being revised

Joint German Guideline “Diagnosis and treatment of eating disorders”

German Society for Psychosomatic Medicine and Medical Psychotherapy (DGPM)
German Society for Eating Disorders (DGESS)
German Society for Child and Adolescent Psychiatry, Psychosomatic Medicine and Psychotherapy (DGKJP)
German Association for Psychiatry, Psychotherapy and Neurology (DGPPN)
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AWMF-registration number: 051/026 category S3

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Preface to the 2nd revised edition of the S3 Guidelines "Diagnosis and Treatment of Eating Disorders"[1]

Stephan Herpertz

The eating disorders anorexia nervosa (AN) and bulimia nervosa (BN), as well as binge eating disorder (BED), OSFED (other specified feeding or eating disorder) and ARFID (avoidant/restrictive food intake disorder), the latter two of which were introduced in 2013 as new eating disorder categories in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, APA 2013), are especially significant in the first half of life. The incidence of both AN (Smink et al., 2012; Steinhausen & Jensen, 2015; Hoek, 2016) and BN (Currin et al., 2005; Zerwas et al., 2015) has remained relatively stable in the last few decades, although studies in children and adolescents indicate a rise of AN in this age group (Smink et al. 2012; Favaro et al. 2009; Steinhausen and Jensen 2015). Together, AN and BN were categorized as the twelfth leading cause of disability-adjusted life years (DALYs) among 15-19-year-old females in countries with a high gross domestic product, out of over 300 physical and mental illnesses (Hoek 2016).

The treatment outcomes for eating disorders, especially AN and BN, are not satisfactory. For instance, in the treatment of AN, recovery rates of just under 50% over the lifetime are achieved (although considerably higher among adolescents). The number of patients in remission increases with the length of follow-up periods, but so too does the death rate, which amounts to approximately 6.0% in the first 10 years after diagnosis (Arcelus et al. 2011; Hoang et al. 2014).

Guidelines – historical overview

In the year 2000, the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN) published a guideline for the diagnosis and treatment of eating disorders in Germany for the first time (Fichter et al. 2000). This was followed the same year by a guideline from the German Society of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP; Herpertz-Dahlmann et al. 2000). Both guidelines corresponded to development stage 1, i.e., they were developed by expert groups from the respective professional societies with the aim of making recommendations for the diagnosis and treatment of eating disorders, which had previously been approved by the board of the respective professional societies. In the autumn of 2003, a conference of members of the German Society for Psychosomatic Medicine and Psychotherapy (DGPM) decided to develop an evidence-based guideline for eating disorders in Germany according to development stage 3.

This led, in the spring of 2004, to the first meeting of a group of interested physicians and psychologists in Berlin, with the aim of forming a working group to develop an evidence-based guideline on the diagnosis and treatment of eating disorders in Germany.

[1] Text passages are adopted from the German-language article: Herpertz S. & Herpertz-Dahlmann B. S3-Leitlinien Diagnostik und Therapie der Essstörungen–Update, Psychotherapeut 2017;3:230-233.

The working group was represented by five professional societies DGKJP, Section for Clinical Psychology and Psychotherapy of the German Psychological Society (DGPs), DGPM, DGPPN, and the German College of Psychosomatic Medicine (DKPM). The individual members of the working group were authorized by their respective societies to act as elected representatives for the development of the scientific guidelines for the Association of the Scientific Medical Societies in Germany (AWMF) (http://www.awmf.org/leitlinien/aktuelle-leitlinien.html). In 2010, the S3 guideline for the diagnosis and treatment of eating disorders was made available online by the AWMF (Register-No. 051/026; http://www.awmf.org/leitlinien/detail/ll/051-026.html); in the same year, it was also published in book format (Herpertz et al. 2011). With the aim of communicating the contents of the evidence-based guideline to patients and their families, in 2015, the patient guideline was published both online and in book form, this time under the auspices of the German Society for Eating Disorders (DGESS; Zeeck & Herpertz 2015). In addition to reformulating the scientific guideline to be comprehensible for laypersons, the patient guideline also addresses care structures and supports communication with professional care providers in the health care system, from family doctors to medical or psychological (child and adolescent) therapists.

With regard to the revision of the S3 guideline, i.e., its second edition, the elected representatives of the individual professional societies, as well as patient spokespersons, took part in a two-day consensus conference in Essen on the 23rd and 24th of November, 2017 led by the AWMF. The thematic structure of the guideline broadly corresponds to the first edition and covers chapters on epidemiology, diagnostics, the therapeutic relationship, AN, BN, BED, physical sequelae, and methodology. In line with the DSM-5 (APA, 2013), two new eating disorder categories have been added: “other specified feeding or eating disorder” (OSFED), which also includes “night eating syndrome”, and “avoidant/restrictive food intake disorder” (ARFID), together with replace the old category of “eating disorders not otherwise specified” (EDNOS). With regard to therapy studies on AN, BN, and BED, meta-analyses were performed based on a systematic literature search and assignment of pre-determined quality criteria (evidence level 1).

The problem of evidence

The development of guidelines is oriented to the principles of evidence-based medicine. However, evaluating the efficacy of psychotherapy, which is the treatment method of choice for eating disorders, according to the principles seen as standard in somatic medicine is not a straightforward undertaking.

Hermeneutics (ancient Greek ἑρμηνεύειν hermeneuein: “explain”, “interpret”, “translate”) and thus processes of construction and reconstruction, are attributed with great importance in psychotherapy, in contrast to somatic medicine. The concept of understanding in the sense of an inner experience, which is relevant in psychotherapy and dates back to Dilthey (1974), broadly lacks scientific objectivity and particularly falls short regarding the criterion of testability, which is essential in the natural sciences. The diagnostic and therapeutic concepts in psychotherapy are incumbent upon two fundamentally different models. Psychotherapy is based on the “psychological model”, which is distinguished by the following characteristics:

- Tendency to emphasize psychological and social factors
- Tendency for dimensional thinking
- Tendency to view disorders as an extreme of normal functioning
- Tendency to prioritize psychologically grounded interventions, and finally
- Emphasis on the importance of the therapist as a person and on the therapeutic relationship

By contrast, the "medical model", which is built on research from the natural sciences, emphasizes biological factors in the etiology and genesis of a disease. This is linked to a categorical thinking and a view of disorders as clearly delimitable pathological states – ideally against the background of transparent causalities. Moreover, the results of psychotherapy research increasingly raise the question of whether individual interventions are the decisive "active ingredients" (Lambert 1992, Grawe et al. 1994, Lambert and Ogles 2004; Lambert and Barley 2002). For instance, the specific technique (psychotherapeutic approach) only accounts for 15-20% of all influencing factors with respect to the treatment outcome (Lambert 1992). The outcome of therapy is influenced much more strongly by, above all, patient variables (such as attractiveness, socioeconomic status, expectations regarding the treatment, degree of defensiveness, demographic characteristics, intelligence, severity of mental disorder, social support etc.). Besides the therapist, however, so-called "general influencing factors" found in all psychotherapeutic approaches are important, such as the quality of the therapeutic working relationship or the imparting of hope. Against this background, the following questions need to be given clearly greater consideration in the future: Which approach is most helpful for which patients, with which characteristics (psychological, social and biological-genetic), and in which stage of their illness? And with which therapist? As yet, we are still unable to answer these questions.

In addition to psychotherapy, pharmacotherapy plays a major role in the treatment of mental disorders. Specifically for the four eating disorder categories, its relevance has been determined in meta-analyses, especially in comparison to the outcomes of psychotherapy.

The outpatient care of patients with eating disorders in Germany does not only take place in the form of individual and group psychotherapy according to the German directives for psychotherapy. Both guided and non-guided structured self-help manuals, the majority of which are based on cognitive-behavioral therapy, are increasingly employed to treat patients with eating disorders. The efficiency of such manuals also needs to be critically examined in order to derive recommendations from them.

Evidence-based guidelines are the result of a systematic process of development, and constitute both scientific (empirical) and practice-oriented recommendations for action. They pursue the objective of supporting care providers and patients within the health care system in making decisions regarding questions of diagnostics and treatment. Accordingly, guidelines serve the

purpose of quality development within the health care system. Guidelines are characterized by practical recommendations that are the result of a thorough scientific and thus transparent analysis of the current state of the art. At the same time, however, they also contain evaluations of study results in terms of their clinical relevance and applicability (Muche-Borowski und Kopp 2011; Qaseem et al. 2012). The German Association of the Scientific Medical Societies (AWMF) speaks of "corridors for action and decision-making", within which the diagnostics and especially the therapy of the individual patient operate, but also within which the patient's preferences are determined and need to be considered in the framework of participatory decision-making. With regard to the quality development of diagnosis and treatment of eating disorders, we hope that with these guidelines, and especially the second, revised edition, we have made a meaningful contribution which will help to improve the successful recovery and quality of life of our patients with eating disorders.

Bochum, Spring 2018

Stephan Herpertz
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Literature

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Special note:
Medicine is subject to a perpetual process of development; therefore, all information, especially relating to diagnostic and therapeutic methods, can always only reflect the state of knowledge at the time the guidelines went to print. With respect to the provided recommendations pertaining to therapy, and the selection as well as dosage of medications, the greatest possible care has been taken. Nevertheless, the user is encouraged to consult the package insert and specialist information of the manufacturer for checking purposes, and in the case of doubt, to consult a specialist. We ask that in the general interest, if questionable discrepancies arise, the user contacts the editorial team. The user retains responsibility for any diagnostic and therapeutic application, medication and dosage.

Off-label use:
In the guideline texts and recommendations for medication, reference is made in the respective chapters to the possible use of medications that are not approved for the respective area of indication (off-label use). Such use is only permissible if the following criteria are met:
1. proven efficacy
2. favorable risk-benefit profile
3. lack of alternatives – compassionate use

Accordingly, off-label use is only permissible for illnesses when there is no treatment alternative. Based on the current state of scientific knowledge, there must be a reasonable prospect of treatment success. Furthermore, there is also a specific duty to inform the patient, pointing out the fact of off-label use and the resulting liability consequences. A shared decision-making is necessary.

Use of pronouns:
Predominantly women suffer from AN and BN. Therefore, the members of the guideline working group decided to use the female pronoun throughout, although a large number of men are also affected by BED.
Each subchapter ends with treatment recommendations, which are oriented to the respective levels of evidence according to the Oxford Centre of Evidence Based Medicine (2001). The strength of the treatment recommendation is divided into A ("We recommend"), B ("We suggest/can be considered"), O ("may") and GCP ("Good Clinical Practice").

Levels of evidence, Oxford Centre of Evidence Based Medicine (2001)	
Level	**Studies on therapy / prevention / etiology**
1a **1b** **1c**	Systematic review of randomized controlled trials (RCT) One RCT (with narrow confidence interval) All-or-none principle
2a **2b** **2c**	Systematic review of well-planned cohort studies One well-planned cohort study or one RCT of lower quality Outcome studies, ecological studies
3a **3b**	Systematic review of case-control studies One case-control study
4	Case series or poor-quality cohort/case-control studies
5	Expert opinion without explicit appraisal of the evidence or based on physiological models / laboratory research

Harbor, R., Miller, J. (2001) A new system for grading recommendations in evidence based guidelines BMJ. 323(7308):334–336

Wording of recommendations

Recommendations in this guideline were classified as „A“ (very strong recommendation), „B“ (strong recommentation), „O“ (weak recommendation) and GCP (good clinical practice). Recommendations were based on the available empirical evidence (see methods section), and could be up- or downgraded after discussion in the expert team according to their clinical relevance, the risk-benefit-ratio, ethical and economic considerations, practicability in everyday life / in different areas of care and the applicability in the German healthcare system.
The wording in the German guideline used „soll“ for a very strong recommendation, „sollte“ for a strong recommendation, and „kann erwogen werden“ (as an example) for weak recommentations. It proved to be difficult to translate these terms adequately into English. Therefore, the English wording that was used is explained in more detail:

- If there is a legal duty to apply a recommendation or if there might be serious consequences of not following the guideline, the recommendation was formulated using „**must**“ or „**has to be** [done/conducted]“.
- If there is a very strong recommendation due to good empirical evidence or high clinical relevance, „**should be offered**“ or „**should be provided**“ was used.
- If the empirical evidence and clinical relevance is less strong, but a recommendation should be seriously considered, weighing up benefits and harms, it was formulated with the wording „**should be considered**“.
- If a recommendation is weak, it was formulated with the wording „**it is recommended**“ or „**it can be justified**“. Here, weighing up benefits and harms is necessary in each individual case.

Contents

I. Epidemiology of Feeding and Eating Disorders

Manfred M. Fichter

1. New developments and explanation of terms

Since the publication of the first AWMF S3 Guideline "Diagnosis and treatment of eating disorders", the new US psychiatric guidelines have been published in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; German edition 2015). In the DSM-5, (childhood) feeding disorders are subsumed in one area in the chapter "Feeding and Eating Disorders". The DSM-5 manual contains diagnostic criteria for the following disorders: pica, rumination disorder, avoidant/restrictive food intake disorder (all three of which predominantly occur in childhood), as well as anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED). The diagnostic criteria, for instance for AN, BN, and BED, have also changed – they have become somewhat broader. This has a direct influence in terms of a moderate rise in incidence and prevalence rates. The change in the diagnostic criteria from the DSM-IV to the DSM-5 is also relevant for other reasons: Most scientific works on incidences and frequency of mental disorders were conducted on the basis of the DSM criteria. In Germany, on the other hand, the International Classification of Diseases (ICD) criteria are relevant both clinically and for the health and pension insurance companies.

Terminology: In order to understand the statements made in epidemiological studies, several terms are important. One important term is the **population** about which a statement is to be made. A population needs to be defined very precisely, for example all citizens in Germany who are eligible to vote, or all adults who have their primary residence in a particular district on a given day. Such populations can be specified even further, e.g. all adult women aged 40-49 years who have their primary residence in a particular district on a given day. As it is often not possible in scientific investigations to capture a whole population using questionnaires or interviews, the concept of the **representative sample** was developed. According to this concept, parts of the population can be captured, e.g. one in ten or a random sample, so that the sample drawn from the population is representative of this population. For instance, in the area of eating disorders, there are studies which examined students in a grammar school; the findings of such studies would not be representative of all young people of that age, as a selection occurred. Once we have established a sample from a clearly defined population, it is necessary within a scientific study to capture the relevant characteristics of interest in a reliable and valid manner. For instance, it is necessary to examine persons with anorexia nervosa in the sample and to assess the relevant diagnostic criteria using a questionnaire or an interview conducted by people who are trained in administering the employed instruments (**case identification**).

Other important terms within epidemiology are incidence, prevalence and mortality rates. **Incidence** means the number of new cases of a particular disease in the population in a specified period of time. The **incidence rate** was standardized as the number of new cases of a disease per 100 000 people in the population per year. Incidence and prevalence rates, and the changes

therein over time, also help to draw conclusions about the etiology of a disease. **Prevalence** refers to the frequency of a disease (e.g. of anorexia) in the population. Based on the period of time to which a prevalence rate occurs, one speaks of point prevalence (today) period prevalence (e.g. one year) or lifetime prevalence (prevalence over the total number of years lived so far). **Prevalence rates** are also important for planning within the health care system. Anorexia is the mental illness with the highest **mortality rate** in the young adult years (Fichter & Quadflieg, 2016). Mortality rates are considerably higher for anorexia than for schizophrenia or depression. BN and BED have substantially lower mortality rates than anorexia. The "crude" mortality rate means the percentage of deceased persons in the examined sample or population. To draw any meaning from statements about mortality, the number of observed deaths among persons with a particular disease has to be related to the expected death rate in the comparison population (same gender, same age). In that case, one speaks of the standardized mortality ratio (SMR).

When considering incidence, prevalence, and mortality rates over time, the problem arises that different diagnostic criteria were used over time and the respective rates are consequently not directly comparable. Questions which laypeople are prone to ask ("Are eating disorders on the rise?") are thus often quite difficult to answer on an epidemiological-scientific basis. BN was described for the first time by Russell in 1979 and was included in the diagnostic criteria of the DSM-III in 1980, meaning that there are no epidemiological studies on BN prior to this time. Similarly, BED was first defined in the DSM-IV in 1994.

1. There are different approaches to achieve as representative a sample as possible. The arguably "cleanest" way is to draw a representative population sample from the residents' registry, which is easily possible in Scandinavian countries and in Germany because all citizens are obliged to register their place of residence.
2. Assuming that sick persons will at some point seek out a doctor or hospital (which cannot be seen as a given in the case of eating disorders), various case registers have been developed and in some cases maintained over many decades. Based on the statistics of the case register, it is then possible to provide details on the incidence- and prevalence-defined disease.
3. Some countries, such as in Scandinavia, possess outstanding disease statistics which go far beyond pure diagnostic statistics. The advantage here is that all patients are covered who were diagnosed and treated on an outpatient or inpatient basis. However, these registers do not include those sick persons who did not consult a doctor or hospital, which is often the case with eating disorders due to the doctor-averse behavior of a considerable number of sufferers.
4. In some countries, like Great Britain, the health system is structured such that almost all citizens are registered with a "General Practitioner" (GP). In many studies from Great Britain, **GP registers** were used to calculate prevalence and incidence rates, which are thus relatively informative.

2. Incidence

In order to determine the incidence of anorexia, case register studies play an important role. Due to the structure of the health care system in Great Britain, British studies with General Practitioners (GPs; family doctors) show a fairly strong resemblance with the methodology of register studies. In table 1 (in the appendix) as well as figure 1, the **incidence rates** are mainly presented for cases per year per 100,000 persons in the population. As such, the figures provided are comparable. The higher the incidence, the greater is the rate of new cases of AN or BN. The surveys on AN by Theander (1970, 1985) reach back to 1931. Over the examined time period from 1931 to 1960, a clear increase in treated cases of **AN** is apparent among women in Southern Sweden. The Monroe County case register in the USA by Jones, Fox, Babigian and Hutton (1980) also shows a corresponding increase in incidence for the 1970s compared to the 1970s. The same applies for the Zurich case register (Milos et al., 2004). In the Danish case register, the incidence rate was still low in 1970, and then increased substantially in 1980 and 1989. For the archive of medical records of a clinic in Rochester/USA for the period from 1950 to 1989, Lucas, Crowson, O'Fallon and Melton (1999a) also reported a gradual increase in incidence rates for anorexia. The reported data for the years 1935 to 1949 fall outside of this pattern and possibly constitute a methodological artifact. According to Milos et al. (2004), the incidence of first-time hospitalization due to AN in the Swiss Canton of Zurich rose steadily from 4.0 per 100,000 residents (1956 to 1958) to 16.5 per 100,000 residents (1973 to 1978), before rising less sharply to 19.7 per 100,000 residents (1993 to 1995). According to Currin, Schmidt, Treasure and Jick (2005), the incidence rate in England from 1998 to 2000 also remained constant at this level, at 20.8 per 100,000 residents. In a larger Dutch sample of male and female patients under GP care, Van Son, Hoeken, Bartelds, van Furth and Hoek (2006) found an incidence rate of 7.4 for the period from 1985 to 1989 and of 7.7 per 100,000 person years from 1995 to 1999. Keski-Rahkonen et al. (2007) reported on a twin cohort of girls aged from 15 to 19 years, and found a high incidence rate of 270 per 100,000 person years (95% confidence interval =180-360). This finding was substantially outside of the expected range. Table 1 and figure 1 indicate that the incidence rate of AN has increased since 1930 – and principally in the 1960s – from 0.1 to approx 5.0 per 100,000 persons in the population. In the decades since 1970, the incidence rate of AN has remained relatively stable (Smink et al., 2016) – without a further increase. For BN, by contrast, a tendency for an increase can be discerned in Western Europe over the last three decades (Hoek, 2016).

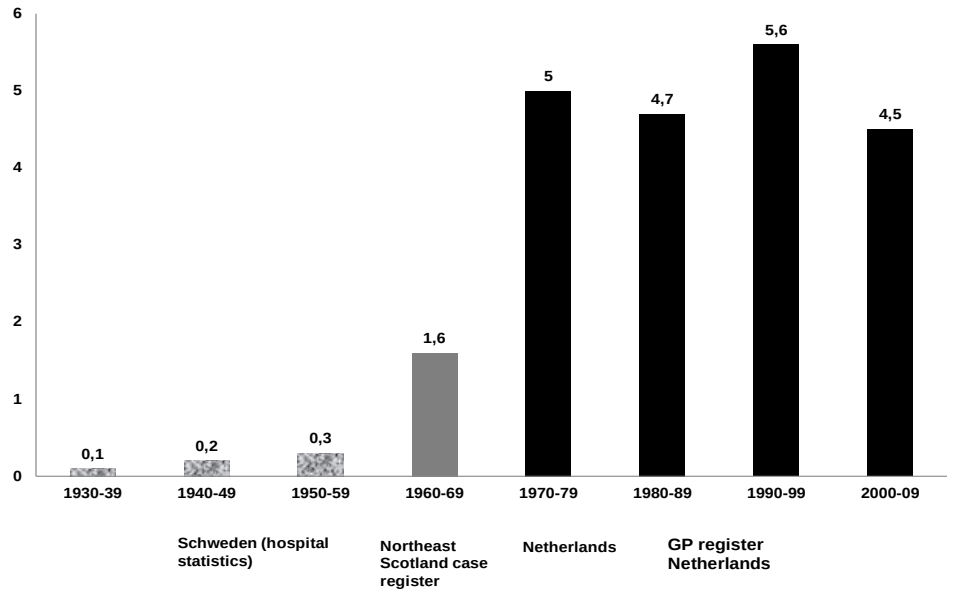

Fig. 1 Change in the annual incidence rate (per 100,000 persons) of anorexia nervosa in Western Europe over the decades (modified from Hoek, 2016), Sweden (hospital statistics); Northeast Scotland case register; Netherlands; GP register Netherlands

There are few available data on the incidence of **BN**. Currin et al. (2015) reported results over time in women aged between 10 and 39 years. The annual incidence rate rose continuously from 1989 to 1993: the highest annual incidence rate (over 60 per 100,000 inhabitants) occurred in 1996; in the following years it declined substantially. Zerwas et al. (2015) reported an incidence rate for BN in young women of 66.3 per 100,000 residents (national Danish research register).

Data on **BED** and **Eating Disorder Not Otherwise Specified** (EDNOS) are very limited.

3. Prevalence

An overview of selected important studies on the prevalence of AN, BN and BED as well as eating disorder not otherwise specified can be found in table 2. Particularly for AN and BN, the prevalence figures are a great deal higher for women than for men. Moreover, there appears to be an issue of selectivity in terms of the treated prevalence, insofar as men with BN and AN are less likely to seek treatment than women. Due to different sampling methods and different assessment instruments, the prevalences in this table are not immediately and directly comparable.

3.1. Anorexia nervosa

For women with **AN**, the 12-month prevalence rate for the risk age between 15 and 35 years lies at approx. 0.4% (DSM-5). Only the aforementioned study by Keski-Rahkonen et al. (2007) in a Finnish twin cohort reported substantially higher lifetime prevalence (2.2%) and incidence rates.

3.2. Bulimia nervosa

The 12-month prevalence for **BN** in adult women in North America lies at approx. 1.5 % (Hudson, Hiripi, Pope & Kessler, 2007). In men, the prevalence is around ten times lower. The prevalence of BN among adolescents (e.g. because the age at onset has not yet been reached) is lower than that of adults (Swanson, Crow, Le Grange, Swendsen & Merikangas, 2011; Kessler et al., 2012; Piazza et al., 2016; and in Germany Nagl et al., 2016 and Hammerle, Huss, Ernst & Bürger, 2016). Overweight in adolescence constitutes a risk factor for BN (Flament et al., 2015).

3.3. Binge eating disorder

For BED, the 12-month prevalence in adults lies at 1.6% for women and 0.8% for men. Accordingly, the proportion of men is not as vanishingly small compared to many other eating disorders. BED is more frequent among persons who have received treatment for overweight or obesity (Davis, 2015). In North America, BED occurs with the same frequency in black and white persons – which is not the case for anorexia and bulimia nervosa. The lifetime prevalence of BED in childhood and adolescence lies at 1.6%; the onset of the disorder was found to lie at a median age of 12.6 years (Swanson et al., 2011). As with BN, prevalence rates of BED also rise with increasing age (Stice, Marti, Shaw & Jaconis, 2009; Allen, Byrne, Oddy & Crosby 2013). In overweight individuals taking part in weight loss programs, the prevalence of BED is increased (Glasofer et al., 2007). Girls are somewhat more frequently affected than boys (Nicholls, Chater & Lask, 2000; Marcus & Kalarchian, 2003). In a study of adolescents taking part in a long-term rehabilitation measure due to extreme obesity, 57% of the girls and 35% of the boys suffered from binge eating (Ackard, Fulkerson & Neumark-Sztainer, 2007). In investigations which also included children and referred exclusively to inpatient measures, up to a third of children and adolescents reported binge-eating episodes. Thus, the risk of binge eating is higher in sufferers who require a more intensive (inpatient) treatment. In the framework of a large epidemiological study which examined all five-year-olds born in one particular year, 2% of all participants and 6% of obese children (BMI ≥ 90th percentile) showed binge-eating behavior (Lamerz et al., 2005).

There are no useable epidemiological results on **rumination disorder** according to the DSM-5 (Delaney et al., 2015).

In the DSM-5, **pica** and **Avoidant/Restrictive Food Intake Disorder** (ARFID) are defined as feeding or eating disorders included in the chapter Feeding and Eating Disorders of the DSM-5 criteria. Both are essentially attributed to feeding disorders and predominantly concern the area of child psychiatry. Nevertheless, pica can also occur in adult women during pregnancy or the postpartum period (Fawcett, Fawcett & Mazmanian, 2016). With regard to ARFID, at the time of writing, there was virtually no well-grounded literature on the frequency of this disorder. It appears to be rather infrequent, although there are hints that disorders with avoidance or restriction of food intake in the broader sense are by no means rare (Kurz, van Dyk, Dremmel, Munsch & Hilbert, 2016).

3.4. Eating Disorder Not Otherwise Specified (EDNOS)

The residual group of eating disorder not otherwise specified (EDNOS) according to the DSM-IV criteria is the largest group, covering 60% of all eating disorders (Fairburn & Bohn, 2005). The prevalence rates vary widely here due to the specific group composition: the residuals of the three main eating disorders AN, BN and BED, but additionally above all "subclinical" eating disorders which nevertheless often require treatment. In a large epidemiological survey of female students aged 12 to 23 years in Portugal, the point prevalence of EDNOS amounted to 2.37%. EDNOS accounted for 77% of all eating disorder diagnoses in this study (Machado, Machado, Gonçalves & Hoek, 2007). In a Spanish study, the prevalence of EDNOS among 13-15-year-old adolescents lay at 4.9% for girls and 0.6% for boys (Rodriguez-Cano, Beato-Fernandez, Belmonte-Llario, 2005). A study in Greek females and males aged 12-21 years examined the presence of an eating disorder in the home country (Veria, N=2920) and in Germany (as children of "guest workers"). Female Greeks in Greece had a lifetime prevalence of EDNOS of 19.4% (female Greeks in Germany 13.8%); the prevalence of EDNOS was substantially lower in boys (2.7% in Greece and 0.0% in Germany) (Fichter, Quadflieg, Georgopoulou, Xepapadakos & Fthenakis, 2005).

3.5. Other Specified Feeding or Eating Disorder according to DSM-5 (OSFED)

As the EDNOS category in the DSM-IV was so broad and expansive, in the DSM-5 criteria, other specified feeding or eating disorders have been defined more succinctly. These are:

1. **Atypical AN** (all criteria for AN are met, with the exception that body weight lies within or above the normal range).
2. **BN of low frequency and/or limited duration** with less frequent symptoms.
3. **BED of low frequency and/or limited duration**
4. **Purging disorder**, i.e. recurrent purging behavior in order to influence weight or shape (e.g. self-induced vomiting, abuse of laxatives, diuretics or other medications) in the absence of binge eating. Purging disorder: Munn-Chernoff et al. (2015) reported a prevalence rate of 3.77 % for a twin study and Micali et al. (2017) found a 12-month prevalence rate of 0.23% in women in a population-based sample over a period of 10 years. However, the section on purging disorder requires clearer diagnostic criteria. The 12-month prevalence for milder forms of eating disorders among middle-aged women

amounted to 0.35% for atypical AN, 0.44% for (subthreshold) BN and 0.38% for (subthreshold) BED (Micali et al., 2017).

5. **Night Eating Syndrome**, recurrent episodes of nighttime eating in the form of eating after nocturnal awakening or of excessive food intake following the evening meal. Sufferers are aware of the eating and are able to recall it. The nighttime eating can be better explained by external influences, e.g. changes in the individual sleep/wake rhythm or regional social norms. In a study of Swedish twins, Tholin et al. (2009) reported a prevalence of night eating syndrome of 4.6% in men and 3.4% in women. Sufferers with night eating syndrome showed increased obesity and sleep problems. The DSM-5 developments have stimulated research into night eating syndrome (Saraçh et al., 2015). The prevalence of night eating syndrome is especially high in obese patients in whom bariatric surgical interventions are planned. In a population sample of 2,460 persons (aged 14-92 years) in Germany, de Zwaan, Müller, Allison, Brähler and Hilbert (2014) found a prevalence of 1.1% based on the "Night Eating Questionnaire" (NEC).

4. Mortality

According to a meta-analysis, the mortality rate for AN is considerably higher than that for depression and schizophrenia; indeed, for AN, it is the highest of all mental disorders (Harris & Barraclough, 1998). A distinction is made between a "Crude Mortality Rate" (CMR; percentage of deaths in a sample) and the much more meaningful "Standardized Mortality Ratio" (SMR). To calculate the SMR, the mortality rate of the age group and for the respective time period are also considered, with values above 1.0 indicating above-average mortality and values below 1.0 indicating below-average mortality. Birmingham, Su, Hlynski, Goldner and Gao (2005) reported an SMR of 10.5 (95 % CI: 5.5–15.5) for 326 Canadian AN patients. In 524 AN patients in Northeast Scotland, Millar et al. (2005) found an SMR of 3.3 (95 % CI: 2.2–4.9). Fichter, Quadflieg and Hedlund (2006) reported a CMR of 7.7% in 103 female AN patients for a 12-year period. In a Swedish study, the CMR of hospitalized AN patients was longitudinally compared across two time periods (Lindblad, Lindberg and Hjern, 2006). The AN mortality rate for the period from 1977 to 1981 amounted to 4.4%, and decreased to 1.2% for the later time period from 1987 to 1991 (possibly due to improved treatment options in Sweden). However, a Norwegian study found an increase in "AN-related deaths" for the period from 1992 to 2000, from 6.5 to 9.9 per 100 000. In general, conventional death certificates have been found to be of limited reliability for studies on the cause of death. More recent investigations show that mortality rates for bulimia nervosa and binge eating disorder are substantially lower than those for AN (Fichter et al., 2006; Fichter, Quadflieg and Hedlund, 2008). In a meta-analysis of 43 follow-up BN studies, Nielsen (2003) found an aggregated SMR of 1.6% (95 % CI: 0.8–2.7). In a recent, very large and important study, Fichter & Quadflieg (2016) reported on a very large longitudinally examined clinical sample with mortality data on eating disorders. The standardized mortality ratio (SMR) adjusted according to population data showed the following results: The SMR was strongly increased for AN, at 5.35 (normal = 1.0); for BN, an SMR of 1.49 was calculated, and for BED, the SMR was 1.50. Mortality is thus excessively increased for AN and substantially increased for BN and BED.

5. Specific risk groups

A series of studies have shown that black women in the USA are much less likely to develop anorexia than white women, even though they are exposed to a similar pressure to be thin, at least on the part of the media. Apparently, therefore, there are particular subcultural factors that play a protective role here. Bulimia nervosa is also substantially more frequent in white women than in **black women** in the USA. By contrast, binge eating disorder and other forms of binge eating appear to be equally as widespread among blacks and whites in the USA (Striegel-Moore et al., 2003; Striegel-Moore et al., 2005). Persons at risk include first, adolescent girls in Western industrialized countries. Button, Aldridge and Palmer (2008) reported on a very large sample (N = 2554) from one region over a period of 21 years starting in 1987, and found fairly constantly that approx. 5% of those treated for eating disorders were male. Further risk factors are being overly conformist in childhood and a lack of development of positive self-esteem and body image. These girls or young women are therefore particularly sensitive to societal norms and are more likely to yield to the pressure to be thin than women with positive self-esteem. Due to their excessive conformity and lack of self-esteem, persons at risk are more likely to go on diets or try to lose weight in another way, and may therefore ultimately develop an eating disorder.

Compared to **men**, women between the ages of 12 and approx. 35 years have a substantially increased risk (at least 12-fold) of suffering from AN or BN. In samples of persons who have been treated for eating disorders, men are even scarcer, in population samples somewhat more frequent than the ratio of 1:12. In a population-based study in the USA, Husdon et al. (2007) found a lifetime prevalence of 0.5% for BN in adult men (women 1.5%). In a North American study, the proportion of men showing BN was found to be higher than in earlier studies (Hoek & van Hoeken, 2003). Although women are also more frequently affected by binge eating disorder (BED) than men, in adults, the proportion of men nonetheless lies at 30 to 40%.

A particular risk of disorder has further been shown in some specific groups. This applies to people who undertake **excessive exercise** or competitive sport, as well as those who partake in serious classical ballet or competitive dancing (Arcelus, Witcomb & Mitchell, 2014). For such people, there is a greater focus on a lower body weight, which increases the risk of developing AN (see review by Sundgot-Borgen, Fasting, Brackenridge, Torstveit & Berglund, 2003). Dancing with a high physical effort, as is the case for instance with ballet dancing, requires a strong degree of physical fitness, thinness and bodily control. Jockeys who take place in horse races also have an increased risk, as a lower body weight is a clear advantage for reaching the finish line first. Boxers and wrestlers are divided into weight classes and it is not uncommon for them to try to starve themselves down into a lower weight class before competitions. According to a study by Klungland Torstveit and Sundgot-Borgen (2004), athletes who take part in "leanness sports" competitions are at greater risk of eating disorders than athletes whose competitions take place in "nonleanness sports". In the sports sciences, there is the concept of a *female athlete triad*. Healthy athletes show an optimal supply of energy from food, eumenorrhea and a healthy bone structure. Through increased (athletic) energy consumption or reduced calorie intake, this triad can move in the direction of 1) lower availability of energy

with or without eating disorder, 2) osteoporosis, and 3) functional hypothalamic amenorrhea. Nattiv et al. (2007) wrote a review on behalf of the American College of Sports Medicine, which found that competitive athletes are at risk of a lower availability of energy if they a) undertake calorie reduction diets, b) exercise excessively over a longer period of time, c) are vegetarians, or d) substantially limit their range of nutrition (Cobb et al., 2003; Manore, 1999). Sundgot-Borgen and Klungland Torstveit (2004) examined 1620 competitive athletes of both genders as well as 1696 controls in Norway with regard to the emerging likelihood of an eating disorder using a two-stage approach. The prevalence of eating disorders was higher in competitive athletes than in controls. Among competitive athletes, it was higher in women than in men. Among the different types of sports, the prevalence of eating disorders was relatively highest for sports that showed a dependency on thinness and body weight. The same results were found by Byren & McLean (2002) in Australia. Sundgot-Borgen and Klungland Torstveit found a subclinical or clinical eating disorder in 13.5% of all competitive athletes and in 4.6% of controls. Eating disorders were found particularly among women in esthetic sports, at 42% (compared to endurance sports, technical sports or ball sports). For men, eating disorders were most frequent in "anti-gravity sports" (22%).

A new frequently asked question refers to the relationship between eating disorders and **diabetes mellitus**. A distinction is made between type I diabetes (onset mostly in adolescence, destruction of β-cells of the pancreas with consequent absolute insulin deficiency) and type II diabetes, which normally occurs in the second half of life and is frequently linked to obesity. In patients with type I diabetes, this generally occurs before the emergence of the eating disorder, in patients with type II diabetes generally afterwards. According to Herpertz (2008), anorexia and type I diabetes do not co-occur more frequently, but type I diabetes and bulimia nervosa do co-occur more often. "Insulin purging" refers to the reduction in the (generally evening) insulin dosage in order to lose weight. It is described as "vomiting over the kidneys". In persons with eating disorders and type I diabetes, "insulin purging" is not infrequent, which can considerably complicate the treatment both of the diabetes and of the eating disorder (Neumark-Sztainer et al., 2002; Colton, Olmsted, Daneman & Rydall, 2004; Grylli, Hafferl-Gattermayer, Schober & Karwautz, 2004; Goebel-Fabbri et al., 2008).

6. Do anorexia and bulimia exist in developing countries?

There are empirical studies from Singapore (Lee, Pathy & Chan, 2005), Hong Kong and Japan (Pike & Mizushima, 2005) which indicate that also in Eastern industrialized regions, eating disorders are approximately as frequent as in Western industrialized nations. There are also hints that eating disorders are on the rise in relation to the industrialization and urbanization in Arabic countries and in the not yet highly developed Asian countries (Pike, Hoek und Dunne, 2014). An increase can also be found overall especially in developing or emerging countries. Studies have been conducted on the Fiji Islands (Becker, Gilman & Burwell, 2005), among black people on Curaçao, in Morocco, Mexico and in Malaysia: In these places, the frequency of eating disorders is a great deal lower than in Western industrialized nations (Keski-Rahkonen, Raevuori & Hoek, 2008). If anorexic and bulimic eating disorders do occur in these developing countries, they are predominantly found in affluent families – thus in families where

there is an abundance of food. As an example, a study conducted on the Caribbean island of Curaçao (Hoek et al., 2005) found a relatively low overall incidence of AN, at 1.82 (95 % CI: 0.74–2.89) per 100,000 person years. Among black people, who make up the majority of the island's inhabitants, not a single case was found.

Acknowledgement: I wish to thank Prof. Dr. Tanja Legenbauer and Prof. Dr. Anja Hilbert for their input on this text.

Table 1: Incidence of AN and BN per year per 100 000 population

Authors	Total	Men	Women	Region	Source	Time period (year)	Age group
a) Anorexia nervosa							
Theander (1970)	–	–	0.10	Southern Sweden	Hospital archive	1931–1940	all
	–	–	0.20			1941–1950	all
	–	–	0.45			1951–1960	all
	–	–	0.24			1931–1960	all
Jones et al. (1980)	0.35	0.20	0.49	Monroe County (USA)	Case register+	1960–1969	all
	0.64	0.09	1.16		Hospital archive	1970–1976	all
Martz et al. (2001)	0.55		6.76	Zurich (CH)	Hospital archive	1963–1965	12–25 yrs
Milos et al. (2004)	1.12		16.75	Zurich (CH)	Hospital archive	1973–1975	12–25 yrs
	1.43		16.44	Zurich (CH)	Hospital archive	1983–1985	12–25 yrs
	1.17		19.72	Zurich (CH)	Hospital archive	1993–1995	12–25 yrs
Møller-Madsen & Nystrup (1992)	0.42		3.37	Denmark	Case register	1970	15–24 yrs
	1.36		11.96			1980	15–24 yrs
	1.17		8.97			1989	15–24 yrs
Currin et al. (2005)	4.70	0.70	8.60	GB	GP	2000	all
Keski-Rahkonen et al. (2007)	–	–	270.00	Finland	Twin register	Born 1975–1979	15–19 yrs
Lucas et al. (1999b)	9.10	3.40	15.00	Rochester, MN	Hospital archive	1935–1949	all
	4.30	0.80	7.60			1950–1959	all

		7.00	1.20	12.80			1960–1969	all
		7.90	1.40	14.50			1970–1979	all
		12.00	1.20	22.90			1980–1989	all
		8.30	1.50	15.00			(1935–1989)	all
Zerwas (2015)	broad criteria	60.5	7.7	116.5	Denmark	Nat. research register	Born 1989-06	16-20 yrs
	narrow criteria	40.4	4.6	78.4	Denmark	Nat. research register	Born 1989-06	16-20 yrs
b) Bulimia nervosa								
Currin et al. (2005)		6.60	0.70	12.40	GB	GP	2000	all
Zerwas (2015)	BN	28.2	5.8	66.3	Denmark	Nat. research register	Born 1986-06	16-20 yrs

Table 2: Prevalence of AN, BN and BED

Authors	Prevalence			Persons		Method		
	Overall	Men	Women	Sample	Age (yrs)	*N*	Screening[a)]	Criteria
a) Anorexia nervosa								
Råstam et al. (1989)	–	0.09	0.47	School students	15	2.136	Growth Tab. +	DSM-III
	–	0.00	0.23				questionnaire	DSM-III-R
Wittchen et al. (1998)	0.10[c)]	0.00[c)]	0.30[c)]	Population sample FRG	14–24	1.528	M-CIDI	DSM-IV
	0.60[d)]	0.10[d)]	1.00[d)]					
Fichter et al. (2005)	0.30[e)]	0.00[e)]	0.59[e)]	School students (Greece)	13–19	2.920	ANIS/SIAB-Ex	DSM-IV
Machado et al. (2007)	–	–	0.39	School students	12–23	2.028	EDE-S	DSM-IV
Hudson et al. (2007)	0.00[c)]	0.00[c)]	0.00[c)]	Population sample USA	>18	2.980	WHO-CIDI	DSM-IV
	0.60[d)]	0.30[d)]	0.90[d)]					
Keski-Rahkonen et al. (2007)	–	–	2.20[d)]	Twin cohort (Finland)	25	2.881	EDI/short-SCID	DSM-IV
Taylor et al. (2007) Blacks	0.17[d)]	0.20[d)]	0.14[d)]	NSAL household sample USA	>18	5.191	WMH-CIDI	DSM-IV-TR
Alegria et al. (2007) Latinos	0.08[d)]	0.03[d)]	0.12	NSAL household sample USA	>18	2.554	WMH-CIDI	DSM-IV-TR
Nicdao et al. (2007) Asians	0.08[d)]	0.05[d)]	0.12	NLAAS household samp. USA	>18	2.095	WHO-CIDI	DSM-IV
Ackard et al. (2007) US various	–	0.00[e)]	0.04[e)]	US Middle & High School	14.9 ± 1.7	4.746	Survey Quest.	DSM-IV
Zachrisson et al. (2008) 1991	–	–	0.10[d)]	Norway ♀	36.9 ± 12	1.537	Self-rating	DSM-III-R/IV
2004	–	–	0.20[d)]	Norway ♀	40.4 ± 13	1.466	Self-rating	DSM-III-R/IV
b) Bulimia nervosa								
Garfinkel et al. (1995)	–	0.10[d)]	1.10[d)]	Population sample Ontario	15–65	8.116	WHO-CIDI	DSM-III-R

Wittchen et al. (1998)	0.30[c]	0.00[c]	0.70[c]	Population sample	14–24	1.528	M-CIDI	DSM-IV
	0.90[d]	0.00[d]	1.70[d]	FRG	14–24	1.493		
Fichter et al. (2005)	0.93[e]	0.68[e]	1.18[e]	School students (Greece)	13–19	2.920	ANIS/GHQ	(DSM-IV)
Hudson et al. (2007	0.30[c]	0.10[c]	0.50[c]	Household sample USA	>18	2.980	WHO-CIDI	DSM-IV
Taylor et al. (2007) Blacks	0.20[d]	0.97[d]	1.90[d]	NSAL household samp. USA	>18	5.191	WHM-CIDI	DSM-IV-TR
Alegria et al. (2007) Latinos	1.61[d]	1.34[d]	1.91[d]	NSAL household samp. USA	>18	2.554	WMH-CIDI	DSM-IV-TR
Nicdao et al. (2007) Asians	1.09[d]	0.71[d]	1.42[d]	NLAAS household samp. USA	>18	2.095	WHO-CIDI	DSM-IV
Ackard et al. (2007) US various	–	0.17[e]	0.34[e]	US Middle & High School	14.9 ± 1.7	4.746	Survey Quest.	DSM-IV
Zachrisson et al. (2008) 1991	–	–	2.00[d]	Norway ♀	36.9 ± 12	1.537	Self-rating	DSM-III-R/IV
2004	–	–	4.10[d]	Norway ♀	40.4 ± 13	1.466	Self-rating	DSM-III-R/IV

c) Binge Eating Disorder

Hudson et al. (2007)	1.20[c]	0.80[c]	1.60[c]	Household sample USA		2.980	WHO-CIDI	DSM-IV
	2.80[d]	2.00[d]	3.50[d]					
Taylor et al. (2007) Blacks	1.66[d]	0.78[d]	2.36[d]	NSAL household samp. USA	>18	5.191	WHM-CIDI	DSM-IV-TR
Alegria et al. (2007) Latinos	1.92[d]	1.55[d]	2.31[d]	NSAL household samp. USA	>18	2.554	WMH-CIDI	DSM-IV-TR
Nicdao et al. (2007) Asians	2.04[d]	1.35[d]	2.67[d]	NLAAS household samp. USA	>18	2.095	WHO-CIDI	DSM-IV
Ackard et al. (2007) US various	–	0.34[e]	1.91[e]	US Middle & High School	14.9 ± 1.7	4.746	Survey Quest.	DSM-IV
Zachrisson et al. (2008) 1991	–	–	0.90[d]	Norway ♀	36.9 ± 12	1.537	Self-rating	DSM-III-R/IV
2004	–	–	0.70[d]	Norway ♀	40.4 ± 13	1.466	Self-rating	DSM-III-R/IV

d) EDNOS (DSM-IV)

Fichter et al. (2005)	8.30[e]	2.71[e]	13.55[e]	School students (Greece)	13–19	2.980	ANIS/GHQ	DSM-IV
Machado et al. (2007)	–	–	2.37[e]	School students (Portugal)	12–23	2.028	EDE-S	DSM-IV
Zachrisson et al. (2008) 1991	–	–	6.30[d]	Norway ♀	36.9 ± 12	1.537	Self-rating	DSM-III-R/IV

2004	–	–	5.00[d)]	Norway ♀		40.4 ± 13	1.466	Self-rating	DSM-III-R/IV

[a)] EAT = Eating Attitudes Test; EDE-S = Eating Disorders Examination, Screening Version; ANIS = Anorexia Nervosa Inventory Scale; BCDS = Bulimic Cognitive Distortions Scale; DIS = Diagnostic Interview Schedule; CIDI = Composite International Diagnostic Interview
[b)] cumulative lifetime prevalence
[c)] 12-month prevalence
[d)] lifetime prevalence
[e)] point prevalence

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II. Diagnosis of Eating Disorders

1. Diagnosis of psychological symptoms

Silja Vocks, Ulrich Schweiger, Anja Hilbert, Ulrich Hagenah, Brunna Tuschen-Caffier[2]

1.1. Early identification[3]

Patients with eating disorders should receive help at the earliest opportunity. To achieve this, it is necessary to identify the disorders in a timely manner, and not wait until the patient herself or persons close to her show an active desire for change or obvious complications have arisen. Early detection is facilitated by the public availability of valid information about the psychopathology of eating disorders and treatment options. At the beginning of their illness, patients with eating disorders often have no contact with physicians for psychiatry, psychosomatic medicine and psychotherapy, psychological psychotherapists or child and adolescent psychotherapists, but they do have contact with specialist physician groups in the areas of general medicine, dentistry, gynecology and obstetrics or pediatric and adolescent medicine. Therefore, it is important that all of these professional groups are alert to the symptoms of eating disorders.

If any respective indications are evident, a physician or psychologist should consider the possibility of an eating disorder, determine body height and weight, and ask screening questions to identify suspected cases. Eating disorder-related questionnaires can provide support in the realm of early detection (see below). Particular attention should be paid to the following groups of people:

- Patients with a low body weight or significant weight loss
- Patients with obesity and/or significant weight gain
- Patients with amenorrhea or infertility
- Patients with dental damage
- Patients who have attended a consultation due to worries about their weight but who are of normal weight
- Overweight patients
- Patients with gastrointestinal symptoms which cannot be clearly attributed to another medical cause
- Children and adolescents with faltering growth
- Patients who work in the entertainment, fashion or food industry
- Competitive athletes

[2] Harriet Salbach-Andrae was a co-author of an earlier version of this chapter.

[3] Parts of chapters 1.1 and 1.2 have been previously published in a similar form in the following book chapter: Schweiger, U. (2015). Diagnostik von Essstörungen. In Herpertz, S., de Zwaan, M. & Zipfel, S. (Hrsg), *Handbuch Essstörungen und Adipositas* (S. 36-42). Berlin: Springer.

- Children and adolescents whose parents are worried about their weight and eating behavior.

For early detection, the primary physician should ask the patient about eating behavior and weight course in a targeted and age-appropriate manner (GCP).

1.2. Physical and psychological characteristics

1.2.1. Underweight or overweight

For a more detailed diagnosis in the case of a suspected eating disorder, the patient should be weighed and measured in underwear and without shoes using a calibrated instrument. The interpretation and evaluation of the measurement values should be undertaken using appropriate formulae (BMI = kg/m^2), normal ranges or age-related percentile curves (for more details, see the S3 guideline "Prevention and treatment of obesity"; Wirth, Wabitsch, & Hauner, 2014). In addition to the current weight, the weight course (e.g. speeed of weight loss) is important.

1.2.2. Body weight and self-esteem

To be able to correctly evaluate the patient's account of her eating behavior and the associated cognitions (i.e. intensive preoccupation with food and food-related themes, fear of being fat, desire to lose weight etc.), it is also important to be aware of the normative age-related attitudes and the cultural background. Restrictive eating behavior can be motivated by esthetic or sporting ideals, but also by ascetic ideals, i.e. the notion of approaching spiritual goals through self-control and abstention. However, restrictive eating behavior can also be motivated by associated aversive experiences or disinterest in food. From a differential diagnostic perspective, it is necessary to discuss a genuine lack of appetite or an increased appetite, for instance in the framework of severe depressive episodes or physical diseases. A self-appraisal as being "too fat" is also common among healthy women and men as well as girls and boys in the Western world (Cooper, Deepak, Grocutt, & Bailey, 2007). The inappropriate or pathological aspect does not arise solely from this self-appraisal, but also from the fact that such thoughts occupy considerable space (e.g. in the form of time-intensive processes of worry), the sufferer is unable to gain any critical distance from them (cognitive fusion), the thoughts substantially reduce the sufferer's self-esteem, or they trigger dysfunctional behavior (e.g. vomiting).

1.2.3. Restriction of caloric intake

Eating disorders typically encompass a range of target-oriented behaviors which serve to reduce weight or to maintain it at a low level:

- Checking behavior, i.e. highly frequent weighing, in order to closely monitor changes in body weight, highly frequent checking of the circumference of body parts using measuring tape, of skin fold thickness, or checking one's appearance in the mirror including with the aim of maintaining the motivation for food restriction.
- Avoidance of high-calorie, fatty or carbohydrate-based foods
- Skipping meal components such as dessert or skipping a whole meal
- Chewing and spitting out food
- Balancing meals by acquiring knowledge about calories and calorie counts and weighing all foods
- Avoidance of foods whose calorie count cannot be clearly determined, such as complex dishes prepared by others
- Use of sweeteners, fat substitutes and "diet" products
- Use of pharmacological appetite suppresants, nicotine, cocaine or other stimulants for appetite control
- Changes in mealtime schedules, for instance by limiting intake to one mealtime per day or through a self-imposed structure with a multitude of small meals
- Excessive fluid consumption before meals in order to limit food intake
- Fluid restriction in order to limit food intake, e.g. through mouth dryness
- Selection and consumption of unattractive foods or foods rendered inedible, for example by adding salt or hot spices
- Use of disgust conditioning in order to block the intake of attractive foods (e.g. by imagining that chocolate has been contiminated by mouse droppings)
- Not eating in the company of others in order to avoid distraction when eating or other social influences
- Use of constricting abdominal belts, restrictive clothing or tensing the muscles in order to generate a premature feeling of fullness
- Use of tongue piercings or self-injuries in the oral cavity in order to impede food intake.

1.2.4. Binge eating

The term "binge" describes an episode of food intake in which the usual control over eating is lost or not practiced. In an objective binge eating episode, an amount of food is consumed that goes beyond the realm of a normal meal in terms of the amount of calories. The diagnostic manuals of the DSM and ICD do not define a precise calorie threshold. The average number of calories, which was measured in binge eating episodes under controlled conditions, lies in the range between 3000 and 4500 kcal (Wolfe, Baker, Smith, & Kelly-Weeder, 2009).
Food intake that is unplanned, uncontrolled or undesired but which does not constitute an objectively unusual amount can also be subjectively perceived as binge eating (Fairburn & Wilson, 1993). Binge eating typically involves foods which the person usually forbids herself from eating. In the case of a long-term eating disorder, binge eating epsiodes are often precisely planned, i.e. foods suitable for bingeing are bought and stored and it is ensured that nobody will disturb the person during the binge (Abraham & Beumont, 1982).

1.2.5. Compensatory behavior

Compensatory behavior refers to a range of target-oriented behaviors that serve to rapidly remove consumed energy or fluids from the organism. All measures that promote vomiting or diarrhoea are summarized in this regard as "purging behavior".

- Self-induced vomiting can take place following mechanical irritation of the pharynx, supported by chemical substances which promote vomiting (e.g. Radix, Ipecacuanha, saline solutions) or automatically
- Herbal or synthetically manufactured laxatives
- Herbal or synthetically manufactured diuretics
- Thyroid hormones (to increase the basal metabolic rate)
- Exercise and exposure to cold or heat (e.g. saunas)
- Skipping insulin in patients with type I diabetes in order to induce renal loss of glucose

1.2.6. Evaluation of behaviors

Some behaviors which occur in eating disorders can also be observed in healthy women and men, but also even in girls and boys during childhood, and above all from adolescence (e.g. dieting, induced vomiting, intensive exercise for weight control). The evaluation of behaviors as clinically relevant can therefore not be solely based on frequencies or intensities. Rather, in each individual case, it is necessary to check whether the specific behavior gives rise to a relevant impairment or threat to physical health, psychosocial functioning or subjective distress.

1.3. Diagnosis

If an eating disorder is suspected, it should be formally checked whether the criteria for an eating disorder are met according to an operationalized diagnostic system of the respective current version of the ICD or DSM. Further diagnostics should include structured clinical interviews or checklists (see below). To adequately help all persons suffering from an eating disorder, it is important to also apply the diagnostic categories of atypical eating disorders or eating disorders not otherwise specified (EDNOS). Health care epidemiological studies show that the current main ICD categories only capture approximately 40 to 60% of patients with a clinically significant eating disorder. When applying the criteria of the DSM-5, the proportion of EDNOS diagnoses lies at around 25% (Fairburn & Cooper, 2011).

1. If an eating disorder is still suspected following preliminary examinations, categorical diagnostics should be systematically performed using the current diagnostic criteria of the DSM or ICD, ideally using guidelines or validated diagnostic interviews. (GCP)
2. In the framework of differential diagnosis, a timely co-evaluation by a medical psychotherapist, psychological psychotherapist or child and adolescent psychotherapist should be performed. (GCP)

1.4. Approaches for the categorical and dimensional diagnosis of psychological symptoms

At the beginning of treatment, a comprehensive valid and reliable diagnossis of the psychological symptoms is essential for determining indications and for treatment planning. The diagnosis of psychological symptoms also assumes an important role in the course of treatment and after treatment completion, in order to assess the progress and outcome of therapy in the sense of quality assurance. First, this chapter therefore presents structured clinical interviews for diagnosis according to the ICD and DSM, with a focus on eating disorder-specific as well as general instruments. In addition to this approach of categorical diagnosis, the chapter also describes various self-report questionnaires which can be used to dimensionally quantify eating disorder symptoms and associated symptoms. The description of the eating disorder-specific procedures in text form is supplemented by a table which lists the procedures focused on in the text and further includes psychometric procedures for categorical and dimensional diagnostics (table 3). For each procedure, the table includes sources, scale names, numbers of items and literature references to studies assessing the reliability and validity of the respective instrument.

Table 1: Overview of eating disorder-specific structured interviews and self-report questionnaires for adults and children and adolescents

Name of interview/questionnaire	Authors	Subcales (No. of items)	Validation study/studies
Instruments for categorical diagnosis in adults			
Eating Disorder Examination (EDE)	*Original version:* Fairburn & Cooper, 1993 *German translation:* Hilbert et al. 2004; Hilbert & Tuschen-Caffier, 2006a, 2016a	1. Restraint (5) 2. Eating concern (5) 3. Shape concern (8) 4. Weight concern (5)	Hilbert et al., 2004
Structured Inventory for Anorexic and Bulimic Disorders Expert Interview (SIAB-EX) *[Strukturiertes Inventar für Anorektische und Bulimische Essstörungen zur Expertenbeurteilung*]	Fichter & Quadflieg, 1999a, 2001, 2004; Fichter et al., 1998a	1. Body image and slimness ideal 2. general Psychopathology and social integration 3. Sexuality 4. Bulimic symptoms 5. Measures to counteract weight gain, fasting and substance abuse 6. Atypical Binges	Fichter & Quadflieg, 2001
Instruments for categorical diagnosis in children and adolescents			
Eating Disorder Examination for Children (ChEDE) *[Eating Disorder Examination für Kinder]*	*Original version:* Bryant-Waugh et al., 1996; Fairburn & Cooper, 1993	1. Restraint (5) 2. Eating concern (5) 3. Shape concern (8) 4. Weight concern (5)	Hilbert et al., 2013; Watkins et al., 2005

	German translation: Hilbert, 2016a; Hilbert et al., 2013		

Instruments for dimensional diagnosis in adults

Body Checking Cognitions Scales (BCCS)	*Original version:* Mountford et al., 2006 *German translation:* Neubauer et al., 2010	1. Objective verification (6) 2. Reassurance (4) 3. Safety beliefs (4) 4. Body control (4)	Neubauer et al., 2010
Body Checking Questionnaire (BCQ)	*Original version:* Reas et al., 2002 *German translation:* Vocks et al., 2008	1. Overall appearance (10) 2. Specific body parts (8) 3. Idiosyncratic checking (5)	Steinfeld et al., 2017b; Vocks et al., 2008
Body Image Avoidance Questionnaire (BIAQ)	*Original version:* Rosen et al., 1991 *German translation:* Legenbauer et al., 2007b	1. Clothing (9) 2. Social acitivities (4) 3. Eating restraint (3) 4. Grooming and weighing (3)	Legenbauer et al., 2007b; Steinfeld et al., 2018
Eating Attitudes Test (EAT)	*Original version:* EAT-40, Garner & Garfinkel, 1979; EAT-26, Garner et al., 1982 *German translation:* e.g. EAT-26D, Meermann & Vandereycken, 1987; EAT-8, Richter et al., 2016; EAT-13, Berger et al., 2012; Rainer & Rathner, 1997; Tuschen-Caffier et al. 2005	e.g. EAT-26D: 1. Dieting (13) 2. Bulimia and food preoccupation (6) 3. Oral control (7)	Berger et al., 2012; Richter et al., 2014, 2016
Eating Disorder Examination-Questionnaire (EDE-Q)	*Original version:* Fairburn & Beglin, 1994 *German translation:* Hilbert & Tuschen-Caffier, 2006b, 2016b; Hilbert et al., 2007, 2012 *German short version:* Hilbert & Tuschen-Caffier, 2016b	1. Restraint (5) 2. Eating concern (5) 3. Shape concern (8) 4. Weight concern (5)	Hilbert et al., 2007, 2012 English short version: Eating Disorder Examination-Questionnaire 8 (Kliem et al., 2016)
Eating Disorder Inventory (EDI, EDI-2)	*Original version:* Garner et al., 1983; Garner, 1991 *German translation:* Paul & Thiel, 2004; Rathner & Rainer, 1997; Rathner & Waldherr, 1997	1. Drive for thinness (7) 2. Bulimia (7) 3. Body dissatisfaction (9) 4. Ineffectiveness (10) 5. Perfectionism (6) 6. Interpersonal distrust (7) 7. Interoceptive awareness (10) 8. Maturity fears (8) 9. Asceticism (8) 10. Impulse regulation (11) 11. Social insecurity (8)	Kappel et al., 2012; Paul & Thiel, 2004; Salbach-Andrae et al., 2010

Three-factor-Eating-Questionnaire (TFEQ) *[Fragebogen zum Essverhalten, FEV]*	*Original version:* Stunkard & Messick, 1985 *German translation:* Pudel & Westenhöfer, 1989	1. Cognitive restraint (21) 2. Disinhibition (16) 3. Hunger (14)	Pudel & Westenhöfer, 1989
Body Shape Questionnaire (BSQ) *[Fragebogen zum Figurbewusstsein, FFB]*	*Original version:* Cooper et al., 1987 *German translation:* Waadt et al., 1992	Total score (34)	Pook et al., 2002, 2009
Body Image Questionnaire (BIQ) *[Fragebogen zum Körperbild, FKB-20]*	*Original version (German):* Clement & Löwe, 1996	1. Rejecting body evaluation (10) 2. Vital body dynamics (10)	Albani et al., 2006
Questionnaire for Assessing One's Own Body [Fragebogen zur Beurteilung des eigenen Körpers, FBeK]	*Original version (German):* Strauß & Richter-Appelt, 1996	4-Scale model: 1. Attractiveness/self-confidence (15) 2. Accentuation of physical appearance (12) 3. Insecurity/concern (13) 4. Physical/sexual discomfort (6) 3-Scale model: 1. Insecurity/discomfort (19) 2. Attractiveness/self-confidence (13) 3. Accentuation of body/sensitivity (20)	Brähler et al., 2000; Dähne et al., 2004
University of Rhode Island Change Assessment Scale (URICA) *[Fragebogen zur Erfassung der Veränderungsbereitschaft, FEVER]*	*Original version:* McConnaughy et al., 1989 *German translation:* Hasler et al., 2003	1. Precontemplation (8) 2. Contemplation (8) 3. Action (8)	Hasler et al., 2003; von Wietersheim & Hoffmann, 2011
Questionnaire for The Assessment of Dysfunctional Cognitions in Eating Disorders [Fragebogen zur Erfassung dysfunktionaler Kognitionen bei Essstörungen, FEDK]	*Original version (German):* Legenbauer et al., 2007a	1. Body and self-esteem (11) 2. Restriction and diet rules (9) 3. Eating and loss of control (8)	Legenbauer et al., 2007a
Frankfurt Body Concept Scales (FBCS) *[Frankfurter Körperkonzeptskalen, FKKS]*	*Original version (German):* Deusinger, 1998	1. Health (6) 2. Grooming and taking care of functioning (8) 3. Physical efficacy (10) 4. Body contact (6) 5. Sexuality (6) 6. Self-acceptance of one's body (6) 7. Acceptance of one's body by others (4) 8. Physical appearance (14) 9. Dissimilating body processes (4)	Deusinger, 1998
Multidimensional Body-Self-Relations	*Original version:* Cash, 2000	1. Appearance evaluation (7) 2. Body areas satisfaction scale (9)	Vossbeck-Elsebusch et al., 2014

Questionnaire Appearance Scales (MBSRQ-AS)	*German translation:* Vossbeck-Elsebusch et al., 2014	3. Appearance orientation (12) 4. Overweight preoccupation (4) 5. Self-classified weight (2)	
Munich Eating and Feeding Disorder Questionnaire (Munich ED-Quest)	*Original version (German):* Fichter et al., 2015	1. Preoccupation with figure and weight (33) 2. Bingeing and vomiting (12) 3. Inappropriate compensatory behaviour (15)	Fichter et al., 2015
Stages of Change Questionnaire for Eating Disorders (SOCQ-ED)	*Original version (German):* von Brachel et al., 2012 *Following:* *Anorexia Nervosa Stages of Change Questionnaire* (ANSOCQ; Rieger et al., 2000, 2002) *Bulimia Nervosa Stages of Change Questionnaire* (BNSOCQ; Martinez et al., 2007)	13 items: each designates one symptom (e.g. vomiting, great importance of shape and weight) Assessment of current stage of change (per item), different stages: 1. Precontemplation 2. Contemplation 3. Preparation 4. Action 5. Maintenance 6. Termination	von Brachel et al., 2012
Structured Inventory for Anorexic and Bulimic Disorders Self-Report [Strukturiertes Inventar für Anorektische und Bulimische Essstörungen zur Selbsteinschätzung, SIAB-S]	*Original version (German):* Fichter & Quadflieg, 1999a, 2001	1. General psychopathology and social integration 2. Bulimic symptoms 3. Body image and slimness ideal 4. Sexuality and body weight 5. Measures to counteract weight gain, fasting and substance abuse 6. Atypical binges	Fichter & Quadflieg, 1997, 1999b; Fichter et al., 1998b
Instruments for dimensional diagnosis in children and adolescents			
Anorectic Behavior Observation Scale (ABOS)	*Original version:* Vandereycken & Meermann, 1984 *German translation:* Salbach-Andrae et al., 2009 *German short version:* *Eating and Activity Questionnaire for Parents* (EAQP; Thiels & Schmitz, 2009)	1. Unusual eating behavior (16) 2. Bulimic-like behavior (7) 3. Hyperactivity (7)	Salbach-Andrae et al., 2009; Vandereycken & Meermann, 2003
Anorexia Anxiety Sclae [Anorexie-Angst-Skala, AAS]	*Original version (German):* Schulze & Keller, 2009	1. Weight-associated anxiety (8) 2. Other anxieties (9)	Schulze & Keller, 2009
Eating Disorder Examination-Questionnaire for Children (ChEDE-Q) *[Eating Disorder*	*Original version:* TODAY Study Group, 2007 *German translation:*	1. Restraint (5) 2. Eating concern (5) 3. Shape concern (8) 4. Weight concern (5)	Hilbert et al., 2008

Examination-Questionnaire für Kinder]	Hilbert, 2016b; Hilbert et al., 2008 *Deutschsprachige Kurzversion:* Kliem et al., 2017		
Eating Disorders in Youth-Questionnaire (EDY-Q)	*Original version (German):* Kurz et al., 2015, 2016; van Dyck et al., 2013; van Dyck & Hilbert, 2016	1. Food avoidance emotional disorder (3) 2. Selective eating (3) 3. Functional dysphagia (2) 4. Pica, rumination disorder(2) 5. Early-onset feeding or eating disorders (2)	Kurz et al., 2015, 2016; van Dyck et al., 2013
SCOFF	*Original version:* Morgan et al., 1999 *German translation:* e.g. Berger et al., 2011	Five items: 1. Sick (deliberate vomiting) 2. Control (loss of control over eating) 3. One Stone (weight loss) 4. Fat (body image distortion) 5. Food (impact of food on life)	Berger et al., 2011; Botella et al., 2013; Herpertz-Dahlmann et al., 2008, 2015; Richter et al., 2017; Solmi et al., 2015
Weight Concerns Scale (WCS)	*Original version:* Killen et al., 1993, 1994 *German translation:* Grund, 2003	WCS Scale (5): − Worry about shape − Fear of gaining weight − Last time on a diet − Importance of weight − Feeling of fatness	Grund, 2003; Killen et al., 1994

1.4.1. General instruments

1.4.1.1. Instruments for categorical diagnosis in adults

Diagnostic Interview for Mental Disorders (DIPS)

The Diagnostic Interview for Mental Disorders (DIPS; Margraf, Schneider & Ehlers, 1994; Schneider & Margraf, 2008; Margraf & Cwik, 2017; Margraf, Cwik, Suppiger & Schneider, 2017) is used for the assessment and diagnosis of the most important mental disorders for the clinical domain. On the whole, the inter-rater reliability can be described as very good. The procedure is streamlined by the use of branch instructions. The administration of the DIPS requires training, reading of the manual and compliance with the rules contained therein. The particular benefit of the DIPS for the user in the framework of diagnosing eating disorders lies in the systematic assessment of comorbidity. The limitation of the procedure lies in the fact that it exclusively assesses diagnostically relevant symptoms. The interview can also be administered in routine clinical practice. The questions on eating disorders refer first to body height, current weight, and highest and lowest weight in adulthood. Further questions include: "Has there ever been a time when you weighed much less than other people thought you ought to weigh, or when you lost a lot of weight?" or "Do you have binge eating or phases of ravenous appetite in which you eat much more than other people would eat under similar circumstances?". Subsequently, the criteria for anorexia nervosa, bulimia nervosa and binge eating disorder are assessed. The DIPS and the short version Mini-DIPS are now available in

adapted versions according to the DSM-5 (Margraf & Cwik, 2017; Margraf et al., 2017). These are freely available from the following links: http://dips.rub.de; http://mini-dips.rub.de

Structured Clinical Interview for DSM-IV (SCID), Axis I and II disorders

The Structured Clinical Interview for DSM-IV (SCID), Axis I and II disorders (Fydrich, Renneberg, Schmitz, & Wittchen, 1997; Scholz & Wittchen, 2006) is a comprehensive and complex diagnostic interview for the assessment and diagnosis of selected pschological syndromes and disorders as they are defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) on Axis I (acute mental disorders) and Axis II (personality disorders). In addition, coding options are provided for Axis III (physical disorders), Axis IV (psychosocial impairment) and Axis V (psychosocial functioning). The inter-rater reliability of the interview can be described as good to very good. Administering the SCID requires training, reading of the manual and compliance with the rules contained therein. The particular benefit of the SCID for the user in the framework of diagnosing eating disorders lies in the systematic assessment of comorbidity. The limitation of the procedure lies in the fact that it exclusively assesses diagnostically relevant symptoms. The interview can also be administered in routine clinical practice. The questions referring to eating disorders are: “Have other people ever said that you are too thin?” and “Have you ever had eating binges where you had the feeling that you could not control your eating behavior?”. In section H, the criteria for eating disorders, their subtypes and the stage of disease are then documented: H1 to H10 anorexia nervosa, H11 to H24 bulimia nervosa and H24 to H38 binge eating disorder. The procedure is streamlined through the use of branch instructions. There is now an English-language version of the SCID adapted to the modified diagnostic criteria of the DSM-5 (First, Williams, Karg & Spitzer, 2015); a version of the SCID translated into German is currently being developed (Beesdo-Baum, Zaudig & Wittchen, 2019).

International Diagnostic Checklists (IDCL)

The International Diagnostic Checklists for DSM-IV and ICD-10 (IDCL; Hiller, Zaudig, & Mombour, 1997) provide the possibility, for research and practice, to conduct a standardized and economical assessment of findings according to the classification systems DSM-IV and ICD-10 (two sets of checklists/IDCL for ICD-10 and IDCL for DSM-IV). Particularly for diagnosticians who are already experienced in standardized interviews (such as the SCID), the IDCL enable an even quicker procedure. The test-retest reliability and the inter-rater reliability for all examined disorder groups are satisfactory to good. Each checklist refers to one diagnosis. The particular benefit of the IDCL for the user in terms of the diagnosis of eating disorders lies in the systematic assessment of comorbidities with a simultaneously very high time-efficiency in routine clinical practice. The limitation of the procedure lies in the fact that it exclusively assesses diagnostically relevant symptoms. Due to the lack of branch instructions, the structure of the checklists does not allow for a complete implementation, meaning that experience with other, more highly structured diagnostic procedures is helpful in the preparation.

1.4.1.2. Instruments for categorical diagnosis in children and adolescents

Diagnostic Interview for Mental Disorders in Children and Adolescents (Kinder-DIPS)
The Diagnostic Interview for Mental Disorders in Children and Adolescents (Kinder-DIPS) is a supplement to the Diagnostic Interview for Mental Disorders (DIPS), which was designed for adults. It consists of a child version, in which the child or adolescent is surveyed directly, and a parallel parent version, in which a parent or other caregiver is surveyed (Schneider, Unnewehr & Margraf, 2008). The Kinder-DIPS is seen as a reliable (Kappa values: .50–.89, Yule's Y-values: .60–.81 for the test-retest reliability of the major diagnostic categories) and valid instrument for diagnosis according to the criteria of the DSM-IV or ICD-10. Analogously to the DIPS, the use of the Kinder-DIPS requires training, reading of the manual and compliance with the rules contained therein. With respect to the diagnosis of eating disorders, the particular benefit of the DIPS lies in a reliable assessment of psychological comorbidities. The Kinder-DIPS can be employed in practice and in research institutions. A limititation of the instrument lies in the considerable amount of time required for its administration. A version of the DIPS adapted to the DSM-5 is now available (Schneider, Pflug, In-Albon & Margraf, 2017) and can be freely accessed from the following link: http://kinder-dips.rub.de

Kiddie-Sads-Present and Lifetime Version (K-SADS-PL)
The German version (Delmo, Weiffenbach, Gabriel & Poustka, 2000) of the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL; Chambers et al., 1985; Kaufman et al., 1997) is a semi-structured diagnostic interview which was developed to assess current and past episodes of mental disorders in children and adolescents according to the DSM-III-R and DSM-IV. An adapted revision for the DSM-5 is now available (Kaufman et al, 2016), and can be accessed from the homepage of the first author (https://www.kennedykrieger.org/patient-care/faculty-staff/joan-kaufman), although it is not available in the German language. To rate the symptoms, probes and objective symptom criteria are provided. Inter-rater reliability (93 to 100 % agreement) and test-retest reliability (Kappa values: .63-1) have been found to be good to excellent (Kaufman, Birmaher, Brent, Ryan & Rao, 2000). For a reliable and valid administration of the K-SADS-PL, special training is necessary. In terms of the diagnosis of eating disorders, the particular benefit of the K-SADS-PL lies in the reliable assessment of psychological comorbidities. It can be employed in both inpatient and outpatient settings. Somatoform disorders cannot be diagnosed with the K-SADS-PL, which constitutes a limitation of the instrument. A further limitation lies in the high amount of time required to administer the K-SADS-PL.

1.4.2. Eating disorder-specific instruments

1.4.2.1. Instruments for categorical diagnosis in adults

Through the use of interview guidelines such as the Diagnostic Interview for Mental Disorders (DIPS; Margraf et al., 2017) or the Structured Clinical Interview for DSM-IV (SCID; Wittchen, Zaudig & Fydrich, 1997), the reliability of diagnoses can be considerably increased (cf. e.g.

Wittchen, Semler, Schramm & Spengler, 1988). However, the two most widely used interview guidelines for the area of mental disorders in the German-speaking area – the DIPS (Margraf et al., 2017) and the SCID (Wittchen et al., 1997) – often do not offer sufficient information for treatment planning, especially in the case of eating disorders. Therefore, guidelines have been developed which not only cover the diagnostic criteria of eating disorders but additionally also provide further, indirect treatment-relevant information, such as information about patients' individual diet rules (see also table 3). In contrast to questionnaire procedures, the number of interview guidelines in the area of eating disorders available in the German language is very limited: Only for two interviews (Eating Disorder Examination [EDE] and Structured Inventory for Anorexic and Bulimic Disorders expert rating interview [SIAB-EX]) are detailed evaluation findings available which are valid for the German-speaking area.

Eating Disorder Examination (EDE)

The Eating Disorder Examination (EDE; Fairburn & Cooper, 1993; German version: Hilbert, Tuschen-Caffier & Ohms, 2004; Hilbert & Tuschen-Caffier, 2006a, 2016a) is a structured expert interview for the diagnosis and assessment of the specific psychopathology in eating disorders which is widely and internationally used in research and practice. The specifically assessed eating disorder-related psychopathology comprises restrictive eating behavior, which might be expressed in fasting, slimming diets or in other restraint eating. Parameters of restraint eating, for example the attempt to avoid food intake for long periods of time or to follow diet rules, are captured in the EDE Restraint scale. Further abnormalities in the area of eating such as impaired concentration due to preoccupations with food or feelings of guilt when eating are described in the Eating Concern scale. A further central feature is disturbances in the evaluation of shape and weight (Shape Concern, Weight Concern). This is expressed in an increased level of importance placed on shape and weight for one's self-esteem, in inpaired concentration due to preoccupation with shape and weight, or in the fear of becoming fat(er) (see table 3 in Appendix). Besides the items of the four scales of the EDE, 14 diagnostic items enable a differential diagnostic classificaiton of anorexia nervosa, bulimia nervosa or binge eating disorder according to the criteria of the DSM-5 (in addition, diagnosis can also be made according to the ICD-10). Moreover, optionally, with the help of further items, sociodemographic data and characteristics on the development and maintenance of eating problems can be recorded. With regard to the psychometric properties of the EDE, the inter-rater reliability of the subscales lies between $.92 \leq r \leq .99$ and that of the items between $.80 \leq \kappa \leq 1.00$ (Hilbert et al., 2004). The internal consistencies of the subscales lie at $.73 \leq$ Cronbach's $\alpha \leq .86$ (total score: $\alpha = .93$). Thus, overall, the reliability of the EDE can be described as high. High correlations between the EDE subscales Shape Concern and Weight Concern and other self-report scales on body image speak in favor of convergent validity. The EDE subscales Restraint and Eating Concern show significant associations with the eating behavior recorded in food diaries, such as frequency of meals or binge eating, or of nutrient intake. The subscales of the EDE distinguish between groups with different eating disorder diagnoses, which points to disriminant validity. Moreover, the subscales of the EDE are sensitive to changes through psychological psychotherapy. To administer the EDE, in addition to a detailed manual, there is also an interview guideline, a coding sheet, an evaluation sheet as well as a diagnosis sheet (Hilbert & Tuschen-Caffier, 2006a, 2016a). The materials are freely

available in electronic form (http://www.dgvt-verlag.de/e-books/1_Hilbert_Tuschen-Caffier_EDE_2016.pdf). The EDE is very well suited for the diagnosis of eating disorders in adults within clinical psychological practice and research. It takes approximately 45 minutes to administer. As is the case when performing expert interviews in general, a reliable and valid implementation of the expert interview is optimized if, in addition to working through the manual, special training is completed. An advantage of the interview lies in its specific focus on eating disorders, meaning that barely any redundancy arises when it is used in combination with the above-mentioned general structured interviews. Moreover, with a duration of 45 to 60 minutes, the amount of time required to perform the EDE is reasonable for patients. If less time is available for diagnosis, it is further possible to limit the EDE solely to the diagnostic questions.

Structured Inventory for Anorexic and Bulimic Eating Disorders Expert Interview (SIAB-EX)

As an expert interview, the Structured Inventory for Anorexic and Bulimic Eating Disorders (Fichter & Quadflieg, 1999a; Fichter & Quadflieg, 2001; Fichter & Quadflieg, 2004; Fichter, Herpertz, Quadflieg & Herpertz-Dahlmann, 1998) allows for both the assessment of eating disorder-specific symptoms and the asessment of symptoms which frequently accompany eating disorders, such as anxieties and impairments in social competence. Thus, in contrast to the EDE, the SIAB-EX is not exclusively targeted at the psychopathology of eating disorders, but is additionally geared towards associated symptoms of eating disorders. The SIAB-EX is suitable for the diagnosis of eating disorders in adults and adolescents within clinical-psychological practice and research. It takes between 30 and 60 minutes to administer. The internal consistencies of the subscales indicate predominantly homogeneous subscales (total score for current diagnoses: Cronbach's $\alpha = .92$; past diagnoses: $\alpha = .93$). The subscale structure derived from principal components analysis supports the construct validity of the SIAB-EX. Furthermore, convergent validity of the procedure has been demonstrated by correlations with conceptually related self-report scales. In part, the subscales of the SIAB-EX and the EDE show substantial convergence. Sensitivity to change of the SIAB-EX is supported by significant symptom improvements following inpatient psychotherapy and weight loss. The instrument is very well suited for diagnosis, treatment planning and longitudinal assesments. To enable a reliable and valid administration of the expert interview, a comprehensive manual is available, with "anchor examples" from practice and definitions.

1.4.2.2. Instruments for categorical diagnosis in children and adolescents

The Eating Disorder Examination for Children (ChEDE; German: Hilbert, 2016a; Hilbert et al., 2013; Engl: Bryant-Waugh, Cooper, Taylor & Lask, 1996; Fairburn & Cooper, 1993) is an adapted version of the Eating Disorder Examination, for children and adolescents aged 8-14 years (EDE; German: Hilbert & Tuschen-Caffier, 2006a, 2016a). The ChEDE assesses the specific eating disorder psychopathology using child-appropriate language with four subscales on restraint eating, and on concerns about eating, weight and shape (22 items). Fourteen diagnostic items allow for the diagnosis of eating disorders according to the DSM-5. Psychometric testing of the German translation of the ChEDE in samples of 8-17-year-old

children and adolescents with anorexia nervosa, binge eating disorder, loss of control eating, overweight and obesity as well as chronically ill children and adolescents without eating disorders showed excellent inter-rater reliabilities both for the subscales ($.98 \leq r_{icc} \leq .99$) and for the items ($.80 \leq r_{icc} \leq 1.00$) (see Hilbert et al., 2013). The internal consistences lay at $.70 \leq$ Cronbach's $\alpha \leq .88$ for all subscales apart from the Restraint scale, for which the internal consistency amounted to Cronbach's $\alpha = .62$, and were thus predominantly good. Convergent validity determined using correlations with conceptually related self-report procedures lay in the moderate to high range. The subscales distinguished between children and adolescents with different eating disorders or eating disorder symptoms and those without eating disorders. These results indicate that the German version of the ChEDE is suitable for a reliable and valid assessment of eating disorder psychopathology in children and adolescents. The limitations of the ChEDE include the overall time required for its administration (approx. 45 minutes). For diagnostic purposes, this can be reduced by solely using the items relevant for diagnosis. The ChEDE manual, including interview guidelines, coding and evaluation sheets as well as diagnosis sheets, is freely available in electronic form (http://www.dgvt-verlag.de/e-books/3_Hilbert_ChEDE_2016.pdf). An additional ChEDE module on the diagnosis of avoidant/restrictive food intake disorder, which was specified for the first time in the DSM-5, is currently being prepared.

1.4.2.3. Instruments for dimensional diagnosis in adults

In addition to the categorical or classification-based assessment of eating disorders, the symptoms of an eating disorder and associated characteristics can further be dimensionally quantified by means of questionnaires, e.g. to estimate the degree of severity of particular symptom areas for the purpose of treatment planning or to measure the success of psychotherapy. In this respect, a substantial number of procedures are available, of which only a selection are described in greater detail in the following. The selection of questionnaires was primarily based on whether the respective procedures are widespread, can be meaningfully and well implemented in the clinical context, and on their availability. A brief description of these and further German-language questionnaires for the dimensional diagnosis of eating disorders and associated characteristics for adults as well as children and adolescents is presented in table 3, listed alphabetically. The instruments outlined in the table are available in German, are mostly disseminated internationally, and have been psychometrically tested (for a further review, see Steinfeld, Bauer, Hartmann & Vocks, 2017; Tuschen-Caffier, Pook & Hilbert, 2005). The symptom areas associated with eating disorder pathology in the narrower sense, which are assessed in the listed questionnaires, include, for example, body image disturbances in anorexia and bulimia nervosa (for a more detailed overview, see Steinfeld, Bauer, Waldorf, Hartmann & Vocks, 2017) or the motivation to change/ambivalence regarding the eating disorder (for a more detailed overview, see Hötzel, von Brachel, Schlossmacher & Vocks, 2013; von Wietersheim & Hoffmann, 2011).

Eating Disorder Examination-Questionnaire (EDE-Q)

The Eating Disorder Examination-Questionnaire (EDE-Q) by Fairburn and Beglin (1994; German translation: Hilbert & Tuschen-Caffier, 2006b, 2016b; Hilbert, Tuschen-Caffier,

Karwautz, Niederhofer & Munsch, 2007; Hilbert, de Zwaan & Brähler, 2012) is the questionanaire version of the structured expert interview Eating Disorder Examination (EDE; Fairburn & Cooper, 1993). Analagously to the EDE, the EDE-Q assesses features of the specific psychopathology of eating disorders with four subscales. The Restraint scale and the Eating Concern scale describe problems with eating behavior, such as restricting food intake by following dieting rules or feelings of guilt when eating. The Weight Concern scale and the Shape Concern scale ask about characteristics of a negative body image, such as an increased level of importance attached to shape and weight for self-esteem. The 28 items of the EDE-Q correspond to the compulsory questions of the EDE. All items refer the the past 28 days. Like in the EDE, 22 items are allocated to the four subscales. Frequencies and/or intensities are rated on 7-point anchored rating scales (0 = no days/not at all to 6 = every day/markedly). A further six items which are not allocated to scales assess the occurence and frequencies of diagnostically relevant core features such as binge eating, self-induced vomiting or abuse of diuretics and laxatives. The EDE-Q is suitable for adults and adolescents and allows for the assessment of self-report of the specific eating disorder psychopathology in clinical-psychological practice and research. The EDE-Q can be employed descriptively or as an initial screening instrument in a multistage diagnostic process. Compared to the EDE, the use of the EDE-Q can be seen as particularly indicated if a structured expert interview like the EDE cannot be administered for economical reasons. The EDE-Q generally takes less than 15 minutes to complete. The EDE-Q is evaluated by calculating subscale mean scores and evaluations of individual diagnostic items; an overall (mean) score from the 22 items of the subscales can be calculated. The psychometric evaluation showed good internal consistencies of the subscales, from $.80 \leq$ Cronbach's $\alpha \leq .93$ (cf. Hilbert et al., 2007, 2012). Over a period of three months, the test-retest reliability of the subscales lay at $.68 \leq rtt \leq .74$. The reliability of the EDE-Q can therefore be described as good. The factor structure of the EDE-Q has been broadly replicated. Normative values for the German population were established based on a representative sample of men and women aged 14 years and over (Hilbert et al., 2012). A short form for the assessment of global eating disorder pathology with eight items has been developed and validated in two representative samples (Kliem et al., 2016). Limitations pertain to the fact that – as with all self-report scales – the EDE-Q cannot be used for clinical diagnosis, but is employed solely as a screening instrument and to depict the course of eating disorders from the patient's perspective. The EDE-Q cannot be used as a substitute for a structured expert interview for diagnosis (EDE or SIAB-EX). The EDE-Q is freely available electronically, including the short form and the necessary materials for evaluation (http://www.dgvt-verlag.de/e-books/2_Hilbert_Tuschen-Caffier_EDE-Q_2016.pdf).

Eating Disorder Inventory (EDI, EDI-2)

The Eating Disorder Inventory (EDI; Garner, Olmstead & Polivy, 1983; German translations by Paul & Thiel, 2004; Rathner & Waldherr, 1997 among others) aims to assess symptoms which are frequently linked to the disorders of anorexia nervosa or bulimia nervosa. The most recent version available in German (EDI-2; Garner, 1991) comprises 91 items on 11 scales [(1) Drive for thinness, (2) Bulimia, (3) Body dissatisfaction, (4) Ineffectiveness, (5) Perfectionism, (6) Interpersonal distrust, (7) Interoceptive awareness, (8) Maturity fears, (9) Asceticism, (10) Impulse regulation and (11) Social insecurity]. Through this expansion, ultimately only around 25% of the items now refer to the primary symptoms of eating disorders. There are several

versions of the EDE and EDE-2 (e.g. Paul & Thiel, 2004; Rathner & Rainer, 1997; Rathner & Waldherr, 1997), the most widespread of which is probably the version by Paul and Thiel (2004). Independently of item coding and translation variant, there is a high correspondence in the psychometric findings on the EDI (e.g. Rathner & Waldherr, 1997; Thiel et al., 1997). For instance, the internal consistencies of the three scales (1) Drive for thinness, (2) Bulimia and (3) Body dissatisfaction are good to very good in clinical groups. In non-clinical groups, and especially in male participants, only the values on the scale "Bulimia" fall into the suboptimal range. The discriminant validity of the three scales is demonstrated by mean differences between clinical and non-clinical groups. The findings on factorial validity, by contrast, are inconclusive. This might predominantly be attributable to the fact that the "Drive for thinness" scale also captures aspects of dissatisfaction with shape, as shown by results on the construct validity. The sensitivity to change of the procedure is supported by a series of therapy studies demonstrating partial improvements in the scale scores. The utility for routine clinical practice has been demonstrated particularly for the eating disorder-oriented subscales "Drive for thinness", "Bulimia" and "Body dissatisfaction". These scales also show good psychometric properties. The EDI-2 by Paul and Thiel (2004) has also been psychometrically tested in adolescents (Salbach-Andrae et al., 2010). The values for internal consistency can be rated as high for the group of patients and as satisfactory to adequate for the female and male control groups. Comparisons of mean scores on the individual scales of the EDI-2 between patients with eating disorders and control participants demonstrated that the EDI-2 can differentiate well between the different groups of adolescents. Limitations of the EDI-2 lie in the fact that not all subscales show good psychometric properties. Moreover, it is a self-report instrument, bringing the commonly associated limitations (e.g. response tendencies). In the English-speaking area, there is already a revised and extended version (EDI-3; Garner 2004), although a German translation and validation has not yet been published.

Three-factor-Eating-Questionnaire (TFEQ)

The Three-factor-Eating-Questionnaire (TFEQ) (Fragebogen zum Essverhalten; FEV; Pudel & Westenhöfer 1989) is the German version of the Three-Factor Eating Questionnaire (TFEQ; Stunkard & Messick, 1985). The questionnaire comprises 44 items which are answered dichotomously with "true" or "false", 13 items which are rated on a 4-point scale from "never" to "always", and three questions with six to eight response options. The procedure enables the assessment of the three factors of eating behavior "cognitive restraint", "disinhibition" and "hunger" . The questionnaire has good internal consistency. Reference values are available for large population samples. However, the factor structure of the questionnaire is a matter of debate, with only the factor "cognitive control" being well-recognized. Overall, the TFEQ is the most commonly employed questionnaire for examining eating behavior across the world. The questionnaire is suitable for quantifying the extent of restrictive eating behavior and the disturbability of eating behavior in the course of therapy.

Structured Inventory for Anorexic and Bulimic Eating Disorders Self-Report (SIAB-S)

The Structured Inventory for Anorexic and Bulimic Eating Disorders Self-Report by Fichter and Quadflieg (SIAB-S; 1999a, 2001) is the questionnaire version of the expert interview SIAB-EX. Using this procedure, both symptoms of eating disorders and symptoms of mental disorders which are frequently associated with eating disorders can be assessed from the

perspective of the patients. The 87 items of the SIAB-S correspond to the items of the expert interview (SIAB-EX), with the difference that they are formulated in order to be generally comprehensible to laypersons. The subscale allocation also broadly corresponds to the SIAB-EX. For each item, the respondent is first asked about the current extent of a symptom referring to the past three months; subsequent questions pertain to the more distant past. The SIAB-S is suitable for the diagnosis of eating disorders in adults and adolescents in clinical-psychological practice and research. It takes 30 minutes to complete. The internal consistencies of the subscales of the SIAB-S can be predominantly evaluated as satisfactory. In part, the subscales of the SIAB-S are substantially correlated. The convergent validity of the SIAB-S has been confirmed by a series of content-based plausible correlations with conceptually related self-report questionnaires and the EDE. Furthermore, the subscale structure of the SIAB-S derived from principal components analysis indicates the construct validity of the procedure. The content-logical validity of the procedure is given. The diagnostic sensitivity of the SIAB-S in terms of differentiating between defined eating disorders (anorexia and bulimia nervosa) and eating disorders not otherwise specified has been demonstrated. The sensitivity to change of subscales of the SIAB-S and the total score is supported by significant changes following inpatient psychotherapy and after follow-up periods of several years (e.g. Fichter & Quadflieg, 1997, 1999b; Fichter, Quadflieg & Gnutzmann, 1998). Reference values are predominantly available for women. Limitations emerge – as with all self-report scales – through the fact that while the procedure can be used as a screening instrument and to quantify the course of eating disorders, it cannot be used as a substitute for expert rating using structured diagnostic tools (e.g.. EDE or SIAB-EX).

Munich Eating and Feeding Disorder Questionnaire (Munich ED-Quest)

The Munich Eating and Feeding Disorder Questionnaire (Munich ED-Quest) by Fichter, Quadflieg, Gierk, Voderholzer and Heuser (2015) was specifically developed to take into account the reformulation of the DSM-5 (and ICD-11) for diagnostic purposes and to assess the symptom severity of eating and feeding disorders in clinical practice and research. The questionnaire is available in its original German version and in an English translation. It can be used for persons between the age of 12 and 65 years. Using 65 items, the questionnaire captures attitudes and behaviors which frequently occur in persons with eating or feeding disorders. Several items are broken down into subquestions. Most of the items are rated on a severity scale from 0 (not at all or never) to 4 (very severe or very often). Moreover, the frequency of binges and compensatory measures are assessed. Most of the items assess the current state (last three months) and the worst state in the past from prepuberty to 3 months before completion of the questionnaire. As such, the worst state over the lifetime is assessed. The three subscales are calculated as scale mean scores and are differentiated according to these time periods. The subscale “preoccupation with figure and weight” captures the preoccupation with shape, body weight and weight loss. The subscale “bingeing and vomiting” refers to the severity and frequency of binges, their emotional consequences, as well as vomiting and nighttime eating. The subscale “inappropriate compensatory behavior” assesses behaviors such as the use of laxatives and diuretics with the aim of avoiding weight gain, including insulin abuse. For the following diagnoses of eating disorders according to the DSM-5 (ICD-11), there is a standardized algorithm which was validated through an expert interview: anorexia nervosa (restricting type and binge-eating/purging type), bulimia nervosa, binge eating disorder,

avoidant/restrictive food intake disorder (criteria A and C without exclusion criteria), rumination disorder, atypical anorexia nervosa, bulimia nervosa (of low frequency and/or limited duration), binge eating disorder (of low frequency and/or of limited duration), purging disorder, purging disorder according to the criteria of Keel and Striegel-Moore (2009), night eating syndrome. The Munich ED-Quest was validated in 605 women and men with eating disorders. The internal consistencies of the subscales yielded very good values, from .89 to .98 (Cronbach's α). The test-retest reliability was very high, with values of at least .89, and the questionnaire also showed a high sensitivity to change. Comparison and norm values (means/standard deviations, percentiles) are available for the 605 men and women treated for eating disorders – also separately for anorexia nervosa and bulimia nervosa. In addition, data are also available for clinical control persons (patients without eating disorders but with psychosomatic illnesses) and for 547 young women without eating disorders. The Munich ED-Quest and all documents necessary for its evaluation are available in German and English at http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/forschung/forschungsfelder/ essstoerungen/evaluation/index.html

1.4.2.4. Instruments for dimensional diagnostics in children and adolescents

Eating Disorder Examination-Questionnaire for children (ChEDE-Q)

The Eating Disorder Examination-Questionnaire for children (ChEDE-Q; German version Hilbert, 2016b; Hilbert, Hartmann & Czaja, 2008; English version TODAY Study Group, 2007) is an adapted version of the Eating Disorder Examination-Questionnaire EDE-Q (German version Hilbert & Tuschen-Caffier, 2006b, 2016b; English version Fairburn & Beglin, 1994), for children aged 8-14 years, based on the Eating Disorder Examination for Children (ChEDE; German: Hilbert, 2016a; English: Bryant-Waugh et al., 1996; Fairburn & Cooper, 1993). Using 22 items formulated in child-appropriate language, the ChEDE-Q assesses the specific eating disorder psychopathology on the four subscales Restraint, Eating Concern, Weight Concern and Shape Concern. Six diagnostic items provide information about the extent of core diagnostic features, for example binges or self-induced vomiting. The German translation of the ChEDE-Q was psychometrically tested in a population-based sample of 8-13-year-old children and adolescents as well as in subsamples of children with versus without loss of control eating (Hilbert et al., 2008). Subscales and the total score of the ChEDE-Q were predominantly found to be internally consistent and stable over a period of 7.5 months. The factor structure of the ChEDE-Q was reproduced for the most part. The parameters of the ChEDE-Q were significantly correlated with those of the ChEDE as well as with conceptually related questionnaires. Furthermore, the ChEDE-Q showed good discriminant validity in distinguishing between children and adolescents with and without loss of control eating. A short form of the ChEDE-Q, which assesses global eating disorder psychopathology with eight items, has been developed and validated (Kliem et al., 2017). The German-language version of the ChEDE-Q is thus suitable for the reliable and valid dimensional assessment of eating disorder psychopathology in childhood and adolescence. A limitation is that while the instrument assesses the specific eating disorder psychopathology, it cannot act as a substitute for a structured interview for diagnosis. The ChEDE-Q, including the short form and materials

necessary for its evaluation, are electronically available (http://www.dgvt-verlag.de/e-books/4_Hilbert_ChEDE-Q_2016.pdf). A parent version of the procedure (in the sense of parental assessment of the child's eating behavior) is currently in preparation.

SCOFF questionnaire

The SCOFF questionnaire (Morgan, Reid & Lacey, 1999) contains five items for the screening of eating disorders. The name is an acronym of the five key questions of the English-language original (**S**ick, **C**ontrol, **O**ne Stone, **F**at, **F**ood). In clinical patient populations and especially in female participants up to the age of 40 years, the SCOFF shows high sensitivity and specificity in terms of identifying eating disorders in the general population. In a meta-analysis of 15 studies examining the use of the instrument in different age groups (Botella, Sepulveda, Huang & Gambara, 2013), the authors calculated a pooled sensitivity of .80 and specificity of .93. In representative samples from the general population (Richter, Strauss, Braehler, Adametz & Berger, 2017; Solmi, Hatch, Hotopf, Treasure & Micali, 2015), the questionnaire likewise showed a high specificity (.94 and. 97, respectively). However, in both studies, the sensitivity of the instrument was substantially lower, at .54 (Solmi et al., 2015) and .26 (Richter et al., 2017, age group 14-95 years), meaning that due to the associated rate of false negative assessments, the questionnaire may be less suitable as a screening instrument in the general population. For the German-speaking area, translations are available both for children and adolescents and for adults. In a subsample (n =1895) of the largest representative study on the state of health of 11-17-year-old children and adolescents conducted in Germany to date, the KiGGS study, 29.4% of female respondents and 14.4% of male respondents answered at least two of the five questions positively (BELLA-Studie, Herpertz-Dahlmann, Wille, Hölling, Vloet & Ravens-Sieberer, 2008). Psychometric testing of the questionnaire in 12-year-old boys (N = 382) and girls (N = 425) in the Federal state of Thuringia with the EAT-26D as reference (cut-off: 20 points) showed a satisfactory test-retest reliability (.73) with a maximum accuracy (AUC) of 82%, sensitivity of .79 and specificity of .74 (Berger et al., 2011). In a six-year follow-up investigation of the BELLA cohort, a higher SCOFF score at the baseline assessment proved to be a significant predictor for a higher SCOFF score at follow-up and for the development of overweight and obesity, independently of the BMI at baseline and the BMI of the parents (Herpertz-Dahlmann, Dempfle, Konrad, Klasen & Ravens-Sieberer, 2015). Due to the shortness of the questionnaire, it is very economical to administer and evaluate. The translation used for children and adolescents is freely accessible online, including at the following address: http://www.diabetes-heute.uni-duesseldorf.de/news/index.html?TextID=3973

Anorectic Behavior Observation Scale (ABOS)

The Anorectic Behavior Observation Scale (ABOS; Vandereycken & Meermann, 1984; German translation: Salbach-Andrae et al., 2009) is a multidimensional questionnaire for the parents' (or caregivers') assessment of eating disorder symptoms in children and adolescents. The test consists of 30 items which are answered by the parents (or caregivers) in a closed response format on a 3-point scale. All 30 items are entered into the scale evaluation, which are allocated to three subscales. 16 items are allocated to the subscale "Unusual eating behavior", seven items to the subscale "Bulimic-type behavior" and seven items to the subscale "Hyperactivity". Additionally, the three subscales are aggregated into a total score. The mean internal consistency of the German-language version (Cronbach's α) for the total scale as well

as the three subscales lay between α = .75–.95 across the whole sample. By means of confirmatory factor analysis, the three-factor structure proposed by Vandereycken and Meermann (2003) was confirmed for the German version of the ABOS. Moreover, testing of criterion validity showed that parents of patients with eating disorders reported significantly higher scores compared to parents of the control group (Salbach-Andrae et al., 2009). Due to its clarity and short time to implement (5 to 10 minutes) and evaluate (10 minutes), the questionnaire is quick and easy to administer and does not require special training. The advantage of the instrument lies in the quick assessment of parent reports of the specific eating disorder psychopathology, which is especially essential in childhood and adolescence. The ABOS can be used in clinical practice and within clinical-psychological research. A limitation lies in the lack of standardization of the instrument. A short form of the ABOS comprising 10 items is now available, the Eating and Activity Questionnaire for Parents (EAQP) (Thiels & Schmitz, 2009).

Eating Disorders in Youth-Questionnaire (EDY-Q)

The Eating Disorders in Youth-Questionnaire (EDY-Q; van Dyck & Hilbert, 2016; short form, van Dyck, Dremmel, Munsch & Hilbert, 2015, 2016) is a self-report questionnaire for assessing restrictive eating problems in 8-13-year-old children. The 14 items are based on the criteria for avoidant/restrictive food intake disorder defined in the DSM-5, on the clinical "Great Ormond Street" criteria for this eating disorder (Bryant-Waugh & Lask, 1995) and on the literature on early-onset restrictive eating problems. Twelve of the 14 items of the EDY-Q capture symptoms of ARFID, including its three proposed variants (Bryant-Waugh, Markham, Kreipe & Walsh, 2010): food avoidance emotional disorder, selective eating and functional dysphagia. Two additional items assess pica and rumination disorder and two others assess early-onset feeding or eating disorders which are described in the DSM-5. Each item is rated on a 7-point Likert scale ranging from 0 = "never" to 6 = "always". Scoring can take the form of a total mean score or dichotomized for the presence of symptoms of ARFID including its variants, or descriptively for pica and rumination disorder. Psychometric evaluations of the EDY-Q in children aged 8-13 years (Kurz et al., 2015, 2016; van Dyck et al., 2013) showed an acceptable internal consistency for the total mean score and confirmed the factor structure with the three proposed variants of ARFID. Findings on convergent, divergent and discriminant validity are available. A limitation of the EDY-Q is the still limited database for this instrument. Moreover, as with all self-report scales, while the EDY-Q can be employed to assess central symptoms of ARFID, it cannot be used as a substitute for expert rating in the framework of structured diagnosis (e.g. ChEDE). The EDY-Q and the materials necessary for scoring are freely available online (http://nbn-resolving.de/urn:nbn:de:bsz:15-qucosa-197236). A parent version of the procedure (in terms of the assessment of the child's eating behavior by the parents) is currently being developed.

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2. Diagnosis of physical symptoms

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Medical diagnostics serves the purpose of assessing immediate risk and detecting possible complications of the eating disorder. Further aims are the diagnosis of relevant medical causes of weight loss and vomiting (differential diagnosis) and the diagnosis of relevant comorbid medical diseases.

2.1. Recommended initial diagnostics

Anthropometry

- Height
- Weight
- Pulse
- Blood pressure
- In children and adolescents: pubertal status (according to Tanner stages)

Internal examination

- Auscultation of the thorax
- Palpation of the abdomen
- Assessment of vascular status
- Inspection of the oral cavity, salivary glands
- Inspection of the skin surface
- Ultrasound of the abdomen
- Electrocardiogram
- Possible echocardiography

Neurological examination

- Higher cortical functions (e.g. memory, arithmetic, praxis)
- Stance and gait
- Cranial nerves
- Motor system
- Fine motor skills and coordination
- Sensitivity
- Muscle reflexes
- Autonomic nervous system

Laboratory

- Differential blood count
- ESR, C-reactive protein
- Glucose

- Electrolytes (sodium, potassium, calcium, magnesium, phosphate)
- Renal status (creatinine)
- Liver status (e.g. ALT, AST, ALP, CK, GGT, total and direct bilirubin, PT and PTT)
- Amylase, lipase
- Urine status
- TSH.
- In selected patients, the determination of iron, ferritin, vitamin A, vitamin E, vitamin B12, folic acid, ß-carotine, zinc, copper, selenium, as well as immunochemical or chromatographic drug screening can also be considered.

Further diagnostic steps can result from pathological findings in this initial diagnostic process. Depending on the initial findings and the level of symptoms (underweight, purging behavior), intervals for follow-up examinations can be determined. These intervals can range from daily examination for severely ill patients to an interval of one year. In the case of abnormal findings and clinical signs pointing to comorbid or differential diagnostically relevant medical diseases, the diagnostic paths recommended within the respective disorder guidelines should be followed.

2.1.1. Anthropometry

Body Mass Index (BMI)

In the case of a BMI below 15 kg/m² in adults, a disorder-oriented inpatient treatment with hospital-typical remedial methods should be considered. A very low BMI constitutes a particular risk factor in terms of mortality (Rosling, Sparen, Norring, & von Knorring, 2011). It is important to measure weight using a calibrated instrument, preferably by the attending physician or psychologist him/herself. The patient should be weighed and measured in her underwear without shoes. Delegating this task to assistants or using information provided by the patient herself carries a significant risk of inaccurate evaluation (for instance underestimation of the risk through underweight due to an erroneously low indication of height, or weighing after consuming large amounts of fluids).

As a benchmark for evaluating body weight, the BMI is used. It is calculated according to the formula BMI = body weight (kg)/height (m^2). Accordingly, a person who weighs 60 kg and is 1.70 m tall has a BMI of 20.8 kg/m^2. The literature presents detailed information on the distribution of BMI in various reference populations and age groups and on the relation between BMI and various health risks. For clinical purposes, BMI in adults of both genders can be interpreted using the following classification (WHO Global Database on Body Mass Index, WHO technical report 854):

Severely underweight BMI <16 kg/m^2
Moderately underweight BMI 16 to 16.99 kg/m^2
Mildly underweight BMI 17 to 18.49 kg/m^2
Normal-range BMI 18.50 to 24.99 kg/m^2
Overweight BMI 25 to 29.99 kg/m^2

Obese class I BMI 30 to 34.99 kg/m^2
Obese class II BMI 35 to 39.99 kg/m^2
Obese class III BMI ≥ 40 kg/m^2

From a clinical perspective, severe underweight can be further subdivided into two classes: severe underweight class I, with a BMI of 13.0 to 15.99, and severe underweight class II, with a BMI < 13.0 kg/m^2. The rationale for this lies in the substantially higher mortality in patients with anorexia nervosa who have a BMI below 13.0 kg/m^2

When using the BMI to evaluate the health risk, the following limitations need to be kept in mind: The BMI correlates highly, but not very highly, with fat and muscle mass. The most important moderator of this relationship is exercise. Persons who do intensive weight and endurance training can be overweight or even obese, without having a greater fat depot. Conversely, underweight, physically inactive patients can have a smaller muscle mass than hyperactive patients with anorexia nervosa. When evaluating the health risk associated with a higher BMI, it should be noted that the BMI does not depict the fat distribution between the visceral and subcutaneous fat depot. Accordingly, even normal-weight persons can have an increased visceral fat depot and overweight persons can have a normal visceral fat depot. To evaluate risk inherent in underweight, it needs to be considered that a stable underweight is less risky than a rapid weight loss with regard to cardiovascular risks. Moreover, one must take into account that an increase in the fluid depot, for example in the case of edemas, can mask the risk in the case of underweight.

In children and adolescents, due to age-dependent changes in body proportions, risk is evaluated with the help of age-based BMI percentile tables (Kromeyer-Hauschild et al., 2001). Respective websites to calculate the percentile values are available online (www.pedz.de).

In the treatment of anorexia nervosa in children and adolescents, a primary treatment aim is the restoration of a healthy body weight for an age-appropriate growth, as well as menarche or resumption of menses. However, consensus is lacking with regard to the definition of a healthy body weight. Recent studies indicate that a BMI on the 25th age percentile constitutes a necessary prerequisite for the resumption of menses (Dempfle et al., 2013; Faust et al., 2013). Therefore, reviews suggest the 25th age percentile as a benchmark for the desired target weight of a treatment, and where possible at least the 10th age percentile (Herpertz-Dahlmann, 2017)

In the guidelines of the professional society, a fall below the 10th BMI percentile is defined as a criterion for extreme underweight and a fall below the 3rd BMI percentile as a criterion for an indication for inpatient treatment for children and adolescents (DGKJPP, 2007). Chapter 1.2 Diagnostic criteria addressed the problems of the 5th BMI age percentile as suggested in the preparation of the ICD-11 as a criterion for underweight in greater detail.

In children and adolescents with a high starting weight or overweight/obesity prior to disorder onset, the level of acute risk can be significantly underestimated: While they have often not yet reached the threshold for underweight, or may only fall slightly below this threshold, the often more pronounced weight loss means that they nevertheless show equally severe physical and psychological symptoms (e.g. level of bradycardia, circulatory instability, psychological comorbidity, suicidal risk) to patients with typical anorexia nervosa (Sawyer, Whitelaw, Le Grange, Yeo, & Hughes, 2016).

In line with the guidelines of the European Childhood Obesity Group (ECOG), the Working Group of Obesity in Childhood and Adolescence recommends the use of the 90th and 97th percentile of the aforementioned reference data as the threshold for defining overweight and obesity, respectively (Wabitsch & Moß, 2009). Extreme obesity is defined as a BMI > 99.5th percentile. This purely statistical specification of the cutoffs enables, when using the new reference sample for German children and adolescents, an almost continuous transition to the aforementioned fixed thresholds in adulthood.

Heart rate, blood pressure and orthostatic test
Bradycardia with a heart rate below 40/minute, tachycardia with a heart rate above 110/minute, a blood pressure below 90/60 mmHg, a decline in blood pressure of > 20 mmHg or an increase in heart rate of > 20 in the orthostatic test are risk indicators in which the necessity of inpatient treatment should be assessed. Approximately 43% of patients with anorexia nervosa have a heart rate below 60/minute and around 17% below 50/minute.

Body temperature
Up to 22 % of patients with anorexia nervosa show hypothermia, with a temperature below 36.0°C. A centrally measured body temperature of 36.0°C or lower constitutes a risk indicator and should lead to an assessment of the necessity for inpatient treatment.

Pubertal status
In patients with an early, especially prepubertal onset of anorexia nervosa, the poor nutrition over time frequently leads to a delay or even an irreversible arrest in growth, as well as an absence of the hormonal and physical changes linked to puberty. A pubertal status that does not correspond to the patient's age generally suggests that the illness is not recent. Early menarche is more frequent among early-onset bulimic disorders (Day et al., 2011).

2.1.2. Internal examination

Thorax
A mitral valve prolapse is more frequent in anorexia nervosa. However, it is not possible to derive specific therapeutic consequences from this. Arrhythmogenic effects of a mitral valve prolapse represent an additional risk factor in patients with pronounced underweight. Pericardial effusions, albeit mostly without hemodynamic relevance, are frequently found both in adults and adolescents with anorexia nervosa (Oflaz et al., 2013).

Abdomen
Changes in the gastrointestinal motility are frequent in all forms of eating disorders. An acute abdomen, for instance in the case of acute dilatation of the stomach, is rare. This constitutes an acute life-threatening danger. Particular attention should also be paid to symptoms of chronic inflammatory bowel disease and celiac disease. Especially in the presence of diarrhea and chronic stomach pain, the corresponding diagnostic paths should be followed.

Vascular status
Acrocyanosis is frequent in anorexia. When exposed to cold, these patients are at increased risk of frostbite.

Oral cavity, salivary glands
Patients who vomit are particularly likely to show dental damage with characteristic patterns of erosions, changes in the oral muscosa and enlargement of the parotid glands and salivary glands at the base of the tongue. The concentration of salivary amylase in serum is increased in patients with an eating disorder, depending on the extent of vomiting. Sufferers require regular dental checks, treatment and targeted advice on dental care. The pronounced dental damage can lead to a severe and lifelong health burden. The enlargement of the parotid glands and the salivary glands at the base of the tongue is an important element of visual diagnostics in eating disorders.

Skin surface
Dry skin, hair loss, acne, disorders of skin pigmentation, yellowing of the skin in the case of hypercarotenemia, petichiae, neurodermatic changes, Livedo vasculitis, intertrigo, generalized itching, skin infections and Striae distensae are observed in all forms of eating disorders. Patients with underweight frequently have typical Lanugo hair. Patients who induce vomiting can have calluses on the back of the dominant hand (Russell's sign). Sufferers often do not make the link between the eating disorder and skin changes, sometimes interpreting them as "allergies". Diets derived from this can exacerbate the eating disorder.

Bone density
Bone density is considerably prematurely reduced in anorexia nervosa. A routine examination of bone density cannot be recommended as this does not result in specific further diagnostic or therapeutic consequences. The indication emerges from spontaneous fractures.

2.1.3. Laboratory

Blood count
Around 34% of patients with anorexia nervosa show a mild leucopenia; a more severe leucopenia is rare. Thrombocytopenia is present in approximately 5% of cases. Hematocrit and mean corpuscular volume (MCV) mostly lies in the lower reference range. Marked changes in the blood count are risk indicators. Inpatient treatment must be considered. In a randomized comparison trial of different feeding protocols with very underweight adolescents (BMI at treatment start < 78% mBMI), low numbers of leukocytes prior to treatment start correlated significantly with the phosphate nadir over the course of treatment, and possibly represent a risk marker for the development of hypophosphatemia and a refeeding syndrome (O'Connor, Nicholls, Hudson, & Singhal, 2016).

Electrolytes
In the case of intensive vomiting, but also refeeding, rapid changes in electrolyte concentrations can arise. Particularly with dehydration, potassium in serum may lie in the reference range, but

the intracellular potassium may be considerably reduced. Approximately 20% of patients with an eating disorder show hypokalemia, around 7% hyponatremia and around 6% show low concentrations of potassium. Hypophosphatemia occurs above all in the case of parenteral refeeding, but can also be a consequence of high carbohydrate consumption following a longer period of fasting. Similar associations also apply for hypomagnesemia. A potassium concentration of 3.0 mmol/l is a risk indicator, especially in conjunction with ECG changes. An inpatient treatment must be considered.

Blood glucose

Even in the case of severe malnutrition, the blood glucose is mostly in the lower reference range. In conjunction with other factors such as infectious diseases or intoxications, life-threatening hypoglycemia can arise. A glucose concentration lower than 60 mg/dl is a risk indicator. An inpatient treatment must be considered.

Kidneys

Due to the reduced muscle mass, the concentrations of creatinine in anorexia nervosa typically lie in the lower reference range. Chronic hypokalemia, in particular with persistent vomiting and laxative abuse, can lead to kidney failure due to hypokalemic nephropathy in some patients with an eating disorder. Even if the upper reference range is only slightly exceeded, further diagnostics should be conducted.

Liver

Approximately 12 % of patients show an increased concentration of liver enzymes. An acute severe damage to the liver can occur in anorexia nervosa. If the reference range is exceeded, further diagnostics should be conducted.

Adrenal glands

The secretion of the stress hormone cortisol is regularly increased in anorexia nervosa and in individual cases with other forms of eating disorders. A routine determination of cortisol cannot be recommended because no specific further diagnostic or therapeutic consequences can be derived from this.

Thyroid

Reduced concentrations of triiodothyronine (“low T3 syndrome”) are regularly present in anorexia nervosa and present in individual cases of bulimia nervosa. The recommendation to exclusively determine TSH pertains to the necessity to exclude thyroid diseases that are not directly related to an eating disorder (e.g. Hashimoto’s thyroiditis). A routine determination of T3 cannot be recommended as no specific further diagnostic or therapeutic consequences can be derived from this.

Sex hormones

In the case of anorexia nervosa, reduced concentrations of estradiol, progesterone and luteinizing hormone (LH) are regularly found. Disorders of sex hormone secretion are also frequently found in other forms of eating disorders. A routine determination of sex hormones

cannot be recommended, as no specific further diagnostic or therapeutic consequences can be derived from this.

2.1.4. Neurological examination

Brain imaging

Frequent findings in anorexia nervosa and bulimia nervosa are enlargements of the outer and inner cerebrospinal fluid spaces. There are no available data on binge eating disorder. Routine brain imaging (CT or MRT) cannot be recommended, as specific further diagnostic or therapeutic consequences cannot be derived from this. The indication emerges from abnormalities in the neurological findings.

2.2. Differential-diagnostic considerations

The diagnosis of an eating disorder is only rarely a diagnosis by exclusion. Anorexia nervosa is the most common cause of pronounced underweight in adolescence and young adulthood in Western society. A problem lies in differentiating anorexia nervosa with mild underweight from constitutional forms of underweight. In the case of constitutional underweight, the psychological characteristics of an eating disorder are lacking, endocrine functions are normal, and in particular, amenorrhea is not present. It is difficult to distinguish between binge eating disorder and overweight that is not caused by an eating disorder. Neurological or endocrine disorders that mimic the physical and psychological characteristics of a bulimic eating disorder are rare.

For underweight patients, the following differential-diagnostic considerations should be made:

Tumor diseases (brain, stomach, pancreas, lungs, lymphomas, leukemia)

Endocrine disorders (diabetes, hyperthyroidism, adrenal insufficiency)

Gastrointestinal disorders (celiac disease, cystic fibrosis, esophageal stenosis, chronic occlusion of the superior mesenteric artery, Crohn's disease, ulcerative colitis)

Infectious diseases (tuberculosis, parasitoses, systemic mycoses, HIV)

Other mental disorders (depression, anxiety and obsessive-compulsive disorders, somatoform disorders, schizophrenia, autism spectrum disorders)

Drugs and substance abuse (multiple drug use, heroin, cocaine, amphetamines).

For patients with vomiting, the following differential-diagnostic considerations should be made:

Tumor diseases of the brain (especially hypothalamic tumors)

Endocrine disorders (diabetes, emesis gravidarum)

Gastrointestinal disorders (gastric or duodenal ulcer, chronic pancreatitis, intestinal parasitoses, connective tissue disorders with involvement of the gastrointestinal tract such as scleroderma).

However, the above-mentioned disorders rarely yield a similar temporal pattern of vomiting behavior to that found in a typical eating disorder.

In patients with overweight, the following potential determinants should be considered (Hruby et al., 2016; Schwartz et al., 2017):

Lack of exercise, sedentary lifestyle, large number of hours spent in front of a screen, unfavorable dietary composition, large food portion sizes, skipping breakfast

Poor nutritional quality (junk food)

Consumption of alcohol, cannabis or other appetite-increasing substances

Endocrine disorders (Cushing's syndrome, hypothyroidism, insulinomas)

Neurological disorders (damage to the medial hypothalamus, craniopharyngioma)

Genetic syndromes.

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III. The therapeutic relationship with patients with an eating disorder diagnosis

Stephan Herpertz, Brunna Tuschen-Caffier, Silja Vocks

1. General reflections

A good therapeutic relationship plays a central role in the success of psychotherapy (Crits-Christoph, Gibbons & Mukherjee, 2013). But what does the term "therapeutic relationship" actually mean, and what are the markers of its quality? In the research literature, the therapeutic relationship is defined in classical terms as the collaborative and affective relationship between therapist and patient. The aspect of collaboration refers here to the agreement between patient and therapist with respect to the goals of the therapy and the techniques employed to achieve them. The affective component encompasses aspects such as trust, likability, respect and care between patient and therapist (Crits-Christoph et al., 2013). In accordance with this definition, the therapeutic relationship is usually operationalized in classical terms using the *Working Alliance Inventory* (WAI; Horvath & Greenberg, 1989), which can be employed across different schools of psychotherapy and comprises the scales "development of an affective bond", "agreement between therapist and patient on the tasks of therapy" and "agreement on the goals of therapy".

In the framework of the directives for psychotherapy in Germany, psychotherapy is carried out as individual or group therapy, with the former representing the most commonly practiced form in Germany. While individual therapy concerns a dyad of therapist and patient, group psychotherapy involves a multi-person setting. Accordingly, with regard to the success of a psychotherapy, in the case of individual therapy, it is necessary to take into account the patient variables and therapist variables, the "fit", the psychotherapeutic approach, as well as the therapeutic relationship. For group therapy, in addition to these variables, group-dynamic processes are also relevant.

In psychotherapy process research, attention has traditionally also been paid to therapist variables when examining the therapeutic relationship (Crits-Christoph et al., 2013). To date, there is little research on therapist characteristics which are associated with a positive outcome specifically in the area of eating disorders. Nevertheless, patient preferences have been researched. A qualitative study (Gulliksen, Espeset, Nordbo, Skarderud, Geller & Holte, 2012) reported that patients with AN prefer a therapist who shows acceptance and vitality/is active, focuses on resources, is supportive and shows expertise. Previous investigations also revealed that patients with eating disorders rather prefer female therapists, because the themes of body image and sexuality are often important contents of the therapy (Vocks, Legenbauer & Peters, 2007). Nevertheless, it should be kept in mind that patient preferences regarding therapist characteristics can in no way be equated with therapist variables which also foster the outcome. Equally little is known about the extent to which therapists who show the patients' preferred characteristics actually bring about a greater likelihood of a positive therapeutic relationship; there is a great need for research in this regard.

In the past, research predominantly focused on therapeutic approaches, based on the assumption that "techniques" can be understood as independent from the therapists and patients or the therapeutic relationship. However, differences in techniques are closely linked to differences with respect to therapist and patient variables. In this regard, there is broad consensus among psychotherapists that the therapeutic relationship is an important influencing factor in the treatment of mental disorders. Based on the current state of research, however, the question of causality remains unclear (see below for further details). The American Psychological Association, Division of Clinical Psychology and Psychotherapy also concluded that "Efforts to promulgate best practices or evidence-based practices without including the relationship are seriously incomplete and potentially misleading" (Norcross & Wampold, 2011).

So far, the therapeutic relationship has predominantly been examined from a patient-oriented perspective, with a central focus on characteristics of the therapist such as the degree to which he/she understands and adapts to the patient (accurate empathy), an unprejudiced positive attitude or a non-possessive warmth and affection. On the part of the patients, in the framework of the therapist relationship, their ability to productively engage with the therapy has often been evaluated. From the multitude of currently existing constructs of the therapeutic relationship, the reflections of Gaston (1990) can be emphasized:

1. the patient's affective relationship with the therapist,
2. the patient's ability to collaborate in the therapy,
3. the therapist's empathic understanding,
4. the therapist's involvement,
5. the patient-therapist agreement on the goals and tasks of psychotherapy.

The relation between the therapeutic relationship and the therapy outcome has been examined within psychotherapy research in different treatment settings, both across different disorders and for specific disorders (Crits-Christoph et al., 2013), and has also been the object of numerous studies in the area of eating disorders. The correlation coefficients range from $r = .19$ (psychotherapy in children; Shirk, Karver & Brown, 2011), through $r = .25$ (group therapy; Burlingame, McClendon & Alonso, 2011) to $r = .26$ (couple and family therapy; Friedlander, Escudero, Heatherington & Diamond, 2011). Despite numerous indications of the importance of the therapeutic relationship for therapy success in the context of AN (e.g. Stiles-Shields, Touyz, Hay, Lacey, Crosby, Rieger, Bamford & Le Grange, 2013) and BN (e.g. Accurso, Fitzsimmons-Craft, Ciao, Cao, Crosby, Smith, Klein, Mitchell, Crow, Wonderlich & Peterson, 2015), overall, the findings are inconsistent. In a systematic review (Brauhardt, de Zwaan & Hilbert, 2014), the authors reported an association between the therapeutic relationship and therapy outcome in around half of the reviewed studies in adult patients with eating disorders. In the context of family therapy, however, an association between the therapeutic relationship and symptom reduction was consistently demonstrated.

In spite of these indications of an association between the therapeutic relationship and treatment outcome, also in the context of eating disorders, the question of causality remains unclear. On the one hand, a good therapeutic relationship can be seen as an "ingredient" for a positive outcome; on the other hand, high expectations of the therapy on the part of the patient or also

(first) successes within the treatment might lead to a more positive evaluation of the therapeutic relationship. Moreover, it is conceivable that a third (unknown) factor (e.g. intelligence) influences both the therapeutic relationship and the therapy success (Brown, Mountford & Waller, 2013). First indications of a reciprocity between the therapeutic relationship and the course of therapy in the context of eating disorder treatment were provided by a study which employed multiple measurements of both of these variables (Vrabel, Ulvenes & Wampold, 2015). It was also found that a more positive evaluation of the expected therapy success at the start of treatment predicted a positive therapeutic relationship at various time points over the course of treatment (Stiles-Shields, Bamford, Touyz, Le Grange, Hay & Lacey, 2016).

2. The therapeutic relationship in the treatment of patients with an eating disorder

At the time of seeking psychotherapeutic treatment or at the first consultation, patients with an eating disorder diagnosis are mostly ambivalent about changing their eating problems (e.g. normalizing their eating behavior vs. restrictive eating behavior in order to maintain a low body weight, see below for further details). Moreover, the patient's readiness to openly express her thoughts and feelings associated with the eating disorder is also ambivalent or low at the beginning of treatment – and partly also throughout the whole therapy process (e.g. a patient with AN can find it difficult to address her pride about her low body weight). Furthermore, according to clinical experience, it is not uncommon for patients to experience unsuccessful treatments in the course of their often chronic illness as confirmation of their negative view of themselves (e.g. feelings of low self-efficacy, hopelessness, self-esteem problems). In patients with AN, beliefs with an identity-conferring nature are often observed (e.g. "If I resist eating, I am strong and can be proud of myself"). Feelings of shame can often prevent patients with BN or BED from speaking openly about their eating disorder symptoms, the severity of the symptoms and the associated emotional problems. For men with eating disorders, the therapy motivation can be further impeded by the notion that they are suffering from a purportedly "female" disorder. These examples illustrate that the building of the therapeutic relationship plays an important role for patients with eating disorders.

3. The building of the therapeutic relationship

Given the often ambivalent therapy motivation of these patients, an empathic, nonjudgmental, non-reproachful attitude towards the patient's description of her problems is warranted, especially at the start of treatment. As long as the patient's physical and/or psychological situation does not necessitate direct intervention (e.g. guideline chapter VII "Physical sequelae of eating disorders" and guideline chapter V "Anorexia nervosa", Chapter 2.3.4 "Inpatient treatment" and Chapter 2.3.8 "Compulsory treatment"), the development of a sustainable working relationship should be at the forefront (table 4). Due to the risk of eating disorders becoming chronic, and the associated physical and psychological complications, the treatment motivation is the focal point of the first conversations. This includes detailed and factual information about the eating disorder including its risks, although without scaring the patient.

Especially in patients with AN, cognitive impairments due to cachexia need to be taken into account. Information about the clinical picture should contain in-depth information about symptoms, causes and course as well as potential complications and comorbidities. It is beneficial if the disorder model that is imparted is founded on the intended treatment in terms of content. In a first conversation, in which the patient is informed about treatment options, the various alternatives of promising therapy options should already be outlined (see Chapter V "Anorexia nervosa", Chapter VI, "Bulimia nervosa", Chapter VII "Binge eating disorder"); regional accessibility also needs to be taken into account here.

4. Therapy motivation

A high level of ambivalence towards the eating disorder is especially characteristic for AN and BN (Gale, Holliday, Troop, Serpell & Treasure, 2006). On the one hand, the level of suffering of these patients is not inconsiderable, as they experience a severe limitation of their physical, cognitive and social capabilities, extending to a ubiquitous reduction in performance. On the other hand, the eating disorder often – at least in the short term – includes numerous positive facets for the sufferer, which are not to be underestimated (Legenbauer & Vocks, 2014; Serpell & Treasure, 2002). For instance, the eating disorder often constitutes a more or less efficient method of weight loss or stabilization, which due the high relevance of shape and weight for the sufferer's self-evaluation, as also outlined in the diagnostic criteria of the DSM-5 (APA, 2013), is central. Besides stabilizing self-esteem, the eating disorder symptoms can also serve the purpose of emotion regulation, in particular the regulation of negative emotions, e.g. through binge-eating and purging (Heatherton & Baumeister, 1991). Additionally, patients perceive the ability to renounce food, being thin, and the feeling of success and control as reinforcing (Cockell, Geller & Linden, 2003; Serpell, Treasure, Teasdale & Sullivan, 1999). These numerous positively perceived functions of the eating disorder explain the often low motivation for change and for psychotherapy, with the motivation to change often varying with respect to the different symptoms of an eating disorder (Vitousek, Watson & Wilson, 1998). For instance, sufferers are often prepared to cut down on the eating disorder symptoms, but the motivation to reduce or give up weight control strategies like restrictive eating, excessive exercise and in part also self-induced vomiting, is substantially lower (Treasure, Katzman, Schmidt, Troop, Todd & de Silva, 1999). This varying motivation for change depending on the symptom area is also reflected in the fact that patients with AN tend to perceive their eating disorder as "ego-syntonic", i.e. commensurate with their goals, while patients with BN mostly have a substantially more negative view of their illness and perceive it rather as "ego-dystonic" (Bulik & Kendler, 2000; Vitousek et al., 1998).

This ambivalence regarding the eating disorder symptoms, or low therapy motivation, is part of any treatment of a patient with an eating disorder; presumably, therefore, it is implicitly or explicitly an important aspect of any therapeutic relationship. A further reason for the high clinical significance of a low motivation to change in eating disorders lies in the fact that it predicts both treatment dropout (Bandini, Antonelli, Moretti, Pampanelli, Quartesan & Perriello, 2006; DeJong, Broadbent & Schmidt, 2012) and unfavorable treatment outcomes (Castro-Fornieles, Bigorra, Martinez-Mallen, Gonzalez, Moreno, Font & Toro, 2011; Geller,

Cockell & Drab, 2001; Gusella, Butler, Nichols & Bird, 2003; Rieger, Touyz, Schotte, Beumont, Russell, Clarke, Kohn & Griffiths, 2000; Wolk & Devlin, 2001). A systematic review (Clausen, Lübeck & Jones, 2013) revealed that a higher pre-treatment motivation to change was associated with a stronger improvement in restrictive eating behaviors, bingeing behaviors, and cognitive and affective measures of eating disorder pathology, but not with purging behavior (e.g. vomiting).

For this reason, the measurement of motivation to change – also specific to different areas – is an important part of the diagnostics of eating disorders, both at the beginning and in the course of treatment (Hötzel, von Brachel, Schlossmacher & Vocks, 2013; von Wietersheim & Hoffmann, 2011). The described findings on the prognostic relevance of a low motivation to change also suggest the employment of interventions which directly aim to increase the motivation to change. Such interventions are mostly based on the transtheoretical model of behavior change (Prochaska & DiClemente, 1992) or Motivational Interviewing (Miller & Rollnick, 1991). These two forms of intervention have their roots in the area of addiction, and were conceptually and practically transferred to the area of eating disorders (cf. e.g. Dray & Wade, 2012). Interventions to foster motivation are carried out either prior to the actual psychotherapy (e.g. Gowers & Smyth, 2004) or in parallel to it (Dean, Touyz, Rieger & Thornton, 2008). In terms of content, such programs target reflection on pro and con arguments regarding the eating disorder (cf. Legenbauer & Vocks, 2014). However, the empirical findings on the efficacy of these interventions in increasing motivation to change are inconsistent. While some studies demonstrated positive effects (Hötzel, von Brachel, Schmidt, Rieger, Kosfelder, Hechler, Schulte & Vocks, 2014), others yielded only moderate effects or were unable to demonstrate the superiority of such interventions over standard treatments (Treasure et al., 1999). A systematic review of studies conducted up to 2012 found that these interventions were particularly able to increase the motivation to reduce binge symptoms, but only small affects were demonstrated in terms of giving up compensatory or restrictive behavior (Knowles, Anokhina & Serpell, 2013). Nevertheless, it should be noted that the methodological quality of the studies (e.g. due to an insufficient sample size) is not satisfactory.

In terms of the concrete implementation of strategies to motivate the patient, in accordance with the reactance theory (for an overview, cf. Dickenberger, Gniech & Grabitz, 1993; Eagly & Chaiken, 1993), it can be expected that the more the patient feels pressured by the therapist to change her attitudes or behavior, the more strongly she will defend her beliefs and goals. This means that the more the therapist tries to convince the patient through argument, the more she might combat this with her own line of thinking and argument, in the sense of a "boomerang effect". Especially with regard to food intake, patients feel observed, controlled and pressurized, for example to empty their plate. Therefore, they often employ more or less obvious avoidance strategies (e.g. postponing or cancelling appointments); moreover, they frequently show reactance against the therapist's attempts at change, which they perceive to be unpleasant, for instance by not sticking to agreements (e.g. continuing to exclusively eat low-calorie foods). The aforementioned techniques of Motivational Interviewing derived from addiction therapy (Miller & Rollnick 1991) constitute appropriate methods to build up the intrinsic motivation for behavior change in this regard. Important goals of Motivational Interviewing are the exploration of discrepancies within the conflict of ambivalence and its resolution, often in one

particular direction. In this respect, motivational strategies like contracts, rewards, etc, i.e. extrinsic methods, play less of a role. The main focus is on increasing intrinsic motivation. The ambivalent motivation to change (e.g. wanting to stop binge eating but not wanting to gain weight, see above) should be considered in the conversation throughout the entire treatment. The therapist should avoid slipping into the role of a punitive parent in his/her communication, and monitoring in a "finger-wagging" manner whether the patient is complying with his/her recommendations. Instead, he/she always makes it clear that ultimately, the patient herself is responsible for the therapy success and for the speed of changes. This so-called resistance can be constructively resolved if the therapist takes the patient's thoughts, feelings, goals etc. seriously, puts his/her own position into perspective, and makes it clear that the patient's views are perfectly understandable. At the same time, information that can awaken the motivation to change can be imparted "in passing".

> **Example:** "With any other patient, I would recommend changing their diet, because by experience, this clearly reduces the binges. But you're quite sure that it won't help you…And knowing you as I do, you're not just saying that, you're sure to have had experience or made observations that underpin your view. Let's talk about that first of all,..." (Tuschen-Caffier & Florin, 2012, S. 46).

An essential prerequisite for treatment success is consensus with the patient regarding the treatment modalities. To this aim, it is necessary to develop a treatment plan together with the patient. It is generally useful to explain to the patient that she will make the important therapy decisions and that the psychotherapeutic treatment is reliant on her desire to change and her cooperation.

The building of the therapeutic relationship is also especially important in the treatment of children and adolescents with eating disorders. As the involvement of the parents or guardians in the therapeutic process is seen as essential, the therapist takes care to build up a sustainable therapeutic relationship both with the child/adolescent and the parents, and where necessary further caregivers. Clinical experience suggests that it can be beneficial if the child or adolescent perceives that the relationship between parents/guardians and therapist is a positive one. At the same time, however, the therapist should always ensure that he/she is impartial. In other words, he/she should neither be an ally of the parents/guardian against the child nor vice versa (Borg-Laufs, 2009).

Children and adolescents with eating disorders are often "sent" to treatment at the behest of their parents or guardians; thus, it cannot necessarily be assumed that the child or adolescent is already willing to change the eating disorder. It can even occur that parents/guardians address the inappropriate eating behavior in great detail in front of their child. This can trigger feelings of shame and guilt on the part of the child/adolescent and should be prevented by the therapist. Moreover, family and friends often convey to children/adolescents how dangerous and unreasonable their eating behavior is. This, however, can lead to reactance on the part of the affected children/adolescents. Therefore – similarly to the treatment of adults – it is important that a child or adolescent suffering from an eating disorder learns that the therapist is able to understand her disordered eating and the associated behavior, and will not judge it. When

building the therapeutic relationship, the child's/adolescent's stage of development additionally needs to be considered.

Generally speaking, the therapeutic stance should express a certain equanimity towards the symptoms. The eating disorder has generally already existed for months or even years, not least contributed to by the human organism's ability to compensate for starvation, which cannot be underestimated. An exception to this is acute physical or psychological risk situations, for example in patients with AN, which are often accompanied by an insufficient decision-making ability. In extreme cases, the therapist must consider the possibility of compulsory treatment (Thiel & Paul, 2008; see also chapter 2.3.8 "Compulsory treatment" in guideline chapter V "Anorexia nervosa").

Both outpatient and inpatient treatment of patients with eating disorders can currently still be described as insufficient in Germany, with the often long waiting times necessitating interim care. Generally speaking, it is the general physician who is tasked during this time, similarly to a case manager, with leading the patient through the various areas of care and possibly seeking treatment alternatives. At the same time, the general physician should endeavor to avoid the occurrence of further weight loss. Many patients wish to use such time to "go it alone after all". Such an attempt can be supported as long as the patient is somatically stable, but should realistically be accompanied by compulsory "check-up appointments", for example after four and eight weeks. This type of "open approach" which incorporates the patient's competencies, is often a prerequisite for building up a sustainable motivation for therapy.

5. Specific elements of the dialogue in the diagnostic phase

Before the start of therapy, a detailed diagnosis of the eating disorder pathology, the comorbid mental disorders and medical problems is conducted (see guideline chapter II "Diagnosis of eating disorders". The aim of the diagnostic interview, however, is also to develop a good and sustainable relationship with the patient. Furthermore, a first impression of the symptoms should be gained, after which the patient is informed about the further procedure (e.g. further diagnostic assessments, therapeutic strategies and process). To successfully develop a good rapport, in the first conversation (and throughout the entire therapy), the therapist employs conversational strategies which serve the purpose of depathologizing thoughts, feelings or behaviors which patients are generally reluctant to report, or which they only report under strong feelings of shame or guilt (cf. Frank & Frank, 2009). Experience demonstrates that depathologization helps the patient to be able to speak more openly about difficult themes (e.g. binge eating, vomiting). Moreover, experience has also shown that the therapist is perceived as someone who is obviously well-informed about eating disorders if he/she manages to provide detailed examples. Presumably, this fosters the development of a trustful therapeutic relationship. To round off the first conversation, the patient is informed that she will first have to undergo comprehensive medical and psychological diagnosis to clarify whether psychotherapy is likely to be successful. Likewise, it will only be possible to develop an individual therapy plan once the diagnosis has been established. The implementation of diagnostics thus does not yet imply an agreement for therapy.

Once the further diagnostic assessments have been conducted (see Guideline chapter II "Diagnosis of eating disorders"), the essential diagnostic findings are reported back to the patient and together, an etiological model of the (individual) eating disorder problems as well as the ability to change (therapy model) the problems is developed. When preparing for the psychotherapeutic treatment, the therapist should consider a series of rules for conducting dialogue which can contribute to increasing the motivation for psychotherapy.

For instance, it should be ensured that the patient has a good understanding of and is able to retain the explanatory model, that she finds it credible and is able to accept it for herself (Fiegenbaum, Freitag & Frank, 1992). When imparting a credible explanatory model, a broadly interactive approach is followed. The patient is guided to run through the explanatory model using her own examples. Through concrete questions, she is encouraged to draw her own conclusions, and importantly, is expressly asked to freely voice her reservations, doubts and questions and – if possible – to report on her own experiences which appear to be in conflict with the explanatory model. The therapist's task, following the method of guided discovery, lies in letting the patient answer the open questions herself and to work out the compatibility of her experiences with the model to explain the eating disorder. When conducting dialogue, the therapist takes care to anticipate possible objections and to integrate them into the explanatory model. This also applies to deriving the change model, i.e. for the therapy proposal. The patient is encouraged, irrespective of their practicability, to initially generate as many ideas for changing the problems as possible (e.g. continuing to diet but take vitamin tablets to "compensate for" nutritional deficiencies; eat a more diverse range of foods; do more exercise etc.). Following this, she is asked to imagine that from now on, she is going to change her eating behavior in a health-conducive direction (e.g. eating more regularly and eating a more balanced diet). Questions about her expectations regarding short- and long-term consequences are equally as important as questions relating to her ambivalence (e.g. "which factors speak in favor of or against weight gain?" etc.). At the end of the conversation, the therapist again summarizes the discussed advantages and disadvantages of the therapy and – if the patient's health permits – allows some time for the patient to reflect, during which she can decide for or against the therapy. The autonomy of the decision, the repeated weighing up of advantages and disadvantages of the therapy on the basis of detailed information about the demands of therapy as well as possible consequences of non-treatment (e.g. continuation of the eating disorders; severe physical consequences such as cardiac arrhythmia or even cardiac arrest) have been found to be conducive to generating self-motivation and willingness to cooperate on the part of the patient.

6. Dialogue in the course of treatment

The psychotherapeutic treatment of AN and BN is often a treatment of young people, specifically adolescent girls or young women. This brings with it important treatment implications, especially with regard to the therapeutic relationship (see Fichter & Herpertz, 2008). Adolescence and young adulthood constitutes a time of considerable psychosexual and social challenges. The formation of self-image (or self-esteem) is a continuous process which

begins in early childhood but certainly requires demanding developmental steps of the individual in the life phase of puberty, adolescence and young adulthood. In terms of shaping one's own "private" and professional life, it is a time of significant decisions and of the "adult" life experience that any decision also means, or at least can mean, a decision against something else, which can be felt in the most diverse areas of life. It is therefore all the more relevant to adopt a therapeutic stance which sees no insurmountable differences between a reflected, engaged partiality and the necessary abstinence, and which can allow for a dynamic interplay of psychoeducational and genuine psychotherapeutic treatment strategies. Besides empathetic solidarity, this also includes "putting one's foot down" in the sense of providing structure (e.g. that the regular participation in mealtimes is not discussed). The conflict between autonomy and dependency that is characteristic for this phase of life, and the associated ambivalent relationship towards the parents or guardians, is generally also reflected in the therapeutic relationship and can be utilized productively. Particularly the unspecific predictor variables of the psychotherapeutic process, such as interest, curiosity, commitment, authenticity and reliability are examined very critically against the background of the relationship with the parents/guardians ("Are they really interested, is it genuine, can I rely on them?").

Considerable conflicts with respect to self-esteem, which are characteristic for persons with eating disorders, necessitate a psychotherapy in which the patient's resources are strengthened. The focus should be less on the deficits in the development so far, and more on the abilities and achievements. At the same time, it is necessary to work out the genesis of the problems with self-esteem, which is generally to be sought in interpersonal conflicts, especially with the parents (e.g. high achievement expectations, linking of recognition and affection with performance), in order to ultimately be able to gather corrective experiences. A transference relationship (e.g. paternal or maternal) which is benevolent and fosters the patient's resources provides the opportunity to make positive corrections to self-esteem, which can then be transferred from the therapy to other relationships.

Therapeutic tasks, for example exposure to one's figure or the establishment of a changed eating style, are introduced as tasks through which the patient is able to discover, with the support of the therapist, to what extent the developed explanatory models are appropriate. Experience shows that such therapeutic tasks are linked to ambivalence (e.g. approach motivation on the one hand and avoidance motivation on the other), which can especially necessitate a motivating dialogue. Moreover, in the case of "cumbersome" therapeutic tasks (e.g. continuously filling out food logs), a style of dialogue is required which makes the necessity of the task clear to the patient without appearing to be "lecturing". For instance, the therapist can anticipate the patient's feelings (e.g. annoyance) and behaviors (e.g. filling out the food logs retrospectively for the whole week) and emphasize that it is up to the patient whether she would like to choose the best therapy (i.e. tailored to her own problems) or the second- or third-best therapy. In this regard, it is important that the therapist has internalized this concept of self-responsibility for his/her therapy success as a therapeutic stance and is thus able to authentically impart it to the patient.

Typical for the dialogue with patients with eating disorders is the active consideration of goals, wishes, feelings and thoughts throughout the course of the therapy. This also applies to the

phase of gradually ending the therapy (Hoffmann, 2009). Together with the patient, the therapist takes stock of the therapy goals which have been achieved and, if applicable, the therapeutic steps which are still necessary. Patients should become their own problem-solvers and should be actively included in the process of ending the therapy.

In the case of BED, an independent influence on the therapeutic relationship must be assumed with respect to the substantial overweight which is usually also present. In terms of the therapeutic process, these influencing variables have barely been examined in the past; however, psychotherapists are not immune to the (often unconscious) societal prejudices and discrimination against persons with obesity. Moreover, the understanding of the illness on the part of both the therapist and the patient, especially if they diverge, is likely to have a decisive influence on the therapy process. Monocausal explanatory models ("mind over matter" vs. "heavy-boned") of both the therapist and the patient are not conducive to success and harbor the risk either of discouraging the patient or of "passing the buck" in terms of relinquishing responsibility and thus also self-efficacy. For the psychotherapeutic work, it is much more important to determine, together with the patient, the framework within which weight loss and weight stabilization is possible (weight of parents and grandparents, age at onset of obesity, number of previous, frustrated weight loss attempts etc.). Furthermore, mental disorders and intra- and interpsychic problems in terms of cause and effect should be clarified in order to ultimately strengthen the patient's experience of self-esteem as a person with overweight or obesity. Particularly with regard to self-efficacy as an important determinant of the patient's self-esteem, a therapeutic stance which favors weight stabilization rather than weight loss is advantageous.

7. Informed consent vs. compulsory measures

In rare cases, which almost exclusively concern patients with AN, the cognitive impairments and disorder sequelae mean that it is no longer possible to assume a consequential decision-making ability on the part of the patient. In such cases, the responsibility for treatment decisions has to be assumed by other persons (generally by the physician). These compulsory measures (via placement according to the Mental Health Act, compulsory supervision or the involvement of psychosocial services, cf. Chapter 2.3.8 "Compulsory treatment" in the Guideline chapter V "Anorexia nervosa") should, of course, be explained to the patient.

All necessary treatment steps should likewise be explained to children and adolescents, and their consent should be sought. If minors refuse to participate in treatment, the treatment can also be initiated without explicit consent. However, the treatment then has to be approved by the family courts according to § 1631b of the German Civil Code (see Guideline chapter V "Anorexia nervosa" Chapter 2.3.8.4 "Compulsory treatment of children and adolescents").

8. The role of family and friends

An eating disorder always also harbors interpersonal problems (impacts on family members, partner and friends). Frequently, dysfunctional patterns of interaction between the patient and other members of the family (of origin) can be assumed. Therefore, for all patients, it is necessary to clarify these reciprocal influences in the respective family context early on, during the diagnostic process. Family members and partners often feel helpless and desperate in the face of their loved one's eating disorder. This helplessness is often not a good guide in the attempt to behave "correctly" and helpfully, and often leads to strong feelings of guilt and/or aggressive, reproachful attitudes towards the patient. The integration of family and friends into the therapy should be considered early on, irrespective of the therapeutic approach, under consideration of the patient's age, her interpersonal relationships (family, partner) and the degree of risk of the eating disorder. Moreover, the integration of family and friends provides the opportunity to obtain third-party anamnestic information. For children and adolescents, the integration of the parents into the therapeutic process is among the most important pillars of the treatment. Providing the family members with information has an important, especially fear-allaying function for the treatment. Even prior to the therapy, family and friends require information in order to be able to cooperate effectively. Generally speaking, the information should be provided in the presence of the patient and can include:

- the causes of eating disorders
- the maintaining conditions
- prognosis and expected course
- physical risks and possible consequential damage
- appropriate treatment options
- individual treatment planning
- methods of psychotherapy
- risks and possible side effects of treatment
- recommendations for dealing with the patient

The inclusion of family members can have positive, but also negative impacts on the therapeutic relationship and/or the psychotherapy (e.g. in the case of problematic family constellations such as sexual abuse, experiences of violence; in adolescent patients who want to emancipate themselves from their parents). In the individual case, it is necessary to clarify whether the inclusion of the family is useful or whether it should be forgone despite the considerable positive evidence. In adolescence, the parents should be included in the therapy wherever possible. In the case of outpatient and day-clinic treatment, they are essential "co-therapists". If family members are included in the treatment, it is necessary to adhere to the usual professional parameters (e.g. duty of confidentiality, communication with family members in the presence of the patient, avoiding the formation of coalitions).

In 2015, the German Society for Eating Disorders (DGESS) published patient guidelines that also address the families of persons with eating disorders (Zeeck & Herpertz, 2016). The

Federal Centre for Health Education (BZgA) provides diverse information for families in the form of brochures and on the Internet (www.bzga-essstoerungen.de). Information about themes relating to family members for a multitude of mental disorders is provided, for example, by the Federal Association of Families of People with Mental Illness (BApK, http://www.bapk.de). Patient and family guides can also be found in bookshops. In many large towns and cities, there are contact points, information offices and advisory services in the area of self-help, which provide lists and contact details of self-help groups. Useful information can also be found on many internet portals. However, other internet portals should be viewed critically, especially if they trivialize or even glorify eating disorders, and extol them as a "lifestyle" (e.g. so-called "Pro-Ana" or "Pro-Mia" websites; Gale, Channon, Larner & James, 2016; Rodgers, Lowy, Halperin & Franko, 2016). In the case of psychological strain, feelings of being overburdened or mental disorders of one's own, professional help for family members can also be useful.

Recommendations

Within the framework of the diagnosis and psychotherapy of eating disorders, a sustainable therapeutic relationship should be established.

Patients should receive information about their eating disorder (etiology, pathogenesis), their prognosis, as well as various forms of treatment including the effictiveness and side effects thereof (e.g. with regard to weight). Prevailing treatment standards of the respective institution should be described during a preliminary discussion.

In relation to the ambivalence towards changing the eating disorder symptoms, interventions to increase the motivation to change should be employed at the beginning of and/or during the treatment. For children and adolescents with an eating disorder diagnosis, the inclusion of family members should be considered.

Table 1: Example of aspects of dialogue within the strategy "depathologization" (cited from Tuschen-Caffier et al., 2005)

Type of problem	Examples for depathologization
Failed attempts to lose weight in the case of obesity	Reference to genetic aspects that make it more difficult to reach or maintain a certain weight.
Dieting as a trigger for BN	Dieting is widespread in our society, new diets are constantly being promoted in the media.
Unwillingness to talk about the eating problem in the case of AN	If the patient has been sent by her parents (the doctor etc.), point out that the behavior is easy to grasp and understand. Verbalization of thoughts and feelings that

	the therapist, for example, would have if he was in the patient's shoes (e.g. anger towards the parents, skepticism whether the therapist is secretly an "accomplice" of the parents).
Binge eating in the case of BN	Point out that the body is reacting perfectly normally: If the body doesn't always get enough food and is malnourished, it will catch up on what it needs.
Stress as a trigger for binge eating in the case of BED	Eating is initially a "good" problem solver; you're tired, you distract yourself from unpleasant feelings, food tastes good.

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IV. Anorexia nervosa

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1. Symptoms and diagnostic criteria

1.1. Symptoms

In AN, the emergence or maintenance of underweight occurs due to a restriction of or insufficient increase in energy intake (in the case of growth / intensive exercise). The body weight lies below that expected based on the sufferer's gender, height and age. Despite being underweight, sufferers are afraid of being and/or becoming fat. However, they may not report or consciously perceive this fear. The whole body or parts of the body are deemed as "too fat", despite the underweight (body image disturbance). For most patients, self-esteem depends to a large degree on their shape and weight, and for others, controlling their weight represents success in exerting sufficient self-control.

Food intake is restricted – generally by limiting the amount of food or by a selective choice of foods (avoidance of fats and/or carbohydrates). This may be compounded by excessive exercise, self-induced vomiting or abuse of laxatives, thyroid medications or diuretics. Some patients with type I diabetes accept high blood sugar levels in order to reduce the uptake of sugar into the cells. Many patients develop eating rituals, which most frequently consist of eating slowly, cutting food into small pieces and a highly selective combination of foods. In the course of the illness, bingeing occurs in some patients, which in most cases is accompanied by "purging behavior" (self-induced vomiting, laxative abuse etc.).

The food restriction has consequences on the physical and psychological level. The malnutrition affects most of the important organs, potentially leading to life-threatening states. Among other things, a disturbance of the endocrine system occurs, which in women and girls is reflected in a suspension of menses. Decreased bone density associated with altered hormone levels is often only partially reversible. In children, a delay in puberty with an absence of menarche and a stagnation of physical development and stunted growth can arise. On the psychological level, a positive feeling of lightness, control and euphoria often initially prevails, which later switches to indifference, irritability and depressed mood. Often, rigid thinking, a strong need for control – extending to compulsive thinking and behavior – conflict avoidance and difficulties in dealing with negative affect (above all anger and rage) as well as a lack of spontaneity are apparent. These traits can be strengthened in the case of pronounced underweight.

A large proportion of patients with AN show problematic exercise behavior (Shroff et al., 2006), which can range from a strong psychomotor unrest due to starvation in the case of extreme underweight (Ehrlich et al., 2009), through compulsive exercise (Davis et al., 1993;

Meyer & Taranis, 2011) to exercise addiction in the narrower sense (Cunningham et al., 2016; Zeeck & Schlegel, 2013).
Patients' outwardly visible underweight leads to concerned reactions in their environment, especially from parents, teachers, friends and partners. These reactions – e.g. increased attention – can unintentionally become secondary reinforcers of the illness (Salerno et al., 2016). The danger which the underweight entails is mostly negated by the sufferers themselves; many show little or no insight into their illness. This also explains why patients with AN typically do not seek help of their own volition, but often initially only at the urging of family, friends, teachers or superiors.
As the disorder begins in most cases in puberty and adolescence, it leads to an impairment in psychological and physical development during an important life phase (Herpertz-Dahlmann, 2015a). Delays in school or professional development often arise. If the disorder progresses over many years, AN can become part of the individual's identity which she finds difficult to relinquish.

1.2. Diagnostic criteria

Table 4.1 presents the ICD-10 criteria for AN (F50.0), which are provisionally valid until 2022 They comprise underweight (BMI < 17.5 kg/m² in adults or falling below the 10th age percentile for children and adolescents), body image disturbance, and the presence of an endocrine disorder (or a delay in the sequence of pubertal development steps). A distinction is made between a type with (F50.1) and without (F50.00) active measures for weight loss.
In the ICD-11, underweight will be defined through a BMI < 18.5 kg/m² in adults and falling below the 5th age percentile in children and adolescents (http://www.who.int/classifications/icd/revision/en/). Therefore, the new criteria include a substantially larger group of patients than previously. The underweight cannot be attributable to another illness or the unavailability of food. The revision will be oriented to the US classification system DSM-5. However, the weight criterion for children and adolescents should be seen critically, as a lower threshold is set than for adults, even though the consequences of chronic starvation are more serious for children and adolescents[4]. Measures which hinder the restoration of a normal body weight are subsumed in a second diagnostic criterion – this includes restrictive eating, self-induced vomiting, laxative abuse and excessive exercise. A third criterion refers to body perception: Despite being underweight, the body is perceived either as normal/ "too fat" (body image disturbance), or body weight and shape are central for self-evaluation (see table 4.1).
For the ICD-11, due to the prognostic relevance, a differentiation between two types according to the extent of underweight is suggested: AN with significantly low body weight (BMI < 18.5kg/m² and > 14.0kg/m² or between the 5th and the 0.3rd percentile) as well as AN with dangerously low body weight (BMI < 14 kg/m² or < 0.3rd age percentile), with a distinction between a restrictive type and a "binge-purging type" in each group.

[4] For an adolescent who has just turned 18 years of age, the 5th BMI age percentile corresponds to approx. 17.6 kg/m². For an 17.11-year-old girl (162 cm, 48kg, BMI 18.3 kg/m²: according to Kromeyer-Hausschild (2001): 10th pecentile according to KIGGS (2011): 5th percentile. CDC: 11th percentile.

The revised version of the "Diagnostic and Statistical Manual" (DSM-5; American Psychiatric Association, 2013) contains the following changes from the DSM-IV (see table 4.1): The criterion of an endocrine disorder has been dropped, as it is difficult to apply in female patients before the menarche, in men, and in women taking contraceptives. A fear of weight gain or of becoming "fat" does not necessarily have to be expressed – the criterion is seen as fulfilled if behaviors are observed which interfere with weight gain despite a low weight. Underweight is defined as "significantly low body weight", i.e. a weight which lies below the minimum of normal weight (the minimum of normal weight in adults corresponds to a BMI of 18.5 kg/m²). Furthermore, the DSM-5 no longer speaks of "refusal" to maintain a normal weight because this formulation implies a conscious, willful and controllable management of behavior (Hebebrand & Bulik, 2011). The subdivision into two types (restrictive type, binge-eating/purging type) has been retained and additionally contains a time criterion: The respective behavior must have occurred during the last three months. In addition, a partial or full remission can be coded, as can a level of severity. The latter is primarily defined according to the degree of underweight. The severity of symptoms and the degree of functional impairment, however, should be included in the evaluation (see table 5). It should be noted here that there is not yet a uniform definition of the level of severity, and the criteria vary substantially: The DSM-5 already speaks of extreme AN from a BMI < 15 kg/m², while for the ICD-11, a "significantly low body weight" at a BMI < 14 kg/m² is currently being suggested.

With the respect to the categorization of eating disorders, it should be kept in mind that in the course of illness, transitions between the different forms of eating disorders can occur, which are not considered by the classification systems. It can be assumed that in approx. a third to a half of cases, AN later transitions into BN (Bulik et al., 1997; Eddy et al., 2008). Moreover, the question of the extent to which a division into subgroups of AN is appropriate currently remains unresolved (Peterson et al., 2016).

On a further critical note, male patients with anorexia nervosa are underrepresented in studies, and both the diagnostic criteria and the currently existing instruments to assess body image are oriented to females (Murray et al., 2017).

1.3. Comorbidity

AN frequently shows comorbidities with other mental illnesses, particularly depression, anxiety disorders or obsessive-compulsive disorders (Milos et al., 2003; O´Brien & Vincent, 2003). An increased rate of personality disorders has further been found (Martinussen et al. 2017, Farstad et al. 2016). The few existing studies investigating psychological comorbidity in adolescent patients with AN point to similarly high comorbidity rates (Bühren et al., 2014; Salbach-Andrae et al., 2008; Swanson, 2011).

The assessment of additional disorders provides important hints regarding etiology, type of eating disorder pathology, treatment success and prognosis (Lilenfeld et al., 2006). However, the relationships between symptoms of anorexia and comorbid disorders are complex. To date, it remains unclear to what extent comorbid disorders are the cause or the consequence of AN, or else the result of a mutual predisposing factor. In the course of illness, a reciprocal influence occurs, which needs to be taken into account during therapy.

Data on the prevalence of depressive disorders in AN vary strongly, from 31 to 89 % (Godart et al., 2007); overall, a lifetime prevalence of 40 % (compared to 15.9% in the population) is assumed. The state of starvation appears to play a role in the high prevalence rates, possibly also by exacerbating a predisposition to depressive reactions (O´Brien & Vincent, 2003). Data on the prevalence of obsessive-compulsive disorders lie at 15 to 69 % for lifetime prevalence (Serpell et al., 2002) and at 15 to 29 % for point prevalence in clinical samples (Herzog et al., 1992; Thornton & Russell, 1997). There appears to be a particularly high comorbidity of obsessive-compulsive disorders and AN in males. In a large Swedish register study, females who had first been diagnosed with obsessive-compulsive disorder had a 16-fold increased risk of suffering from AN, whereas males had a 37-fold increased risk (Cederlöf et al., 2015). Around a third of patients with AN show a least one comorbid anxiety disorder (primarily social phobia), of whom around two thirds report that this preceded the AN and already existed in childhood (Godart et al., 2002; Raney et al., 2008; Swinbourne et al., 2012). The prevalence of alcohol abuse or dependency lies between 9 and 25 % and is typically found in the binge/purge subtype (Baker et al., 2010; Bulik et al., 2004; Root et al., 2010). Moreover, patients with AN and their families show increased rates of autism spectrum disorders, although a shared genetic predisposition should not be assumed (Koch et al., 2015). Furthermore, AN patients show an increased risk of developing attention-deficit/hyperactivity disorder (ADHD) and vice versa (Nazar et al., 2016).

In almost a half of adult patients, comorbid personality disorders are present. The four most frequent personality disorders, in descending order of frequency, are obsessive-compulsive, avoidant, dependent and borderline personality disorders (Farstad et al., 2016; Martinussen et al., 2017). Besides categorical personality disorders, there are increased associations between AN and personality traits (dimensional), above all higher perfectionism, neuroticism, avoidance motivation and reward sensitivity as well as low levels of extraversion and self-regulation capacity (Farstad et al., 2016). It is assumed that the type of eating disorder is co-determined by premorbid personality traits.

1.4. Differential diagnosis

Weight loss should always be taken as a serious indicator of a potentially severe physical disease. All diseases which are linked to weight loss are part of the differential diagnostic spectrum of AN.

If psychological causes are present, in most cases, it is sufficient to identify the reasons for the weight loss and reduced food consumption. However, it is possible that a not yet diagnosed organic disease leads to a secondary disorder of eating behavior, meaning that even in cases in which the psychological nature of the eating disorder initially appears to be obvious, differential diagnostic vigilance remains advisable. At this point, only those differential diagnoses are addressed which are especially liable to be confused with AN.

In particular, gluten-sensitive enteropathy, termed “celiac disease” in its child and adolescent form, often gives rise to confusion (Grenet et al., 1972; Leffler et al., 2007a; Leffler et al., 2007b; Ricca et al., 2006). This is due to the early and insidious onset of the disease and the interaction with the resulting nutritional disturbance and the parenting behavior of the parents. Celiac disease leads not only to weight loss and delayed longitudinal growth, but often also to

disordered eating behavior. The occurrence of BN has also been observed in the framework of a gluten-sensitive enteropathy (Jost et al., 2005). For differential diagnosis, the specific gliadin and endomysial antibodies alone are not sufficient. A duodenal biopsy to provide evidence of the characteristic villous atrophy should be carried out in any case of doubt. Often, the diagnosis of gluten-sensitive enteropathy is only made in adulthood, after many years.
The onset of the chronic inflammatory bowel diseases Crohn's disease and ulcerative colitis most frequently occurs between the ages of 14 and 26, and thus at an age when eating disorders are also at their most frequent. While ulcerative colitis is generally correctly identified due to the typical symptoms with bloody diarrhea, the symptoms of Crohn's disease are more diverse and can occasionally be confused with AN.
Endocrinological causes of underweight are not always easy to detect, but mostly show characteristic accompanying symptoms. These disorders include:

- Primary or secondary hypocortisolism
- Hyperthyroidism
- Panhypopituitarism
- Autoimmune polyglandular syndrome

Insulin-deficient diabetes leads to a very rapid weight loss, which cannot be sufficiently explained by reduced appetite and food consumption. The diagnosis is straightforward if the symptoms are correctly interpreted.
Chronic lung or kidney diseases can also lead to an accompanying cachexia, which in individual cases can be confused with AN. A decrease in renal function with pre-uremia can also occur as a consequence of chronic volume loss and of hypokalemia. In such cases, the creatinine levels can be misleading, as in the case of AN, they are correlated with the considerably reduced muscle mass. As pre-uremia is linked to a loss of appetite and a resulting reduction in food intake (Carrero, 2009; Carrero et al., 2008), the joint occurrence of renal failure and anorexia can occasionally be causally related. In such mixed forms of AN and uremic anorexia, dialysis can lead to an improvement in eating behavior.

1.5. Etiology

In etiological terms, AN can be assumed to be multicausal in nature, with an interaction of biological (genetic factors), psychological and environmental factors (family, cultural) (Treasure et al., 2015; Zipfel et al., 2015). The examination of risk factors which are decisive for the etiological understanding is strongly impeded in the case of AN due to the low prevalence of the disorder. The majority of previous longitudinal investigations do not allow for an evaluation of full-blown AN, or for a differentiated consideration of the individual eating disorder groups. Moreover, to date, little is known about the interaction as well as the specificity of individual risk factors.

Sociocultural aspects
AN appears to manifest independently of culture, although the prevalence is higher in Western industrialized nations than in non-industrialized countries (Hoek et al., 2005; Hoek, 2016; Makino et al., 2004; van Hoeken et al., 2016). In contrast to BN, the occurrence of AN on the

African and South American continent is rare, which also suggests differing genetic risks or gene-environment interactions (Kolar et al., 2016; van Hoeken et al., 2016). Sociocultural models of the etiology of eating disorders predominantly see the internalization of the thin beauty ideal propagated in Western countries, and the frequently associated dissatisfaction with one's own body, as risk factors for disordered eating or a reduction in food intake ((Stice & Whitenton, 2002); for an overview, see (Culbert et al., 2015)). Prospective follow-up studies show that young women who are dissatisfied with their own body have an increased risk of developing disordered eating behavior (Ghaderi & Scott, 2001; Killen et al., 1996; McKnight Investigators, 2003). Furthermore, experimental studies have demonstrated that exposure to media which portray a thinness ideal leads to a slight increase in dissatisfaction with one's own body, especially in risk groups (for a meta-analysis, see (Hausenblas et al., 2013)). However, prospective studies have not yet been able to demonstrate that the risk of full-fledged anorexia nervosa also increases.

According to cross-sectional studies, recreational and elite athletes in the esthetically characterized sport types such as gymnastics, ballet and dance, as well as in endurance sports (e.g. distance running) and sports with weight specifications (e.g. boxing, wrestling) can be seen as risk groups for the development of AN (Sundgot-Borgen & Torstveit, 2004; Tseng et al., 2007).

Genetic and neurobiological aspects

The high transmission of AN in families suggests a shared genetic predisposition. Based on twin studies, the heritability of AN is estimated to lie between 48 and 76 % (e.g. (Bulik et al., 2006; Klump et al., 2001; Kortegaard et al., 2001). Compared to women without a family predisposition, female first-degree relatives show an 11-fold higher risk of also developing full-blown AN. Women have an approximately 10-fold higher risk of developing AN compared to men (Jacobi et al., 2004). Moreover, there is mounting evidence that testosterone represents a protective factor in terms of the development of eating disorders, although the biological mechanisms underlying this association remain unclear (Culbert et al., 2015). Preterm birth and perinatal complications appear to slightly increase the risk of developing AN. However, this relationship is subject to controversial debate in the literature, as previous studies have not sufficiently controlled for genetic and environmental factors (Krug et al., 2013; Raevuori et al., 2014).

Molecular genetic investigations suggest that not one individual genetic defect, but rather numerous genes, and to differing extents, contribute to the development of the different phenotypical characteristics of AN (Yilmaz et al., 2015). For many years, the findings on candidate genes of AN were inconsistent, with two genome-wide association studies (GWAS) yielding no significant results (Boraska et al., 2014; Wang et al., 2011). A GWAS published in 2017 (Duncan et al., 2017), showed, for the first time, one significant locus in a gene region on chromosome 12 (rs4622308), for which significant loci have already been found for type 1 diabetes and autoimmune diseases. Results on a comparison between an earlier GWAS on AN (GCAN, Borasko et al., 2014) and another on Body Mass Index (GIANT, Lock et al., 2015) point to possibly similar gene variants for a lower BMI which also predispose to AN (Hinney et al., 2017). Similar comparative approaches (genetic correlations) yielded positive genetic associations with schizophrenia, obsessive-compulsive disorders, neuroticism, autoimmune diseases and educational level, as well as indications of negative associations with metabolic

markers such as unfavorable lipid phenotypes (Bulik-Sullivan et al., 2015; Duncan et al., 2017; Mas et al., 2013). Data from a Finnish register study supported the indications regarding autoimmune diseases (Raevuori et al., 2014), although this association also seems to applies to other mental illnesses.

The state of acute underweight is associated with changed levels of a multitude of hormones and other signal peptides. For instance, leptin, sex hormones and thyroid hormones are strongly reduced, while cortisol and the appetite-stimulating hormones ghrelin and Agouti related Protein (AGRP) are increased (Merle et al., 2011; Schorr & Miller, 2016). The extent to which these changes merely reflect an adaptation response to acute underweight or are predisposing factors for the disorder remains to be clarified.

Besides the molecular-biological and endocrinological investigations, the structural and functional imaging of the brain (PET, structural/functional MRI) opens up new possibilities to gain a better understanding of the neurobiological aspects of AN. In persons with underweight, clear and relatively global reductions of grey (and presumably also white) matter are found, which are completely or partially reversible with weight gain (Bernardoni et al., 2016; King et al., n.d.; Seitz et al., 2016). The results of studies using functional magnetic resonance tomography are heterogeneous, but there is increasing evidence of changes in brain regions that can be related to reward and cognitive control (O'Hara et al., 2015; Phillipou et al., 2014; Wierenga et al., 2014). In recovered patients, changes have been found in the serotonergic and domapinergic neurotransmitter system in the area of the prefrontal and medial temporal cortex as well as the ventral striatum, pointing to a possible dysregulation in the reward system and in affect regulation (Kaye et al., 2013).

Individual and developmental-psychological factors

Disordered eating behavior (e.g. feeding disorder) as well as increased gastrointestinal problems in infancy and toddlerhood are associated with a higher risk of developing AN (Kotler et al., 2001; Marchi & Cohen, 1990; RåStam, 1992). Mainly based on retrospective studies, the following characteristics have been discussed as potential risk factors for the development of AN: increased drive for thinness and restrictive eating (Jacobi et al., 2004; Stice, 2002; Striegel-Moore & Bulik, 2007), lower self-esteem and a negative self-concept (Bulik et al., 2006; Jacobi et al., 2004), affective lability and negative affectivity (Bulik et al., 2006; Cervera et al., 2003; Seidel et al., 2016), an anxious-avoidant or obsessive-compulsive personality style (Anderluh et al., 2003; Cassin & Ranson, 2005; Lilenfeld et al., 2006) as well as insecure attachment patterns (Jewell et al., 2016). According to a recent prospective longitudinal study, the combination of increased drive for thinness and increased anxiety/depressiveness at the age of 16-17 years predicts increased occurrence of AN at the age of 19-20 years (Peñas-Lledó et al., 2015). Difficulties in expressing and processing socio-emotional signals and in affect regulation (Caglar-Nazali et al., 2014; Treasure & Schmidt, 2013) as well as a cognitive style characterized by cognitive inflexibility and a strong attention to detail (Lang et al., 2014; Wu et al., 2013) are also increasingly being discussed as potential risk factors. For instance, an impaired cognitive flexibility and a reduced ability to interpret socio-emotional signals was also found in first-degree relatives of AN patients (Holliday et al., 2005; Kothari et al., 2015; Kothari et al., 2013). From a developmental-psychological perspective, given the primary onset of the disorder in puberty, it is discussed whether girls who develop AN have greater difficulties in coping with age-typical developmental steps. Significant in this developmental stage are, among other

factors, dealing with physical maturation and the associated change in body image as well as the development of a sense of identity as a woman, the separation from primary caregivers and the development of an autonomous, adult self (Gander et al., 2015).

Family-related factors

The longitudinal studies conducted to date do not allow for a differentiation of the extent to which particular family structures and interactions constitute a risk for the development of AN, or are the consequence of the disorder (Button et al., 1996; Calam, 1998; Holtom-Viesel & Allan, 2014). Cross-sectional studies suggest that pathological family structures and functions are associated rather with the severity and chronicity of AN and are less of etiological relevance (Jacobi et al., 2004; Raenker et al., 2013). See also "Prognostically relevant factors" in this regard.

Prognostically relevant factors

So far, there are no prospective investigations specifically examining the influence of prognostically relevant factors, or their experimental change, with respect to the course of symptoms. Information on prognostically relevant and maintaining factors are largely based on observational and intervention studies.

Research on predictors has revealed that a lower BMI, a long duration of illness, and higher age at the time of the study are associated with an unfavorable course (Vall & Wade, 2015; Zerwas et al., 2013). Among the psychosocial predictors which have been linked to a favorable course are purging behavior (or impulsivity), high self-esteem, a lower eating disorder psychopathology, a high treatment motivation and the lack of comorbid depression and trait anxiety (Berkman et al., 2007; Vall & Wade, 2015). Moreover, psychotherapy studies have indicated a lower response in patients with an avoidant personality disorder (Zerwas et al., 2013). Insufficient weight gain in the early phase of treatment was linked to a lower remission rate after one year (Nazar et al., 2017). Moreover, excessive-compulsive exercise appears to be related to higher dropout rates, poorer treatment outcomes and higher relapse rates (Bratland-Sanda et al., 2010; Smith et al., 2013; Solenberger, 2001; Strober et al., 1997b). Family therapy intervention studies have repeatedly shown that pathological family interactions – such as a high degree of parental criticism – are associated with a more negative outcome (Eisler et al., 2007; Holtom-Viesel & Allan, 2014; Rienecke et al., 2016). Furthermore, the consequences of starvation appear to substantially contribute to the maintenance of psychopathology and illness (Treasure et al., 2015).

1.6. Course of illness

Generally speaking, the course of illness reaches over several years and is highly variable. Recovery in the first two years is rare. In a study by Herzog et al. (Herzog et al., 1997), the mean duration until recovery lay at six years. However, the available longitudinal studies refer to patients who utilized medical or psychological help. There are barely any data on untreated cases, meaning that the rate of spontaneous remission is largely unclear. A Finnish longitudinal study in twin cohorts showed that 50% of cases of AN were not even detected by the health care system. After five years, 67 % showed a normalized weight, were menstruating again, and

indicated neither binges nor self-induced vomiting (Keski-Rahkonen et al., 2007). Nevertheless, many sufferers continue to show clear problems in the longer term even after remission, in the area of social integration and interpersonal relationships (Wentz et al., 2009). A review by Steinhausen (2002), which included 119 studies with 5590 patients, reported recovery rates of just under 50 %, while 30 % of patients achieved partial remission and 20 % showed a chronic course. In the longer term, 60-73% reached an appropriate weight. A further review by Berkman et al. (2007) included 22 longitudinal studies on AN: A prospective cohort study (Gothenburg study; N = 51) reported a good outcome according to the Morgan-Russell criteria (symptom severity was rated according to weight, menstruation status, psychological and social situation) in 50 % of patients; 10 % showed a chronic course after ten years. Case series which applied the same criteria found a good outcome in 28 to 58 % and a poor outcome in 11 to 42 % of cases (follow-up periods between six and twelve years) (Berkman et al., 2007). The comparability of studies is limited due to the different definitions of remission and treatment outcome (Pike, 1998) as well as the fact that in general, only treated patients were assessed.

Overall, AN shows the highest mortality rate of all mental disorders, due to suicide and consequences of malnutrition. A meta-analysis revealed that the standardized mortality rate lies at 5.9% (Arcelus, 2011). Worldwide, from among over 300 assessed physical and mental illnesses, AN and BN together lay in 12th place as a primary reason for disability-adjusted life years (DALY´s) among 15-19-year-old girls (Erskine et al., 2016; Hoek, 2016). A Swedish study in patients in inpatient treatment indicated, however, that mortality rates are declining. The authors related this to an improved care in specialist units (including, among other things, nutrition management, suicide prevention) (Lindblad et al., 2006).

The prognosis for young patients, or those with an illness onset before the age of 16 years, has clearly improved over the last two decades, and in most cases appears to be more favorable than in adult patients or those with an illness onset in adulthood (Herpertz-Dahlmann, 2015b). However, there is only a limited number of follow-up studies. In individual cases, a complete recovery following a first episode can be observed, especially when the physical and social development has been unremarkable up until that point, and the development of the eating disorder was preceded by an identifiable, burdensome life event (e.g. loss of a family member) (North et al., 1997). In 10-year follow-up studies (Herpertz-Dahlmann et al., 2001; Strober et al., 1997b; Wentz et al., 2001) and an 18-year follow-up study (Wentz et al., 2009), for the first time, no deaths were found in follow-ups of adolescent cohorts in first inpatient treatment.

2. Therapy

For the treatment of AN, there are essentially three possible treatment settings: the inpatient setting, the partial inpatient/day-clinic setting, and the outpatient setting. More intensive treatment settings (inpatient therapy, day-clinic treatment or a combination of therapy approaches in the outpatient framework, e.g. individual and group therapy as well as body psychotherapy) are indicated if the development process within outpatient psychotherapy has stagnated or a deterioration has even occurred. This can refer both to weight development (which is the most important parameter) and to the psychological and/or social situation.

As the recovery process generally encompasses a period of many months – if not years (see section 1.6), an "overall treatment plan" is necessary, in which different settings can constitute successive stages of therapy. Due to the danger of chronification, treatment should take place as quickly as possible and primarily have a psychotherapeutic orientation, but should also consider physical and nutrition-related problems in addition to psychological aspects (Hay et al., 2014). As treatment should take place as early and in as timely a manner as possible, in the case of longer waiting times for outpatient psychotherapy, it may be necessary to consider day-clinic or inpatient treatment in order to combat chronification. In individual cases, due to physical risks or a low insight into the illness, an inpatient treatment can be necessary as an initial treatment stage (Wilson et al., 2000), meaning that the principle of "stepped care" is not appropriate in all cases for AN.

The treatment of AN almost always involves several treatment providers: besides psychotherapists (individual and family sessions), a general practitioner/family doctor or specialist physician, and where necessary social workers, nutritionists, and special therapists (e.g. body therapists). A close coordination between these treatment providers is necessary – particularly in the outpatient area and across sectoral boundaries. However, due to the framework conditions of the health system in Germany, this does not always take place to a sufficient degree. A continuity of treatment (as few changes as possible in the responsible contact partners) should be striven for.

General practitioners/family doctors and specialist physicians play a key role in the initial detection of AN and in the accompanying physical care. They should motivate sufferers to accept specialist psychological care. An additional social-therapeutic support can be helpful if there are problems regarding school, training, job or living situation. For children and adolescents, it should be carefully checked on a case-by-case basis whether patients are still physically capable, for instance, of taking part in physical education classes or of attending school. Incremental limitations are often necessary in the framework of outpatient treatment in order to counteract a further weight loss.

Any consulted nutritionist should have expertise in dealing with patients with AN. Patients themselves often have in-depth knowledge about nutrition (especially calorie contents), but are not able to implement this in a healthy form in everyday life. Detailed counting of calories, or support of a diet rich in raw foods, which may be advisable in other persons, are counterproductive for patients with AN. In some cases, however, it can be difficult to differentiate between food intolerances, eating habits (vegetarians, vegans), or selective food choices caused by the eating disorder.

Families and important caregivers are often heavily burdened. If there are no reasons to speak against it (e.g. lack of consent of the patient), these persons should be provided with sufficient information and support. For children and adolescents, it is essential to incorporate family members into the treatment.

Advice centers offer low-threshold options for dialogue, which can be a first step in seeking help for patients with AN. In this respect, advice center employees are tasked with providing information and referral to psychotherapeutic treatment. Psychotherapeutic interventions in narrower sense are reserved for licensed psychotherapists. The respective advice center should have experience in dealing with patients with anorexia and be subject to regular quality assurance.

Residential groups play a role in Germany particularly in supporting adolescents and young adults as well as in caring for chronically ill patients. Placement in a therapeutic residential group should be considered, for example, if support in the home environment is not sufficient or conducive to health. A residential group can also be considered, however, if an eating disorder has become chronic, which has led to a pronounced social isolation and/or problems in coping with everyday life. Suitable residential groups should show a specific concept for caring with persons with eating disorders. For adolescents, the youth welfare service is responsible, through § 35a SGB VIII of the German Social Code (integration assistance for minors with mental illness), which must be applied for by the caregivers to the youth welfare office of the place of residence ("place of habitual residence"). Children and adolescents are eligible. Over the age of 18, integration assistance as support for young adults (§ 41 SGB VIII) can also be continued over the age of 21, but must first also be applied for by patients upon reaching legal adulthood. In the case of a threat of or already existing chronification, outpatient or inpatient integration assistance is necessary, if during the inpatient treatment, a stabilization of symptoms and of the living situation has not been achieved to the extent that a reintegration into the living environment existing before the illness is possible. Here, issues of jurisdiction often arise, which have to be solved on a case-by-case basis.

Care gaps or shortfalls exist in Germany with regard to specific offers for patients with a severe, long-lasting course of illness, in the treatment of severely underweight patients with a need for medical supervision (internal-psychosomatic medicine wards) and in terms of specific offers for patients who first need to be motivated to undergo treatment (e.g. as they can be provided in the framework of specialized outpatient clinics).
An observational study indicated that specialized outpatient offers contribute to reducing the overall rates of inpatient admissions as well as of treatment costs (House et al., 2012).

2.1. Treatment aims

The aims of treatment for AN are as follows:

a.) the restoration and maintenance of a body weight appropriate for the patient's age and height
b.) a normalization of eating behavior
c.) treatment of the physical sequelae of eating behavior and underweight
d.) influencing the difficulties underlying the disorder on the emotional, cognitive and interactional level
e.) fostering social integration, which is often linked to "catching up" on missed developmental steps.

The procedure and objectives of treatment should be openly discussed against the background of the often fluctuating motivation and strong ambivalence (detailed information and education), to enable, if possible, an agreement between patient, therapist and where necessary family members. In very rare cases, a treatment against the patient's will can be necessary (see section 2.1.2.).

In the case of a *still short duration of illness*, the normalization of eating and weight is of the highest priority in order to prevent chronification. As insight into the illness is often limited – particularly in children and adolescents – guardians or close family members also need to assume, and often also enforce, important tasks and decisions in the first treatment phase with regard to the treatment to be conducted. On the other hand, an important task of adolescence is to develop autonomy. This means that with increasing stabilization of weight and eating behavior, the patient's ability to deal with conflict and to set boundaries should be strengthened, and it is also necessary to address conflicts with close attachment figures.

Despite intensive therapeutic efforts, the majority of patients show residual symptoms of the disorder following treatment, necessitating respective information prior to treatment and a good aftercare. The end of any AN treatment should include a "relapse prevention" (Fairburn, 2008). Among other things, patients should be prepared for the fact that a renewed strengthening of their symptoms might occur following therapy, but that this does not have to spell disaster if they are able to draw on the coping patterns developed in therapy.

Of central importance in AN is the consideration of deficits in social and/or school and professional integration. Interventions which can be helpful in this regard are those which foster (re-)integration, such as school visits or work trials when the patient is still in the clinic, the discharge from inpatient treatment to a subsequent day-clinic treatment stage, an accompanying support by a social worker or supervision in a residential group specializing in patients with eating disorders.

For patients with a "*severe and enduring anorexia nervosa*" (Robinson et al., 2015), it is necessary to decide individually and together with the patient to what extent the aim of treatment can be a normalization of weight and eating behavior in the sense of recovery (this can still be possible after many years of illness), or whether the primary focus should be on improving quality of life, social integration and physical state in the sense of reducing and limiting the negative consequences of the eating disorder (Hay et al., 2014). This is a flexible ("very small steps, achievable goals") procedure that is aligned to the individual patient, which takes into account general influencing factors such as credibility, empathy, acceptance and understanding (Hay et al., 2014; Kaplan, 2002).

2.1.1. Prerequisites for treatment

Generally speaking, patients with AN are highly ambivalent towards changing their weight and eating behavior. The psychological consequences of hunger and underweight (e.g. cognitive impairments, rigidity, depressivity) additionally impair the ability to show insight into the disorder, the treatment motivation and the collaboration in the therapeutic process (Treasure et al., 2015). The symptoms of the eating disorder are often largely perceived as ego-syntonic (Kaplan & Garfinkel, 1999; Vitousek et al., 1998). Accordingly, premature treatment dropout constitutes a frequent problem in the treatment of AN (Mahon, 2000), and the motivation for change has proven to be a relevant predictor of treatment outcome (see e.g. Carter et al., 2012; McHugh, 2007).

In children and adolescents, the still limited ability for introspection and insight in this age group further reduces the willingness for treatment. At the same time, patients at the beginning of puberty reach a situation of physical danger more rapidly due to the still significantly lower

body fat percentage. Therefore, for this age group, the time frame for outpatient treatment – if eating and weight do not quickly improve – is narrower. In the case of an illness-related cognitive impairment due to the starvation process or severe weight phobia, a treatment also without explicit consent of the adolescent should be initiated even if there is not yet any immediate life-threatening danger (see chapter 2.1.2 "Compulsory treatment"). This leads to an disorder-determined limitation of autonomy which must be tackled later on with the adolescent, but also with the family. In this age group, it is also important not to overlook the severity of illness in patients with atypical AN, if they do not fulfill the full criteria for AN despite considerable weight loss (premorbid overweight). These patients do not significantly differ from patients with typical AN in terms of severity of physical symptoms and psychiatric comorbidity (Sawyer et al., 2016).

2.1.2. Compulsory treatment

If patients with AN are in physical danger and simultaneously unwilling to undergo medically necessary treatment, it needs to be clarified whether symptoms and disorder sequelae are impairing their cognitive faculty and decision-making abilities to such an extent that interventions against their will in the sense of compulsory treatment are necessary. Therapists' fears that such a step may endanger the therapeutic alliance and consequently the long-term prognosis can complicate and delay the decision to initiate compulsory measures.

Reviews (Clausen & Jones, 2014; Elzakkers et al., 2014) as well as a follow-up approx. 20 years following compulsory inpatient treatment (Ward et al., 2015) indicate that the overall effects of compulsory and non-compulsory treatments are comparable, and the mortality and suicide rates do not significantly differ between the two groups. In the short term, compulsory treatment appears to be helpful (Elzakkers et al., 2014); little is known so far about longer-term effects. Clausen and Jones (Clausen & Jones, 2014) mention the following determinants for compulsory treatments in AN: longer duration of illness, higher psychiatric comorbidity, more previous hospital stays and more frequent self-harm. Compulsory treatment is evidently less a sole reaction to the severity of eating disorder symptoms and more a response to the complexity of an AN patient's situation as a whole.

As compulsory treatment violates protected freedom and physical integrity according to German Basic Law Article 2 section 2, the presence of legal requirements needs to be carefully checked. For adult patients in Germany, the general conditions of compulsory treatment under civil law are regulated under the prerequisites of the § 1896 BGB in the § 1906 BGB and require the institution of guardianship through the guardianship court. Any present patient decrees need to be heeded according to § 1901a BGB. If patients are below the age of consent, the guardians (generally the parents) must apply to the family court for approval of treatment with deprivation of liberty according to § 1631b BGB. If considerable self-endangerment "cannot be otherwise averted", accommodations according to the legal foundations of the accommodation laws of the Federal states constitute an alternative.

Custodianship

The institution of a legal custodianship represents a first step of external control if a patient with anorexia nervosa is not sufficiently able to care for herself. A custodian cannot be appointed against an adult's free will. A custodianship can also be considered if a patient has reached an average BMI during inpatient treatment after starting from a very low BMI, but is still underweight and has been discharged. In the case of a professional custodian, the custodian should be a person who has experience in the area of eating disorders. Due to the particular burden of the affected families and the often complex family dynamics, strong consideration should be given to whether a family member assumes the custodianship. In Germany, upon application of the legal custodian, a compulsory treatment under inpatient conditions can be approved. According to the custodianship law, compulsory treatments are possible not only in psychiatric settings but also in other clinics and settings. Information on the practical procedure is provided by the responsible custodianship court at the local court as well as the public health authority and the social-psychiatric service.

Compulsory hospitalization/closed accommodation

If the eating disorder has reached a life-threatening extent or it must be feared that considerable damage to health has emerged (self-endangerment), a compulsory treatment needs to be considered. The approval of compulsory measures in accordance with § 1906 BGB in the framework of a remedial treatment presupposes that the patient is 1. incapable of consent, 2. previous attempts have been made (and documented) to convince her of the necessity of the medical treatment, 3. the compulsory medical treatment is necessary for the best interests of the patient in order to avert the threat of substantial damage to health, 4. the substantial damage to health cannot be averted by any other measure which is reasonable for the patient, and 5. the anticipated benefit of the compulsory medical treatment considerably outweighs the anticipated adverse effects.

Force feeding/restraint

Force feeding can be necessary if patients in the stage of extreme starvation are impaired to such an extent that they are no longer able to perceive their risk, and at the same time have grave fears of consuming food. If the patient is no longer able to ensure sufficient food intake, and nutrition via a gastric tube cannot be tolerated, the safeguarding of nutrition is generally possible through the use of coercion (e.g. restraint). For patients with a longer-lasting necessity of tube feeding, a PEG can represent an alternative over time.

In some patients, coercive treatments can be necessary despite a higher BMI due to other acute physical complications such as electrolyte imbalances following laxative abuse, cardiac arrhythmia, physical diseases such as diabetes mellitus or also in the case of alcohol or drug abuse and acute suicidal risk.

The patient should be included in the decision on the type of food intake. Restraint should be limited to the absolute minimum necessary degree and should be suspended as early as possible. At the latest when the patient is discharged, she should be capable of assuming responsibility for sufficient nutrition.

In situations in which an inpatient compulsory treatment or nutrition takes place against the patient's will, the interventions should be conducted in a specialized setting, which is also able to ensure intensive internistic supervision and has experience in treating AN.
A compulsory treatment should be conducted with the greatest possible respect for the patient's dignity and under careful consideration of all available alternatives.

Compulsory treatment in children and adolescents

Inpatient admission against the patient's express will is rarely necessary in adolescent patients. Preliminary outpatient discussions are often helpful in convincing guardians/close family members and the adolescents themselves of the necessity of inpatient treatment. If nevertheless required, accommodation associated with deprivation of liberty according to § 1631b BGB must be applied for by the guardian (generally the parents) to the responsible family court of the place of residence ("place of habitual residence"). If, despite immediate danger, the guardians refuse a necessary inpatient treatment, in order to avert child endangerment, there is a possibility for emergency placement according to § 42 SGB VIII through the youth welfare office, which in the case of immediate danger can also be implemented until the end of the following day against the adolescent's will with measures entailing deprivation of liberty. In such cases, however, the youth welfare office must procure clarification from the family court in this time window. When the age of maturity is reached during an inpatient treatment – if it can be assumed that treatment with liberty-depriving measures will be necessary beyond the 18th birthday – a precautionary appointment of a custodian according to § 1908a BGB can ensue, which comes into effect when the patient reaches the age of maturity. A compulsory treatment of children and adolescents with AN should take place in a department for child and adolescent psychiatry/psychosomatic medicine as well as, if necessary, in close cooperation with a pediatric and adolescent medical intensive care unit.

2.2. Treatment approaches and methods

General efficacy of psychotherapeutic methods

After it became widely recognized that psychological causes play a fundamental role in the development of AN, both psychodynamic as well as cognitive-behavioral and family therapy approaches were developed. Over the past few decades, new approaches have also emerged, and the interest in technology-based interventions (including internet-based and mobile interventions) has strongly increased. An overview of treatment for AN is provided, for example, in reviews by Zipfel et al. (Zipfel et al., 2015), Treasure et al. (Treasure et al., 2015) and Herpertz-Dahlmann et al. (Herpertz-Dahlmann et al., 2015). Most treatment approaches nowadays take all areas into consideration: behavioral problems (e.g. lack of mealtime structure, eating rituals, selective food choices) and cognitive distortions of patients, psychodynamic aspects (self-esteem and body-esteem, development of gender identity, dealing with affect, regulation of closeness and distance in relationships, obsessive-perfectionistic personality traits), the physical consequences, as well as family and other important relationships. It can be assumed that beyond the various psychotherapeutic approaches, an approach specific to AN combined with a focus on weight normalization is an essential impacting factor. So far, there is no empirical evidence that female and male sufferers with AN

should receive differential treatment; however, gender-specific themes and needs should be considered in the therapy (Carlat et al., 1997).

Overview: Empirical evidence on psychotherapeutic treatment

A systematic literature search yielded 43 randomized controlled trials (RCTs) on the psychotherapeutic treatment of AN up until February 2017 (see table 4.2). Six further RCTs examined mixed eating disorder samples (Dingemans et al., 2014; Salbach-Andrae et al., 2009; Simon et al., 2013; Stein et al., 2013; Steinglass et al., 2014a; Vocks et al., 2011). Four studies investigated relapse prevention or an intervention following inpatient treatment (Fichter et al., 2012; Godart et al., 2012; Parling et al., 2016; Pike et al., 2003). Thirteen studies referred to inpatient or day-clinic treatment settings (Brockmeyer et al., 2014; Dalle et al., 2013a; Eckert et al., 1979; Geist et al., 2000; Goldfarb et al., 1987; Herpertz-Dahlmann et al., 2014; Hibbs et al., 2015; Madden et al., 2015b; Pillay & Crisp, 1981; Weizman et al., 1985; Whitney et al., 2012) or included a treatment arm with inpatient intervention (Crisp et al., 1991; Gowers et al., 2007). Two Cochrane reviews summarize the evidence for outpatient psychotherapy (Hay et al., 2015) and for family-based interventions ((Fisher et al., 2010); up to January 2008).

Due to the in part very low methodological quality, particularly of the older studies, we conducted our own meta-analysis in which studies with very low quality were excluded (Zeeck et al., 2018). This did not reveal any approach to be superior to others (outcome criterion: weight gain). For children and adolescents, studies on family-based approaches were predominant, for adults, approaches in the individual setting. Thirteen RCTs were entered into the analyses (studies in adults: 622 participants, studies in adolescents: 625 participants). To compare treatment outcomes in different treatment settings and age groups, naturalistic studies were also included (38 studies, 1164 participants). Weight gains were significantly higher in the studies of children and adolescents than in those which primarily included adult patients. With regard to treatment settings, significantly higher weight gains can be expected in the inpatient realm than in outpatient treatment (see below). As no previous studies have compared specific therapeutic approaches with untreated control groups, however, the ability to evaluate the efficacy of specific procedures in AN is generally limited. Moreover, the study results could only be evaluated with regard to weight (BMI), as further parameters (eating disorder pathology, depressiveness, quality of life etc.) were at times not measured or were measured using different instruments.

Overall, the evidence base has grown considerably in recent years, and studies with a higher methodological quality are now available (for the original version of the guidelines, a literature search yielded 23 RCTs up to mid-2008). For children and adolescents with AN, increasingly clearer evidence for the efficacy of family-based approaches can be found (larger number of RCTs which show positive effects of treatment over time), even though a comparison with an individual therapeutic approach in the meta-analysis based on the few studies that could be included did not yield a significant difference (Zeeck et al., 2018).

With regard to adults, four manualized treatment approaches can be mentioned, for which moderate evidence is available and which have shown clear improvements in the relevant areas (weight, eating disorder pathology) (at least one RCT with good methodological quality and a sufficient number of cases: enhanced cognitive behavior therapy (CBT-E), focal

psychodynamic psychotherapy (FPT), Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA) and Specialist Supportive Clinical Management (SSCM) (see also (Zipfel et al., 2015)). So far, no approach has proven to be superior to the others (Hay et al., 2015; Zeeck et al., 2018; Zipfel et al., 2015).

Generally, patients with greater disorder severity (those with higher levels of underweight) are treated in more intensive care settings (day clinic, inpatient): While the starting weights in outpatient psychotherapy studies lay at an average BMI between 16 kg/m² and 17 kg/m², inpatients began with a BMI < 15 kg/m² (Zeeck et al., 2018).

In the outpatient framework. average weight gains of 0.04 BMI points (or 0.08 in adolescents) per week can be expected (this corresponds to 105 g/week at a height of 1.68 m or 195 g/week in adolescents with a height of 158cm). In inpatient treatments, a weekly weight gain of 0.19 BMI points (corresponding to 537g/week) in adults and of 0.25 (615g/week) in adolescents is shown. Effect sizes and weight gains are overall higher in the treatment of children and adolescents (Zeeck et al., 2018).

2.2.1. Approaches in line with the German directives for psychotherapy

2.2.1.1. Cognitive behavioral therapy

Six studies were found which examined the efficacy of outpatient cognitive (CT, COT)[5], behavioral (BT, EBT) or cognitive-behavioral (CBT) interventions (total number of cases N=95; (Bachar et al., 1999; Ball & Mitchell, 2004; Channon et al., 1989; McIntosh et al., 2005; Serfaty et al., 1999; Treasure et al., 1995). A study by Pike et al. (2003) examined cognitive-behavioral interventions as relapse prevention following inpatient treatment. Generally, a total of 20 outpatient sessions was offered. Overall, it is difficult to estimate the effects due to a lack of untreated control groups and insufficient follow-up periods as well as small case numbers. Some studies did not provide important information about treatment outcome, or also included subsyndromal cases. Moreover, the procedures are not consistent across the examined treatment arms. In a group of patients with severe and enduring AN, Touyz and colleagues (2013) compared CBT-AN (case number N=31) with Specialist Supportive Clinical Management (SSCM, see 2.2.4). Although these two therapy approaches modified for this subgroup were similarly successful at the end of treatment, CBT-AN was superior 6 and 12 months post-treatment with regard to eating disorder-specific symptoms and social integration.

CBT-E

According to Fairburn (Fairburn, 2012), CBT-E (Cognitive Behavior Therapy - Enhanced) is a development of cognitive behavioral therapy which is based on a "transdiagnostic" model of eating disorders. In a multicenter randomized-controlled psychotherapy trial in adult patients with AN (ANTOP study, (Zipfel et al., 2014)), CBT-E was found to be effective (case number

[5] CT=cognitive therapy: COT = cognitive orientation treatment; BT=behavioral therapy: EBT = educational behavioral treatment.

N=80); regarding the achieved weight gain, however, no significant difference was found compared to a focal psychodynamic psychotherapy (FPT, see 2.2.2) and an optimized[6] treatment as usual (TAU-O). Nevertheless, compared to TAU-O, CBT-E led to a more rapid weight gain up to the end of treatment and a greater improvement in eating disorder-specific psychopathology.
Due to the methodological quality of the study and the comparatively high case number, it can be assumed that CBT-E is highly likely to be effective in adult patients.

For adolescence, there are not yet any randomized controlled trials for CBT-E. In addition to the components employed for adult patients, CBT-E for adolescents also includes the caregivers. Two open studies with 46 outpatients and 27 inpatients, respectively, showed substantial improvements with respect to weight gain and eating disorder psychopathology (Dalle Grave et al., 2013a; Dalle Grave et al., 2014).

2.2.1.2. Psychodynamic therapy

There are three older randomized controlled trials on psychodynamic therapy approaches, with small case numbers (total cases N = 44; (Bachar et al., 1999; Dare et al., 2001; Robin et al., 1999). These approaches focused less on concrete symptoms and more on their importance with respect to the life history, personal development and important relationships (including the therapist). The three trials examined different samples: The patients in the study by Robin and colleagues (1999) were children and adolescents without an average illness duration under one year, while Dare et al. (2001) examined adults with an average illness duration of over six years. In a study with a larger number of cases (N=60) by Lock et al. (2010), an approach following the manual of Robin et al. (“adolescent-focused therapy”, AFT) in the individual setting was compared with family-based treatment (age of patients: m = 14.4). No difference emerged with regard to the remission rates at the end of the therapy, but the family-based approach was found to be superior at follow-up (6 and 12 months). Patients who were treated with AFT achieved a higher weight at the end of therapy, although this difference was no longer present at follow-up. A further study by Crisp et al. (1991) compared a psychodynamic approach (individual therapy + inclusion of family, N=20), which integrated cognitive-behavioral elements and nutritional counseling (Gowers et al. 1994), with inpatient therapy, outpatient group therapy and a group which received in-depth diagnostics (“one-off”). All three treatment regimes proved to be effective after one year, with significantly higher weight gains than in the “one-off” group. Fundamentally, the studies indicate that psychodynamic therapy approaches are effective.

Focal Psychodynamic Psychotherapy (FPT)
A more recent manualized psychodynamic therapy approach conceived for anorexia patients with moderate underweight (BMI > 15 kg/m^2) (FPT; Friedrich et al. 2014), which comprises 40 outpatient sessions, was found to be effective regarding weight gain and in terms of a

[6] TAU-O encompassed an intensive diagnostic clarification at the eating disorders center, motivation and support in the search for outpatient psychotherapy, regular GP monitoring and 4 intensive check-ups and follow-up assessments at the center.

combined outcome measure (weight and eating disorder-specific psychopathology) at 1-year follow-up (case number N=80; (Zipfel et al., 2014)). Although no significant difference in weight course emerged between the three investigated therapy arms (FPT, CBT-E, TAU-O), the FPT arm was superior to an optimized treatment as usual (TAU-O) with respect to remission rates after one year.
Due to the methodological quality of the study and the comparatively large sample size, FPT can be assumed to be highly likely to be effective.

Psychoanalysis
There is no empirical evidence on the efficacy of classical psychoanalytical treatment of AN.

2.2.2. Further (evidence-based) psychotherapeutic approaches

2.2.2.1. Family-based approaches

The largest number of available studies pertain to family-based therapeutic interventions (case number up to February 2017, total N=796). Almost all studies on family-based therapy were conducted in samples of children and adolescents. The majority were oriented towards the concept of the Maudsley Hospital in London and actively addressed dealing with weight and eating within the families as well as the processes of autonomy typical for adolescence. The only study to include adults (age > 18 years) is the study by Dare et al. (2001).
Family-based interventions were examined in comparison with indvidual therapy approaches (Ball & Mitchell, 2004; Dare et al., 2001; Lock et al., 2010; Robin et al., 1994; Russell et al., 1987), or different approaches were compared with one another: e.g. family discussions with the whole family vs. separate discussions with the patient and the rest of the family (Eisler et al., 2000; Le Grange et al., 2016; Le Grange & Eisler, 1992). The studies by Russell et al. (1987) as well as Lock et al. (2010) provide evidence to suggest that in children and adolescents, family-based approaches are more successful than an individual therapy approach. The other studies showed no differences. In the study by Lock et al. (2010), an RCT with 121 adolescents, family-based therapy was compared with individual therapy ("adolescent-focused therapy", AFT). After 6 and 12 months, significantly more patients in the FBT group were in remission (defined by a normal weight and scores within one standard deviation in the Eating Disorder Examination procedure) compared to the AFT group (Lock et al., 2010). At 4-year follow up, the number of remissions had substantially risen in the AFT group, meaning that a significant difference was no longer present (Le Grange et al., 2014). However, it was only possible to examine 65% of the original sample after 4 years. In the study by Russell et al. (Eisler et al., 1997; Russell et al., 1987), family-based therapy proved to be more beneficial in patients with an illness onset ≤ 18 years of age, while patients with a later age of onset were more likely to benefit from an individual therapy approach.

The studies by Eisler et al. (2000) and le Grange et al. (1992) showed, on average, no difference between an approach in which parents and children/adolescents were seen separately compared

to in joint sessions. However, a separated approach proved to be more beneficial in the subgroup showing a higher extent of maternal criticism (Eisler et al., 2007). A further RCT study which compared parent-focused therapy (in which parents and child were treated separately) to family-based therapy (in which parents and child were treated together) did not reveal any discrepant therapy effects 6 and 12 months post-treatment (Le Grange et al., 2016). The patient herself was monitored by a nurse, while the parents met with a therapist.

Lock et al. (2005) compared different doses of family therapy interventions (10 vs. 20 sessions), and found no significant differences in the outcome. However, there were indications that patients from nonintact families and those with severe obsessive-compulsive features benefit more from longer-term treatment.

Caregivers of patients who had not achieved sufficient weight gain after the first sessions of family-based therapy received additional intensive coaching in a further controlled study (albeit with unbalanced randomization!). The patients with additional parental coaching achieved a similarly high recovery rate in this study to patients who had responded to the family-based therapy early on (Lock et al., 2015)

The majority of the US-American studies were conducted as outpatient therapy studies. In this respect, it must be noted that a considerable proportion of the patients had already been treated as inpatients before or during the family-based treatment. A not inconsiderable proportion additionally received medications; in part, the randomization was unbalanced (Lock, 2015). Moreover, the average BMI at study start in the American patients was higher than that in European studies.

The group led by Eisler (Eisler et al., 2016) conducted the first randomized trial comparing family-based therapy (FBT: with one single family) with multifamily therapy (MFT). At the end of treatment, the MFT outperformed the FBT with respect to recovery rate (Morgan & Russell criteria), although all patients had previously received family therapy, meaning that the results need to be interpreted with caution. At 18-month follow-up, there was no longer a significant difference between the two treatments.

An investigation (RCT) of systemic family therapy and FBT yielded no significant differences with regard to remission rates. However, FBT was linked to a quicker weight gain and lower costs (Agras et al., 2014). Patients who suffered from obsessive-compulsive symptoms benefited more from systemic therapy. In a French study of 60 patients (Godart et al., 2012), which compared systemically oriented therapy components in post-hospitalization treatment with treatment as usual (TAU) revealed that the post-hospitalization systemic therapy was superior to TAU.

Overall, family-based approaches can be assumed to be highly likely to be effective in children and adolescents. The vast majority of studies followed the Maudsley approach.

2.2.2.2. “Specialist Supportive Clinical Management” (SSCM)

SSCM combines supportive therapy with unspecific, but in-depth clinical management by an eating disorder specialist. Compared to CBT and IPT, SCCM focuses even more strongly on psychoeducation, eating behavior and weight (McIntosh et al., 2016). In one study ((McIntosh et al., 2005); N=16), SSCM proved to be superior to two specific psychotherapy approaches (CBT and interpersonal therapy, IPT), although this could not be confirmed in a long-term

follow-up (Carter et al., 2011). Another study (Touyz et al., 2013) found that patients with severe and enduring AN were able to benefit from SSCM (N=32). In a comparison of SSCM and a new outpatient treatment approach specifically conceived for AN, the Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA, see 2.2.5), both groups ((Schmidt et al., 2012); case number for SSCM N = 37) showed a similarly good progression. This was confirmed in a larger sample in the so-called MOSAIC trial (Schmidt et al., 2015, 2016).
SSCM can be considered as highly likely to be effective.

2.2.2.3. Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA)

MANTRA is a new, anorexia-specific therapeutic approach which was developed by the work group of U. Schmidt and colleagues at the Maudsley Hospital in London. It is an empirically based, cognitive-interpersonal approach. According to MANTRA, the following 4 factors, linked to underlying obsessive-compulsive (or avoidant) personality traits, are of central importance in the maintenance of AN: 1. a rigid, detail-focused style of thinking characterized by a fear of making mistakes, 2. problems in the socio-emotional area, 3. positive beliefs about the utility of anorexia, and 4. unfavorable reactions of friends and family. A first RCT ((Schmidt et al., 2012), case number for MANTRA N=34) found no significant differences between MANTRA and SSCM (see 2.2.4) in terms of outcomes, but found that MANTRA showed certain weaknesses (more frequent necessity for additional inpatient or day-clinic treatment). However, in the subsequent larger MOSAIC trial ((Schmidt et al., 2015, 2016); N = 72), MANTRA was preferred by patients over SSCM. Although no significant difference emerged between the two groups with regard to weight gain, patients with more severe symptomatology were able to achieve higher weight gain in the MANTRA group than in the SSCM group.
MANTRA can be considered as highly likely to be effective.

2.2.3. Other psychotherapeutic approaches

2.2.3.1. Interpersonal therapy (IPT)

Only one study in the outpatient setting was found for interventions with interpersonal therapy (total cases N = 21; (McIntosh et al., 2005)). As the study also included subsyndromal cases, did not include a follow-up, and the baseline data were not provided separately for the treatment arms, it is not possible to evaluate the effects. The study by McIntosh hinted at a superiority of the specialized therapy approaches (IPT[7], CBT) compared to the control group (SSCM), but this was only significant in the completer analysis.
So far, there is insufficient evidence for IPT.

[7] IPT = Interpersonal Therapy

2.2.3.2. Client-centered psychotherapy

No empirical evidence is available.

2.2.3.3. Integrative approaches

There are two studies (total number of cases: N = 36; (Dare et al., 2001; Treasure et al., 1995)) on an integrative psychotherapeutic approach ("cognitive-analytic therapy", CAT), which includes both cognitive-behavioral elements (addressing the function of behavior and dysfunctional thought patterns) and psychodynamic elements (tackling interpersonal difficulties and sense of self, work on the transference relationship (Ryle et al., 1990). Both studies examined adult patients with AN. In the investigation by Dare et al. (2001), CAT and family therapy were superior to a "routine treatment". Treasure et al. (1995) showed that CAT performed better than an educational-behavioral approach according to the patients' subjective judgment; however, no significant difference emerged in the overall treatment outcome. In sum, there are initial indications for the effectiveness of CAT.

2.2.3.4. Body-oriented methods

Only one randomized controlled trial can be found which tested the efficacy of body-oriented methods. The study was carried out in children and adolescents with an average illness duration of less than one year (case number: N = 13; (Wallin et al., 2000)). All patients received family therapy and the target group additionally received either "body awareness therapy" or not. No additional effect of the body therapy was apparent. However, due to methodological limitations, no conclusions can be drawn from the findings.

2.2.3.5. Combination of distinct psychotherapeutic approaches

Four studies explicitly chose a combination of approaches in order to compare them with one individual approach (total number of cases: N = 110; (Crisp et al., 1991; Gowers et al., 2007; Hall & Crisp, 1987; Wallin et al., 2000)). Individual or group therapy was combined with family therapy and dietary counseling, or family therapy was combined with body awareness therapy. The studies did not yield any clear indications for the superiority of a combined approach. However, it should be noted as a limitation that almost all studies on the treatment of AN employed additional elements apart from the approach being tested (short discussions, consultations with the family practitioner, dietary counseling, counseling of family members, temporary hospitalizations etc.). The "pure" treatment with one approach rather constitutes the exception, not only in clinical practice but also in the review of randomized controlled trials.

2.2.3.6. Technology-based approaches

According to the review by Schlegl and colleagues (2015), internet-based interventions can be applied for relapse prevention in AN. However, efficacy has only been demonstrated in one RCT so far (Fichter et al., 2012, 2013). The so-called "VIA" program encompassed nine modules plus email contact with a therapist over a period of nine months. In a pilot study (n=16), Giel et al. (2015) examined a post-inpatient relapse prevention program (RESTART) which is based on the Maudsley Model of Anorexia Nervosa Treatment (see 4.2.2.2.3.) and includes 10 manualized video conference sessions. The program was easy to implement and was very well accepted by patients. Several case studies (Yager, 2001, 2003) suggest that internet-based interventions (e.g. email) can be an effective therapeutic approach in the outpatient treatment of AN.

2.2.4. Other treatment approaches and methods

2.2.4.1. Cognitive remediation therapy (CRT)

A multitude of studies and several meta-analyses have demonstrated that AN is associated with a reduced cognitive flexibility ("set-shifting") as well as a strong detail-oriented information processing (Lang et al. 2014; Wu et al. 2014). CRT is a treatment module with which these cognitive functions can be improved in a targeted manner through exercises (quickly switching between various rules and demands; increasing the level of abstraction of complex information), behavior experiments (also in the form of homework) and meta-cognitive elements (reflection on one's own thinking styles) (Tchanturia et al. 2014; Danner et al. 2015; Lindvall Dahlgren & Rø, 2014). To date, four small to medium-sized randomized controlled intervention trials and one controlled trial on CRT in AN have been published. These vary substantially regarding the examined samples (AN vs. mixed eating disorder sample, inpatients vs. outpatients, etc.), the applied dosage (8-30 sessions), the comparison groups (CBT, TAU, food exposure, unspecific cognitive training) and the primary endpoints (neurocognitive parameters, eating disorder symptoms, food intake, dropout rate). Two proof-of-concept studies revealed a short-term improvement regarding neurocognitive parameters (Brockmeyer et al. 2014; Lock et al. 2013). In the largest study to date, which compared an adjuvant procedure to standard treatment with standard treatment alone, patients with eating disorders (not only AN) showed stronger improvements in quality of life at the end of treatment and in eating disorder symptoms at 6-month follow-up (Dingemans et al., 2014). Although overall, some of these results appear to be promising, the clinical utility remains to be demonstrated in larger randomized controlled trials.

2.2.4.2. Exposure-based approaches

Given that food- and body image-associated fears are among the core symptoms of AN and that abnormal anxiety conditioning processes are attributed with an important role in the etiopathogenesis of the disorder (Guarda et al., 2015), exposure-based interventions represent a promising but so far under-researched approach to the treatment of AN (Koskina et al., 2013). Long established in the treatment of bulimic eating disorders, food exposure in AN has only been examined in two small randomized controlled trials to date (Steinglass et al., 2014; Levinson et al., 2015). These provided first hints that an exposure treatment leads to the consumption of a larger amount of food during a test meal and to a greater reduction in associated anxiety. Moreover, an augmentation with D-Cycloserine may potentially strengthen the effects of food exposure (D-Cycloserine is an N-methyl-D-aspartate receptor agonist which facilitates extinction learning) (Levinson et al., 2015). Body image-related anxieties represent a further target for exposure-based approaches in AN (Koskina et al., 2013). To date, however, there is only preliminary evidence from experimental studies that in-vivo exposure (mirror- or video-based), or else exposure approaches based on virtual reality scenarios, are associated with a short-term improvement in mood, self-esteem and body image-related symptoms, and the effects in part appear to be unspecific (Ferrer-Garcia & Gutierrez-Maldonado, 2012; Gutiérrez-Maldonado et al., 2010; Keizer et al., 2016). Moreover, processes of attentional control, re-evaluation and feedback-based correction of misperceptions probably play a greater role in body image exposure than habituation and extinction learning (Koskina et al., 2013; Luethcke et al., 2011; Alleva et al., 2015).

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2.2.4.3. Physical activity-related and exercise therapy interventions

With regard to physical activity- and exercise-related interventions, the following approaches should be distinguished: physiotherapeutic interventions with the aim of strengthening the muscles, improving mobility and fostering bone structure, programs which allow an incremental increase in physical activities adapted to the physical situation, as well as exercise therapy programs in the proper sense (Cook et al., 2016; Zeeck & Schlegel, 2013). The latter include, besides guided physical activity, psychoeducation and targeted work on changing problematic exercise behavior (promoting positive, healthy body experience and reflection on dysfunctional attitudes to exercise; quasi-experimental studies: (Calogero & Pedrotty, 2004; Schlegel et al., 2012; Schlegel et al., 2015)). So far, the evidence is very sparse, but initial findings suggest positive effects (reduction of obsessive-compulsive-excessive exercise, favorable influence on eating disorder pathology as well as compliance; reviews (Cook et al., 2016; Hausenblas et al., 2008; Zunker et al., 2011)). Overall, there are no indications that supervised exercise programs impair weight gain.

2.2.4.4. Self-help

One Cochrane review has been conducted on self-help (Perkins et al., 2006), although this considers all eating disorders and does not include a single study on AN. In summary, the authors cautiously formulate that "*Self-help may have some utility as a first step in treatment*". In an RCT (n=354), a fully automated internet-based self-help program ("featback") using self-monitoring and feedback in sufferers with self-reported eating disorder symptoms led to an improvement in eating disorder-related and comorbid psychopathology, but not with regard to anorexic symptoms (Aardoom et al., 2016). The authors conclude that the program is possibly more suitable for sufferers with bulimic symptoms.

Summary: Evidence on treatment procedures and methods for AN

- Psychotherapy is the treatment procedure of first choice in AN (EL 1b; (Zeeck et al., 2018; Zipfel et al., 2015))
- There is moderate evidence that the following specific psychotherapeutic approaches are effective: in adults, enhanced cognitive-behavioral therapy (CBT-E), focal psychodynamic therapy (FPT), Maudsley Model of Anorexia Nervosa Treatment (MANTRA) as well as Specialist Supportive Clinical Management (SSCM); in children and adolescents, family-based therapy following the Maudsley approach (EL1b; (Zeeck et al., 2018)).
- There is no sufficient evidence that one of these approaches is superior to another (EL 1b; (Zeeck et al., 2018)).
- There is no sufficient evidence that for children and adolescents, one particular approach within family therapy (joint sessions with the patient or separate sessions with patient and parents) is more effective than the other (EL 1b; (Fisher et al., 2010; Zeeck et al., 2018)); however, there are indications that in the case of a strong degree of critical parental comments, it may be more beneficial to see parents and patient separately (EL 1b; (Eisler et al., 2007)).
- There is limited evidence that specialist services lead to a reduction in inpatient admissions and to a cost reduction (EL 3; (House et al., 2012)).
- There is limited evidence that cognitive remediation therapy as an adjuvant procedure improves eating disorder symptoms as well as quality of life (EL 1b; (Brockmeyer et al., 2014; Lock et al., 2013)).
- A low motivation to change the eating disorder is associated with lower treatment success and a higher risk of treatment dropout (EL 1a; see, among others, systematic review by Vall & Wade, 2015; Carter et al. 2012; McHugh 2007)

2.2.5. Nutrition therapy

Weight gain

The restoration of a healthy body weight constitutes one of the most important therapeutic objectives in AN (cf. chapter 2.1). Both in adolescent and adult patients with AN, a higher weight gain during inpatient treatment or a higher weight at discharge represents a favorable prognostic factor for the short-term and long-term course of illness (Baran et al., 2015). However, there is not yet any uniform, evidence-based approach with respect to nutrition management (Marzola et al., 2013). Guidelines pertaining to the refeeding of anorexic patients are differently interpreted and applied in different institutions and countries (see table 4.3) (Herpertz-Dahlmann et al., 2015).

The weekly weight gains strived for in Germany are listed for different target groups and treatment settings in chapter 2.2 ("Empirical evidence"). With regard to the desired rate of weight gain, the approaches in different countries currently differ substantially from one another: The moderate weakly increase of 500g/week which is practiced in Germany is in contrast to the Anglo-Saxon countries, which recommend an increase of 1-2kg per week in the inpatient setting.

Target weight

The target weight represents a healthy weight for an individual, which should be strived for and maintained in the longer term.

Adolescents

As a basic principle, it can be stated that a healthy body weight has been achieved when menses resumes (American Psychiatric Association, 2006). However, in many patients, amenorrhea endures at the end of treatment despite weight restoration, and younger patients as well as those with an illness onset before the menarche show a higher risk of longer-term amenorrhea (Dempfle et al., 2013). For this reason, with the aid of scientific foundations, an individual target weight should be set for each patient by the therapist (Herpertz-Dahlmann et al., 2015). In various studies, the achievement of the 15th-25th age-adjusted BMI percentile was associated with resumption of menses (Dempfle et al., 2013; Faust et al., 2013; Golden et al., 2008; Herpertz-Dahlmann et al., 2014). Instead of applying a strictly defined target weight, some clinicians prefer to define a weight range which lies close to the 25th BMI percentile (Herpertz-Dahlmann et al., 2015) in order to permit physiological weight fluctuations and take the focus away from a particular weight number.

Adults

A healthy weight in adults should lie in a range above the minimum weight of 18.5 kg/m^2 defined by the WHO. As such, a normal weight stretches across a broad range (BMI 18.5 – 25 kg/m^2). The resumption of menses can be seen as a crude measure of physical recovery in this regard. If, in adults, the eating disorder began after reaching physical maturity, the premorbid weight is a suitable indicator. A healthy weight is present if the body weight remains stable without restriction and compensatory behavior.

Start of refeeding, and refeeding syndrome

The early phase of refeeding following a sustained period of starvation is seen as critical, as health problems can arise which are subsumed under the term "refeeding phenomena". "Refeeding syndrome" represents a serious metabolic dysregulation which can be fatal (Mehanna et al., 2008). Signs of this syndrome, which predominantly occurs in the first weeks of treatment, are shifts in fluids and electrolytes which can occur as a consequence of the endocrine and metabolic changes at the beginning of refeeding (Mehanna et al., 2008). A central hallmark of the syndrome is hypophosphatemia, although further electrolytes, glucose metabolism and thiamine supply also play a role (Crook et al., 2001). The drastic malnutrition is accompanied by depleted intracellular phosphate stores. Upon refeeding, and the associated shift from catabolic fat burning to anabolic carbohydrate metabolism, phosphate is increasingly used. This causes a critical decline of the intracellular concentration of ATP and consequently the energy supply to the cells. The diverse resulting clinical consequences range from severe organ dysfunctions, through rhabdomyolysis, to seizures, delirium, coma and death. In the literature, several cases of refeeding syndrome in AN patients are described, for example by Norris et al. (Norris et al., 2012). However, refeeding syndrome is still lacking a precise definition. Due to this lack of definition, clear information on the prevalence of refeeding syndrome in the refeeding of patients with AN is scarce (Mehanna et al., 2008). The incidence of hypophosphatemia in adolescent patients during refeeding was reported as lying at 14% in adolescents and 28% in adults (O'Connor & Nicholls, 2013; Ornstein et al., 2003). Awareness of the risk of undesired refeeding phenomena, the appropriate steering of energy intake, as well as medical monitoring of electrolytes and their adequate supplementation during the early stage of refeeding are essential in order to avoid complications.

Initial energy intake

With respect to an appropriate initial energy intake, there is currently no general consensus, which leads to inconsistent approaches. This is evidenced by a considerable range of initial energy intake currently employed, from 125 to 3264 kcal/d (O'Connor & Nicholls, 2013; Pettersson et al., 2016; Slogan et al., 1962). Since awareness of the above-described refeeding syndrome, for a long time, a low initial energy intake was recommended for patients with AN ("start low, go slow"). However, this approach is coming under increasing criticism. A low initial energy intake leads, to begin with, to additional weight loss and prolongs the duration of the hospital stay (Garber et al., 2012, 2013). A scientific basis for the very restrictive feeding guidelines for the initial calorie intake is lacking, and presumably the starting BMI and a lower number of leukocytes are better predictors of complications than the level of initial calorie intake (O'Connor & Nicholls, 2013). An RCT comprising 36 adolescent AN patients demonstrated that a higher initial energy intake was associated with a higher weight gain, but did not lead to a higher rate of complications (O'Connor et al., 2016). Similarly, in a cohort study of 800 cases, Redgrave et al. (2015) concluded that it is not the speed of weight gain, but rather the level of cachexia that predicts refeeding phenomena. Study protocols in which a high initial calorie intake was compared with low-calorie feeding (e.g. 1764 vs. 1093 kcal/d; (Garber et al., 2013)), or with a high energy intake in the first week of 3264+/- 196kcal followed by a gradual reduction to 2622+/-331kcal (Pettersson et al., 2016) showed no difference regarding the occurrence of refeeding phenomena, but that better weight progress was achieved in the

high-calorie variants. Moreover, in a review by Garber et al. (2016), results of a systematic literature review on the different refeeding strategies at the start of therapy were evaluated. Among other things, the authors derived the following recommendations:

1) For patients with mild to moderate malnourishment[8] a low initial energy intake is too conservative.
2) Higher initial energy doses are not associated with an increased risk of refeeding syndrome provided that electrolytes, fluid balance and cardiovascular parameters are closely monitored and controlled.

Nevertheless, it should be noted that in many of the cited works, the recommendations are based largely on studies from the Anglo-Saxon area, where hospital stays, linked to a quicker weight gain, are customary. It is unclear whether the findings from other countries can be transferred to Germany, and which of the approaches is linked to a better outcome in the longer term.

Fluid balance
In this regard, there are two sources of errors which need to considered particularly in the beginning phase in order to critically evaluate the weight development. Many patients have hypovolemia at the start of treatment (Caregaro et al., 2005; Comerci, 1990). Recurrent vomiting, abuse of laxatives and diuretics, as well as a reduced urge to drink, lead to dehydration, which can be clinically detected through lower serum sodium concentrations and a relatively high hematocrit. Appropriate water intake consequently leads, due to the fluid influx into the cells, to weight gain, without a corresponding increase in the fixed body mass per se. In addition, there is often a dysregulation in the renin-angiotensin-aldosterone mechanism (Ehrlich et al., 2006; Tey et al., 2005), which leads to a strong tendency towards hyper-hydration (see also chapter 8). Weight gains particularly at the beginning of treatment often do not reflect a true increase in body mass, i.e. the intracellular body mass, but are rather caused by a disproportionate increase of the extracellular volume. Linked to this is a strong tendency towards edema formation, occasionally also the development of ascites and pericardial effusions. Weight gains especially in severely underweight patients should therefore be accompanied by regular clinical testing of the edema tendency, and better still by measuring the body composition. For everyday clinical practice, multi-frequency bioelectrical impedance analysis is best suited to measuring the extracellular volume (Mika et al., 2004).

2.2.6. Nutritional management in patients with severe malnutrition

Refeeding of patients with severe AN is complex, and requires a specialized, medical management by a trained team. When determining the initial calorie intake, it should be considered that especially in severely underweight patients, a sufficiently high energy intake to remedy the risky sequelae of cachexia (bone marrow depression, hepatopathy, renal dysfunctions, cardiovascular function) is necessary. As yet, there is no uniform procedure for

[8] In this respect, not only the current BMI, but also the extent of malnutrition as well as the extent and speed of weight loss in the last months should be considered.

patients with an extremely low BMI. There is a current need for research in order to identify the biochemical, behavioral and anthropometric markers for a safe and appropriate procedure in the refeeding of severely malnourished patients.

2.2.6.1. Delivery form and food composition

Delivery form

Liquid food

As far as possible, the refeeding should be delivered orally and with a diverse, mixed range of foods. However, problems frequently arise in this regard, which due to the often threatening physical constitution of the patients necessitate special measures to ensure a sufficient food intake. One treatment option which still remains close to the desired oral feeding is the use of liquid food (Imbierowicz et al., 2002). Often, liquid food is given following oral food intake in order to balance the difference between expected and achieved energy amount (Garber et al., 2016). The nutritional components fats, proteins and carbohydrates should be provided in a balanced form. The liquid food should enable a complete provision of electrolytes, micronutrients and vitamins. The different energy density of the products needs to be taken into account. For this reason, the food needs to be prescribed in a calorie-controlled rather than a volume-controlled manner.

However, oral nutrition places high demands on digestion, which can be impaired due to the underweight. Liquid food offers the possibility to supply larger amounts of calories in a concentrated form. At the same time, the accruing volume of food is comparatively low. Moreover, the largely broken down nutritional components in liquid food are easy to digest. On the other hand, this type of feeding can maintain the avoidance of normal food (Hart et al., 2013).

Tube feeding

Nasogastric tubes are a further option with which to ensure sufficient nutrition, also when the patient is not willing or able to feed herself orally to a sufficient extent. The use of nasogastric (NG) tubes is an invasive measure which requires the patient's consent. Possible complications are incorrect positioning with aspiration, irritation in the nose and throat area and gastrointestinal intolerance reactions when the tube nutrition is applied too quickly. When placed for a longer period of time, mucosal lesions can arise in the nose or in the posterior pharyngeal wall.

The review by Garber et al. (2016) examined the utility of nasogastric tube feeding. Currently, it is unclear whether a combination of oral food intake and NG tube is superior to completely oral food intake. This uncertainty is predominantly due to methodological weaknesses of the studies conducted so far, which were not designed to determine an independent effect of the type of nutritional provision. While the NG tube is suitable for increasing energy intake, studies with and without NG tube showed a comparable weight gain. Presumably, the patient's acceptance of the tube plays a crucial role. A controlled trial by Rigaud (2007) tested normal

nutrition against tube nutrition over two months. After one year, the relapse rate was comparable in the two groups and the tube was well accepted.

If forced feeding (see chapter 4.2.1.2) becomes necessary, nasogastric tubes are poorly tolerated by some patients. In such cases, a percutaneous endoscopic gastrostomy (PEG) tube offers an alternative. Although it is clearly more invasive than the nasogastric tube, PEG is seen as entailing few complications. For underweight patients with a poor general physical condition, as is the case with force-fed AN patients, however, complication rates are likely to be higher. This should be carefully considered when weighing up the risks of forced feeding. Although the PEG tube belongs to the range of treatment alternatives in the case of severe AN, there are only a small number of case reports on its successful application (Malfi et al., 2006; Neiderman et al., 2000).

2.2.6.2. Medical monitoring of critical electrolytes and vitamins in the refeeding phase

Phosphate

In renally healthy patients, phosphate can be provided during refeeding, for preventive purposes. There are many reports of critical situations during the refeeding of AN patients (Birmingham et al., 1996; Cariem et al., 1994; De Cock et al., 2006; Fisher et al., 2000; Haglin, 2001; Huang et al., 2001; Ornstein et al., 2003; Sato et al., 2004; Sheridan & Collins, 1983; Van Dissel et al., 1992; Wada et al., 1992; Winston & Wells, 2002). Ornstein et al. (2003) followed 69 adolescent patients with moderate to severe AN during inpatient treatment. 27% had hypophosphatemia according to laboratory tests, of whom 6% had more severe hypophosphatemia (serum phosphate < 2.5 mg/dl). All patients with more severe hypophosphatemia were also severely underweight. After one week of normalized nutrition, phosphate levels were back in the normal range in most patients. The symptoms of hypophosphatemia can develop very quickly and then rapidly become life-threatening, with myolysis, heart failure, arrhythmia and impairment of consciousness. For this reason, hypophosphatemia should be detected before symptoms emerge. It should be considered that the determination of serum phosphate does not provide reliable information about the available phosphate concentration in the cells. Phosphate is an electrolyte, which shows an approximately 14-fold higher concentration in the cells than in serum.

Potassium and chloride

Frequent vomiting, but also abuse of diuretics and laxatives, leads to considerable losses of potassium and chloride. Hypokalemia can lead to life-threatening cardiac arrhythmia. In this respect, the increases in potassium stress between higher intracellular and lower extracellular concentration of this electrolyte is decisive for the associated cardiac risk. The chronic potassium depletion in the bulimic form of AN and in bulimia nervosa frequently also lead to a decrease in the intracellular potassium concentration, such that even in the case of severe hypokalemia in serum, life-threatening arrhythmia can remain absent. The potassium stress in the case of known serum potassium can best be determined with electrocardiogram recording. The visible signs of hypokalemia in the ECG correlate with the concentration difference (extra-

/intracellular) (Bonne et al., 1993; Koh et al., 1989). Persisting hypokalemia is generally a sign of continued vomiting and should be discussed with the patient. Hypokalemia requires a balancing out until normokalemia is reached, and besides potassium, the chloride deficiency should also be balanced out. For this purpose, potassium chloride is more suitable than potassium carbonate.

Sodium

Depleted sodium levels are mostly a sign of polydipsia, which can be habitual but can also be consciously employed to suppress the feeling of hunger and for weight control. Depleted sodium levels should therefore be regulated through the normalization of fluid intake and not through exogenous sodium intake. In some cases, hyponatremia also emerges through a SIADH (syndrome of inappropriate antidiuretic ADH secretion), caused by treatment with psychotropic drugs, especially SSRIs, SNRIs and neuroleptics. Due to this dangerous side effect, the corresponding medications should be halted in such cases. A forced (in the case of parenteral application) normalization of depleted sodium and potassium levels in the case of overhydration must not be conducted as this is linked to a risk of pontine myelinolysis (Amann et al., 2001; Sugimoto et al., 2003). The sodium concentration should only be increased by around 4 to 6 mmol/l per day (Ayus et al., 2015). By contrast, an appropriate use of table salt in the framework of normal nutrition should be unproblematic.

Magnesium

Symptoms of hypomagnesemia resemble the symptoms of severe anorexia: muscle weakness, adynemia, constipation, cardiac arryhthmia and cramps. Magnesium deficiency is frequent in AN (Birmingham et al. 2004; Fonseca & Havard, 1985; Hay et al., 1989). Therefore, checking the serum magnesium and possibly also oral administration can therefore be useful. With regard to calcium metabolism and vitamin D metabolism (see chapter 8).

Thiamine

Thiamine is required in the mitochondria in order to transfer pyruvate as coenzyme A to the citrate cycle. With the restoration of energy supply to the cells, an increased need for thiamine thus also arises. Thiamine can only be stored in the body to a very limited degree. By contrast, no hypervitaminoses are known. Wernicke-Korsakoff encephalopathy is characterized by the triad of encephalopathy, disorders of the oculomotor system and ataxia of gait. It is caused, in a manner that is not yet completely understood, by a thiamine deficiency. Although thiamine deficiency and thus Wernicke-Korsakoff encephalopathy occurs most frequently in chronic alcoholism, it can also arise in other forms of malnutrition and undernourishment. The phase of refeeding is seen as especially hazardous. There are numerous case reports of vitamin B1 deficiencies in AN (Cooke et al., 2006; Doraiswamy et al., 1994; Elmer et al., 2011; Morcos, 2003; Peters et al., 2007; Renthal et al., 2014; Scarpellini et al., 2012; Watanabe et al., 2009). Serum thiamine determination is unreliable and cannot dispel the suspicion of encepalopathy caused by thiamine deficiency. As such, a preventive oral administration of vitamin B1 is to be recommended in the case of a very low starting weight.

2.2.6.3. Macro- and micronutrients

Macronutrients

Patients with AN are undernourished not only quantitatively but also qualitatively. The macronutrient composition in current studies corresponds to that recommended for the general population (25-35% fat, 50-60% carbohydrate, 15-20% protein; (Garber et al., 2016)). In a review by Marzola et al. (2013), the following, pragmatic recommendations are made:

- Increase the variety of food and the energy density
- Consume protein with a high biological quality
- Choice of protein sources which patients find less challenging (usually plant-based proteins, fish and chicken)
- Ensure that essential fatty acids are consumed
- Complex carbohydrates (bread, rice, potatoes)
- Fruit, juices and vegetables

A nutritional analysis to precisely determine individual nutritional deficiencies would require the use of targeted laboratory analyses and questioning of supplementation practices, in addition to retrospective and prospective nutritional records (Setnick, 2010). This procedure is laborious and thus rarely feasible in everyday clinical practice. Therefore, common practice is to rather refrain from a separate intake of individual nutrients, under the assumption that the reintroduction of a balanced diet covering the patient's needs is sufficient to counter the deficits in most cases. In the following, nutritional components are mentioned which need to be given particular consideration and in some cases should be additionally supplemented.

Micronutrients

Besides the obvious lack of energy and dietary fats, various different vital micronutrients such as minerals and vitamins are also lacking (Hadigan et al., 2000; Rock & Curran-Celentano, 1994). A review by Setnick et al. (2010) addressed micronutrient deficiencies in patients with eating disorders. As each patient maintains her own dietary habits, frequently over long periods of time, there is no conclusive list of nutritional deficiencies common to all patients. Many patients predominantly avoid all fatty foods, which leads to a lack of fat-soluble nutrients. Others, by contrast, additionally or predominantly limit their consumption of carbohydrates and/or sugar ("low carb"), while some avoid meat and dairy products, without supplementing the vegetarian diet with appropriate plant-based alternatives. In some cases, patients consume excessive amounts of certain foods (e.g. raw fruit and vegetables), or always and repeatedly eat a very restricted selection of foods, which can lead to an extremely high consumption of certain nutrients. Furthermore, many patients themselves supplement with vitamins or minerals. In view of these differing practices, it is hardly surprising that individual studies reach different results.

In the following, only the trace element iron will be addressed (for zinc deficiency see section 4.2.2.7.3). Anemia is a frequent in AN (Devuyst et al., 1993). Its true prevalence is possibly

underestimated due to hemoconcentration and hypovolemia. Anemia in AN has multifactorial causes: bone marrow depression, substrate deficiency, folic acid deficiency, vitamin B12 deficiency and also iron deficiency can all play a role. The role of each of these factors varies on an interindividual basis.
Iron deficiency only plays a role in a smaller proportion of patients (Nova et al., 2006). Iron consumption is especially reduced in patients with a vegetarian diet. On the other hand, iron loss is reduced due to amenorrhea.

Vitamins
Anorexia patients often have a one-sided diet, and many take particular care to consume foods that are rich in vitamins. Mostly, however, nutrition nevertheless remains so unbalanced that the findings on vitamin supply and on vitamin status of AN patients are contradictory and inconsistent (Mira et al., 1989; Thibault & Roberge, 1987; Van Binsbergen et al., 1988). More recent investigations point to a greater deficiency above all of water-soluble vitamins, in particular from the B-complex (Hadigan et al., 2000; Levine et al., 2007; Moyano et al., 1998; Rock & Vasantharajan, 1995). Many but by no means all AN patients show signs of reduced vitamin supply of thiamine, niacin, riboflavin and folic acids. From the available findings, it is not possible to draw a general recommendation on vitamin substitution in the case of moderate underweight. An insufficient vitamin intake can generally be offset by a balanced and sufficient diet.

2.2.6.4. Refeeding during and at the end of therapy

Increasing energy requirements in the course of therapy
Due to different and interindividual metabolic changes, the energy requirements vary not only from patient to patient but also in the different phases of treatment. The formulas for calculating the basal metabolic rate derived from normal-weight and overweight patients are therefore not suitable for application in AN. While the initial weight increase due to the reduced basal metabolic rate in the so-called “hunger metabolism” is often possible or indicated by low amounts of energy, the energy requirements usually rise substantially in the later treatment phase. As there are no evidence-based data on the concrete level of requirements, the guidelines on this point are mainly based on clinical experience. Studies suggest that AN patients require between 5000 and 10000 excess calories in order to gain 1 kg of weight (Kaye et al., 1988; Marzola et al., 2013). However, the indication of requirements in the form of excess calories is limited, because the basal metabolic rate is strongly altered and cannot be reliably estimated in AN patients using the customary prediction formulas (Cuerda et al., 2007; Forman-Hoffman et al., 2006; Polito et al., 2000; Scalfi et al., 2001). The range cited in various guidelines stretches from 5-100 kcal/kg/kg. At the upper end of the range, this can be equated with an energy intake of up to 5000 kcal/d. The precise reasons for this broad range remain unclear, but the following factors have been discussed: physical activity, individual differences in the efficiency of energy utilization, thermoregulatory processes, composition of the synthesized tissue, fluid shifts, age and treatment phase (Marzola et al., 2013). Besides the metabolic changes and the resultantly

high energy needs, however, a lack of compliance (restriction, compensatory behaviors) can also erroneously suggest a high need.

Due to the difficulties in reliably calculating the energy requirements, in the later phase of refeeding, the estimation of the respective requirement based on weight gain is useful: In the case of a lack of weight gain, an increase in energy intake is advisable.

2.2.6.5. Refeeding in the outpatient setting

Nutritional therapeutic counseling to support patients in normalizing their eating behavior appears to be highly useful across all therapy phases and thus also in the outpatient setting. Especially at the end of inpatient therapy, it is important to adapt and consolidate the newly learned behaviors to daily life on an individual basis. Nutritional counseling can help the patient to select or prepare appropriate meals with the aim of eating a regular and balanced diet that covers her needs.

2.2.6.6. Vegetarian and vegan diets

There are not currently any evidence-based specific nutritional recommendations for patients with AN (Marzola et al., 2013). For the time being, therefore, it appears useful to draw on nutritional recommendations for the general population as a benchmark for patients with eating disorders. The German Nutrition Society (DGE) evaluates an ovo-lacto vegetarian diet as a suitable long-term diet both for adults and for adolescents, but emphasizes the need to select foods carefully, in order to avoid nutrient deficiencies especially in adolescents. If a patient has decided on a vegetarian diet, it is recommendable to explore the motives for this decision during psychotherapy. If children and adolescents eat a purely plant-based diet, in which they refrain completely from animal products, they are described as vegans. The DGE deems a vegan diet to be unsuitable for the whole of childhood (http://www.dge.de/presse/pm/kinder-vegetarisch-ernaehren-ja-oder-nein/). According to the DGE, adults who nevertheless wish to eat a vegan diet should take a vitamin B12 preparation on a long-term basis, ensure that they consume an adequate amount above all of the critical nutrients, and possibly use enriched foods and nutrient preparations. For this purpose, they should consult a qualified nutrition specialist, and the supply of critical nutrients should be regularly checked by a medical practitioner. A further aspect that appears to make a vegan diet problematic for patients with eating disorders is that vegans have to constantly and comprehensively deal with the theme of nutrition, which can hinder recovery from an eating disorder.

2.2.7. Pharmacotherapy

Overall, the evidence on pharmacotherapy for AN is unsatisfactory, both for antidepressants and for antipsychotics. As the studies conducted to date differ strongly in terms of design (acute therapy vs. relapse prevention, controls against placebo vs. controls against other pharmaceuticals; considerable differences in the employed basic treatment), it is not possible

to conduct a meta-analysis. A primary endpoint was weight criteria: extent of weight gain, speed of weight gain, duration of treatment until weight restitution and number of patients who achieved a sufficient weight gain. With regard to antipsychotics, only studies with very small sample sizes are available. Only a small number of studies employed longer follow-up observation periods, although these are necessary to be able to evaluate the clinical significance of weight effects under pharmacotherapy. Due to the low number of controlled trials, in the following, case studies are also included, although these usually describe much larger effects than those found in controlled studies. Only those substances are mentioned for which at least one controlled trial is available (table 4.4).

2.2.7.1. Antipsychotics

More recent studies on the group of antipsychotics address second-generation antipsychotics (for reviews, see (Aigner et al., 2011; Brewerton, 2012; Frank & Shott, 2016; McKnight & Park, 2010; Miniati et al., 2016)). Among this group, the antipsychotic olanzapine particularly stands out with respect to the evidence base. Thus, for the group of second-generation antipsychotics, first, a closer look at the study findings on olanzapine will be taken, while further substances in this group will be summarized. Subsequently, for the sake of completeness, an overview will be provided of the state of evidence for first-generation antipsychotics.

Second-generation antipsychotics

Olanzapine

Olanzapine belongs to the group of atypical neuroleptics. It can – especially at high dosages – cause extrapyramidal-motor symptoms (EPMS), but the risk of agranulocytosis is far lower than for clozapine. With indication-appropriate treatment, olanzapine very often leads to considerable weight gain in normal-weight or overweight patients. The assumption is that insulin action is impaired and thus the carbohydrate metabolism is disrupted. There is no evidence that olanzapine acts directly on the hypothalamic regulatory mechanisms of body weight. Due to this favorable range of side effects for the treatment of AN, various clinical trials have been conducted on the use of olanzapine in AN.

A series of uncontrolled case studies (Barbarich et al., 2004; Boachie et al., 2003; Ercan et al., 2003; La Via et al., 2000; Malina et al., 2003; Mehler et al., 2001; Powers et al., 2002; Wang et al., 2006) have shown that olanzapine leads to a clear weight gain. In the case study with the highest number of described cases (Barbarich et al., 2004), however, the weight gain was substantially lower than in all other case studies. In an RCT comparing olanzapine with chlorpromazine, olanzapine was not found to be superior with respect to weight gain (Mondraty et al., 2005). An RCT in adolescents found no superiority of olanzapine over placebo with respect to weight gain with a study duration of ten weeks (Kafantaris et al., 2011). A further controlled trial in which olanzapine was used as an additional treatment compared to treatment as usual for all study participants found no difference regarding weight gain (Brambilla et al., 2007). However, the patients treated with olanzapine (comparison condition: treatment with chlorpromazine) showed a significant improvement in anorexia-typical cognitions (measured

with the Eating Disorder Inventory, EDI). In a further randomized controlled trial (Bissada et al., 2008) (N=34), both groups took part in an inpatient treatment program over ten weeks. The olanzapine group received differing doses of olanzapine. Compared to the group which did not receive olanzapine, the group receiving olanzapine showed significantly better weight gain and a greater decrease in obsessive symptoms. A further RCT found a significant superiority of olanzapine over placebo with respect to weight gain after a treatment duration of eight weeks, although this difference can only be described as marginal in terms of the extent of weight gain (Attia et al., 2011). Olanzapine is generally initially used at a low dose of 2.5mg, which can be increased if necessary.

Further second-generation antipsychotics

For risperidone, there is one RCT (N=40), which examined the duration until achievement of a target weight as compared to placebo. Risperidone was not superior regarding weight-related outcome measures or regarding other psychometric variables (Hagman et al., 2011).
With regard to quetiapine, there is one RCT and one open study, whose quality was rated as low. A very small RCT on quetiapine found no difference between verum and placebo regarding weight and eating disorder psychopathology (Powers et al., 2012). An open-label naturalistic study on quetiapine – in addition to treatment as usual – showed trends towards a better weight development and a good tolerability of the substance (Court et al., 2010).
For sulpiride, which occupies an intermediate position between first- and second-generation antipsychotics, there are two controlled trials, which independently showed a better weight gain in groups treated with sulpiride than with other psychotropic drugs (Ruggiero et al., 2001) or placebo (Vandereycken, 1984). As a limitation, it should be mentioned that in the study by Vandereycken (1984), the weight gain was only better initially, and not following the crossover of the treatment arms. In a study by Ruggiero et al. (Mondraty et al., 2005; Ruggiero et al., 2001), the weight gain, which was on average a little over 4kg, was significantly greater than for fluoxetine and clomipramine, but still unsatisfactorily low, and lower than in psychotherapy studies.

First-generation antipsychotics

Cassano et al. (2003) described the administration of haloperidol as an adjunctive treatment to standard treatment over a total of 6 months (N=13). Therapy effects that were solely attributable to haloperidol could not be identified.
For pimozide (Orap®), an antipsychotic with a particularly adverse range of cardiac-related side effects and thus limited suitability for the treatment of AN, two smaller controlled studies (Vandereycken & Pierloot, 1982) did not show improved weight gain upon administration of pimozide.

Overview antipsychotics

Although weight gain is described as a side effect of many neuroleptics, it has not yet been demonstrated that this is also an – in this case desirable – effect of antipsychotic treatment in the case of AN. Nevertheless, antipsychotics are utilized in many clinics and occasionally also

in outpatient treatment. The aims in this respect have more to do with the psychomotor-dampening main effects of this group of medications. They serve to reduce stress conditions, the often pronounced urge for movement and the circular thinking around eating disorder-related themes such as eating or shape and weight.
From the available case studies, application reports and clinical practice, the following principles can be derived for antipsychotic administration in AN:

1. The required dosage is generally low.
2. The indication is derived from symptoms which accompany the AN. The necessary duration of pharmacological treatment thus depends on the course of these symptoms and not on the eating disorder diagnosis.
3. Antipsychotics with a low range of extrapyramidal side effects are preferred.
4. Compliance is crucial for the utility of such medications. The benefit of the medication must be communicable to the patient.

Summary: Empirical evidence on treatment with antipsychotics

Overall, the state of study findings on the treatment of AN with antipsychotics is highly unsatisfactory. There are five systematic reviews (Aigner et al., 2011; Brewerton, 2012; Frank & Shott, 2016; McKnight & Park, 2010; Miniati et al., 2016), which show similar results. Olanzapine is described as the antipsychotic with the presumably clearest effect on AN, although an effect on the core symptoms of AN have not yet been conclusively demonstrated. However, olanzapine appears to have an effect on the associated symptoms such as compulsions.

- There is no evidence that neuroleptics contribute to improved weight development in AN (EL 1a).

- There is limited evidence that obsessive-compulsive symptoms and circular thoughts are favorably influenced by olanzapine (EL 2a).

4.2.2.7.2. Antidepressants

Tricyclic antidepressants

Potential toxicity and the range of side effects are the main reasons why tricyclic antidepressants are nowadays rarely used in the treatment of AN. In more recent studies, these medications tend to rather play a role as a comparison condition.
Clomipramine, a tricyclic antidepressant, is at least theoretically an interesting substance for the treatment of AN given its use in the treatment of obsessive-compulsive disorders. In a study from 1980, Lacey and Crisp (1980) did not find an improved weight gain compared to placebo in patients treated with 50 mg of clomipramine. However, they did describe an improved appetite and larger food intake with simultaneously higher urge for movement in the verum arm. In a further study, however, clomipramine (average approx. 60 mg) performed worse than sulpiride with respect to weight gain (Ruggiero et al., 2001).

Amitriptyline, which used to be one of the most frequently prescribed antidepressants for the treatment of depression, with a broad anticholinergic side effect profile and frequent weight gain, unselectively inhibits the reuptake of monoamines in the synaptic cleft. Based on several case reports with a positive weight progression (Kendler, 1978; Mills, 1976; Moore, 1977; Needleman & Waber, 1976), in 1985, Biedermann and colleagues (1985) conducted the first controlled trial (average dosage 115 mg) in AN. A better weight gain compared to placebo was observed. In a later study by Halmi et al. (1986), amitriptyline (up to 160 mg) was employed as a comparison arm together with placebo compared to cyproheptadine (see below). In this study arm, there was a tendency for improved weight gain, but this was not significantly better than in the placebo arm, and poorer than under cyproheptadine. In a controlled study, Brambilla et al. (1995c) examined *nortriptyline*, the active metabolite of amitriptyline, compared to fluoxetine (see below) and did not find any differences between the two medications.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine inhibits the uptake of serotonin from the synaptic cleft and has direct effects on 5-HT_{2C} receptors. At very high doses, fluoxetine can also inhibit noradrenaline reuptake. In contrast to most other antidepressants, weight gain is not one of the typical side effects of fluoxetine. Fluoxetine has the longest half-life of all antidepressants (fluoxetine 4-6 days, active metabolite norfluoxetine 4-16 days) and a substantial interaction potential (inhibition of CYP2D6, to a lesser extent also inhibition of CYP3A4). Likely due to the established position of fluoxetine in the treatment of bulimia nervosa, there are several studies on this substance. Compared to placebo, Attia et al. (Attia et al., 1998) found no improvement in weight development in a randomized controlled trial. Regarding the active form of AN, the weight effects of fluoxetine were not better compared to amineptine (Brambilla et al., 1995c) (amineptine is an atypical tricyclic antidepressant, with a strong stimulating effect, which is now no longer manufactured.) The same research group likewise found no difference between fluoxetine and nortriptyline regarding the restrictive form of AN (Brambilla et al., 1995a). However, these two controlled trials were very small (N= 6 vs. 7 active form of AN; N= 15 vs. 7 restrictive form of AN). Thus, for the initial weight gain, there is no evidence for a benefit of fluoxetine.

Two controlled studies, by contrast, suggested advantages of fluoxetine administration for relapse prevention. However, for the study by Halmi et al. (1999), only six-month outcomes are available, although the study was designed for one year. In the study by Kaye et al. (2001), the number of dropouts was very high, especially in the placebo group. At best, these two studies provide indications of a possible positive effect of fluoxetine in terms of relapse prevention. In a more recent, well-designed study by Walsh et al. (2006), however, no benefit of fluoxetine treatment following weight normalization was found. This finding is in accordance with a clinical longitudinal follow-up study over 24 months by Strober et al. (1997a) of 33 patients, in which fluoxetine did not show better courses when retrospectively compared with the courses of other patients without fluoxetine. Pharmacologically plausible are case reports that AN developed upon administration of fluoxetine due to bulimia nervosa (Oliveros et al., 1992; Vaz & Salcedo, 1994). This danger of an SSRI-induced anorexia may be present for other substances of this group (Sagduyu, 1997).

Citalopram has a much shorter half-life compared to fluoxetine and a more favorable interaction potential. In a study by Calandra et al. (1999) (N=6 patients with AN), citalopram

(20mg) was employed together with systemic therapy. In the uncontrolled study, the scale scores on the Eating Disorder Inventory (EDI) improved, but no systematic change in weight was found. In the only existing controlled study on citalopram (Fassino et al., 2002), compared to a waiting control group, significant changes in patients' psychopathological burden such as depressive symptoms were found, which were attributable to citalopram, but the weight development was comparable in both groups. The study was afflicted by a high number of treatment dropouts.
Sertraline also has a low interaction potential and a favorable side effect profile compared to other SSRIs. There is only one controlled, but not randomized study (Santonastaso et al., 2001), which described an improvement in depressive symptoms, self-perception and perfectionism in the group treated with sertraline. Again, however, weight development did not differ from the control condition.

Overview: Evidence on treatment with antidepressants

Although the evidence base for antidepressants is somewhat better than for antipsychotics, it is still not sufficient for deriving recommendations for treatment with this class of medications. The efficacy of antidepressants, as suggested in a considerable number of case studies, is rather likely to be attributable to the concomitant treatments that were often conducted in parallel rather than to the antidepressants themselves. The study findings give no reason to hope that better studies with the respective substances would bring about a fundamental change to the conclusion: There is no evidence for a specific efficacy of antidepressants in the treatment of AN if the focus is on weight-related criteria.

Nevertheless, antidepressants are regularly used in anorexia treatment within clinical practice in order to treat concomitant symptoms of AN such as depressive disorders or obsessive-compulsive symptoms. The scientific basis for this is essentially extrapolated from studies that were conducted in patients without eating disorders. There is no sufficient evidence to justify this practice. Depressive and obsessive-compulsive accompanying symptoms are also caused by the low body weight and can improve through weight gain even without an additional specific therapy (Dowson, 2004; Jordan et al., 2008; Meehan et al., 2006).

Furthermore, the risk of side effects in antidepressant pharmacotherapy is increased in AN due to several specific factors:
1.) Body weight is lower; the volume of distribution is lower.
2.) Oral intake is rendered more diffi
cult given the irregular eating behavior and the recurrent vomiting.
3.) Due to the already existing cardiac difficulties, cardiac side effects are more dangerous (see guideline chapter 8 "Physical sequelae of eating disorders").
4.) Electrolyte imbalances are more frequent. Accordingly, the risk of overlooking an induced syndrome of inappropriate antidiuretic hormone secretion (SIADH) is higher.

Specific considerations in children and adolescents

Based on the available data, the treatment of depressive symptoms in children and adolescents with AN in the state of starvation is not recommended, as there are no indications that an additional administration of antidepressants in the case of underweight (< 10th BMI percentile)

accelerates or improves treatment progression (guidelines of the German Association for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, 2007).

There are barely any data on the safety of antidepressants in children and adolescents who are underweight. If depressive symptoms persist following sufficient weight rehabilitation, a supplementary treatment with a serotonin reuptake inhibitor can be considered. In Germany, only fluoxetine is permitted for the treatment of moderate to severe depression in this age group.

Summary: Empirical evidence on treatment with antidepressants

The five available placebo-controlled studies (Attia et al., 1998; Biederman et al., 1985; Halmi et al., 1986; Lacey & Crisp, 1980; Walsh et al., 2006) did not find a superiority of antidepressants either with respect to weight change or for the broader area of eating disorder symptoms. The other three studies (Brambilla et al., 1995b,c; Ruggiero et al., 2001) compared antidepressants with other antidepressants and did not find any differences. It is also unclear which dosages should be employed. While fluoxetine was given at the high dose tested for bulimia nervosa, other SSRIs were given at the standard dose. In the controlled studies, tricyclic antidepressants were employed at rather low doses. Overall, the evidence remains unchanged since the Cochrane review from 2006, which considered most of the aforementioned studies (Claudino et al., 2006).

- There is no evidence for the specific efficacy of antidepressants in AN (EL 1a)

2.2.7.3. Other pharmaceuticals

Appetite stimulants

Cyproheptadine (Peritol®), a serotonin antagonist, was primarily developed as an anti-allergic medication. However, it emerged that it stimulates the appetite. Despite the well-evidenced weight-increasing effect of cyproheptadine in other nutrition disorders, the results for AN are ambiguous. As with the aforementioned group of psychotropic drugs, there are case reports suggesting a weight efficacy of cyproheptadine (Benady, 1970; Goldberg et al., 1979; Mainguet, 1972; Silbert, 1971). However, the controlled studies in this regard only found a weight-increasing effect for subgroups of AN (Goldberg et al., 1980; Halmi et al., 1986; Kibel, 1969).

For the group of cannabinoids, there are studies on *tetrahydrocannabinol (THC)* and the cannabinoid-receptor 1 (CB1) agonist *dronabinol*. Cannabinoids bind to receptors whose importance and function in the human organism is not yet completely understood. For AN, primarily the CB1 receptors are likely to play a role, which are found on nerve cells in the basal ganglia, cerebellum and hippocampus. As the brain regions in which the CB1 receptor is predominantly found play an important role in memory (hippocampus and cerebellum) as well as in the regulation of movement, it is reasonable to assume that endocannabinoids influence processes of learning and movement. Research findings show that the presence of the CB1 receptor is necessary for the extinction of negative memories. Therefore, it is suspected that endocannabinoids play an important role in anxiety disorders. For eating disorders, the role of

this receptor type is important with regard to the regulation of motility and appetite. An involvement of the endocannabinoid system in AN is demonstrated in the increased blood levels of endocannabinoids in AN (in contrast to BN) (Monteleone et al., 2005). There is only one controlled crossover study (N=11) on the use of *THC* in AN (Gross et al., 1983), which found no effect on weight gain. An RCT on the CB1 agonist *dronabinol* demonstrated, over a very short investigation period (4 weeks) in a small sample with a crossover design, a significant superiority of dronabinol over placebo regarding weight gain, although this was rather low from a clinical perspective (1 kg vs. 0.34 kg). Further publications from the work group examining this sample refer to endocrinological changes or changes in motor activity (increase under dronabinol compared to placebo), which might limit the potential use of this substance (Andries, et al., 2014; 2015a,b).

Lithium

Lithium has been used since the mid-20th century as a mood stabilizer in bipolar affective disorders and as an antidepressant augmentation strategy. For use in the therapeutic area, the tolerability is good, but due to the low therapeutic index, there is a risk of potentially lethal lithium intoxication in the case of overdose. A known and frequent side effect of lithium treatment is weight gain, which suggests its use in AN. Besides two case reports (Barcai, 1977; Stein et al., 1982), there is one smaller controlled study on the use of lithium in AN (Gross et al., 1981). However, due to methodological weaknesses of the study, the reported improved weight gain in the lithium group has to be called into question.

D-cycloserine

D-cycloserine is a glutamatergic N-methyl-d-aspartate (NDMA) receptor agonist, which in experimental approaches can strengthen the effects of exposure therapy via the improvement of emotional learning. In an RCT with a pilot nature, a substantially higher weight gain under D-cycloserine with exposure was described compared to a placebo condition (Levinson et al., 2015). However, the study shows considerable methodological weaknesses, as only 19.4% of patients had a baseline BMI of less than 18.5 kg/m² (mean baseline BMI of 20.24 kg/m^2).

Anxiolytics – Benzodiazepines

Benzodiazepines bind to central nervous system inhibiting GABA receptors and exert anxiolytic, muscle-relaxant, anticonvulsive and sleep-promoting effects. Due to the anxiolytic active component, there is at least theoretical reason to assume that administration will influence fears in relation to food intake in AN. However, a high potential for dependence and negative effects on learning processes, which play an important role in the therapy process, strongly limit this treatment approach. With regard to *alprazolam*, there is one controlled study (Steinglass et al., 2014b) with an extremely short observation period (only two administrations at two mealtimes; N=20). No difference compared to placebo was found regarding amount of food and anxiety.

Nutritional supplements - Zinc

Zinc is among the trace elements that are essential for the metabolism. The recommended daily intake amounts to 15 up to a maximum of 100 mg. If this maximum intake is exceeded, intoxication symptoms such as nausea, vomiting or diarrhea can arise. Zinc fulfills many different functions in the body. It is found in traces in numerous foods such as meat, fish, milk products, wholemeal products, oilseeds, and various salad types. Despite the multitude of foods containing zinc, the unbalanced and poor nutrition in AN frequently also leads to zinc deficiency (Ainley et al., 1986; Bakan, 1979; Bakan et al., 1993; Casperet al.1978, 1980; Dinsmore et al., 1985; Humphries et al., 1989; Katz et al., 1987; Lask et al., 1993). Nevertheless, zinc deficiency was not found in every investigation (Van Binsbergen et al., 1988; Varela et al., 1992), meaning that a diagnosis of AN can in no way be equated with zinc deficiency. This is also corroborated in a recent work reporting that of 153 patients with AN, zinc deficiency was found in only 3 cases (2.1%) (Achamrah et al., 2017).

The symptoms of zinc deficiency are diverse, and include, for instance, growth disorders, anemia, hair loss, dry skin and brittle nails. Above all, however, zinc deficiency leads to hypogeusia up to ageusia[9], to lack of appetite and to weight loss, and hence causes a clinical picture resembling that of AN. There are indications that lack of appetite is linked to an attenuated release of the neuropeptide Y in the hypothalamus (Levenson, 2003).

There are a series of case studies (Bakan, 1979; Birmingham & Gritzner, 2006; Bryce-Smith & Simpson, 1984; Safai-Kutti, 1990; Safai-Kutti & Kutti, 1986a; Su & Birmingham, 2002; Yamaguchi et al., 1992) which in part report dramatic weight gains following zinc substitution in AN. However, these may have been exceptional cases in which a manifest zinc deficiency contributed to malnutrition. Accordingly, a meaningful use of zinc substitution in AN would be limited to cases in which a zinc deficiency is actually present. In the thus far only controlled trial on zinc supplementation, Birmingham et al. (Birmingham et al., 1994) found that weight gain was twice as high for 100mg zinc/day compared to placebo, but the weight gain was nevertheless only moderately significant.

Oxytocin

Oxytocin plays a central role in the neurobiological mediation of social behavior, appetite, anxiety and stress. In AN, a reduced concentration of oxytocin in the cerebrospinal fluid is found during starvation. In light of these findings, studies have investigated the effect of oxytocin on food intake and emotion recognition. The studies by the work group led by Kim et al. (2014, 2015) on the effect of oxytocin in eating disorders found, in a double-blind within-subject crossover design, no effects of the hormone on calorie consumption and emotion recognition in AN, while oxytocin did elicit these effects in BN. Ultimately, the results were interpreted such that in the framework of starvation in AN, emotional processes are suppressed. However, the methodological quality of both of the studies by the work group were rated as low and very low, respectively.

Combination therapy

There are no randomized controlled trials comparing a psychotherapeutic treatment of AN with a combination of psychotherapeutic plus psychopharmacological treatment.

[9] Loss of taste functions

2.2.8. Experimental procedures

Neuromodulation

In light of the improved understanding of the underlying neurobiological factors in AN, neuromodulatory methods to treat AN are increasingly being examined (Brockmeyer et al., 2018; McClelland et al., 2013a). These include, above all, deep brain stimulation (DMS) as a minimally invasive procedure, and repetitive transcranial magnetic stimulation (rTMS) as well as transcranial direct-current stimulation (tDCS) as non-invasive procedures. In a non-controlled clinical study (n=16) on deep brain stimulation over one year, half of the examined patients with a severe, chronic course achieved a relevant weight increase (BMI > 17g/m²) and improvements in anxiety and obsessive-compulsive symptoms (target region: subgenual cingulate cortex). However, several undesired effects were also observed, including seizures and infections (Lipsman et al., 2017). Besides the subgenual cingulate cortex, in an individual case study and a small case series, the ventral striatum and the nucleus accumbens were also selected as target regions for brain stimulation. So far, there are no published and only one ongoing small randomized controlled trial on DBS in AN. Moreover, it is largely unclear which brain regions are suitable targets for DBS in AN (Treasure & Schmidt, 2013). For rTMS, two case series and one randomized placebo-controlled pilot trial (with a single therapy session) showed that the intervention was associated with a short-term reduction of AN symptoms as well as an improvement in affect, although in all patients who were followed further, in part substantial weight losses occurred over time (van den Eynde et al., 2013; McClelland et al., 2016; McClelland et al., 2013b). Further assessments of the efficacy of rTMS are currently underway within several ongoing randomized controlled trials. With regard to tDCS in AN, so far, there is only one case series, in which a sustained improvement in AN symptoms was observed in half of the patients following the intervention (Khedr et al., 2014). To date, these are experimental approaches which only play a role within research contexts.

3. Treatment settings

For an overview on treatment settings and the framework conditions in Germany, see also Chapter 2. So far, there are only two systematic reviews on a comparison of treatment settings (Madden et al., 2015a; Meads et al., 2001). Due to methodological shortcomings of the available original literature and the heterogeneity of studies, it is not possible to draw any definitive conclusions, although Madden et al. (Madden et al., 2015a) interpret the evidence such that given the comparable effects, less intensive settings, which are more economical, are preferable in the treatment of AN. A corresponding recommendation was incorporated into the guidelines of the Royal Australian and New Zealand College of Psychiatrists (Hay et al., 2014). It should be taken into account that framework conditions and programs of inpatient treatment can differ greatly between different countries, and the quality of outpatient care also does not necessarily correspond to that which is examined in randomized controlled trials. Thus, based on the current data, an evidence-based decision for a particular setting is only possible to a limited extent in the treatment of AN; rather, the decision should be broadly based on clinical experiences and

expert opinion (Fairburn, 2005; Vandereycken, 2003). The recommendations on indication criteria for day-clinic or inpatient treatment are presented in sections 3.2 and 3.3.

3.1. Outpatient treatment

See section 2.2 for treatment approaches and methods as well as the available evidence on their efficacy.

3.2. Day-clinic treatment

Day-clinic treatment phases often follow the inpatient treatment phase in the therapy of AN, and serve the purpose of preparing the patient for the transition to outpatient treatment ("step-down" approach). While inpatient treatment means removing the patient from the context of her everyday life, a day-clinic treatment entails a daily switch between intensive treatment in the clinic and a return to the everyday life situation (Zeeck & Hartmann, 2008). As such, a day-clinic treatment decreases the disadvantages and risks of a longer-term hospitalization and emphasizes the patient's personal responsibility through a substantially lower degree of external control and supervision and a constant confrontation with possible difficulties in the everyday life situation.

Day-clinic treatments as part of specialized programs can also be considered in patients who can no longer be sufficiently looked after in the outpatient setting or whose outpatient therapy process has stagnated. As such, a day-clinic stay means a temporary intensification of an outpatient therapy process. It enables complex interventions on the psychological and physical level, including support in nutrition (generally speaking, two main meals and two snacks are offered in the clinic, on 4-5 days per week).

A day-clinic treatment can be considered in patients at moderate risk with *chronic* AN, in whom an outpatient treatment is not sufficient to overcome interpersonal and social problems – especially if these patients have already repeatedly undergone inpatient treatments and should remain in close contact with their everyday life situation.

An overview of day-clinic treatment programs for eating disorders is provided by Zipfel et al. (2002), Friedmann et al. (2016) as well as Hepburn & Wilson (2014). As program elements and the underlying theoretical orientations vary greatly, these are difficult to compare with each other. Moreover, treatment intensity and treatment duration is also very variable, ranging from 6-12 hours per day, for 4-7 days per week, over a total of 3-26 weeks (most frequent: 10-16 weeks, see (Friedman et al., 2016)).

Only a small number of empirical studies have compared day-clinic and inpatient therapy. A multicenter randomized controlled trial compared specialized inpatient treatment (average 14.6 weeks) in adolescents with a three-week inpatient and subsequent specialized day-clinic treatment (average 16.5 weeks in the same setting) (Herpertz-Dahlmann et al., 2014). A procedure following a "step-down" approach was not inferior to the continuous inpatient treatment regarding weight gain and reduction of eating disorders 12 months after the end of therapy, and also entailed lower costs. The inpatient-day-clinic group even showed greater improvements with respect to well-being and psychosexual development. One advantage lies

in preserving the patient's integration within the family and the social environment. The treatment in the "step-down" condition ensued in the same treatment team and with close integration of family members.
So far, there are no randomized studies comparing day-clinic with outpatient treatment in AN. Most of the studies on day-clinic treatment are observation studies without a comparison or control group, which often do not report separate data for the different groups of eating-disordered patients (for overviews see (Friedman et al., 2016; Hepburn & Wilson, 2014)). An exception to this is the small case-control study comparing inpatient and day-clinic therapy (Zeeck et al., 2006). Overall, the available observation studies indicate that day-clinic treatment is effective in AN but that weight gains are lower than in the inpatient setting (Abbate-Daga et al., 2015; Goddard et al., 2013; Treat et al., 2008; Zeeck et al., 2006), see also a meta-analysis including naturalistic studies (Zeeck et al., 2018). Stronger weight gains appear to be achieved when there is a high motivation, the patient has a short illness duration and a lower illness severity, or the setting resembles an inpatient treatment through the combination with supervised living groups, an intensive inclusion of family members or a 7-day program (Gerlinghoff et al., 1998; Howard et al., 1999; Kaplan & Olmsted, 1997). In terms of the question of the optimal dosage and treatment duration, there is not yet sufficient available evidence (Friedman et al., 2016).

Summary: Evidence on partial-inpatient/day-clinic treatment of AN

- There is limited evidence that day-clinic treatment within a specialized therapy program is effective (EL 4; (Friedman et al., 2016; Hepburn & Wilson, 2014)).
- For adolescents (14-18 years) with a short duration of illness, a combined treatment with short inpatient admission and subsequent specialized day-clinic treatment ("step-down") is not inferior to a continuous inpatient treatment (EL 1b; (Herpertz-Dahlmann et al., 2014)).
- For adult patients with AN and substantial underweight, a day-clinic treatment appears to lead to lower weight gains compared to an inpatient treatment (EL 4; (Abbate-Daga et al., 2015; Treat et al., 2008; Zeeck et al., 2006)).

3.3. Inpatient treatment

Inpatient treatment is more often necessary in the case of AN than in other eating disorders. This applies especially to adult patients. The reasons for this are the physical risk and the continuous supervision of eating behavior often necessary due to the marked ambivalence and anxiety regarding weight gain (Bodell & Keel, 2010), as well as the treatment in a multiprofessional team which work in close collaboration. A psychosomatic-psychotherapeutic hospital treatment or a psychiatric-psychosomatic hospital treatment in children and adolescents is defined through particular characteristics and encompasses a combination of different interventions which are aligned to each other (see also Operation and Procedure Code

OPS)[10], which need to be supplemented by disorder-oriented elements. A hospital treatment can also be necessary in patients with less severe underweight if they have a serious psychological comorbidity (e.g. trauma-related disorders, borderline personality disorders), a severe behavior problem (e.g. extreme "purging" behavior, excessive-compulsive exercise, self-harm) or were originally in a high weight range but have lost a lot of weight in a relatively short period of time. Further advantages of inpatient therapy are that the treatment takes place in a group and that it can enable scope for development away from problematic family contexts. On the other hand – especially in children and adolescents – the risks inherent in a longer-term hospitalization and the interruption of regular schooling need to be taken into account (Gowers et al., 2000, 2010). Towards the end of an inpatient therapy, it is of vital importance to prepare the patient to transfer the achieved changes to everyday life in a targeted manner, for instance through a day-clinic treatment stage following the inpatient phase ("step-down", see above) and a timely planning of the outpatient follow-up treatment.

A main goal of inpatient treatment lies in physical stabilization, for which a sufficient weight gain is a prerequisite. Studies suggest that in the treatment of adult patients, as high a weight as possible (BMI > 18 kg/m²) should be strived for in order to reduce the risk of relapse (Baran et al., 1995; Howard et al., 1999; Steinhausen et al., 2008). For children and adolescents, an orientation to the 25th BMI age percentile taking into account premorbid BMI data is generally accepted. The aim is menarche or the resumption of menses (American Psychiatric Association, 2006; Dempfle et al., 2013; Golden et al., 2008). An inpatient treatment enables an intensive psychotherapeutic accompaniment of the patient during weight gain, which is generally linked to strong fears, feelings of powerlessness and helplessness.

Three ideal-typical phases of inpatient treatment can be distinguished: At the *beginning of therapy*, the focus is on motivating the patient and providing concrete help regarding eating and weight gain. In this phase, the treatment serves to provide support in the case of fears and strong ambivalence, to put dysfunctional beliefs into perspective, and to encourage the patient to change her eating behavior. In the *further course of treatment*, there should be increasing work on the central psychological problem areas and their relation to the symptoms (Herzog & Zeeck, 2001; Pierloot et al., 1982). A stepwise intensification of the program must be oriented to the patient's resilience and approachability and her physical situation. As relapses are frequent following inpatient treatment phases, the *final phase* should be sufficiently long and should concentrate on preparing the patient for discharge. This includes planning the outpatient follow-up therapy, the anticipation of relapses and difficulties after discharge, practice elements (shopping, preparing meals, restaurant visit, weekend breaks) and experiencing a phase in

[10] This encompasses for adults – if there is not a necessity for an integrated clinical-psychosomatic-psychotherapeutic complex treatment (OPS 9-642) or intensive treatment (OPS 9-61) due to physical risk – a therapy target-oriented treatment by a multiprofessional team (physicians, psychologists, special therapists/social workers, nursing staff) with weekly team meetings and a minimum of 3 therapy units of individual and group therapies led by physicians and psychologists, as well as weekly visits from specialist physicians (psychosomatic-psychotherapeutic complex treatment, OPS 9-63).
For children and adolescents, OPS encompasses, as a regular treatment with mental and psychosomatic disorders and behavioral disorders in children (OPS 9-656) and adolescents (OPS 9-666) or with a risk of somatic decompensation as an intensive treatment (OPS 9-672), a therapy target-oriented treatment by a multiprofessional team (physicians, psychologists, child and adolescent psychotherapists, special therapists, educational-nursing staff) with weekly visits and team meetings, and therapy units in the form of individual and group sessions led by physicians and psychologists with the children and adolescents as well as their parents and/or caregivers from the milieu of origin.

which weight is no longer continuously rising but can rather be maintained (Lay et al., 2002). There are indications that compared to adults, adolescents show a quicker weight gain and a stronger symptom improvement during inpatient treatment (Castro-Fornieles et al., 2007; Goddard et al., 2013; Zeeck et al., 2018).

Adult patients who are admitted with extreme underweight (BMI < 13 kg/m²) often do not achieve the otherwise aimed for target weight during an inpatient treatment. In these patients, a readmission following an appropriate period of time (in the sense of interval therapy) can be indicated.
For patients with a chronic course and who are very socially isolated, an inpatient (or also day-clinic) treatment can have the goal of achieving a stabilization on a level with a high quality of life by structuring the daily routine and rebuilding social contacts (see e.g. (Rø et al., 2004). For these patients, the concern regarding the physical situation is often not with normalizing weight but rather with a medical stabilization to the fullest possible extent. The therapy goals should be developed individually (see section 2.1).
For patients with other mental disorders (e.g. borderline personality disorder, PTSD), a hierarchization of therapy aims may be necessary (oriented to the degree of risk from the respective symptom). In such cases, the therapeutic approach should contain elements that are aligned to the guidelines for the respective comorbid disorder. For children and adolescents, however, not least due to the physical and developmental sequelae, the aim of weight normalization should not be deferred.

The general conditions for inpatient treatments differ widely in the European countries (Richard, 2005). Both in Great Britain and in Germany, the inpatient admission rates rose substantially in female adolescents with AN between 2010 and 2014 (National Health Service Statistics 2015, Bundesamt für Statistik, September 2015). In Germany, treatment days due to AN increased by approx. 5.5 days for 10-14-year-olds and by approx. 3.5 days for 15-18-year-olds between 2000 and 2013 (Bundesamt für Statistik, September 2015). Overall, the increasing economic pressure has led to a shortening of treatment times and discharge at a lower BMI (Suarez-Pinilla et al., 2015). There are indications that this development is associated with an increase in relapses and a reduction of inpatient therapy to "weight and crisis management" (Wiseman et al., 2001). Especially in the case of first-time hospitalizations, however, it should be ensured that patients reach an adequate weight in order to avoid rehospitalizations and chronification (Willer et al., 2005). Inpatient treatment should not be seen as a "last resort", but rather as a treatment option that encompasses specific therapeutic options (Vandereycken, 2003).
A naturalistic German multi-center study on the inpatient treatment of eating disorders showed that the risk of relapses was lower in patients treated in specialist clinics (Kaechele et al., 2001; Richard, 2001; Richard, 2005b).

Treatment components

Generally speaking, the offer of inpatient therapy programs in Germany is integrative and multimodal, meaning that it contains symptom-oriented components (agreement on a target weight, treatment contracts, weekly targets for weight gain, work with food diaries, mealtime

support and cooking support etc.), medical supervision, and components targeting the patient's psychological difficulties. A development away from inflexible, rigid programs towards procedures which consider the individual development of each patient is apparent. Concrete work on eating behavior ("mealtime support"), which is often difficult to change, and on the fears associated with eating, is a cornerstone of inpatient anorexia treatment. This work includes the adherence to a mealtime structure, the stipulation of quantities of food as well as practice elements (relating to eating rituals and food selection as well as an increasing independence in terms of dealing with eating). Studies on exposure and response-prevention techniques (see section 4.2.2.4.2) have yielded first empirical hints for the efficacy of concrete work on anxiety-triggering eating situations. However, such work is time- and personnel-intensive. It requires experienced, further qualified staff and a sufficient staff-to-patient ratio. Depending on the extent of physical risk, patients should be regularly (generally 1-3x/week) weighed in the morning, at approximately the same time, wearing light clothing (underwear). Additionally, it can be agreed that further weighing appointments will take place unannounced, in order to uncover and address "cheating" (e.g. by drinking water).

It is difficult to empirically assess which treatment components need to be included in inpatient treatment programs. However, there is consensus that they must contain medical supervision, nutrition management, body therapy approaches, elements specifically aligned to changing eating behavior and weight, therapy options with a non-verbal approach (creative/music therapy) as well as individual and group psychotherapy, which should be led by an experienced treatment team working in close collaboration with each other. In a cohort study, the introduction of symptom-oriented treatment elements and a structured treatment agreement with patients led to 70% of patients achieving the specified target weight, compared to 20% previously (Herzog et al. 1996).

In the treatment of children and adolescents, family-based interventions are essential (see section 4.2.2.2.1; (Espie & Eisler, 2015)). Several randomized controlled trials have examined therapy components which were offered in addition to various "standard programs", such as particular types of nutrition management, behavioral therapy interventions (desensitization), social skills training, emotion skills training, cognitive remediation therapy (CRT), an additional pharmacotherapy or family therapy interventions (for an overview see: (Suarez-Pinilla et al., 2015)). Studies on CRT as an "add-on" intervention showed that patients' cognitive flexibility improved in the short term ((Brockmeyer et al., 2014; Davies et al., 2012), see also section 4.2.2.4.1). In the treatment of children and adolescents, it can be assumed that family-based interventions contribute to therapy success by providing the caregiver with guidance in giving the patient concrete support (Herpertz-Dahlmann et al., 2014; Madden et al., 2015b). For patients with problematic exercise behavior (excessive, compulsive), a supervision of the exercise should take place and a tiered exercise program or sports therapy group should be offered ((Calogero & Pedrotty, 2004); see also section 4.2.2.4.3). It can be assumed that a sport/exercise offer which is adapted to the physical situation also increases compliance in patients who tend to secretly circumvent exercise bans (Cook et al., 2016; Zeeck & Schlegel, 2013). The offer of a body therapy can be especially beneficial in the phase of fear of weight gain. Two studies on mirror exposure pointed to potential positive effects of such an intervention (Key et al., 2002; Vocks et al., 2007). Art therapy also plays an important role (Ganter et al., 2009).

Therapeutic contracts

Therapeutic contracts are almost always part of specialized treatment programs (see e.g. (Godart et al., 2009; Zeeck & Hartmann.A, 2008)). Generally, therapeutic contracts include a target weight, targets for weekly weight gains, and possibly information on rules and participation in the therapy program. They appear to be superior to unstructured procedures with respect to weight gain (Herzog et al., 1996). For inpatient treatment, weight restitution should be sought, meaning reaching a BMI ≥ 18.5 for adults, and the 25th BMI age percentile for children and adolescents, but at least the 10th BMI age percentile (see also section 4.2.2.5). The target weight should generally be set within this range, although in justified individual cases (e.g. planning of interval treatment with an extremely low starting weight), it is possible to deviate from it. Programs that are too rigid, which insist on a strict adherence to weight targets without tackling the patient's fears and ambivalence, should be avoided (Herzog et al., 2004; Touyz et al., 1984, 1987). They lead to a superficial adaptation of the patient, who often loses weight again following discharge. Internationally, weight targets of 500-1000 g weight gain per week in the inpatient setting are recommended (American Psychiatric Association, 2006; National Institute of Clinical Excellence, 2004). Investigations on characteristics of the weight curve progression indicate that weight development in the first weeks enables a good prediction of therapy outcome – and thus also the identification of risk patients who are ambivalent or who only have limited motivation (Boehm et al., 2016; Hartmann et al., 2007; Remschmidt & Müller, 1987; Wales et al., 2016). The achieved weight should be maintained for a certain period of time prior to discharge in order to reduce the risk of later relapses and hospitalizations (Lay et al., 2002). If patients do not adhere to the targets for weight gain over a longer period of time or lose substantial weight again prior to discharge, an early discharge for therapeutic reasons can be useful. However, this should always be linked to an offer of readmission following a preliminary discussion and renewed assessment of motivation (either in the sense of a short "therapy break" with predetermined duration or in the sense of an "interval treatment").

Treatment duration

Only a small number of studies have examined predictors of treatment duration (Maguire et al., 2003; Nozoe et al., 1995; Strik Lievers et al., 2009) and predictors of the costs of an inpatient stay (Haas et al., 2012). The findings suggest that a psychological comorbidity (personality disorder, affective disorder), previous inpatient stays and a lower BMI at admission are associated with longer treatment durations and higher costs.

There is no direct empirical evidence from which to derive the most beneficial treatment duration; however, there are indications that several factors need to be considered. An aim of an inpatient treatment episode should be the achievement of an adequate weight. Therefore, treatment durations of several months can be expected when patients are admitted at a very low weight. The possibility of an "interval treatment" with renewed admission within an agreed time frame can be considered on a case-by-case basis and might be helpful. The results of a naturalistic multicenter study indicated that older patients with a long illness duration should

rather be treated for longer in order to achieve a good therapy outcome (sufficient weight gain, reduction of the eating disorder)[11] (Kaechele et al., 2001).

Trajectory and predictors of trajectory

A more recent study was able to identify subgroups of patients with different weight trajectories during inpatient treatment: a negative quadratic trajectory, a negative quadratic trajectory with fast weight gain, and a positive linear trajectory with slower weight gain (Makhzoumi et al., 2017). While most patients could be categorized into the first group, the latter group were more likely to achieve complete weight restoration at discharge. Another study found, by contrast, that patients with an initially higher BMI and those who quickly gained weight (0.5-1 kg/week within 6 weeks) had a substantially better prognosis regarding the achievement of complete weight restoration (Wales et al., 2016). In adult patients, comorbid depressive symptoms and a high motivation to change proved to be positive predictors of a clinically significant improvement in the framework of inpatient treatment, while a high body dissatisfaction, difficulties in impulse regulation and social insecurity were negative predictors (Schlegl et al., 2014). In adolescent patients, comorbid depressive symptoms and a high body dissatisfaction emerged as negative predictors of a clinically significant improvement (Schlegl et al., 2016). With regard to the long-term trajectory, a low starting weight is linked to an increased risk of chronification and increased mortality rates 1 to 9 years after treatment (Hebebrand et al., 1997; Pinter et al., 2004). One single study on relapses during the transition from inpatient to day-clinic therapy revealed that a long duration of illness (> 6 years), amenorrhea of more than 2.5 years as well as a lower weight at both admission and discharge were negative predictors (Howard et al., 1999).

In adolescent patients, the following factors predicted the necessity for rehospitalization: alcoholism of the parents, further AN cases in the family, an eating disorder in early childhood, periodic hyperactivity, slow weight gain at first-time hospitalization and low BMI at first discharge (Steinhausen et al., 2008).

Treatment dropouts

Due to patients' strong ambivalence regarding treatment, the risk of premature dropouts is generally high (Zeeck et al., 2005). The following factors are linked to an increased risk of dropout: a higher severity of eating disorder symptoms (Castro et al., 2004; Huas et al., 2011; Kahn & Pike, 2001), the bulimic subtype and a pronounced impulsivity (Fichter et al., 2006; Kaechele et al., 2001; Kahn & Pike, 2001; Woodside et al., 2004), marked fear of growing up (Woodside et al., 2004; Zeeck et al., 2005), strong worries about weight (Woodside et al., 2004) as well as a lower desired weight (Huas et al., 2011), a comorbid personality disorder, having one's own children and a lower educational level (Huas et al., 2011; Pham-Scottez et al., 2012; Roux et al., 2016). Patients with comorbid depression, by contrast, show a lower risk of treatment dropout (Roux et al., 2016; Zeeck et al., 2005). Moreover, early treatment dropouts appear to be characterized by a specific profile of risk factors: low desired weight, strong mistrust, and impulsive behavior (alcohol consumption,

[11] Note: Patients with a chronic course, in whom the objective is placed more on improving quality of life and social integration than on curing anorexia nervosa, also benefit from day-clinic treatment and a lower therapy dose.

suicide attempts) (Huas et al., 2011). In adolescent patients, the following factors are linked to an increased risk of dropout: a one-parent household, a strong dietary restriction, and a low initial body weight (Hubert et al., 2013; Roux et al., 2016).

Relapses

Fichter et al. (Fichter et al., 2006) found a renewed deterioration of general psychopathology and eating disorder pathology two years after inpatient treatment, but continuous improvements after six and twelve years. At the 12-year follow-up, the degree of improvement was comparable to that at discharge (28% good outcome, 25% moderate outcome, 40% chronically ill, 7% deceased). This roughly corresponds to the findings of an earlier study (Eckert et al., 1995). The majority of relapses occur within one year after discharge (Eckert et al., 1995; Isager et al., 1985; Strober et al., 1997b), with the highest risk between 4 and 9 months post-discharge (Carter et al., 2012). Patients who were able to maintain their weight in the first year after discharge, by contrast, go on to relapse in only 8% of cases (Eckert et al., 1995). The following predictors of relapse have been identified: low desired weight, long illness duration, bulimic subtype, increased body-related control behavior, reduction in motivation to change during treatment, as well as low motivation to change at discharge (Carter et al., 2012; Richard et al., 2005). In a 10-year follow-up following inpatient treatment of children and adolescents, 69% showed a good course, 23% a moderate course and 8% a poor outcome (Herpertz-Dahlmann et al., 2001).

A study of 212 adolescent patients (average age 14.9 years) found that 44.8% had to be rehospitalized at least once (Steinhausen et al., 2008).
Due to the risk of relapses, it is necessary to prepare the patient for the subsequent outpatient phase prior to discharge from inpatient treatment – for instance by spending weekends at home, practice discharges or a day-clinic treatment phase. Patients should have maintained the achieved target weight for some time. It is helpful to agree on interventions in the case of relapse (including readmission) with all persons involved before such cases occur.

Interventions for relapse prevention

There are a small number of randomized controlled trials on interventions following inpatient treatment. A one-year cognitive-behavioral psychotherapy was superior to an approach with "nutritional counseling" in adult patients with AN. One year after inpatient treatment, 44% of the group which received posthospitalization cognitive behavioral therapy achieved a good outcome, compared to 7% in the case of posthospitalization nutritional counseling (Pike et al., 2003). An internet-based offer as an adjunct to outpatient psychotherapy also appears to contribute to a more favorable course (Fichter et al., 2012). Posthospitalization offers, preferably through the clinic, can also be seen as beneficial; in these, the therapeutic relationship which developed during the inpatient stay is not abruptly stopped, but rather maintained over a transition period (e.g. post-inpatient individual or group sessions).

A randomized controlled trial by Russell et al. (Russell et al., 1987) showed that patients with an illness onset before the age of 19 years and a short course of illness benefited more from a

family-based therapy following hospitalization – in contrast to older patients, in whom an individual, supportive approach proved to be more favorable. In a randomized controlled trial, adolescents showed a significantly better treatment success 12 and 18 months post-hospitalization if they were offered, in addition to a multidimensional program (individual and family sessions), family sessions which did not focus on the eating disorder symptoms but rather explicitly on intra-family dynamics (Godart et al., 2012).

Summary: Evidence on inpatient treatment of AN

The available empirical evidence on the efficacy of inpatient treatment compared to outpatient therapy is very limited (Fairburn, 2005; Madden et al., 2015a; Meads et al., 2001; Vandereycken, 2003). This is primarily due to the fact that a randomization of very underweight patients into an outpatient or untreated control group does not appear to be ethically justifiable. Only two randomized controlled trials have compared inpatient treatment with outpatient options (Crisp et al., 1991; Gowers et al., 2007), but their findings need to be interpreted with great caution. Overall, it is apparent that studies on inpatient treatments examine patients with a substantially lower BMI than do studies on outpatient interventions (Zeeck et al., 2018). A further limitation is that the general conditions for inpatient treatments vary strongly depending on the health system, making it barely possible to compare studies from different countries.

- So far, there is no sufficient evidence regarding which elements of inpatient treatment are indispensible and which effects they achieve.
- There is limited evidence that the introduction of clearly structured symptom-oriented treatment components (weight guidelines, target weight) leads to higher success rates (EL 3; (Herzog et al., 1996)).
- There is limited evidence that a weight stabilization phase prior to discharge is linked to a longer outpatient period before the next rehospitalization (EL 4; (Lay et al., 2002)).
- There is limited evidence that discharge below a weight of BMI 18–20 kg/m² is associated with an increased rate of rehospitalizations and a higher risk of osteoporosis in the long term (EL 4; (Baran et al., 1995; Gross et al., 2000)).
- There is evidence that a one-year cognitive-behavioral intervention following inpatient treatment is superior to a procedure with “nutritional counseling” (EL 2a; (Pike et al., 2003)).
- There is evidence that in children and adolescents with an illness onset < 19 years and an illness duration of < 3 years, family-oriented interventions should be part of treatment following an inpatient episode; the interventions should predominantly also address the intra-family dynamics. Older patients with a late illness onset benefit more from individual therapy (EL 3; (Godart et al., 2012; Russell et al., 1987)).
- There is evidence that an internet-based relapse prevention in addition to outpatient interventions can contribute to preventing the eating disorder symptoms from increasing again following discharge (EL 2a; (Fichter et al., 2012))

Recommendations for the treatment of anorexia nervosa

General

- Patients with AN should be offered treatment as early as possible in order to avoid the disorder becoming chronic (GCP).
- The treatment of AN should be disorder-oriented and consider the physical aspects of the illness (GCP).
- Comorbid disorders should be systematically assessed and considered in the treatment (GCP).
- In the treatment, patients should be informed that the recovery process can encompass a period of many months to several years (GCP).
- Outpatient, day-hospital and inpatient treatments should take place in institutions or with therapists who have expertise in treating eating disorders (GCP).
- The involved care providers (e.g. registered therapists, advice centers, hospitals, family doctors/GPs, nutritional counselors) should ensure a close consultation and communication (GCP).
- A central therapeutic objective in the treatment of patients with AN is the normalization of body weight. Recommended target weights are the 25th BMI percentile for adolescents and a BMI $\geq$ 18.5 kg/m² for adults (GCP).
- To evaluate the medical risk or physical complications, in addition to weight development, further assessment parameters such as laboratory values and physical signs must be assessed (see guideline chapter 8 "Physical sequelae of eating disorders") (GCP).
- Depending on their physical status, patients with AN should be actively and regularly encouraged to attend progress check-ups (GCP).
- Patients with AN should receive advice on the appropriate amount and composition of food (GCP).
- Generally, patients with AN show strong ambivalence with respect to changing their weight and eating behavior. Therefore, work on motivation and ambivalence is a central task, which should be continued throughout the entire treatment process (EL 1a; A).
- If there are no explicit reasons to suggest otherwise, for children and adolescents with AN, the guardians or close family members/caregivers should receive in-depth information about the illness and treatment options, and should be included in the treatment (EL Ib; A).
- A compulsory treatment of patients with AN should only be used in the case of acute self-endangerment and once all other interventions have been exhausted (GCP).

Outpatient treatment

- The outpatient treatment of first choice in patients with AN should be an evidence-based psychotherapy (for children and adolescents: family-based therapy; for adults: FPT, CBT-E, MANTRA, SSCM)[12], led by therapists experienced in the realm of eating disorders (EL Ib; B).

[12] FPT = Focal Psychodynamic Psychotherapy; CBT-E = Cognitive-Behavior Therapy, Enhanced; MANTRA = The Maudsley Model of Anorexia Nervosa Treatment for Adults; SSCM = Specialist Supportive Clinical Management

[Note: In the German directives for psychotherapy, only psychodynamic psychotherapy, cognitive-behavior therapy and systemic psychotherapy are approved methods for the indication "eating disorder"]

- Nutritional counseling should not be provided as a sole treatment; this also applies to interventions employed following inpatient treatment (EL 2b; B).
- In the outpatient setting, a weight gain of 200-500mg/week is highly recommended. Some flexibility in this regard is possible (GCP).
- Prior to outpatient psychotherapy, the general conditions of the treatment should be discussed with the patient (and where appropriate the guardian): e.g. dealing with weighing, procedure in the case of weight loss, contacts with family doctor/pediatrician/gynecologist, dealing with the family (GCP).
- A primary objective of outpatient treatment of patients with AN should be the normalization of eating behavior and weight, as well as work on the related psychological and psychosocial problems (GCP).
- Following outpatient psychotherapy, follow-up appointments should be offered by the psychological or medical psychotherapist, child and adolescent psychiatrist/ psychotherapist or the attending (family/pediatric) physician. These should take place at regular intervals over a period of at least one year, and should have the aim of maintaining the treatment outcome as well as relapse prevention (GCP).
- If development deteriorates or stagnates during outpatient psychotherapy, more intensive treatment options (e.g. inpatient treatment; potentially also day-hospital treatment or a combination of treatment approaches in the outpatient setting) should be offered in a timely manner (GCP).

Day-hospital treatment

- In the following cases, a day-hospital treatment should be considered (GCP):
  – For preparing patients to transition to the outpatient situation following an inpatient treatment ("transfer" of the achieved changes to everyday life; "step-down"); day-hospital treatment should be delivered with disorder-specific expertise and within the same treatment team wherever possible.
  – For well-motivated patients without comorbidity and only moderate underweight (BMI > 15kg/m² or > 3rd BMI age percentile in children and adolescents), in whom outpatient treatment does not prove to be sufficient (intensification of outpatient treatment).
  – For patients with a chronic course and repeated inpatient stays in the past, if the aim is to improve social integration and daily structure.

- Further treatment in a day-hospital - following inpatient treatment with sufficient stabilization of the physical status - should be considered in children and adolescents, if the day-hospital treatment can ensue with disorder-specific expertise within the same treatment team, and if a close integration of family members is guaranteed (EL 1b; A).

Inpatient treatment

- Inpatient treatment has to be offered if one or more of the following criteria are present (GCP):
  – rapid or sustained weight loss (> 20 % over six months)
  – severe underweight (BMI < 15 kg/m^2, or below the 3rd age percentile in children and adolescents)
  – sustained weight loss or insufficient weight gain over three months (earlier for children and adolescents) despite outpatient or day-hospital treatment
  – social or family factors which strongly hamper the healing process (e.g. social isolation, problematic family situation, insufficient social support)
  – pronounced mental comorbidity
  – suicidality
  – severe bulimic symptoms (e.g. abuse of laxatives/diuretics, severe binge eating with vomiting) and/or excessive urge to exercise, which cannot be mastered in the outpatient setting
  – physical risk or complications
  – low insight into the illness
  – excessive demands in the outpatient setting (too little structure in the guidelines regarding mealtime structure, amount of food, feedback on eating behavior; for children and adolescents: breakdown of family resources)
  - necessity for treatment by a multi-professional team (multi-modal treatment program integrating psychological and medical treatment methods as well as social work and creative arts therapies) within a hospital setting (psychosomatic/psychiatric hospital treatment).

- Inpatient treatment should take place in institutions that are able to offer a specialized, multimodal treatment program (EL 4; A).

- The following disorder-specific treatment components should be provided within the framework of a specialized day-hospital/inpatient treatment program, beyond the features of a psychosomatic-psychotherapeutic hospital treatment or a psychiatric-psychosomatic hospital treatment in children and adolescents (GCP):
  – Disorder-oriented psychotherapy (in the individual and group setting)
  – Disorder-oriented nutrition management (cf. Chapter 2.2.16.)
  – Interventions which target a change in behavior regarding weight, eating and where appropriate exercise (including supervision of eating and clear agreements/"contracts" between patient and treatment team regarding a target weight and weekly weight gain)
  – Medical treatment and regular medical rounds with discussion of weight trajectory
  – Disorder-oriented body therapy and where appropriate sport therapy
  – Integration of the family, at least for children and adolescents

- Within the overall treatment plan, in the case of inpatient treatment, a weight restoration should be striven for (for adults: BMI ≥ 18.5 kg/m², for children and adolescents: the 25th BMI age percentile, but at least the 10th age percentile). Nevertheless, an individual target

weight can also be set under consideration of further factors (e.g. duration of illness, premorbid weight) (GCP).

- In the case of inpatient treatment, a weight gain of 500-1000g/week is highly recommended (GCP).
- Patients should be regularly weighed (generally 1-3x/week) in the morning on an empty stomach, at around the same time and in light clothing (underwear) (GCP).
- To reduce the likelihood of relapses in the final stage of inpatient therapy, the aim should be for the patient to at least maintain the achieved weight over a certain time. Moreover, the patient should be prepared for the transfer to the outpatient setting (EL 4; B).
- Due to an increased risk of relapse, particular attention should be paid to the transfer between settings (above all into less intensive settings: inpatient → outpatient) and that a networking with outpatient further treatment providers is actively sought (CGP). Particularly beneficial are options, which facilitate the transfer to the outpatient setting, such as post-inpatient groups or internet-based therapy (EL 4; B). To prepare for the transfer to the outpatient setting, also a (re-)integration into the school and work environment should be sought (GCP).
- Inpatient treatment should be followed by outpatient psychotherapy. For children and adolescents, this (if there are no serious reasons to suggest otherwise) should be a family-oriented psychotherapy (EL 2a; A)

Pharmacotherapy

- Neuroleptics and antidepressants should not be used only in order to achieve weight gain in AN (EL 1a; A).
- If thinking is considerably restricted to weight concerns and eating, and hyperactivity cannot be mastered, an attempt to employ neuroleptics at low doses can be justified in individual cases (mainly olanzapine (EL 2a; O)). In this regard, pharmaceuticals with a low extrapyramidal impairment should be preferred. The treatment indication should be limited to the duration of the aforementioned symptoms (no long-term treatment) and only applies in the framework of the overall treatment plan. In this regard, the patient must be informed about the nature of off-label use (GCP).

Nutrition management

- If medical monitoring is guaranteed, for patients with mild to moderate AN, an initially low calorie consumption with stepwise increases is not necessary for safe weight gain (avoidance of refeeding syndrome) (EL 2a; evidence statement). Initial calorie intake should lead to a sufficient weight gain, taking the acceptance of the patient into account (GCP).
- The energy intake for the weight gain to be expected is highly variable. It should be individually tailored to the patient and the treatment phase, and continuously monitored (GCP).
- The refeeding of severely malnourished patients with AN must be conducted in the inpatient setting, with close medical monitoring (lab, heart/circulation parameters, fluid balance) (GCP).

- To ensure a sufficient food intake, especially at the beginning of therapy, liquid food can be used as a supplementation (or if necessary also as a replacement) to a not yet sufficient normal nutrition. (EL 3; O). Products should be used that are suitable for complete nutrition, i.e. which contain all components of normal nutrition in balanced amounts.
- If refeeding through a regular food or liquid intake proves to be insufficient, liquid food and gastric tube feeding should also be considered (GCP).
- In the case of severe starvation, regular checks of the phosphate serum level must be conducted. There should be either an increased oral supply of phosphate (via food supplements or the oral administration of sodium monohydrogen phosphate) or a substitution oriented to the serum level. Kidney function should be noted in this regard (CGP).
- In the treatment of AN, serum potassium levels should be checked regularly. Furthermore, in the case of decreased values, checking signs of hypokalemia and ruling out cardiac arrhythmia is mandatory. Finally, hypokalemia should be compensated by exogenous, preferably oral administration of potassium chloride (GCP).
- A hypo- or hypernatremia should first be compensated through the normalization of the fluid balance with normal sodium intake through food. Particularly with parenteral sodium administration, a rise in serum sodium must not exceed 6 mmol per day (GCP).
- In the case of a very low starting weight, an initial substitution of vitamin B1 for preventive purposes should be considered (GCP).
- Iron substitution should only be considered if iron deficiency anemia has been established (low ferritin) (GCP).
- In the case of vitamin deficiencies (especially thiamine [B1], riboflavin [B2], niacin [B3], folic acid [B9]) and vitamin D), a vitamin substitution should take place (GCP).

Table 1: Criteria for AN according to ICD-10, ICD-11 (proposal) and DSM 5

ICD-10 (1993)	Proposal ICD-11 (2018)	DSM 5 (2013)
F 50.0 Body weight at least 15% below expected weight or body mass index ≤ 17.5 kg/m² Weight loss is self-induced through: – avoidance of high-calorie foods and/or – self-induced vomiting – self-induced purging – excessive exercise – use of appetite suppressants, diuretics etc. Body image disturbance; excessive notion of being/becoming too fat; a very low weight threshold is set Endocrine disorder (hypothalamic-pituitary-gonadal axis), manifests, for example, in amenorrhea If onset is prepubertal, the sequence of pubertal development steps is delayed, e.g. growth ceases, primary amenorrhea. **F 50.00** (AN without active measures for weight loss) no vomiting, no abuse of laxatives or diuretics **F 50.01** (AN with active measures for weight loss) Self-induced vomiting, laxative abuse or similar, binge eating may occur	**6B10** • Underweight (BMI < 18.5kg/m² or < 5th age percentile), that is not due another illness or the unavailability of food • Persistent pattern of behaviors which hinder the restoration of a normal body weight (restrictive eating behavior, self-induced vomiting, laxative abuse, excessive exercise), which are typically accompanied by a fear of weight gain • Disturbance in the perception of one's own shape or body weight, or undue influence of body weight and shape for self-evaluation **6B10.1** AN with significantly low body weight • BMI between 18.5 and 14.0 kg/m² (between 5th and 0.3rd age percentile for children and adolescents) • 6B10.11: restrictive type • 6B10.12: binge-purging type **6B10.2** AN with dangerously low body weight • BMI < 14.0 kg/m² (age percentile in children and adolescents < 0.3.) • 6B10.21: restrictive type • 6B10.22; binge-purging type	**307.1** **(A)** Restriction of energy intake relative to requirements leading to a significantly low body weight (weight lies below the minimum of normal weight or, for children and adolescents, less than that which is minimally expected). (B) Intense fear of gaining weight or becoming fat, or persistent behavior that interferes with weight gain, despite significantly low weight (C) Disturbance in the way in which one's body weight or shape is perceived, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight **Restrictive type:** During the last 3 months, no recurrent episodes of binge eating or no "purging" behavior **Binge-Eating / Purging type:** During the last 3 months, recurrent episodes of binge eating or "purging" behavior **In partial remission:** After full criteria were previously met, Criterion A has not been met for a sustained period, but either Criterion B or C is still met. **In full remission:** After full criteria were previously met, none of the criteria have been met for a sustained period of time. **Severity:** For children and adolescents, the corresponding BMI percentiles should be used. The level of severity may be

		increased to reflect clinical symptoms, the degree of functional disability or the need for supervision. • Mild: BMI ≥ 17 kg/m² • Moderate: BMI 16 – 16.99 kg/m² • Severe: BMI 15 – 15.99 kg/m² • Extreme: BMI < 15 kg/m²

Table 2: Randomized controlled trials on psychotherapy of AN

Study	Design	Therapy arms	Cases (N /arm)	Drop-outs	Measurement time points	Sample	Endpoints (primary, secondary)	Results	Notes/study quality
Agras et al. 2014 Lock et al. 2016	RCT	Family-based treatment (FBT)	78	20 (+ 4 before start of intervention)	Baseline, end of therapy Follow-up: 6 mths and 1 yr	A DSM IV Age: 15.3 yrs 0% > 18 yrs Female: 89.2% Illness duration: 1.1 yr Weight: 81.9% IBW Restrictive: 55.7%	<u>Primary</u>: % ideal body weight, Remission (≥ 95% IBW)	No difference regarding primary endpoint	Study quality: moderate No information on how many patients were assessed at follow-up, no consideration of dropouts in the power analysis, unclear for how many patients objective weight data were available, approx. ¼ of patients dropped out, partly contradictory info. on dropouts
		Systemic family therapy (SyFT) 16 sessions over 9 months	80 (164 pat. were random.)	20 (2 before start of intervention)			<u>Secondary</u>: Costs, days in hospital, initial weight gain	FBT > SyFT regarding: quicker weight gain, fewer hospital days, lower costs, pat. with OCD benefited more (weight) from SyFT	
Bachar et al. 1999	RCT	Self psychological treatment (SPT)	7	1	Baseline, end of therapy Follow-up: 1 yr	E/A DSM IV Age: 18.1 yrs % > 18 yrs? Female: 100%	<u>Primary:</u> DSM-SS (Symptomatology Scale for AN and BN) EAT 26 BSI	SPT > COT (DSM-SS, EAT 26, Selves Questionnaire	Study quality: very low Weight at end of therapy?; no ITT analysis; type of randomization not reported; low case

						Illness duration: 2.9 years Weight 16.4 BMI Restrictive: ? %	Selves Questionnaire		number; only 2 completers in SPT; additional nutritional counseling Overall: Results not usable due to low case numbers
		Cognitive orientation treatment (COT)	6	4			<u>Secondary:</u> No differentiation between primary and secondary		
Ball & Mitchell 2004	RCT	Cognitive-behavior therapy (CBT)	13	4	Baseline, end of therapy FU: 6 mths	E/A, SY DSM -5 Age: 13–23 yrs % > 18 yrs? Female: 100% Illness duration: ? yrs Weight: 16.3 BMI Restrictive: 64 %	<u>Primary</u>: % good outcome = within 10 % ABW and menstruation	No group diff. ~ 60 % at therapy end and at 6-mth. FU.	Study quality: very low Also included subsyndromal patients; no info. on blinding and type of randomization, only completer analysis; small case number
		Behavior family therapy (BFT)	12	3			<u>Secondary</u>: Among others: Morgan &Russell, EDE, EDI, BDI, STAI, self-esteem, fam. communication.	No group diff.	
Bergh et al. 2002	RCT	Computer Support (CE)	10	?	Baseline, then every 3 mths	E/A DSM -IV Age: 16 yrs. % > 18 yrs? Female: ?	<u>Primary</u>: Time until remission	Average time for whole group (AN+BN): 14.4 mths; only 1 pat. in control gp achieved remission (mean	Study quality: very low Number of dropouts, number of remitted patients and procedure and analysis methods unclearly described; waitlist controls: waited 7–21 mths, 70 % (14/20) of pats. in the control gp left the

						Illness duration: 2 yrs Weight: 15.0 BMI Restrictive: ? %		waiting time 17.5 mths)	study and sought treatment elsewhere; intervention of little relevance, for 4 patients CE under standard conditions
		Waitlist controls	9	?			<u>Secondary</u>: -		
Brockmeyer et al. 2014	RCT (pilot study)	Treatment as usual (TAU: inpatient or outpatient) + cognitive remediation therapy (CRT)	20	9	Baseline, end of therapy	E DSMIV Age: 23.6 / 26.7 yrs % > 18 yrs? Female: ? Illness duration: 7.9 / 6.8 yrs Weight: 14.7 BMI Restrictive: 79 / 95%	<u>Primary</u>: Cognitive flexibility	CRT > NNT	Study quality: Moderate Limited mainly by completer rather than ITT analysis (pilot study), case number
		Treatment as usual (TAU: inpatient or outpatient) + nonspecific neurocognitive therapy (NNT)	20	6			<u>Secondary:</u> Acceptance	No diff.	
Channon et al. 1989	RCT	Outpatient management (OM)	8	1 (FU)	Baseline, after 6, 12, 18 mths	E Morgen & Russell criteria Age: 23.8 yrs % > 18 yrs? Female: ?	<u>Primary:</u> Morgen & Russell score	No gp diffs.	Study quality: very low No ITT analysis, small case number, no blinding, one therapist for all patients (who also conducted assessments), no absolute scores indicated for
			8	1 (FU)			<u>Secondary:</u>	No gp diffs.	

		Cognitive behavior therapy (CBT)				Illness duration: 5.3 yrs Weight: 15.3 BMI Restrictive: ? %	EDI, BDI, bulim. symptoms		post and follow-up outcome: patients improved, no superiority of one setting
		Behavioural treatment (BT)	8	0					
Crisp et al. 1991 (Gowers et al. 1994)	RCT	"one-off"	20	0	Baseline, after 1 yr FU: 5 yrs	E DSM III-R Age: 22 yrs 100 % > 18 yrs Female: 100% Illness duration: 3.3 yrs Weight: 15.5 BMI Restrictive ? %	<u>Primary:</u> Weight	Weight gain lower in "one-off" than in other gps	Study quality: moderate Type of randomization and blinding not described: no CONSORT statement; "one-off" group had longest illness duration; many dropouts in inpatient group; here also fewer experienced treatment providers (see Crisp 2002)
		Inpatient therapy	30	12					
		Family discussions + individual therapy + nutritional counselling (outpatient)	20	2			<u>Secondary:</u> Morgan & Russell score	No group diffs.	
		Group therapy+ Nutritional counseling (outpatient)	20	3					
Dalle Grave et al. 2013	RCT	13 wk inpatient + 7 wk day-clinic therapy CBT-Ef	42	5	Baseline, end of therapy	E / A DSM IV Age: 23.4 yrs	<u>Primary:</u> Completion of treatment	No diff. Overall, 90% completers	Study quality: high

		(cognitive-behavior therapy enhanced / CBT-E focusing on eating disorder symptoms)			6 and 12 mths after end of therapy	29% < 18 yrs Female: 78% Illness duration: 5 yrs Weight: 14.3 BMI Restrictive: approx. 2/3			
		13 wk inpatient + 7 day-clinic CBT-Eb (CBT-E "broad": focus on eating disorders symptoms + affect intolerance, perfectionism, self-esteem, interpersonal problems)	38	3			<u>Secondary:</u> BMI	No diff.; Improvement in ED symptoms and general psychopathology remains stable to follow-up	
Dare et al. 2001	RCT	Routine treatment (RT)	17	4	Baseline, after 1 yr (end of therapy)	E DSM -IV Age: 26.3 yrs % > 18 yrs? Female: ? Illness duration 6,3 yrs	<u>Primary:</u> Weight	Overall: Specialized therapies > routine treatment; Focal analytic therapy and FT > RT	Study quality: low Blinding unclear; overall small case number; high dropout rate; no follow-up; 12 patients (15 %) temporarily admitted to inpatient treatment
		Cognitive-analytic therapy (CAT)	22	9					
		Family therapy	21	5			<u>Secondary:</u>	No gp diffs.	

		Focal analytic therapy	19	7		Weight: 15.4 BMI Restrictive: ? %	Morgen & Russell score, Dropouts		
Eckert et al. 1979	RCT	Behavior management (BM) (inpatient)	40	?	Baseline, end of intervention (after 35 days)	? DSM ? Age: ? % > 18 yrs? Female: ? Illness duration: ? Weight: ?% Restrictive: ? %	<u>Primary:</u> Weight	No gp diffs.	Study quality: very low Diagnostic criteria? Sample insufficiently described, interventions (clinics) and methods not sufficiently described, dropouts not mentioned, no follow-up
		Standard treatment (ST) (inpatient)	41	?			<u>Secondary:</u> -		
Eisler et al. 2000 (Eisler et al. 2007) Prelim. study: Le Grange et al. 1992	RCT	Conjoint family therapy (CFT)	19	2	Baseline, end of therapy FU.: 1 yr, 5 yrs	A DSM –IV Age: 15.5 yrs % > 18 yrs? Female: 97.5% Illness duration: 1 yr Weight: 74.3%ABW Restrictive: 75%	<u>Primary:</u> Not clearly defined Morgen & Russell score?	Trend for better outcome in SFT (76 % vs. 47 % "good + intermediate")	Study quality: moderate Stratification according to extent of parental criticism; 5-year follow-up reported in Eisler et al. 2007; ITT analysis, dropouts not sufficiently described, low case number
		Separated family therapy (SFT)	21	2			<u>Secondary</u> EDI, EAT, SMFQ, RSE, MOCI, , FACES-II, SCFI	CFT: somewhat more "psychological change" (mood, compulsiveness, psychosex. level.); After 5 yrs: no gp diff.; with high	

								maternal criticism, poorer course in CFT (Eisler et al. 2007)	
Eisler et al. 2016	RCT	Multi-Family Therapy (MFT)	86	9	Baseline, 3 mths, 12 mths (end of therapy) 18 mths (6 mths after therapy)	A DSM-IV Age: 15.7 yrs % < 18 yrs: Not specified Female: 91% Illness duration: 0.8 yrs Weight: 15-8 BMI (%mBMI 78) Restrictive: ? %	<u>Primary:</u> Morgen & Russell Scale (end of therapy)	MFT-AN > FT-AN (75% vs. 60% good or moderate outcome)	Study quality: high
		Single-Family Therapy (SFT)	83	9			<u>Secondary:</u> Morgan & Russell after 18 mths Weight EDE, BDI, Rosenberg Scale Satisfaction Parents: Experience of Caregiving Inventory	No group diffs. apart from MFT-AN > FT-AN for %mBMI after 18 mths	
Fichter et al. 2012	RCT	Internet-based relapse prevention (RP) after inpatient therapy over 9 months	128	7	Baseline (time of discharge), End of intervention	E / A DSM IV Age: 24.0 yrs % < 18 yrs: not specified Female 100%	<u>Primary:</u> BMI difference	RP > TAU (but only in completer analysis)	Study quality: low no ITT analysis, weight partially captured by self-report, no control for center effects, additional interventions unclear
			130	8			<u>Secondary:</u>		

		Treatment as usual (TAU)				Illness duration: ? Weight: 17.8 BMI Restrictive: 55.9%	SIAB-Ex, -S EDI-2 Morgan & Russell BSI (Brief Symptom Inventory)	RP > TAU on the SIAB-EX sexual anxieties and bulimic symptoms, otherwise RP not superior	
Geist et al. 2000	RCT	Inpatient therapy + family therapy in a group	?	?	Baseline, end of intervention (after 4 mths)	A, SY Clinical judgment (DSM IV) Age: ~ 14.5 yrs 0% > 18 yrs Female: 100% Illness duration: ? Weight: 77.2 /74.9 %IBW Restrictive: ? %	<u>Primary:</u> Weight	No gp diffs.	Study quality: very low Low case number; Randomization, dropouts, stat. methods not sufficiently described; no follow-up; no blinding; effects of strict inpatient regime mask the effects of the family intervention (days: 8-107 inpatient treatment); 5 pats. rehospitalized following first discharge; 79 % of all inpatients refused to participate
		Inpatient therapy + family therapy	25 pat. random.	?			<u>Secondary:</u> EDI-2, CDI, BSI, FAM-III	No gp diffs.	
Godart et al. 2012	RCT	Post-hospitalization intervention TAU	30	7	Baseline After 18 months.	A DSM -IV Age 16.6 yrs % > 18 yrs? Female: 100 % Illness duration: 16.6 mths Weight 16.9 BMI	<u>Primary:</u> Morgen & Russell criteria	TAU + FT > TAU	Study quality: moderate Contradictory information on dropouts; among others, problematic power calculation, selection criteria for sample unclear
		TAU + family therapy with focus on family dynamics (TAU+FT)	30	5			<u>Secondary:</u> BMI, Menstruation, EDI	TAU + FT > TAU for reaching 10th BMI percentile	

						Restrictive 86.7 %	Re-hospitalization SAS (social integration) GOAS Total score	and resumption of menses	
Goldfarb et al. 1987	RCT	Desensitization (inpatient)	4	?	Baseline, 6 and 18 mths after discharge)	E/A, SY DSM-III Age: 17.4 yrs % > 18 yrs? Female: ? Hospital duration 1.2 yrs Weight: 17.0 BMI Restrictive: ? %	<u>Primary:</u> ?		Study quality: very low Only one therapist (psychology student), extremely low case number (data from additional 11 patients from completed files, only 7 randomized), vague inclusion criteria, interventions not clearly differentiated, randomization procedure unclear, no blinding, no ITT analysis; dropouts?
		Relaxation therapy (inpatient)	3	?			<u>Secondary:</u> Rosenberg Self-esteem Scale, Goldfarb´s "fear-of-fat" Scale Overall outcome rating after 18 mths	Relax > DS and "Routine" regarding self-esteem, fear of fat after 6 mths, also in overall outcome after 18 mths	
		"Routine"	11 (histor. control)	?					
Gowers et al. 2007 (Gowers et al. 2010)	RCT	Inpatient therapy	57	29	Baseline, after 1 yr, after 2 yrs FU 5 yrs (Gowers et al. 2010)	A Clinical diagnosis acc. DSM-IV Age: 15 yrs 0% > 18 yrs Female 92%	<u>Primary:</u> Morgan & Russell Scale	In ITT analysis no gp differences after 1 and 2 yrs	Study quality: moderate In the specialized outpatient gp. 10 pts were temporarily hospitalized (plus 4 of those who did not begin treatment), from the TAU gp, 7 patients were
		Specialist outpatient therapy	55	14					

		TAU	55	17		Illness duration: 1.1 yrs Weight: 15.3 BMI% Restrictive: 76%	<u>Secondary:</u> HoNOSCA (-SR), EDI, FAD, MFQ	No gp differences; Poorest acceptance: inpatient therapy After 5 yrs, outpatient therapy more cost-effective than inpatient	temporarily hospitalized, plus 10 others who had dropped out, Dropout rate > 20%
Hall & Crisp 1987	RCT	Individual therapy + Family sessions	15	1	Baseline, after 1 yr	E/A DSM? Age: 19.6 yrs % > 18 yrs? Female: 100% Illness duration: 1.4 yrs Weight: 15.2 BMI Restrictive: ? %	<u>Primary:</u> Weight	No group difference	Study quality: low Diagnostic instrument unclear, no blinding, type of randomization unclear, no ITT analysis, very variable duration of therapies (range 84-168 days); DA gps also received family discussions and psychiatric discussions (15 min) from therapists of the other therapy arm
		Dietary advice (DA)	15	4			<u>Secondary:</u> Morgan & Russell Score Crown-Crisp-Experiential Index (CCEI)	in PG group, 4 pats. with full remission after 1 year, none in DA gp; PG: stronger improvement in social and sexual funct.	
Herpertz-Dahlmann et al. 2014		Inpatient therapy	85	10	Baseline, discharge, FU: 1 yr	A DSM IV Age: 15.3	<u>Primary:</u> BMI (Baseline → 1 yr)	DP not inferior to IP	Study quality: high

		3 weeks inpatient therapy + day-clinic (« step-down »)	87	25		0 % > 18 yrs Female: 100% Illness duration: 53.7/ 42.4 wks Weight: 2.2 / 1.8 BMI percentile Restrictive: 86% / 83%	<u>Secondary:</u> Costs Morgan & Russell criteria EDI-total score Number of readmissions BSI	DP: more cost-effective DP > IP psychosexual development and psychological well-being	
Hibbs et al. 2015 (Magill et al. 2016)	RCT	Inpatient or day-clinic therapy + ECHO (for caregivers)	86 (134 caregivers)	17 (after 1 yr)	Baseline, discharge FU: 6 mths, 1 yr, 2 yrs	A / E DSM IV Age: 24 yrs % > 18 yrs? Female: 85% Illness duration: 6.3 yrs Weight: 14.4 BMI Restrictive: 30% BMI: 14.4	<u>Primary</u>: Relapse rate after 1 yr (ECHO)	Lower relapse rate for ECHO	Study quality: low No structured interview for diagnosis, only self-rating, no blinding
		Inpatient or day-clinic therapy (TAU)	92 (134 caregivers)	16 (after 1 yr)			<u>Secondary:</u> BMI Quality of life ED pathology Distress	QoL, ED pathology, better in ECHO gp after 6 mths but not 1 yr or 2 yrs after discharge; also more positive effects on caregivers, but which are no longer significant after 1 yr	
Le Grange et al. 1992	RCT	Conjoint family therapy (CFT)	10	?		A, SY DSM III-R	<u>Primary:</u> Weight,	No gp diffs.	Study quality: very low

		Separate family therapy (Fam)	8	?	Baseline, after 16 wks, after 32 wks	Age: 15.3 yrs 0 % > 18 yrs Female: 89% Illness duration: 1.1 yrs Weight: 77.9 % ABW Restrictive: 87.8%	<u>Secondary:</u> Menstruation, EAT, Morgan & Russell Scale, SCFI, EE, FACES-II	No group diff.; poorer outcome associated with higher fam. dissatisfaction and higher degree of critical comments in the family	Randomization methods not described, no ITT analysis, very small case number
Le Grange et al. 2016	RCT	Family-based therapy (FBT)	55	9	Baseline, end of therapy 6 and 12 mths post-treatment	A DSM IV Age: 15.5 yrs 0 % > 18 yrs Female: 87.7% Illness duration: 10.5 mths Weight: 16.5 BMI Restrictive: ? %	<u>Primary:</u> Remission rate at end of therapy (BMI + EDE)	PFT superior at end of therapy (trend), but no longer at FU	Study quality: moderate Randomization unclearly described, high dropout rates
		Parent-focused therapy (PFT)	52	8			<u>Secondary:</u> EDE-Total score % median BMI	No gp differences	
Lock et al. 2005	RCT	Family-based therapy “low dose”	42	10	Baseline, after 6 mths, after 12 mths (end of therapy)	A, SY DSM-IV Age: 15.2	<u>Primary:</u> Weight, EDE,	No gp differences	Study quality: high

		Family-based therapy "high dose"	44	7		0 % > 18 yrs Female: 89.5% Illness duration 1 yrs Weight: 17.1 BMI Restrictive: 82%	<u>Secondary:</u> YBC-ED, CBCL, Family Environment Scale	Longer therapy more beneficial with clear compulsive traits and non-intact families	However, no follow-up, stratified according to illness duration¸ higher BMI at start
Lock et al. 2010 Le Grange et al. 2014 Ciao et al. 2015	RCT	Adolescent-focused individual therapy (AFT)	60	4	Baseline, end of therapy, after 6,12 mths, Long-term FU	A DSM-IV Age: 14.4 0% > 18 yrs Female: 91% Illness duration: 1 yr Weight: 16.1 BMI Restrictive: 83%	<u>Primary</u>: Rate of patients in full remission	End of therapy: no gp diff; after 6 and 12 mths: FBT > AFT	Study quality: moderate High dropout rate in FBT, no blinding, high number of patients temporarily hospitalized (not considered in analyses: 37% in AFT and 15% in FBT)
		Family-based treatment (FBT)	61	13			<u>Secondary:</u> Weight ED pathology	BMI percentile and change in ED pathology at end of therapy: FBT > AFT (but no longer at follow-up)	
Lock et al. 2013	RCT	Cognitive remediation therapy (CRT) for 2 mths + 16 sessions cognitive-behavior therapy (CBT) for 4 mths	23	3 (up to 8th session)	Baseline, 8 wks, End of therapy	A/E Clinical judgment (DSM IV) Age: 22.7 yrs % > 18 yrs? Female: 89%	<u>Primary:</u> Dropout rates	In the first 2 mths fewer dropouts under CRT	Study quality: moderate Small case number, dropout rate > 20 % in CBT, diagnosis based on clinical judgment, no absolute values for BMI

						Illness duration: 6.4 yrs Weight: 17.5 BMI Restrictive: ? %			
		Cognitive-behavior therapy (CBT) für 6 Mo	23	8 (up to 8th session)			<u>Secondary:</u> Cognitive abilities, BMI, EDE, BDI, Rosenberg Self-Esteem Scale among others	Cognitive abilities CRT > CBT, no diffs. in other outcomes	
Lock et al. 2015	RCT	Family-based therapy	10	2	Baseline, End of therapy	A DSM IV Age: 14.6 yrs 0 % > 18 yrs Female: 91% Illness duration: 1 yr Weight: 16.2 / 82.4 %IBW Restrictive: ? %	<u>Primary:</u> Dropout rates, number of attended sessions	No gp diffs.	Study quality: very low Too small case numbers to answer research question, study design problematic
		FBT or FBT + IPC («intensive parental coaching» = 3 sessions with focus on meals in patients with insufficient weight gain after 4th session)	23 FBT 12 FBT+IPC	5 FBT 2 FBT+IPC			<u>Secondary:</u> Expectations ED pathology, Weight	No gp diffs.	

Madden et al. 2015a,b	RCT	«Weight restoration» WR (up to 90% exp. KG) + 20 outpatient settings	41	8	Baseline,discharge, end of outpatient sessions DU: 6, 12 mths	A DSM IV Age: 14.9 yrs 0 % > 18 yrs Female: 95.1% Illness duration: 7.6 mths. Weight: 78.3 % EBW Restrictive: 69.5%	<u>Primary:</u> Number of inpatient treatment days after first admission (to FU 12 mths)	No group difference	Study quality: moderate Allocation concealment not given; clear sample differences in two participating centers
		«Medical stabilization » MS (inpatient up to medical stabilization) + 20 outpatient sessions	41	5			<u>Secondary:</u> Total number of inpatient treatment days up to FU (12 mths); Number patients with full remission (weight > 95% KG) + EDE total score 1 SD of mean	WR: more inpatient treatment days and post-hospital family sessions up to 12-month FU	
Mc Intosh et al. 2005 (Carter et al. 2011)	RCT	Specialist supportive clinical management (SSCM)	16	5	Baseline, end of therapy FU: > 5 yrs (Carter et al. 2011)	A/E, SY DSM-IV Age: 23 yrs % > 18 yrs? Female: 100% Illness duration: Weight: ?% Restrictive: ?	<u>Primary:</u> Global AN rating	SSCM > CBT/IPT in completer analysis, otherwise n.s. No group diffs in FU	Study quality: moderate Randomization method not described; no follow-up; Sample description insufficient, dropout rate > 20%
		Interpersonal Therapy (IPT)	21	9			<u>Secondary:</u> Weight		

							HDRS, GAF EDE EDI	EDE "restraint": CBT, SSCM > IPT GAF: SSCM > CBT, IPT	
		Cognitive-behavior therapy (CBT)	19	7					
Parling et al. 2016	RCT	Acceptance Commitment Therapy (ACT)	24	11	Prior to day-clinic admission, before randomization /end of DC treatment, after intervention FU. 6, 12, 18, 24 mths after end of treatment FU : after 5 yrs	E, SY DSM-IV Age: 25.7 yrs 100% > 18 yrs Female.: 98% Illness duration ?: Weight: 17.5 / 18.1 BMI (before rand.) Restrictive: ? %	<u>Primary:</u> Remission (BMI + EDE-Q)	No gp diffs.	Study quality: very low Target acc. to power analysis: inclusion of 120 patients; only 43 recruited; dropout rate for ACT 45.8%, 80-90% subsyndromal AN
		TAU After 9-12 weeks day-clinic treatment (DC)	19	3			<u>Secondary</u>: EDI BSQ Quality of life(QOLI) Rosenberg Self-Esteem	No gp diffs.	
Pike et al. 2003	RCT (relapse prevention)	Cognitive-behavior therapy (CBT) after inpatient therapy	18	0	Baseline, end of therapy	E DSM-IV Age: 26.1 / 24.3 yrs 100 % > 18 yrs? Female: 100%	<u>Primary:</u> Relapse rate	CBT > NC CBT: 22% relapses: vs. 53 %	Study quality: moderate Blinding? No follow-up, small case number, dropout defined as dropping out within first 10 of 50 sessions

		Nutritional counselling (NC) after inpatient therapy	15	3		Illness duration 7.6 / 7.3 yrs Weight: 15.6 BMI Restrictive: approx. 52% Patients included when inpatient treatment successfully completed (≥ 90 % IBW, no medical probs, eating behav normalized)	<u>Secondary</u>: "Failure rate": (relapses + dropouts)	"Failure rate": 22 % (CBT) vs. 73 % (NC)	
Pillay & Crisp 1981	RCT	Inpatient therapy + social skills training (SST)	13	3	Baseline, after 1 yr	A/E DSM? Age: 23.7 yrs % > 18 yrs? Female:%? Illness duration: ? Weight: 15.4 BMI Restrictive: 56%	<u>Primary:</u> ? Weight, CCEI (Crown & Crip-Index: self-report) Social Questionnaire (SAD, FNE) Social Situations Questionnaire	No gp diffs.	Study quality: very low DSM?; no blinding; type of randomization unclear; no ITT analysis; small case number; dropout rate > 20%, no validated outcome measures
		"Placebo" (inpatient therapy)	20	8			<u>Secondary:</u> ?		

Rhodes et al. 2008	RCT	TAU	10	38% relating to data overall	Hospital discharge, end of 20-session outpatient intervention	A DSM? Age: 12-16 yrs 0% > 18 yrs Female:100% Illness duration: 5% > 1 yr Weight: 82.5% IBW (discharge weight) Restrictive: not specified	<u>Primary:</u> % IBW	No gp diff.	Study quality: very low Very small sample, only 1 session in addition to outpatient therapy, no follow-up, no power analysis, no CONSORT statement
		Additional parent-to-parent consultation (one-time, in addition to 20 sessions of therapy, after hospital discharge)	10				<u>Secondary:</u> Morgan & Russel Scale Parent vs. Anorexia Scale (PVA) Depression Anxiety and Stress Scale (DASS)	No gp diffs.	
Robin et al. 1999	RCT	Ego oriented individual therapy (EOIT)	18	1	Baseline, end of therapy FU: 1 yr	A DSM III-R Age: 13.4 / 14.9 yrs 0 % > 18 yrs Female: 100% Illness duration: < 1 yr. Weight: 16.6 / 15.2 BMI Restrictive: ? %	<u>Primary:</u> Weight (BMI)	BFST > EOIT	Study quality: low Small case number, no blinding, no ITT analysis, no CONSORT statement
		Behavioral family systems therapy (BFST)	19	1			<u>Secondary</u>: Menstruation EAT EDI-2 (three scales), BDI PARQ (family)	BFST > EOIT: menstruation, otherwise no group differences	

Russell et al. 1987	RCT	Family-based therapy after inpatient therapy	41	6	Baseline, after 1 yr	E/A DSM-III Age: 21.8 yrs % > 18 yrs? Female: %? Illness duration: 3.8 yrs Weight: 89-5% ABW (discharge weight) Restrictive: ? % 4 subgroups compared: 1 group with BN and 3 with AN stratified according to age at onset and illness duration (</> 18 age of onset; </> 3 yrs illness duration)	<u>Primary:</u> Morgan & Russell score	Family therapy (FT) more favorable for patients with illness onset < 18 yrs and < 3 yrs ill; individual therapy more favorable for patients illness onset > 19 yrs	Study quality: low No blinding, randomization not described, no ITT analysis; 30% temporarily hospitalized; medication prescribed if depressive; average treatment duration: 1 yr, no follow-up
		”Focal supportive therapy” (FST) after inpatient therapy	39	10			<u>Secondary:</u> Menstruation Weight		
Schmidt et al. 2012	RCT	Maudsley Model of Anorexia Nervosa	34	10	Baseline, end of therapy FU: 1 yr	E, SY DSM-IV Age 26.6 yrs	<u>Primary:</u> BMI (after 1yr)	No gp diffs.	Study quality: high However: dropout rate > 20%)

		Treatment for Adults (MANTRA)				100% > 18 yrs Female: 93% Illness duration: 6.7 yrs Weight: 16.4 BMI Restrictive: 63.4%			
		Specialist supportive clinical management (SSCM)	37	16			<u>Secondary:</u> ED symptoms (EDE) Neuropsych. problems	No grp diffs, but more inpatient and day-clinic admissions under MANTRA	
Schmidt et al. 2015 (Schmidt et al. 2016)	RCT	Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA)	72	18	Baseline, 6 mths and 12 mths after randomization FU: 2 yrs	E, SY DSM-IV Age: 26.7 yrs 100% > 18 yrs Female: 97.9% Illness duration: 8.3 yrs Weight: 16-6 BMI Restrictive: 31 %	<u>Primary:</u> BMI (after 1 yr)	No gp diffs.	Study quality: high However: dropout rate > 20%)
		Specialist supportive clinical management (SSCM)	70	29			<u>Secondary:</u> Remission rates Acceptance ED symptoms (EDE) DASS-21 OCI CIA Neurocognition	No gp diffs, but acceptance of MANTRA > SSCM, MANTR: trend for superiority in severely	

								ill patients. (BMI)	
Serfaty et al. 1999	RCT	Cognitive therapy (CT)	25	2	Baseline, after months	E/A?, SY DSM-III-R Age: 21 yrs % > 18 yrs? Female: 94.3% Illness duration 5 /2.2 yrs Weight: 16.2 / 17.0 BMI Restrictive: 80%	<u>Primary:</u> Weight	DA was not accepted by patients	Study quality: very low No ITT analysis, no blinding, in the DA group all participants are dropouts, no follow-up, clear differences between groups in illness duration (baseline)
		Dietary advice (DA)	10	10			<u>Secondary</u>: EDI BDI Dysfunctional Attitude Scale (DAS) Locus of Control of Behavior Scale (LCB)		
Touyz et al. 2013	RCT	Cognitive-behavior therapy (CBT)	31	1 (+1 before intervention)	Baseline, end of therapy FU: 6, 12 mths	E DSM-IV Age: 33.5 yrs 100% > 18 yrs Female: 100% Illness duration: 16.6 yrs Weight: 16.2 BMI Restrictive: 74.6%	<u>Primary</u>: Quality of life (EDQOL) SF-12 BDI Social integration (WSAS)	No group differences at end of therapy; CBT-AN > SSCM after 6 mths on WSAS	Study quality : high
		Specialist supportive clinical management (SSCM)	32	2 (+1 before intervention)			<u>Secondary:</u> BMI EDE ANSOCQ Health care utilization	CBT-AN > SSCM after 12 mths in reduction of ED pathology (EDE) and willingness to	

		(both modified for "enduring AN")						change (ANSOCQ)	
Treasure et al. 1995	RCT	Educational behavioral treatment (EBT)	16	6	Baseline, end of therapy FU: 3, 6, 9, 12 mths	E ICD-10 Age: 25 yrs 100% >18 yrs Female: 96.7% Illness duration: 4.4 yrs Weight: 15.3 BMI Restrictive: ca. 50%	<u>Primary:</u> Morgan & Russel scale	No gp diff.	Study quality: moderate Dropout rate > 20% Small case number
		Cognitive analytic treatment (CAT)	14	4			<u>Secondary:</u> Selfevaluation Improvement	CAT > EBT in subjective evaluation	
Wallin et al. 2000	RCT	Family based therapy	13	?	Baseline FU: 2 yrs	A DSM-IV Age: 14.2 yrs 0% >18 yrs Female: ? % Illness duration: 1 yr Weight: 15.5 BMI Restrictive: ? %	<u>Primary:</u> GCS (Global Clinical Score n. Garfinkel et al. 1977)	No effect of BAT	Study quality: very low No correlation, no ITT analysis, randomization not described, 4/13 patients temporally hospitalized (12-142 days) very small case number, dropout not described
		Family based therapy + body awareness therapy (BAT)	13	?			<u>Secondary:</u> EDI, Ch-EAT, VSE	Improved body image in patients with previously disturbed body image	
Weizmann 1985	RCT	Behavioral therapy (BT) inpatient treatment	5	?	Baseline, end of therapy	A DSM-III Age: 16 yrs	<u>Primary:</u> Weight	No gp diff.	Study quality: very low No follow-up, insufficient details on sample and methods,

		Pimozid (inpatient treatment)	5	?		0% >18 yrs Female: ?% Illness duration: ? Weight: ? Restrictive: ? %	<u>Secondary:</u> Prolactin level	No gp diff	case number too small to interpret
Whitney et al. 2012	RCT	3-day-workshop for 2 families additionally to inpatient program (FDW)	1-> 20 yrs 25 FDW	3	Baseline, 6 mths, 3 yrs	A/E ? DSM ? Age: ? 0% >18 yrs Female: 98% Illness duration: 5-10 yrs Weight: 13.2 BMI Restrictive: ? %	<u>Primary:</u> BMI	No gp diff.	Study quality: low Sample < 30 per arm, Insufficient sample description, no ITT-analysis, no description of inpatient program
		Weekly to 14d family sessions additionally to inpatient program, 3 follow-up sessions (IFW)	23 IWF	3			<u>Secondary:</u> SEED, IIP burden of relatives	No gp diff.	
Zipfel et al. 2014	RCT	Cognitive behavioral therapy 'enhanced' (CBT-E)	80	17	Baseline, 4 mths after start of therapy, end of therapy (10 mths) FU: 3, 12 mths	E, SY DSM-IV Age: 27.7 yrs 100% >18 yrs Female: 100% Illness duration: 61% > 6yrs Weight: 16.7 BMI Restrictive: 53%	<u>Primary:</u> Weight (end of therapy + 1yr)	No group difference, post 10 mths quick weight improve in CBT compared to TAU	Study quality: high Although drop-out rate > 20%
		Focal psychodynamic therapy (FPT)	80	8			<u>Secondary:</u> Global outcome (remission rate) EDI-total-score	Post 1 yr: higher remission rate in FPT than TAU	
		TAU-O (ambulatory	82	29					

		therapy with experienced therapists)							

Abbrevations

General: *?* no information available, *gp* group, *gp diff.* group difference; *yr* year, *mths* months, *E* adult pat. (>18 years), *A* children and adolescent (< 18 years), *SY* inclusion subsyndromal pat (referred to used classification-system), *Age* always in years, Illness-duration in years, *% active* part of pat. of active/bulim. subtype, *EL* evidence-level, *pre* e.g. inclusion in study, *post*, at end of active treatment, *cat.* catamnesis, *mths*, months, *yr/yrs* year/years, *SH* selfharming behavior, *outpat.* outpatient treatment, *inpatient.* inpatient treatment, *fam* family, *RCT* randomized controlled trial, *ABW* average body weight, *IBW* Ideal Body Weight, *MPMW* Matched Population Mean Weight, *ITT* intention-to-treat, *OCD* Obsessive-Compuslive Disorder, *AN* Anorexia nervosa, *BN* Bulimia nervosa, *ED* eating disorder

Treatment: *TAU* „treatment as usual", *OM* „outpatient management", *SPT* „self psychological treatment", *CBT* cognitive behaviortherapi, *BFT* „behavioral family therapy", *FBT* family-based therapy, *SyFT* systemic familytherapy, *CE* computerbased eatingtraining, *FT* family therapy, *ET* Einzeltherapie, *DC* „dietary counselling, *OGT* „outpatient group treatment", *RT* „routine treatment", *CAT* „cognitiv-analytic therapy", *Focal analytic*, *BM* „behavior management", *SB* Standard-Behandlung, *CFT* „conjoint family therapy", *SFT* „separated family therapy", *FGP* „family group psychotherapy", *DS* sensibilisierung, *EnT* Entspannungstherapie, *PG* individuelle Therapie + Familiensitzungen, *DA* „dietrayadvice", *NSCM* „non-specific clinical management", *IPT* interpersonel therapy, *NC* „nutritional couselling", *SST* „social skills training", *EOIT* „ego oriented individual therapy", *BFST* „behavioral family systems therapy", *CT* cognitive therapy, *EBT* „educational behavioral treatment", *BAT* „body awareness therapy", *VT* spezifisches Verhaltensmodifikationsprogramm, *CRT* cognitive remediationstherapy, *MFT* Multi Family Therapy, *SSCM* Specialist Supportive Clinical Management, *MANTRA* Maudsley Model of Anorexia Nervosa Treatment for Adults MANTRA

Measures: *M&R* Morgan & Russell-Scales, *MRAOS* Morgan and Russell Average Outcome Scale, *EAT* Eating Attitudes Test, *BSI* Brief Symptom Inventory, *ESE* Eating Disorders Examination, *EDI* Eating Disorder Inventory, *BDI* Beck Depression Index, *STAI* State-Trait-Anxiety-Inventory, *SMFQ* Short Mood and Feeling Questionnaire, *RSE* Rosenberg Selfesteem-Scale, *MOCI* Maudsley Obsessive Compulsive Index, *FACES* Family Adaptability and Cohesion Scale, *SCFI* Standardized Clinical Family Interview, *FAM* Family Assessment Measure, *CDI* Childrens Depression Inventory, *EE* Expressed Emotion Ratings, *YBC-ED* Yale-Brown-Cornell-Eating Disorder-Scale, *CBCL* Child Behavior Checklist, *SCID* Structured Clinical Interview for DSM IV, *PARQ* Parent Adolescent Relationship Questionnaire, *GCS* Global Clinical rating Scale, *Ch-EAT* Childrens Eating Attitutde Test, *VSE* Visual Size Evaluation, *HoNOSCA* Health of the Nation Outcome Scale for Children und Adolescence, *FAD* Family Assessment Device, *MFQ* Mood and Feelings Questionnaire, *DASS-21* Depression Anxiety Stress Scale, *OCI-R* Obsessive Compulsive Inventory-Revised, *CIA* Clinical Impartment Assessment, *BSI* Brief Symptom Inventory, *SIAB* Strukturiertes Inventar für Anorektische und Bulimische Essstörungen, *ANSOCQ* AN stages of change questionnaire

Table 3: Recommended weight gains in the different guidelines

American Psychiatric Association (USA)	2–3 pounds (lb)/week (inpatient), equivalent to 0.9 – 1.4 kg

	0.5-1 lb/week (outpatient), equivalent to 0.2 - 0.5kg
National Institute for Clinical Excellence (NICE) guidelines for AN (England)	0.5-1 kg/week (inpatient) 0.5 kg/week (outpatient)
Dutch guidelines (adolescents)	0.5-1.5 kg (clinical setting) Up to 2.0 kg/week (somatic, clinical setting) 0.5–1.0 kg/week (outpatient)
Spanish guidelines	> 0.5 kg/week to 1 kg/week

Table 4: Trials on pharmacotherapy in AN

Study	Design	Treatment arms	Cases (N /Arm)	Dropouts	Measurement time points	Sample	Objects (primary, secondary)	Results	Notes/ study quality
Andries et al. 2014 Dronabinol in Severe, Enduring Anorexia Nervosa: A Randomized Controlled Trial	RCT crossover double-blind Duration: 12 weeks, but only 8 weeks intervention	I: Dronabinol-Placebo	11	0	Daily weight 1st and 4th week EDI-2	N = 23 DSM IV-TR: AN Age > 18 years Duration of ES > 5 years Same psychological and somatic treatments for inpatients and outpatients N = 13 (54%): at least 1 further psychotropic drug, of which n = 10 (77%) SSRI	<u>Primary</u>: Weight change (average)	Slight weight increase Dronabinol	Study quality: moderate No precise data on age and weight No information on comorbidities and no distinction btwn restrictive/purging Short intervention duration No info on which pts in which arm received further psychotropic drugs No precise info on EDI-2 scores, only result Small effect: just 1kg in 4 weeks (CI .40-1.62) => additionally: CI of placebo and intervention group overlap Sequence of intervention has no effect: Intervention
		II: Placebo-Dronabinol Dose: 2x2.5mg daily	13	1			<u>Secondary</u>: Scores on EDI-2	No sig. differences/ changes	

									(whether placebo or dronabinol) brings about weight gain
Andries et al. 2015 Effect of dronabinol therapy on physical activity in anorexia nervosa: a randomised controlled trial	RCT Double-blind, crossover Duration: 20 weeks	I: Placebo	24	0	Weight: Baseline, weekly at same time Physical activity: 7 days during final week of intervention Leptin: weekly Cortisol: last day of each intervention	N = 24 DSM-IV-TR Restrictive = 50% Age: 19-62 M = 33.3 (12.7) W = 100% BMI = 15.7 (1.7) Illness duration: M = 15 (11.6) Therapies (psychiatric, psychotherapeutic, somatic) Outpatient: 38% Inpatient: 62%	<u>Primary</u>: Weight in kg	Sig. weight gains during intervention, but only in outpatients	Study quality: moderate Participants both patients of an eating disorder clinic and outpatient participation in therapy of the clinic (Inpatients: n = 15; 62%; Outpatients: n = 9; 38%) Illness duration: sig. differences btwn outpatients and inpatients (outpatients longer ED) + time span 5-50 years Comorbidity: only mentioned that patients with ED as main diagnosis
		II: Dronabinol 2x2.5mg daily	24	0			<u>Secondary</u>: ES symptoms EDI-2 Physical activity by means of accelerometer Leptin concentration in plasma (P-leptin) Cortisol concentration by UFC	EDI-2 no differences With dronabinol longer physical activity (moderate to strong effort) + stronger intensity of activity => longer in outpatients and more intensive in inpatients.	
Andries et al. 2015	RCT Cross-over,	I: Dronabinol-Placebo	24	0	Last day of intervention: Cortisol	N=24 DSM IV-TR: AN	<u>Primary:</u> Weight/BMI	Sig. weight change (BMI increased)	Study quality: low

Changes in IGF-I, urinary free cortisol and adipokines during dronabinol therapy in anorexia nervosa: Results from a randomised, controlled trial	double-blind Duration: 12 weeks, but only 8 inter-vention	2x2.5mg daily				W = 100% Age: Median = 28 (Interquart. [23.5-42.0]) Illness duration: Median = 10,5 [7-18] BMI: 15.7 (±1.7) IBW: 74.7% (±8.1%) Same underlying therapeutic treatment			Primary outcome: very small effect (0.23 ± 0.5 change in BMI) Confidence intervals vary wide Short intervention Insufficient explanations for effects of indirect associations or influences (leptin, adiponectin, dronabinol etc.) No info on comorbidity, further psychotropic drugs + distinction restrictive/purging
		II: Placebo-Dronabinol	24	0			<u>Secondary:</u> - IGF-I, bioactive IGF & binding protein - Cortisol - Leptin & Adiponectin	IGF: no direct effect of dronabinol on hormones → indirect: Relation between weight and hormones Cortisol: sig. lower value with dronabinol & association with leptin Leptin: sig. higher value after 3 weeks Adiponectin: No sig. diffs	
Attia et al. 1998 Does Fluoxetine Augment the Inpatient Treatment of Anorexia Nervosa?	Rand-omized placebo-controll. double-blind study Average duration:	Group I: Fluoxetine (target dose 60mg; dose 56.0, SD11.2) + inpatient PT (individual, group therapy, structured mealtime program,	15	2	Weight: 3x/wk Anorexic behaviour scale, CGI, BDI: 1x/Wo. BSQ, EAT, SCL-90: pre, after 4 wks, post	N = 31 Female, 26.2 yrs (SD 7.4) AN (DSM-III-R), Restr: 12 Binge/purge: 19 Inpatient Th.	<u>Primary</u>: Target weight: 90% of ideal weight (acc. to Metropolitan Life Insurance Tables, 1959)	Pre-post: No gp differences (n.s.) Pre-post overall (N= 31): Sig diffs in all gps regarding all all outcome criteria except subscale CGI	Study quality: moderate 4 participants from each group dropped out before reaching target weight or before 7 weeks, but still included in analysis. Self-rating of one participant was not analyzed

	7 wks (or until achievement of 90% "ideal body weight" for min. 1 wk.)	controlled weight gain) Average duration: 36.1d (SD 14.1)			Yale-Brown-Cornell Eating Disorder scale: pre, post Plasma samples: after 4 weeks	Weight pre: 32.9kg BMI = 15.0; Group differences: not specified		"global improvement" Weight post: 39.5kg, BMI = not specified, Group diffs: not specified.	
		II: Placebo + inpatient PT ebd. Average duration: 37.4d (SD 13.8)	16				<u>Secondary:</u> Sig. improvement of group 1 on following scales: CGI, (subscales "illness, Eating disorder, Global improvement"), ABS, BDI, BSQ, EAT, SCL-90 (subscales depression, obsessive-compulsiveness, general symptoms), Yale-Brown-Cornell Eating Disorder Scale (Preoccupation, Ritual, Total)	Pre-post overall (N= 31): Sign. Changes in both groups regarding all outcome criteria apart from CGI subscale "global improvement"	

Attia et al. 2011 Olanzapine versus placebo for out-patients with anorexia nervosa	RCT Double-blind placebo-controll-ed Duration: 8 weeks	I: Olanzapine Dose: increased every two weeks, finally M = 7.95mg (2.70) daily	11	3	Weekly weight and questionnaire scores	N = 17 Female = 96% 1 man: Olanzapine Age: M = 27.7 (9.1) DSM IV: AN Almost 50% also took antidepressants	<u>Primary:</u> Weight/BMI	Sig. weight increase through olanzapine	Study quality: low No info on comorbidity, illness duration, therapeutic interventions & type of antidepressants Small sample size Diffs btwn PANSS & subscale BSQ between the patients (from New York and Toronto) No differentiation restrictive/purging No additional interventions alongside, only medication administration
		II: Placebo	12	3			<u>Secondary:</u> Scores on BAI, BDI, EDI-2, YBC-EDS	No sig. differences	
Barbarich et al. 2004 Use of Nutritional Supplements to Increase the Efficacy of Fluoxetine in the	Rand-omized placebo-controll. double-blind study Duration: 26 wks	Group I: Nutritional supplement + Fluoxetine (20-60mg) Nutritional supplement: 2.3g Tryptophan/d,	15 Restr. /purging type of AN: 6	17 Early dropouts (< 4 weeks): 4 Medium dropouts (5-	Weight: 8 wks: 1x/wk, 6 wks: every 2 weeks 12 wks: every 4 weeks Tests: Pre, after 3 and after 6 months	N = 26 Gender: not specified 23.0 ± 6.3 yrs AN, onset at 16.1± 4.6 yrs Restr: 10 Restr. + purge: 6 Binge-purge: 10	<u>Primary:</u> Weight gain/week	Weight gain Gp I: 0.27±0.3kg/wk Gp II: 0.1 ±0.1kg/wk	Study quality: low Contradictory info regarding no. of participants per arm: (Active Group/Placebo Group 14/12 table vs. 15/11 main text.

Treatment of Anorexia Nervosa		1 multivitamin-mineral capsule/day (100% DRD), 4 fish oil capsule/d (600mg docosa-hexaenoic acid, 180mg arachidonic acid)	Binge-purge type of AN: 8	18 weeks): 14 Completion of study: 7 participants group 1 and 2 participants group 2		Participants from "eating disorders programs" from two hospitals (no precise info) Weight pre: not specified	<u>Secondary:</u> Significant improvement of group 1 on following scales: Frost Multidim. Perfectionism Scale, STAI-Y, Y-BOCS	Completion 7 participants in active group and 2 participants in placebo group Dropouts (17) did not differ from completers (9) in variables such as age, onset and duration of ED, BMI. No group differences on all scales (n.s.)	No info on diagnostic instruments, further treatments Following high dropout rate, division into dropout group and completer group
		Group II. "Placebo group" Placebo + Fluoxetine(20-60mg) Placebo: Same number of inactive capsules (starch+ sunflower oil)	11 Restr./purging type: 10 Binge-purge type: 2						
Biedermann et al. 1985	Rand-omized placebo-controll.	Group I. Amitriptyline – (target dose	11	0	Weight: 1x/d, weekly average	N = 43 Gender: not specified	<u>Primary:</u> Weight gain/week	Slight weight gains in all 43 participants, no gp differences	Study quality: low

Amitrip-tyline in the Treatment of Anorexia Nervosa: A Double-Blind, Placebo-Controlled Study	double-blind study + control group without placebo Duration 5 weeks.	3mg/kg/d) + PT (individual therapy, family intervention, supportive psychiatric measures, nutrition program, behavior modification for inpatients)			Tests: Pre, then 1x/wk Plasma level 1x/wk Side effects and blood pressure: 1x/ wk	11-27 yrs (group I 18.4yrs; group II 17.2yrs; group III 15.7yrs) 38 inpatients (6 psychiatric, 32 psychosomatic) 5 outpatients AN (DSM-III): 42 participants Subtypes of AN: not specified Weight pre: Gp I: 38.2±4.2kg Gp II: 35.5±5.8kg Gp III: 35.8±6.7kg % below "Ideal weight" Gp I: 25.0± 7.3% Gp II: 31.0±6.2% Gp III: 27.5±9.6%		Weight post: Approx 2kg increase in all gps (no precise details, only graph)	Control group not selected blindly, comprised participants who refused pharmacological treatment. Due to randomization effects, amitriptyline group had lowest depression rates, placebo group the highest (n.s.) Plasma levels in week 5 were available for 8 participants, for 3, the levels from week 4 were used One participant did not fulfill weight criterion (19% of "ideal weight"), was included in study
		Group II. Placebo + PT ebd.	14				<u>Secondary:</u> Sig. Improvement in group I on following scales: Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-C, depression scale, anxiety scale, endogenous scale) HSCL, (obsessive-compulsive scale), EAT, (restrictive and bulimic factors), Global Severity and Global Improvement Scales	Average amitriptyline dose in week 5: 115mg (± 31) Plasma levels varied strongly in participants with same dose All 3 groups overall only small improvements on the assessed scales No group differences (n.s.)	
		Group III. control group (participants who did not consent to pharmacol. interventions), + PT ebd	18						

Bissada et al. 2008 Olanzapine in the Treatment of Low Body Weight and Obsessive Thinking in Women With Anorexia Nervosa: A Randomized, Double-Blind, Placebo-Controlled Trial	RCT Double blind placebo-controll. Duration: 13 weeks day clinic, of which 10 weeks admini-stration of olan-zapine	I : Olanzapine Dose : M = 6.61mg (2.32) daily	16	2	Weekly weight 1st and 13th week: psychological questionnaire scores	N = 28 Female = 100% DSM IV restrictive = 47% purging = 53% Age: I: M = 23.61 (6.50) II: M = 29.67 (11.59) BMI: I: M = 16.39 (1.13) II: M = 15.93 (1.39)	<u>Primary</u>: Weight/BMI	Sig. weight increase in both groups → with olanzapine quicker gain up to BMI=20	Study quality: moderate No information on comorbidity and illness duration Effects of individual therapies (psychotropic vs. BT) unclear, especially regarding improvement in psychological variables Monitoring of possible undesired side effects (diabetes by measuring glucose levels)
		I : Placebo	18	4			<u>Secondary</u>: Symptoms of anxiety and depression PAI Obsessive-compulsive symptoms Y-BOCS	PAI: significant symptom improvement in both groups → no group differences Y-BOCS: significant symptom improvement → with olanzapine stronger effect on the obsession subscale	
Bloch et al. 2012 Dehydro-epiandroster one treatment effects on weight, bone density,	RCT Double-blind placebo-controlle d Duration: 6 months	I : DHEA Dose : 2x50mg daily	15	2	Baseline and monthly: Weight and psychological variables Baseline and 6th month: Bone parameters	N = 21 Female = 100% DSM IV: AN Age: 17-47 years M = 26.9 (8.2) Weight: 38-57.8	<u>Primary:</u> Weight Bone metabolism (bone density CBM and bone mineral density BMD)	No significant increase in DHEA group (only significant diff between groups in 4th month: DHEA-group had higher BMI)	Study quality: moderate All patients took part in weekly individual and group therapy, as well as nutrition support All patients additionally received 600mg carbonate & 200 IU Vitamin D3

bone metabolism and mood in women suffering from anorexia nervosa — a pilot study						kg M = 45.5 (4.8) BMI: M = 17.7 Illness duration: M = 10.5 (4.4) years		no sig. differences regarding CBM and BMD → only certain bone markers show small effects	No differentiation restrictive/purging + no info on comorbidity Noted that sample too small and intervention too short for such metabolic approaches Possible explanation provided, as illness duration very long in relation to low average age → bones already too severely affected
		II : Placebo	11	3			<u>Secondary:</u> Scores on BDI, EDI, CGI and from physical symptom list	Sig. improvement in BDI- & CGI-E-scores in both groups → Improvement in depressive symptoms already discernible after 3 months → sig. positive relation between weight gain and mood in DHEA group No sig. changes regarding further psychological variables	

Brambilla et al. 1995c Combined Cognitive-Behavioral, Psychopharmacological and Nutritional Therapy in Eating Disorders 2. Anorexia Nervosa – Binge-eating/Purging Type	-	Group I: Fluoxetine (60mg/d) + outpatient therapy + nutritional counseling	6	? (not specified)	Baseline, in mths 1, 2 and 4	N = 13 Female, 23.1±6.8 yrs AN (DSM-IV), only binge-purge. Outpatients Weight pre (BMI): Gp I: 16.7±2.2 Gp II: 16.3±2.8	<u>Primary:</u> Weight/BMI <u>Secondary:</u> EDI, Bulimic Investigation Test, Edinburgh (BITE), HAM-D, HAM-A,	No sig. weight gains in both groups Sig. improvements on EDI, HAM-D, HAM-A, no group differences No change regarding BITE No sig. reduction in bulimic symptoms in both groups. Weight post (BMI): Gp I: 21.1±6.3 Gp II: 17.7±2.6	Study quality: low Open, non-placebo-controlled study Very small samples
		Group II: Amineptine (300mg/d) + outpatient therapy + nutritional counseling	7	? (not specified)					
Brambilla, R. et al. 1995b Combined Cognitive-Behavioral, Psychophar	Rando-mized open study with two groups	Group I: Fluoxetine (60mg/d) + outpatient therapy + Nutritional counseling	15	? (not specified)	Baseline, in mths 1, 2 and 4	N = 22 Female, 21±5yrs AN (DSM-IV), Only restrictive Outpatients	<u>Primary</u>: Weight/BMI	Sig. weight gains in both groups: Gp. I: 26%; Gp II: 58%	Study quality: low Open, non-placebo-controlled study

macological and Nutritional Therapy in Eating Disorders 1. Anorexia Nervosa – Restricted Type	Duration: 4 mths	Group II: Nortriptyline (75mg/d) + Outpatient therapy + nutritional counseling	7			Weight pre (BMI): Gp I: 14.7±1.5 Gp II: 15.9 ±1.9	<u>Secondary</u>: EDI, Bulimic Investigation Test, Edinburgh (BITE), HAM-D, HAM-A,	Sig. improvement on EDI, HAM-D no group differences. Sig. improvement in gp II on HAM-A. No change regarding BITE Weight post (BMI): Gp. I: 16.3±2.6 Gp. II: 18±1.7	Very different group sizes, study provides no reason for this
Brambilla et al. 2007a Olanzapine therapy in anorexia nervosa: psychobiological effects	Double-blind Duration: 3 months	CBT and olanzapine (oral) Dose: 2.5mg daily in 1st month, 5mg daily for remaining 2 months	15	? (not specified)	Baseline, then monthly	N = 30 (originally 35, no info in which condition dropout); recruited from clinics Female = 100%	<u>Primary:</u> Weight/BMI	Sig. weight increase in both groups Sig. highest weight gain in CBT + OLA + AN-BP patients	Study quality: high No information how many dropouts in which condition

		CBT and Placebo (oral)	15			Age: OLA: M = 23.7 (4.8) PL: M = 26.3 (8,.5) OLA: 8 AN restricted, 7 AN bingeing-purging PL: 10 AN restricted, 5 AN bingeing-purging DSM IV: AN Average illness duration in years : OLA: 6.3 (5.0) PL: 4.4 (3.0)	Secondary: EDI-2, YBC, Buss-Durkee scale, Hamilton Rating Scale, TCI, HVA plasma concentration	EDI-2: sign. total, but no gp diffs, subscales Ineffectiveness and Maturity fear only sig. for CBT + OLA YBC: Total: sig., no gp differences Buss-Durkee: total sig, gp difference HRS: total sig., group differences TCI: "persistence" improved for CBT + OLA, group differences HVA Plasma: CBT + OLA increased	
Brambilla et al. 2007b Olanzapine-induced weight gain in anorexia	Randomized placebo-controll. double-blind study	Group I: olanzapine (1st month 2.5mg, 2nd/3rd month 5mg) + Outpatient cognitive-	10	? (not specified)	Baseline, 1 x per month	N = 20 Female, 23±4.8yrs, AN (DSM-IV)	Primary: Weight/BMI	Significant weight gains in both groups, no group differences (n.s.)	Study quality: moderate Small sample No distinction between restrictive and purging

nervosa: Involvement of leptin and ghrelin secretion?	Duration: 3 months	behavioral therapy + nutritional counseling				Subtypes: not specified Outpatients Weight pre: Gp I: BMI = 15.7±2,.1 Gp II: BMI = 16.3±0.7			(unclear whether weekly CBT within the study conducted by therapists already known to patients: only mentioned that precondition for participation was 3-month abstinence prior to psychotherapy or pharmacotherapy) Dose given daily? Not explicitly mentioned No information on dropout No information on previous therapy experience, hospitalizations No precise information on NR (nutritional rehabilitation): how often patients ate per day, calorie counts, etc. Monitoring of NR by patients' families 10 institute employees served as healthy control group (sig. higher BMI values pre and post, sig. higher plasma levels of leptin and ghrelin at baseline)
		Group II: Placebo + outpatient therapy (ebd.)	10				<u>Secondary:</u> Leptin and ghrelin modulation under olanzapine	No time and group differences regarding leptin/ghrelin plasma levels Weight post: Gp I: BMI = 17.1±1.6 Gp II: BMI = 17.5±0.8	

Court et al. 2010 Investigating the effectiveness safety and tolerability of quetiapine in the treatment of anorexia nervosa in young people: A pilot study	RCT, open-label Duration: 12 weeks	I: quetiapine (+ TAU) Dose: 50mg daily, from 4th week max 400mg daily, M=322.5mg	15	5 = 33%	Baseline: physiological data (weight, blood pressure, pulse) + psychological variables weekly: weight, blood pressure and side effects 12th week: physiological variables, psychological variables and side effects Follow-up with assessment of same variables: 26th and 52nd week (here LOCF)	N = 21 Female = 100% DSM IV: restrictive = 71.4% purging = 28.6% Age: I: M = 23.8 (9.4) II: M = 21.0 (3.3) BMI: I: M = 16.9 (1.7) II: M = 16.3 (1.8) Illness duration in months: I: M = 65.4 (96.2) II: M = 30.3 (37.3)	<u>Primary</u>: Health values and possible side effects: UKU Side Effects Rating Scale	no significant change in health variables → high tolerability, as few or mild side effects and minimal EPS + high tolerability despite existing accompanying medication: 9 of 11 patients in gp I additionally took SSRIs and/or benzodiazepines	Study quality: low Patients with comorbid depression took SSRIs and other medication if indicated → sole intake of antipsychotics led to exclusion → precise documentation of how many patients took which additional medication (Table 2) High dropout rate TAU = Combination of CBT, individual and group therapy, and inclusion of family Emerging side effects described and documented/monitored Detailed listing of demographic data and the results of psychological questionnaires per group Small group size No info on comorbidity Improvement of psychopathological scores and increased weight show relatively stable effects across both follow-up points in the quetiapine group
		II: TAU	18	7 = 39%			<u>Secondary:</u> BMI Psychopathological variables, above all body perception (in terms of body image disturbance): EDI-2, MASQ, CES-D, MADS, PWI	Sig. moderate BMI increase in both groups to M = 18.6 kg/m^2 and M = 18.1kg/m² EDI-2: Symptom improvement in both groups, Effect more stable over 12-month FU with quetiapine CES-D and MASQ: sig improvement in depressive and anxiety	

								symptoms (but presumably due to gp diffs at baseline = patients in gp I overall higher psychopathology scores than patients in gp II MADS: no sig. effects PWI: Increased scores in both groups	
DiVasta et al. 2012 The effect of gonadal and adrenal steroid therapy on skeletal health in adolescents and young women with anorexia nervosa	RCT double-blind placebo-controll. Duration: 18 months	I: DHEA + COC Dose: *first 3 months: 50mg DHEA + 0.3mg estrogen daily *then over 15 months: 50mg DHEA + 20µg ethinyl estradiol + 0.1mg levonorgestrel	43	16	All parameters measured: Baseline + after 3, 6, 12 and 18 months	N = 94 Female = 100% Age: M = 18.1 (2.7) BMI: M = 18.0 (1.5) Illness duration in months: Median = 12 Q1-Q3: 1-132	<u>Primary</u>: Areal bone mineral density (aBMD) total body, hips and lumbar spine	Sig. difference between groups → improvement of BMD in all measured areas = total body, hips and lumbar spine through the intervention → under consideration of patients with BMI < 85% the age median: also significant improvement, but trend somewhat more moderate	Study quality: moderate All participants were additionally advised to take calcium (1300mg) and Vitamin D (600IU) daily Possible side effects were not monitored (hirsutism, acne, insulin levels etc.) Patients already taking contraceptives stopped taking them for at least 1 month before study participation No info on comorbidity, diagnostic instrument & additional therapeutic intervention; no differentiation

		II: Placebo	37	18			<u>Secondary</u>: Bone formation by means of osteocalcin BMI Bone resorption markers by means of N-telopeptide Hormones and further anthropometric values: DHEAsulfate, estradiol, IGF-I, total and free testosterone, SHBG	Osteocalcin and N-telopeptide: during treatment different pattern btwn groups but leveled out towards end BMI: no significant differences between groups DHEA sulfate, SHBG, free testosterone: significant increase with treatment IGF-I no change Estradiol: sig. increase in placebo group No side effects observed	restrictive/purging Focus lies on young women (range: 13.3-27.1 years) Mean BMI 18 relatively high Broad distribution regarding illness duration + relatively high BMI (reaching into normal range) Precise info on each measurement regarding number of patients who did not take medication at least once (before 3rd month 39% 6th month: 53% 12th month: 60% 18th month: 48%)

DiVasta et al. 2014 Does Hormone Replacement Normalize Bone Geometry in Adolescents with Anorexia Nervosa?	RCT placebo-controll., double-blind	Same treatment as in DiVasta 2012 "Non-responders": Under 50% regarding outcome criteria at T3	See DiVasta 2012	See DiVasta 2012	Same measurement time points as in DiVasta 2012	Same sample with same demographic data as in DiVasta 2012	<u>Primary:</u> Changes in bone strength via structural geometry of the bones and through HSA program (no secondary outcome criteria in this study)	Improvement in bone health through intervention → axial strength CSA improved → section modulus improved → Bone strength index measured at femoral shaft improved	Study quality: moderate See DiVasta 2012
Fazeli et al. 2014 Teriparatide Increases Bone Formation and Bone Mineral Density in Adult Women	RCT Placebo-controll. Duration: 6 months	I : TPT Teriparatide Dose: 20µg SC daily II : Placebo	10 11	0 0	All parameters measured: Baseline, 3rd and 6th month	N = 21 Female = 100% Age: M = 47 (1,7) BMI: I: M = 17.6 (0.4) II: M = 16.6 (0.4) DSM-IV: AN	<u>Primary:</u> Change in bone mineral density of (BMD) of spine and hip <u>Secondary:</u> Changes in further endocrinological values: P1NP, CTX,	Sig. increase in BMD of spine and hip already after 3rd month compared to placebo Sig. increase in P1NP compared to placebo already after 3rd	Study quality: low Recruitment of participants: special eating disorder clinics, endocrinologists, online announcements =>no information on additional therapeutic interventions No differentiation purging/restrictive; no info on comorbidity

With Anorexia Nervosa						Illness duration: I: M = 20.4 (3.7) II: M = 18.0 (4.3)	Sclerostin, IGF-1 Level BMI or ideal body weight	month; regarding CTX, sclerostin & IGF-1 level: no significant diffs; relation found between low IGF-1 level and increased BMD → Persons with very low IGF-1 level showed greatest change in BMD No sig. diff regarding weight at end of intervention: however, placebo shows trend for more weight gain → unfortunately no exact data on this given (only percentages)	All participants additionally took calcium (1200mg) and vitamin D (400IU) Precise information on side effects → Conclusion: very well tolerated Weight data only reported at start
Garber et al. 2013 Higher Calorie Diets Increase	RCT quasi-experimental Duration: M = 14.9	I: Higher calorie kcal: D1 = 1764 (60) last D = 2893 (64)	28	0	1 x daily: weight, pulse/heart rate, temperature	N = 56 Female = 98% Age: M = 16.2 (0.3)	<u>Primary:</u> Electrolyte and physical values	No refeeding syndrome observed, only: 45% had lower serum phosphorus level	Study quality: moderate Nutritional content of meals: 20% fats, 20 proteins, 60% carbohydrates; in the case of food refusal, then in the form of liquid high-

Rate of Weight Gain and Shorten Hospital Stay in Hospitalized Adolescents With Anorexia Nervosa	(0.9) days 3 meals and 2 snacks	+ quicker increase in kcal: M = 122 (8) daily			2 x daily: electrolyte levels	DSM-IV: AN BMI: M = 16.1 (0.3) Additionally daily: 250mg phosphate 160mg sodium 280mg potassium 1000mg calcium zinc sulfate multivitamin preparation			calorie food (1.06 kcal per mL) No differentiation purging/restrictive, no info on additional therapeutic interventions; no information on illness duration and comorbidity Focus on adolescents with new-onset AN Range BMI: 11.1-21.8 Age: 12.3-20.9
		II: Lower calorie kcal: D1 = 1093 (28) last D = 2642(76) + slower increase in kcal: M = 98 (6) daily	28	0			<u>Secondary:</u> Weight/BMI	I: quicker weight gain and thus also discharge (discharged 5.7 days earlier)	
Gross, H. et al. 1983 A Double-Blind Trial of Delta 9-Tetrahydrocannabinol in Primary Anorexia Nervosa	Randomize double-blind crossover study Duration: 4 weeks Crossover after 2 weeks	Group I. THC (starting dose 7.5mg/d, target dose 30mg/d) + inpatients (individual and group therapy, behavior modification program, therapist-supported food intake)	5 start with THC	3 (group membership not specified)	Weight, calories: 1x/d Tests: 1x/week In week 5: additional administration of highest reached dose THC + subsequent blood samples	N = 9 female, 23.6± 1.8 J. Primary anorexia nervosa (diagnosis according to Feighner et al. 1972) Subtypes: not specified (no vomiting during study)	<u>Primary:</u> Increased calorie intake and weight gain under THC	Substantial weight gain in both groups (approx. 4kg, no exact data), no group differences (n.s.) Clear increase in number of calories per day (Baseline: 1651± 120, week 4: 3401± 234), no group differences (n.s.)	Study quality: low Substances only administered on weekdays (Mo-Fr) Last assessed data of 3 dropouts (in weeks 2 and 3) were included in the study as “outcome data” 8 of the 11 participants recognized the prescribed substance based on the subjectively perceived effect

		Group II. Diazepam (starting dose 3mg/d, target dose 15mg/d) + inpatients ebd.	6 start with diazepam			Inpatient therapy. Weight pre: Gp I: 34.7±1.7kg Gp II: 33.7±1.3kg	<u>Secondary:</u> Changes between groups on following scales: HSCL-90 Goldberg Anorectic Attitude Questionnaire (GAAQ), Goldberg Situational Discomfort Scale (SDS)	Significant changes under THC on following scales: HSCL-90 Somatization, sleep disturbances, irritability Weight post: Both gps approx. 38kg (no precise data, only graph)	3 participants (dropouts) experienced severe dysphoric mood and loss of control under THC
Gross, H. 1981 A Double-Blind, Controlled Trial of Lithium Carbonate in Primary Anorexia Nervosa	Placebo-controll. double-blind study Duration: 4 weeks	Group I: Lithium carbonate (amount not specified) + Behavior modification program	8	? (not specified)	Weight: 1x/d Other measures: 1x/week	N = 16 Female, age: not specified AN (“Primary Anorexia Nervosa” – no information on diagnostic instrument) Subtypes: not specified Weight pre: not specified	<u>Primary:</u> Significant improvements in gp I in following parameters: Weight, daily calorie intake	Higher weight gain in gp I in weeks 3 and 4 Weight post: not specified	Study quality: low short treatment duration No significant side effects observable during the study
		Group II : Placebo + Behavior modification program	8				<u>Secondary:</u> Goldberg Situational Discomfort Scale (SDS), HSCL-90, Goldberg Anorectic Attitude	Improvements in group I on following scales: HSCL-90 (subscale “interpersonal sensitivity”) and GAAQ (subscale “bloated”)	

							Questionnaire (GAAQ), Psychiatric Rating Scale (PRS)		
Hagman et al. 2011 A double-blind placebo controlled study of risperidone for the treatment of adolescents and young adults with anorexia nervosa: a pilot study	RCT Placebo-controll. double-blind	I: Risperidone M = 2.5mg daily Min = 0.5mg increase weekly by 0.5mg Max = 4.0mg	18	? (not specified)	Parameters of ED symptoms: Baseline, after 3 weeks, after every further 4 weeks Parameters for side effects: weekly Lab values: Baseline, after 7 and 11 weeks, after every further 4 weeks	N = 40 Female = 100% Age: M = 16 75% <18 (M = 14.8) DSM-IV: AN BMI: I: M = 15.9 (1.0) II: M = 16.1 (1.3)	<u>Primary:</u> Scores from EDI-2, BIS, CAPT & MASC → Assessment of ES symptoms	Overall no difference and thus no effect on ED and anxiety symptoms through risperidone	Study quality: moderate No information on comorbidity and illness duration; no differentiation purging/restrictive Focus on adolescents (age 12-21) 2 dropouts reported but not mentioned further (N remained the same…) SD only given for each arm Additional therapeutic interventions listed: individual, group and family therapy, nutritional counseling, individualized meal plan 40% additionally took antidepressants + intake of further medically necessary preparations
		II : Placebo M = 3mg	22				<u>Secondary:</u> Time until reaching target weight (90% of IBW) → REE possible side-effects → SAS, AIMS, as well as lab values (liver, prolactin etc.)	No effect on weight gain & no strong side effects through risperidone	
Halmi & Goldberg 1978	Rando-mized study	Group I: Cyproheptadine (Start dose	N of individua l groups	? (not specified)	Weight: 1x/d	N = 81	<u>Primary:</u> Sig. weight gain under	Slight weight gain in group I vs. group II:	Study quality: moderate

Cyproheptadine in Anorexia Nervosa	with 4 groups Duration: 35d	12mg/d, max dose 32mg/d) + behavior modification	not specified		7 days before treatment start (after group randomization): assessment of various "baseline" data	female, age: not specified AN (no official diagnostic manual) Subtypes: not specified Inpatient treatment Weight pre: Substance groups: 5.1kg Placebo groups: 4.32kg	cyprohoeptadine (no specification)	5.11kg/4.23kg (n.s.). Significant improvements under cyproheptadine vs. placebo for following participants: Participants with 2 birth complications, participants with lowest weight, participants with 2 unsuccessful treatments in the past Weight post: not specified	The study with 4 groups was conducted in 3 hospitals – number of participants per hospital not specified (total 81) Diagnostic criteria were determined especially for the study (more specific than DSM-IV criteria) Patients were permitted to receive other non-physiological therapies provided that they did not target weight gain.
		Group II: Cyproheptadine (ebd.) without behavior modification							
		Group III: Placebo + behavior modification					<u>Secondary:</u> -	-	
		Group IV: Placebo without behavior modification							
Halmi et al. 1986 Anorexia Nervosa. Treatment	Rando-mized placebo-controll. double-	Group I: Cyproheptadine (max. 32mg/d) + inpatient treatment (not	24	19 15 from hospital UMH,	Baseline: 1 week Weight: 1x/d	N = 53 female, 20.56 yrs (±5.1) AN (DSM-III),	<u>Primary:</u> Weight(Metropolitan Height-Weight Charts, Target criterion: achievement of	Influencing factors on positive treatment outcome: weight before study start	Study quality: low Sig. difference between 2 hospitals regarding treatment outcomes

Efficacy of Cyproheptadine and Amitrip-tyline	blind study Duration: max. 90 days	precisely specified)		4 from NYHMC (sig difference in N)	All other measures: 1x/week	restr. 39 binge-purge: 33 Inpatient treatment Patients from 2 hospitals (University of Minnesota Hospitals UMH: 46 participants; NY Hospital-Cornell Medical Center NYHMC: 26 participants) Weight pre: not specified	min. 95% "ideal weight")	+ treating hospital. Patients from groups II achieved target weight early than group III. (n.s.) But: Cyproheptadine only led to weight gain in restr. AN, but to a weight loss in binge-purge!	All participants already showed significant weight gains of 1.96kg in the baseline week (7-day pretreatment period) No information on further therapies
		Group II: Amitriptyline (max. 160mg/d) + inpatient treatment	23				<u>Secondary:</u> Side Effects Inventory, HAM-D ABS, HSCL-90, Anorectic Attitude Scale, BDI, Situational discomfort scale	Group 1 showed greater reduction depressive symptoms than. group III (n.s.) Weight post (daily weight gain): Gp I: 0.3±0.19kg Gp II: 0.31±0.17 Gp III: 0.23±0.12	
		Group III: Placebo + inpatient treatment	25						

Kafantaris et al. 2011 A Placebo-Controlled Pilot Study of Adjunctive Olanzapine for Adolescents with Anorexia Nervosa	RCT, Placebo-controlled, double-blind pilot study Duration: 10 weeks	I: Olanzapine Doses: Increases in 2.5mg doses weekly up to max. 10mg daily from 4th week	10	3	Baseline, week 5 & 10: BMI, EDE, YBC-EDS Baseline, week 2, 4, 6, 8 & 10: HDRS & BPRS Weekly: TESS	N = 15 Female = 100% Age: M = 17.1 (range: 12.3-21.8) yrs DSM-IV AN restrictive: 70% EDNOS: 30% BMI: M = 16.4 (1.2) Therapy form: Inpatient: 45% Day-clinic: 30% Outpatient/weekly: 25%	<u>Primary:</u> Weight BMI and median BW %	Weight gain in both groups, but not sig. higher with olanzapine	Study quality: low No info on comorbidity, illness duration Only inpatients and day-clinic patients received 3 meals and two snacks supervised Overall fewer therapeutic interventions in outpatients Focus on adolescents Very small sample + high dropout rate
		II : Placebo	10	2			<u>Secondary:</u> General psychological changes using HDRS & BPRS ES symptoms using EDE & YBC-EDS Side effects using TESS	No sig. changes in either group regarding general psychological and ED symptoms No strong side effects	
Kaye et al. (2001) Double-Blind Placebo-Controlled Administration of Fluoxetine	Rando-mized placebo-controll. double-blind study	Group I: Fluoxetine (20-60 mg/d), Begin 2-4 weeks pre discharge of inpatient treatment	16	6	Weight and assessment: Pre+ 1x per mths (if condition of VPN decreased, data 1x per week)	N = 13 Females Group I 23 yrs (SD 9), Group II 22 yrs (SD 6) AN (DSM-IV) Restrictive: 20	<u>Primary:</u> Improvement in Group I concerning relapse and symptom reduction 1 yr after reaching target weight	Due to high dropout rate 4 groups: 1.'Fluoxetine treatment completers',	Study quality: low Outpat. treatment was up to pat. decision 9 of 12 VPN with outpat. treatment were dropouts,

in Restricting-Purging-Type Anorexia Nervosa	Duration: 1 yr (52wks)					Purge: 15 (No VPN with binge-eating) Outpatient: 12 No PT: 23 Weight pre (avrg body weight, %) Group I: 89% Group II:89%	(90% avrg body weight)	2.'Fluoxetine treatment dropouts' 3.'Placebo treatment completers' 4.'Placebo treatment dropouts' Group I showed sig. improvements in weight between baseline and end of study Weight change post: Gr 1: 5.3% Gr 2: -1.2% Gr 3: 11.2% Gr 4: -0.2%	Very high dropout rate in placebo-group (only 3 of 19 VPN stayed until end of study)
		Group II: Placebo-capsules Begin: ebd.	19	16 Total dropout data (group I+II): Total dropout: 26 4 dropouts not included			<u>Secondary:</u> sig. improvement of group I: HAM-D, HAM-A, Y-BOCS + Y-BOCS-ED Better weight gain in group I compared to group II	Group 1 showed sig. improvements in depression, anxiety, compulsiveness and key symptoms of ED	

				Group I: 6 dropouts Group II: 16 dropouts (each before end of study. results were included in data analysis)					
Kim et al. (2014) The impact of Intranasal Oxytocin on Attention to Social Emotional Stimuli in Patients with Anorexia Nervosa: A Double blind within-subject Cross-over Experiment	RCT Double blind, crossover placebo controll., duration: 4-7d Intake of nasal spray 45 min prior to task: Alter-nating 1d placebo, 1d Oxytocin	I: AN Oxytocin – placebo Dose: 4OIU	31 (13 inpat. 18 out-pat.)	? (n.a.)		N = 64 Female: 100% DSM-IV Age: I: M = 23.10 (9.35) II: M = 22.18 (2.14) BMI: I: M = 15.15 (2.51) II: M = 20.91 (2.22)	<u>Primary:</u> Change in attention in terms of certain stimuli (threatening vs. rewarding)	Increased attention of AN in Oxytocin, if threatening stimuli (angry face) present	Study quality: very low Unclear which other treatments were given 2h prior to spray only water was allowed to be consumed No detail on comorbidity, illness duration, additional medication (only 3 pat. took fluoxetine) No differentiation between restrictive/purging, measurement of possible side effects Large range of BMI in both groups Pat. with AN different illness status Results based on likelihood and do not show proof for long term use of Oxytocin
		II: HC: Healthy controls Oxytocin - placebo	33	? (n.a.)			<u>Secondary:</u> Change in selective attention concerning social stimuli (happy, anger, disgust) Change in psychopathologic values. Measured with EDE-Q, BDI, STAI and AQ Change in weight due to intervention	No change in attention in terms of happy faces in both groups + disgust: without Oxytocin increased attention, with Oxytocin increased disinterest in both groups No change in weight or psychopathologic	

								variables in intervention Conclusion: Different processing of social stimuli in groups →AN: evidence that starvation helps in suppressing emotional processing, Oxytocin could have a small positive effect	
Kim et al. 2015 The impact of Oxytocin on Food Intake and	RCT double blind, crossover placebo controll.	I: AN Oxytocin - Placebo	43	8	1 Test with placebo or Oxytocin, Duration inbetween 4-7d psychological Assessment +	N = 102 Female: 100% Age: I: M = 21.8 (8.4) II: M = 23.0 (5.2) III: M = 22.6 (2.3)	<u>Primary:</u> Reduce of appetite and therefore less calorie food	AN + HC: no difference in eating behav. BN: less calorie food within 24h after Oxytocin	Study quality: low No info on comorbidity, no differentiation between restrictive/purging, no info on medication or other therapeutic interventions

emotion recognition in patients with Eating Disorders: a double blind single dose within-subject cross-over experiment.		II: BN Oxytocin - Placebo	39	5	24 h documentation of food intake per task	DSM-IV BMI: I: M = 15.1 (2.4) II: M = 20.2 (2.5) III: M = 2.9 (2.1) Illness duration in mths: I: M = 43.3 (62.1) II: M = 57.6 (34.7)	<u>Secondary:</u> Increase in social and emotional perception	BN + HC: small effect in emotional and social sensitivity after Oxytocin (v.a. neg. emotion, sad.) AN: no effect	only info that inpat. and outpat.of ED clinic Consideration of menstrual cycle
		III: HC: Healthy Controls Oxytocin – placebo dose 4OIU intranasal	33	0					
Lacey et al. 1980 - Hunger, food intake and weight: the impact of clomi-pramine on a refeeding anorexia nervosa population	Rando-mized placebo control. double blind study duration ca. 76 8+-24 d) d	Group I: Clomipramine (50mg/d) + inpatient therapy (bed rest, daily kcal 2600, individual therapy psychological care	8	2	Weight: 2x/week test/scale 4x/d	N = 13 Female: ? Age: ? AN (no detail on diagnostic) restrictive: 14 purging: 2 inpat. Treatment Weight pre:	<u>Primary:</u> Weight (Target-weight set individually)	All VP reached set weight Group I showed less weight-improvement (in unpublished follow-up group I showed more stable weight-progress than group II Weight post:	Study quality: low Target weight was set individually with each pat. No detail on criteria No detail on measurements (test) Pat. had to stay 24h/d in bed. Hyperactivity was measured with sensors in bed

						Group I: 40.6 (4.6) Group II: 37.7 (5.2)		Group I: 53.93 (4.22) Group II: 52.4 (6.15)	
		Group II: placebo + inpatient ebd.	8	1			<u>Secondary:</u> Scales for hunger, anger, anxiety, excitement, sadness, tension, appetite, restlessness	Group I more stable eating habits and more hyperactivity than group II Group I reported more 'hunger' and 'appetite' after some weeks	
Levinson et al. 2015 D-Cycloserine facilitation of exposure therapy improves weight regain in patients with anorexia nervosa: a pilot randomized controlled trial.	RCT double-blind placebo control. duration: 3 wks/4 sessions	I: placebo + exposure	16	-	After each session + 1mths FU: BMI, SUDS, BDI, EDI-2	N = 36 Female: 97.2% Age: M = 25.4 (R14-49) DSM-IV: 72.2% restrictive Comorbidity: Anxiety 83.3% Depression 77.7.% BMI M = 20.2 (2.02) 80.5% BMI > 18,5	<u>Primary:</u> weight/BMI	Sig. higher weight gain with D-Cycloserin (3 pounds vs. 0,5 pounds) + independently	Study quality: low No detail on illness duration, other therapeutic interventions, food-diary BMI > 20
		II: D-Cycloserine + exposure dose 250mg	20	-			<u>Secondary:</u> anxiety with SUDS (pre, within and post meal = exposure) amount of food	No difference in groups, but less anxiety and more food intake due to exposure	

Malina et al-2003 Olanzapine treatment of AN: A retrospective study	Retro-spective study 1 measure ment	Olanzapin (4.7 (2.4 mg/d) + inpatient ED therapy (n.a. about individual therapy)	18	0	1 measurement Interview + 2 identical questionnaires on pre/post olanzapine treatment	N = 18 Sex: n.a. 22+-7 yrs AN (no detail on diagnostic) Subtype: n.a. Inpatient Weight pre: 38 (6) kg	Retrospective, subjective improvement in AN typical behavior after olanzapine-treatment Questionnaires: compulsiveness, appetite, anxiety before meals, ability and desire to eat, anxiety, daily tiredness, sleep difficulties, mood stability, reaction to weight gain, dizziness after getting up (pre/post olanzapine treatment)	Sig. improvement: compulsiveness, anxiety before meals, reaction to weight gain, mood stability, sleep difficulties weight post: 43(6) kg	Study quality: low 10 pat. more meds during olanzapine treatment Duration of olanzapine intake varied (17 +-20 weeks) No detail on other therapies during olanzapine treatment Retrospective study without control group
Miller et al. 2011 Effects of risedronate and low-dose transdermal testosterone on bone mineral density in	RCT placebo-controll., double blind, duration 12 mths dose: risedrona te 35mg weekly	I: double placebo II: Risedronate + Testosterone	18 20	 -	Baseline + post 1, 3, 6, 9, 12 mths weight, physical activity, hirsutism, acne, marker of bone metabolism, testosterone, ALT	N = 59 Female: 100% Age: I: M = 26.9 (7.2) II: M = 25.2 (6.2) III: M = 25.3 (6.3) IV: M = 27.1 (7.3) Illness duration: I: M = 5.2 (4.3) II: M = 6.3 (6.8)	<u>Primary:</u> Bone density (Hip, spine, radius) marker of bone metabolism (CTX, P1NP)	Increase of bone density with risedronate postanterior and lateral spine + hip) decrease in CTX & P1NP with risedronate no differences with testosterone	Study quality: moderate Dose of testosterone always adapted to lab results Additional intake of Vit D (400IU) and calcium (1200mg) No. of pat. that took contraceptives was documented

women with AN: A randomized, placebo-controlled study	as capsules testosterone 150ug plaster daily	III: Risedronate + Placebo plaster	20	-	baseline + post 6, 9, 12 mths BMD, baseline + 12 mths MAQ physical activity	III: M = 5.1 (5.8) IV: M = 6.6 (5.5) DSM-IV Purging: I: M = 39% II: M = 40% III: M = 50% IV: M = 26% BMI: I: M = 17.9 (1.2) II: M = 17.8 (1.4) III: M = 1.6 (1.2) IV: M = 17.5 (1.8)	<u>Secondary:</u> weight + possible side-effects	no effect on weight higher rates of free and total testosterone connected to increase of lean body mass and strengthening of hip bones no strong side effects	No inf. on additional interventions and food diary BMI high No inf. on comorbidity considered PA (MAQ)
		IV: Testosterone + Placebo capsule	19	-					
Misra et al. 2011 Physiologic estrogen replacement increases bone density in adolescent girls with AN	RCT placebo-controll., double-blind duration 18 mths Inter-vention= physiological/ natural addition of Estradiol IGF-1 not suppressing Dose: BA < 15 yrs	I: AN E +	55	24	Baseline, 6, 12, 18, mths BMD (Hip, spine) body composition weight	N = 90 Female = 100% Age: 12-18 yrs AN: M = 16.5 (0.2) CG: M = 15.6 (0.2) DSM-IV BMI: AN: M = 17.4 (0.1) CG: M = 21.4 (0.5)	<u>Primary:</u> change in bone density (BMD) hip and spine	Sig. increase in bone density with Estradiol (spine and hip) no difference in BMD between AN E+ and CG	Study quality: moderate Consideration of bone age (BA < or > 15 yrs) and specific covariates (height and duration amenorrhea) Additionally, for all daily 1200 ca & 400IU Vit D No differentiation restrictive/purging No info on illness duration, comorbidity AN received day-hospital treatment No severe side effects high BMI focus on adolescents
		II: AN E-Placebo	55	25			<u>Secondary:</u> Weight and body composition	No difference between Group I and II, no difference in BMI, body fat etc. (no change in IGF-1 levels after intervention)	
		III: CG (Placebo) female normal weight	40	11					

	gradual increase of Ethinyl-Estradiol: daily 0-6 M: 3.75 mcg 6-12 M: 7.5 mcg 12-18 M: 11.25 mcg BA> 15 yrs 2x weekly 100mcg 17ß-Estradiol as plaster +2.5 mg Medroxy-progesterone 10 days per month								
Mondraty et al. 2005 Randomized Controlled Trial of Olanzapine in the Treatment of Cognitions	RCT Duration different per VPN	Group I: Olanzapinee (5-20mg, increase) + inpat. treatment (psychiatric contacts, food intake, medication)	8	0	Test: pre + previous to discharge	N = 15 Female: ? 25.3 (7.4) yrs AN (DSM-IV) subtype: ? Inpatient	<u>Primary:</u> sig. improvement of Group I in EDI-2 (subscales: drive for thinness, body dissatisfaction, bulimic symptoms)	Sig. improvement in PI ED specific rumination in group I no group differences in EDI-2	Study quality: low 2 pat. of Gr II did not receive meds, data was included in results 5 pat. of Gr I received SSRIs Gr I had higher amount of pat. with 'purging type' Gr I was not blinded considering meds

in Anorexia Nervosa						Weight (BMI) pre: Gr I: 14.2 (1.9) Gr II: 13.4 (1.2)	Padua Inventory (IP) criteria ED thoughts rumination	weight BMI post Gr I: 16.7 (1.5) Gr II: 15.4 (2.8)	Duration of meds different per pat. Gr I: 46 (31) days Gr II: 53 (26) days
		Group II: Chlorpromazine (25-200mg, increase) + inpatient ebd.	7	0			<u>Secondary:</u> -		
O'Connor et al. 2016 Refeeding Low Weight Hospitalized Adolescents With Anorexia Nervosa: A Multicenter Randomized Controlled Trial.	RCT Duration 10 days	Food intake 1200 kcal/d	18 (2 pat. did not reach 80% of required food intake – naso-gastral tube)	0	Weight: pre breakfast in underwear, baseline, then day 1, 2, 4, 8, 10 Cardiovascular: baseline, then day 4 (12 lead EKG, QTc interval) Blood: glucose, insulin, phosphate, magnesium, potassium, baseline and day 1, 2, 4, 6, 10	N = 36 AN or atypical AN pat.included in study were moderately underfed: < 78% mBMI exclusion criteria: medical state that could influence biochemical and cardiovascular parameters.(diabetes type 1) or atypical antipsychotic or antidepressant meds. Age: M = 13.8 (1.8) Sex: Female: 34 Male: 2 BMI: M = 13.5 (1.1)	<u>Primary:</u> Weight/BMI complications in refeeding (longer QTc interval, low levels of phosphate, potassium, magnesium) refeeding syndrome (indicators for underfeeding) mBMI, WBC, insulin sensitivity etc.	1200kcal group sig higher food intake after 10 days cardiovascular: QTc-interval: after 4 d no sig difference in groups. after 8 d QTc length gone in all pat. HR after 4 d better in both groups no sig. group differences anthropometric measures: mBMI after 4 d no sig differences considering baseline in both groups after 10 d sig change in groups	Study quality: moderate Focus on adolescents No detail on diagnostic manual Post-hoc-analysis

						inpatient recruited from 6 clinics in GB		considering baseline and weight Biochemical measures: phosphate, magnesium potassium: no sig. group differences Hypophosphat-emia: 48 after beginning of refeeding = 28% of the 1200kcal group and 11% of 500kcal group (start of study no hypophosphate-emia in any pat.) no other changes in electrolytes WBC no sig difference after 10 d	
		Food intake 500 kcal/d	18 (2 pat. did not reach 80% of required food intake – nasogastral tube)	0			<u>Secondary:</u> Theoretical predictors for hypo-phosphatemia		

Pallanti et al. 1998 Citalopram in AN	Open trial duration 6 mths	Citalopram (20-max.60 mg/d) + dietary advise at start of study	32	6	1x/week – 1x/mth measurement on an individual basis (min 1/week)	N = 26 Female: n.a. Age: 22.3 (4.0) AN (DSM-IV), all pat. restrictive outpatient Weight pre ('ideal body weight%'): 77.7 (3.7) %	<u>Primary:</u> Weight increase of min. 5%, start of menstruation	Sig. weight increase in all pat., 5 pat. with menstruation, 11 pat. (34.4%) without, Weight post: 81.3 (5.7)	Study quality: moderate Dose of 20mg stayed the same until the end, when pat got better; if no improvement: dose increased to max 60mg/d No detail on further outpatient treatment. Last point of measurement of dropouts was included.
							<u>Secondary:</u> sig. improvement on EDI-2, SCL-90R min. 35%, HAM-D, Y-BOCS	No sig. change in HAM-D and Y-BOCS. Sig improvement in some EDI-2 scales, Pat. with small change with Citalopram started with sig. lower weight. Pat. with good change under citalopram showed more improvement on SCL-90R scales	
Powers et al. 2012 Double blind placebo controlled trial of	RCT placebo control. double-blind duration 8 weeks	I: placebo	9	3	Day 1 vs week 8 differences in mean of groups on BMI, self report + SKID, difference in	N = 10 Age (18-65) M = 34 (13.48) Female = 95.24% BMI = 15.9 (2.27)	<u>Primary:</u> ED symptoms from YBC-EDS & EDI-2	Between groups: no sig. differences Within: in YBC-EDS no sig. difference in	Study quality: low Sample size = 11 only 4 finished quetiapine Recruitment unclear, missing data on occupation, outpatient

Quetiapine in AN					outcome (within & between)	DSM-IV.TR: restrictive = 52.4% comorbidity: depression = 52.4 % compulsiveness = 1/3 specific phobia = 1/3 min 3 other disorders = > 50%		subscales of EDI-2 sig. differences	treatment, illness duration, age of onset) Sociodemographic data only provided for all pat. Analysis of within data: direction unclear Short study duration
		II: Quetiapine doses: M = 177.7mg (90.8)	7	3			<u>Secondary:</u> Obsessive-compulsive symptoms, depression + anxiety symptoms (Y-BOCS, STAI + HAM-D BMI PANSS)	Between: no sig. differences Within: sig differences in HAM-D + STAI-Y trait	
Ricca, et al. 1999 Venlafaxine versus fluoxetine in the treatment of atypical anorectic outpatients: A preliminary study	non rando-mized study 2 groups duration : 6 mths	Group I: Fluoxetine (40mg/d) + outpat. therapy	12	1	baseline, 6 mths	N = 22 Sex: n.a. Age: 19 (3.7) Atypical AN (DSM-IV) Weight pre (BMI): Group I: 15.84 (0.46) Group II: 15.67 (0.59)	<u>Primary:</u> Difference in effects between both meds. Change in weight (BMI)	Sig. weight gain pre-post (no group differences) Weight post (BMI): Gr. I 18.7 (1.1) Gr. II: 18.3 (1.3)	Study quality: low Groups not randomized Pat. of one time period were assigned to group I, patients after this time period were assigned to group II
		Group II: Venlafaxine (75mg/d) + outpat. therapy	12	1			<u>Secondary:</u> SCID, EDE, BDI, STAI	Sig. EDE & BDI reduction (no group diffs) sig. STAI reduction in Gr. II sig. STAI increase in Gr. I no sig. diffs in pat with or without comorbidity	

Ruggiero, et al. 2001 A Single Blind Comparison of Amisulpride, Fluoxetine and Clomipramine in the Treatment of Restricting Anorectics	single-blind study 3 experi-mental groups duration 3 mths	Group I: Clomipramine (57.69 (25.79)mg) + nutrition management inpatient program for weight gain	13	0	T0 baseline T1 3mths	N = 35 Sex: n.a. Age: 23.69-24.5 AN (DSM-IV) only restrictive Inpatient Weight pre: Gr. I: 37.61 (9.8) Gr. II: 40.9 (6.98) Gr. III 38.4 (8.33)	<u>Primary:</u> Sig. changes in: weight (BMI), weight phobia, body schema, amenorrhea und binge-/purging. (scales: DSM-IV, Structured ED Interview from 'long interval follow-up evaluation)	Comparison T0 vs. T1 shows sig. diffs in weight gain between Gr. II and Gr. III (III: highest weight gain) No sig. changes between T0 and T1 in weight phobia, body schema, amenorrhea and binge-/purging. Highest weight gain with aminsulpiride Weight post: Gr I: 38.69 (9.38) Gr. II: 42.7 (7.54) Gr. III 42.62 (10.09)	Study quality: low No detail on other therapies, other meds
		Group II: Fluoxetine (28 (10.23) mg) + ebd.	10	0					
		Group III: Amilsupride (50mg) + ebd.	12	0			<u>Secondary:</u> -	-	
Ruggiero, et al. 2003 Nutritional Management	non rando-mized single-blind	Group I: Fluoxetine (30 (9.35) mg) + nutrition management	21	?	T0 baseline T1 3 mths T2 6 mths T3 12 mths	N = 95 Female 91, male 4 AN (DSM-IV)	<u>Primary:</u> weight (BMI)	Sig. weight gain T0-T3 in both groups. sig increase in BMI (T1,T2,T3)	Study quality: low 40 pat. showed no amenorrhea Gr. I showed higher concern of weight gain at T0 and lower

of anorexic patients with an without fluoxetine: 1-year follow-up	study 2 groups duration 1 yr	inpatient program for weight gain				subtypes: restrictive: 21 Age: 23.36 (4.04) binge-purging: 34 Age: 22.84 (5.01) AN without amenorrhea: 40 age: 24.08 (5.34) Outpatient		in Gr. I compared to Gr. II. weight post (BMI): Gr. I: 19.72 (4.15) Gr. II: 16.52 (3.27)	illness duration compared to Gr. II Fluoxetine was given to pat. that were rated as suitable.
		Group II: nutritional management only	74	?		Weight pre: Gr I: 14.83 (1.53) Gr. II: 14.29 (2.18)	<u>Secondary:</u> weight concerns, vomiting, laxantive-abuse physical activity, drive for thinness (DT), body dissatisfaction (BD), EDI-LIFE, EDI	Sig. improve-ment in Gr. I compared to Gr. II in: physical activity, sig. improvement in fear of weight gain and drive for thinness in Gr. II vs. Gr. I	
Santonastaso et al. 2001 Sertraline in the Treatment of Restricting Anorexia Nervosa: An Open Controlled Trial	Open controll. study duration: 14 weeks FU: 64 weeks	Group I: Sertraline (begin 50mg/d, after 1 mth 100mg/d) + outpatient VT +dietary advise	11	0 (after 14w) 1 (after 64w)	Weight: 2x/mth test and other measures: baseline 14w FU: 52-84w	N = 20 Sex: ? Age: 19.3 (4.7) AN (DSM-IV), all pat. restrictive At study begin outpatient	<u>Primary:</u> weight (BMI) DSM-IV symptoms of AN interviews consid. ED symptoms (preoccupation with food /avoiding food, weight concern, body schema)	Post 14w: 6 pat of each group fulfilled criteria for AN, BMI increased in both groups 17.1 Gr. I and 17.6 Gr. II, Gr. I sig effect on body schema and EDI-scales + SCL.	Study quality: low Pat. not blinded but selected by order. First 11 CG, next 11 sertraline group 2 pat. started binge-/purging during study

						Weight pre (BMI): Gr. I: 15.6 (1.2) Gr. II: 16.4 (0.9)	Self-report measures: EDI, Hopkins Symptom Check List (SCL-58, only compulsiveness, depression, anxiety)	In both groups sig. improvement in eating behavior and ED cognitions FU post 64w:	
		Group II: control group, outpatient ebd.	11	0 (after 14w) 1 (after 64w)			<u>Secondary:</u>	1 pat. Gr. I + 5 pat. Gr. II fulfilled criteria for AN BMI increase 18.4/18.3 no group difference	
Steinglass et al. 2014b The (lack of) Effect of Alprazolam on Eating Behavior in Anorexia Nervosa: A Preliminary Report	RCT placebo controlled double-blind crossover duration: 2 test days within 1 week placebo or Alprazolam	Group I: AN Alprazolam 0.75 mg on test day 1.5 h prior testmeal (975g Strawberrys-shake – 1014kcal)	20	?	Pre/post meal, STAI-S, POMS, post meal amount of food intake	N = 20 Female = 100% Age: 18-60 M = 25.6 (7.8) DSM-V: restrictive = 45% Illness duration: M = 11.1 (8.0) BMI: M = 18.0 (0.6) comorbidity anxiety 25%	<u>Primary:</u> Difference in amount of food intake kcal	No difference	Study quality: moderate Short intervention/ 1 day No normal distribution of data Not enough details Small sample 3 pat. data not included in analysis 10% received fluoxetine Pat. received additional therapeutic intervention, unclear which exactly
		Group II: AN Placebo	20	?			<u>Secondary:</u> Change in anxiety symptoms ad tiredness (STAI + POMS)	No difference in anxiety but increased tiredness in alprazolam	

Strobel et al. 2004 Psychopharmako-therapie mit Clomipram-in und Paroxetin bei jugendlichen Patientinnen mit "Anorexia Nervosa" und „Depressiver Episode" – eine Pilotstudie zu Verträglich-keit, Absetzquote und Verlaufskriterien	Retro-spective study 2 groups	Group I: Clomipramine 75.3 (16.6) mg/d + inpatient avrg stay 87.6d	57 (sub-group 11)	0	1 time point of measurement because of restrospective analysis: basic documentation, multiaxial classification, documentation on progress and outcome	N = 83 (subsample for 2nd study N = 20) Female, 10.9-18.1 yrs AN + depressive episode (ICD-10) Subtypes: n.a. Inpatient Weight pre (BMI) Gr. I: 14.5 (2.3) Gr. II: 14.7 (2.2)	<u>Primary:</u> sig. difference between groups in duration of stay, weight gain (N = 20), side effects, cause for dropping out (N = 83)	part 1 N = 83 side-effects of clomipramine more frequent (15.8%) than with paroxetine (10.3%) clomipramine was dropped sig. more often (14.0%) compared to paroxetine (5.1%) part 2 N = 20 sig longer stay inpatient in Gr. I (96.5d) vs Gr.II (71.9d) sig. faster weight gain in Gr.II weight post (BMI) Gr. I: 2.6 Gr.II: 2.8	Study quality: low Some pat. took clomipramine and paroxetine – therefore sum pat. > N
		Group II: Paroxetine 18.4 (4.7) mg/d + inpatient avrg stay 91.0d	39 (sub-group 9)	0			<u>Secondary:</u> -	-	

Vander-eycken & Pierloot, 1982 Pimozide combined with behaviour therapy in the short-term treatment of anorexia nervosa	Rando-mized placebo control. double-blind crossover study duration: 7w crossover after 3w	Group I: Pimozide (4 or 6 mg) +inpatient BT crossover to placebo after 3w	8	1	Baseline-period: 7-10d avrg. Weight change/d +psychological tests baseline, 3, 7w	N = 17 Female Age: 21.5 AN (DSM-III) Subtypes: n.a. Inpatient Weight pre, both groups: 38.3 (4.8) kg	<u>Primary:</u> avrg. daily weight gain	Sig weight gain in both groups 'responders': 8 pat. 'non-responders': 10 pat. weight post: avrg weight gain in g: Gr.I: 130g Gr.II: 93g	Study quality: low Weight Gr. I (35.5kg) smaller than Gr. II (40.6kg)
		Group II: placebo + inpatient BT ebd. crossover to pimozide after 3w	10	0			<u>Secondary:</u> attitude towards weight gain, compensatory behaviors (Anorectic Behaviour Scale for Inpatient Observation)	'responders'older than 'non-responders', also longer illness duration; small improvements in group I on attitudes towards weight gain and compensatory behavious	
Vander-eycken,, 1984	Rando-mized placebo control. double-blind	Group I: Sulpiride (300-400mg/d) + inpatient ED therapy	?	?	Baseline period: 1w weight 1x/d tests: 1, 3, 7w	N = 18 female Group I: age 23.2 (6.5)	<u>Primary:</u> sig. improve in Gr. I in weight, anorectic behavior scale for inpatient	Gr. I showed decrease in scales of EAT + B.A.T: no group differences	Study quality: low Gr. II began with higher weight than Gr. I – therefore comparison difficult

Neuroleptics in the Short-Term Treatment of Anorexia Nervosa. A Double-blind Placebo-Controlled Study with Sulpiride	crossover study duration: 7w crossover after 3w	crossover to placebo after 3w				Group II: age 23.7 (9.6) AN (DSM-III) Subtypes: n.a. inpatient weight pre: Gr. I: 40.4 (4.6) kg Gr. II: 38.3 (4.3) kg	observation, EAT, B.A.T.	sulpiride increased weight gain in Gr. I weight post: Gr. I: 1 phase: 153.8 (91) 2 phase: 9.6 (51.4) Gr. II 1 phase: 92.6 (49.4) 2 phase: 102.6 (47.5)	
		Group II: placebo + inpatient ED therapy crossover to sulpiride after 3w	?	?			<u>Secondary:</u> -	-	
Walsh, et al. (2006) Fluoxetine After Weight Restoration in Anorexia Nervosa	Randomized placebo controlled double-blind study duration: 1 yr	Group I: Fluoxetine (20-80mg increase) + outpatient BT (45min/1x/w)	49	25	Weight: 1x/w test: 1x/mth	N = 40 Female age: 23 (4.6) AN (DSM-IV) record, BMI baseline min 19 restrictive: 51.6%	<u>Primary:</u> time until recurrent (BMI < 1.5) + group differences in successful therapy over 1 yr	No group differences in all parameters 45% of Gr. I and 43% of Gr. II no recurrent within 52w weight post (BMI): Gr. I: 19.08 (2.1)	Study quality: high Good monitoring of cofounding variables (control of BT sessions, meds and side effects, weight change, mood changes) Pat. without amenorrhea during AN were included

						binge/purge: 48.4% outpatient therapy Toronto (48 pat.) New York (45 pat.)		Gr. II: 18.36 (1.6)	Pat. in Gr. II had sig. higher BMI from beginning Both patients and psychiatrists recognized medication (fluoxetine/placebo) more often than by chance
		Group II: placebo + outpatient BT (45min/1x/w)	44	28			<u>Secondary:</u> sig. increase of Gr. I in weight, BMI, EDI, BDI, BAI, RSE, YBC-EDS, QlesQ	Sig. more pat. from Toronto (56.3%) stayed in study compared to NY (28.9) sig. more pat. with restrictive AN (54.3%) stayed in study compared to binge/purge AN (31.1)	

Abbreviations:
General: *AN* Anorexia Nervosa, *Binge-purge* Binge-eating/purging type of AN, *BN* Bulimia Nervosa, *BT* behavioral therapy, *d* days, *inpat.* inpatient therapy, *n.a.* not available, *m* male, *mths* months, *outpat.* outpatient therapy, *pat.*. patients, *PT* psychotherapy, *Restr* restrictive type of AN, *w.* weeks, *yr/yrs* years
Measures: *ABS* Anorectic Behaviour Scale, *BDI* Beck Depression Inventory, *BSQ* Body Shape Questionnaire, *CGI* Clinical Global Impression Scale, *EAT* Eating Attitude Test, *EDI-2* Eating Disorder Inventory 2, *GAF* Global Functioning Assessment, *HAM-A* Hamilton Rating Scale for Anxiety, *HAM-D* Hamilton Rating Scale for Depression, *HSCL* Hopkins Symptom Checklist, *SCL-90* Symptom Checklists, *STAI* Spielberger State-Trait Anxiety Inventory, *Y-BOCS* Yale-Brown Obsessive Compulsive Scale

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Method report Anorexia nervosa

As the concern was with a revision of the guideline from 2010, the aim was to check the currently available evidence, and where applicable to revise the recommendations should they have changed in the interim. The key questions remain unchanged, and were only supplemented by one question: Given the increasing interest in internet- and technology-based interventions, the available studies pertaining to these interventions were viewed and it was checked whether application-based recommendations could be derived.

To check the current evidence, the following approach was pursued:

- Inclusion of current guidelines: current guidelines of the Royal Australian and New Zealand College of Psychiatrists (ANZJP; Hay et al. 2014), although these are not based on systematic literature reviews. A revision of the English NICE guidelines was underway in parallel, but had not yet been published when the German guidelines were completed. The US-American guidelines (APA, 2006) have also not yet been published in a current, fundamentally revised version.
  For each question, systematic reviews and meta-analysis were searched for and a systematic literature search for primary literature was conducted. The University Library in Heidelberg was given this task (AN and BN). The search strategy was oriented to the search strategies of the original version of the guidelines, although slight changes were necessary due to the change in the literature databases (see below).

- The search initially encompassed the period from 1.11.2005 – 31.01.2016. Due to a delay in the work on the guidelines, the search was updated to the end of February 2017. The search was supplemented by a hand search in the reference lists of current reviews.

First, the identified studies were viewed and roughly coded according to the following criteria: RCT vs. others; anorexia nervosa vs. others; psychotherapy vs. pharmacotherapy vs. others. All new randomized controlled trials were checked with regard to predefined inclusion and exclusion criteria (see below) and then rated with respect to their quality by two independent raters according to the rating scheme used in the first version. In the case of discrepancies in rating, consensus was reached following discussion. The inclusion criteria were as follows (see also Zeeck et al., 2018):

1. At least one arm of the study refers to a psychotherapeutic or pharmacological intervention;
2. Data were reported for at least two measurement time points;
3. Weight data (body weight, BMI) were reported for at least two measurement time points;
4. The sample size is greater than or equal to N_{arms} X 10 (e.g. 11+9 = 20; ≥ 10 x 2);
5. No mixed samples consisting of patients with anorexia nervosa and other eating disorders (or, in such cases, the data have to be separately reported for the subgroup of patients with AN);
6. The second measurement time point lies in a time window of ≤ 3 years after the start of the intervention.

After intensive discussion in the expert group, one exclusion criterion was changed compared to the first version of the guideline: Studies were also allowed to include patients with a weight between BMI 17.5 and 18.5 kg/m². The group of patients with a weight between 17.5 and 18.5 kg/m² shows similar characteristics to the group of patients with a BMI < 17.5 kg/m² (see e.g. Swayer et al 2016) and is also diagnosed as AN according to the new classification in the DSM-5.

The quality evaluation was oriented to GRADE (see e.g. Guyatt et al. 2008), but referred to individual studies. It comprised the following criteria, which were rated as "yes", "no", or "unclear":

(1) Sample size > 30/arm
(2) No indication of recruitment bias
(3) Dropout rate < 20%
(4) ITT analysis
(5) Relevant outcomes were reported (BMI, eating disorder pathology, depressiveness, quality of life)
(6) Validated outcome measures
(7) Allocation concealment
(8) Blinding
(9) Consort Statement
(10) Registered in a register for clinical studies
(11) The examined sample corresponds to the population of interest
(12) The intervention corresponds to the intervention of interest
(13) Endpoints are clinically relevant
(14) The intervention can be implemented and used in the German health system
(15) Acceptance by patients

Here too, in the case of discrepancies between raters, consensus was sought, and an overall quality evaluation was undertaken following discussion (high; moderate; low; very low).
As several new studies on psychotherapeutic interventions have been published since the first version of the guideline, a network meta-analysis was conducted to present the available evidence, which should answer the following questions: Is one psychotherapeutic approach superior to others? Do psychotherapeutic interventions differ in terms of efficacy between adolescents and adults? Which weight gains can be expected in different settings? For the latter two questions, standardized mean change (SMC) statistics were employed, and non-randomized controlled studies were also included (external validity; see Zeeck et al., 2018).
The evidence tables were revised and recommendations were checked regarding whether they can remain or whether they need to be changed regarding the level of recommendation as well as the text. For many clinical questions, literature of a lower evidence level was searched (quasi-experimental studies, observation studies), if no randomized controlled trials were available. For clinical questions on which no empirical evidence could be found, or for which an empirical test is not to be expected or not possible, good clinical practice was developed in the expert group. Some of these (GCP) recommendations were formulated upon consensus in the expert group as "we suggest" or "we recommend" recommendations due to the high clinical significance.
Each of the individual chapters was revised by 2-3 members of the work group. All sections were checked by experts from the area of adult treatment as well as experts from the area of child and adolescent treatment. Within multiple meetings and telephone conferences of the work group, the previously sent suggestions for change (text, evidence rating, recommendations) were discussed and a mutually agreed upon formulation was sought. This discussion explicitly included the question of implementability as well as potential side-effects of a recommended approach. For the section "Nutritional management", a nutritionist was consulted.

Systematic literature search for the chapters Anorexia und Bulimia nervosa

Conducted by: Mr Maurizio Grilli M.A.L.I.S. Library for the Medical Faculty of Mannheim, University of Heidelberg; maurizio.grilli@medma.uni-heidelberg.de

Initial literature search up to 1.11.2016, then supplementary search up to end of February 2017.

Determination of the relevant aspects of the theme

P_1	Anorexia Nervosa
P_2	Bulimia Nervosa
S	Filter document type

Strategy

1	P	Keywords (with subheadings in PubMed)
2	S	
3	P AND S	
4	4 AND time filter	Anorexia from November 2005 For the bulimia search, it is very easy to filter out the publications before 2000 by ordering the hits according to publication year in EndNote in the central area (mouse-click on "Year" in the column of the same name).

Notes

P1 and P2 were separately combined with S. The respective results are also, as desired, saved in separate EndNote libraries.

For the anorexia search, a limitation from 01.11.2005 was always undertaken. If the filter function does not allow day and month to be entered, the whole year of 2015 was set as filter.

The respect number of hits refers to the number before deduplication in EndNote.

Databases searched

- PubMed
- Cochrane Library
- Web of Science Core Collection
- Cinahl
- PsychInfo
- ClinicalTrial.gov (study register)
- ICTRP (WHO study register)

PubMed

P1

"Anorexia/diet therapy"[Mesh] OR "Anorexia/drug therapy"[Mesh] OR "Anorexia/rehabilitation"[Mesh] OR "Anorexia/therapy"[Mesh] OR
"Anorexia Nervosa/diet therapy"[Mesh] OR "Anorexia Nervosa/drug therapy"[Mesh] OR "Anorexia Nervosa/rehabilitation"[Mesh] OR "Anorexia Nervosa/therapy"[Mesh]

OR

(anorexia[tiab] OR anorexic*[tiab]) AND (Treat*[tiab] OR

Therap*[tiab] OR
"disease management"[tiab] OR
rehabilitation[tiab])

P2

"Bulimia/diet therapy"[Mesh] OR
"Bulimia/drug therapy"[Mesh] OR
"Bulimia/rehabilitation"[Mesh] OR
"Bulimia/therapy"[Mesh] OR

"Bulimia Nervosa/diet therapy"[Mesh] OR
"Bulimia Nervosa/drug therapy"[Mesh] OR
"Bulimia Nervosa/rehabilitation"[Mesh] OR
"Bulimia Nervosa/therapy"[Mesh]

OR

(Bulimia*[tiab] OR
bulimic*[tiab])
AND
(Treat*[tiab] OR
Therap*[tiab] OR
"disease management"[tiab] OR
rehabilitation[tiab])

S

"Randomized Controlled Trials as Topic"[Mesh] OR
"Randomized Controlled Trial" [Publication Type] OR
"Controlled Clinical Trials as Topic"[Mesh] OR
"Controlled Clinical Trial" [Publication Type] OR
"Clinical Trials as Topic"[Mesh] OR
"Clinical Trial" [Publication Type] OR
Clinical trial*[tiab] OR
“Clinical studies”[tiab] OR
“Clinical study”[tiab] OR
"Randomized Controlled Trials as Topic"[Mesh] OR
"Randomized Controlled Trial" [Publication Type] OR
"Random Allocation"[Mesh] OR
"Double-Blind Method"[Mesh] OR
"Single-Blind Method"[Mesh] OR
single blind*[tiab] OR
double blind*[tiab] OR
triple blind*[tiab] OR
treble blind*[tiab] OR
single mask*[tiab] OR
double mask*[tiab] OR

triple mask*[tiab] OR treble mask*[tiab] OR “blind single”[tiab] OR “blind double”[tiab] OR Latin square*[tiab] OR "Placebos"[Mesh] OR Placebo*[tiab] OR Random*[tiab] OR "Research Design"[Mesh] OR "Comparative Study" [Publication Type] OR "Evaluation Studies" [Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Cross-Over Studies"[Mesh]

End

	Complete search query
P1	((("Anorexia/diet therapy"[Mesh] OR "Anorexia/drug therapy"[Mesh] OR "Anorexia/rehabilitation"[Mesh] OR "Anorexia/therapy"[Mesh] OR "Anorexia Nervosa/diet therapy"[Mesh] OR "Anorexia Nervosa/drug therapy"[Mesh] OR "Anorexia Nervosa/rehabilitation"[Mesh] OR "Anorexia Nervosa/therapy"[Mesh]))) OR (((anorexia[tiab] OR anorexic*[tiab]) AND (Treat*[tiab] OR Therap*[tiab] OR "disease management"[tiab] OR rehabilitation[tiab])))
P2	((("Bulimia/diet therapy"[Mesh] OR "Bulimia/drug therapy"[Mesh] OR "Bulimia/rehabilitation"[Mesh] OR "Bulimia/therapy"[Mesh] OR "Bulimia Nervosa/diet therapy"[Mesh] OR "Bulimia Nervosa/drug therapy"[Mesh] OR "Bulimia Nervosa/rehabilitation"[Mesh] OR "Bulimia Nervosa/therapy"[Mesh]))) OR (((Bulimia*[tiab] OR bulimic*[tiab]) AND (Treat*[tiab] OR Therap*[tiab] OR "disease management"[tiab] OR rehabilitation[tiab])))
S	("Randomized Controlled Trials as Topic"[Mesh] OR "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [Publication Type] OR Clinical trial*[tiab] OR “Clinical studies”[tiab] OR “Clinical study”[tiab] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Randomized Controlled Trial" [Publication Type] OR "Random Allocation"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR single blind*[tiab] OR double blind*[tiab] OR triple blind*[tiab] OR treble blind*[tiab] OR single mask*[tiab] OR double mask*[tiab] OR triple mask*[tiab] OR treble mask*[tiab] OR “blind single”[tiab] OR “blind double”[tiab] OR Latin square*[tiab] OR "Placebos"[Mesh] OR Placebo*[tiab] OR Random*[tiab] OR "Research Design"[Mesh] OR "Comparative Study" [Publication Type] OR "Evaluation Studies"

	[Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Cross-Over Studies"[Mesh])

Cochrane Library

P1

[mh "Anorexia"/DH] OR [mh "Anorexia"/DT] OR [mh "Anorexia"/RH] OR [mh "Anorexia"/TH] OR
[mh "Anorexia Nervosa"/DH] OR [mh "Anorexia nervosa"/DT] OR [mh "Anorexia nervosa"/RH] OR [mh "Anorexia nervosa"/TH]

OR

(anorexia OR anorexic*):ti,ab,kw AND (Treat* OR Therap* OR "disease management" OR rehabilitation):ti,ab,kw

P2

[mh "Bulimia"/DH] OR [mh "Bulimia"/DT] OR [mh "Bulimia"/RH] OR [mh "Bulimia"/TH] OR
[mh "Bulimia Nervosa"/DH] OR [mh "Bulimia nervosa"/DT] OR [mh "Bulimia nervosa"/RH] OR [mh "Bulimia nervosa"/TH]

OR

(Bulimia* OR bulimic*):ti,ab,kw AND (Treat* OR Therap* OR "disease management" OR rehabilitation):ti,ab,kw

End

	Complete search query

P1	[mh Anorexia/DH] or [mh Anorexia/DT] or [mh Anorexia/RH] or [mh Anorexia/TH] or [mh "Anorexia Nervosa"/DH] or [mh "Anorexia nervosa"/DT] or [mh "Anorexia nervosa"/RH] or [mh "Anorexia nervosa"/TH] OR (anorexia or anorexic*):ti,ab,kw and (Treat* or Therap* or "disease management" or rehabilitation):ti,ab,kw
P2	[mh Bulimia/DH] or [mh Bulimia/DT] or [mh Bulimia/RH] or [mh Bulimia/TH] or [mh "Bulimia Nervosa"/DH] or [mh "Bulimia nervosa"/DT] or [mh "Bulimia nervosa"/RH] or [mh "Bulimia nervosa"/TH] OR (Bulimia* or bulimic*):ti,ab,kw and (Treat* or Therap* or "disease management" or rehabilitation):ti,ab,kw

Notes

The study filter is not needed in this databse. In the Cochrane Library only systematic literature reviews and clinical studies are included.

Web of Science Core Collection

P1

(anorexia OR
anorexic*)
AND
(Treat* OR
Therap* OR
"disease management" OR
rehabilitation)

P2

(Bulimia* OR
bulimic*)
AND
(Treat* OR
Therap* OR
"disease management" OR
rehabilitation)

S

"Clinical trial*" OR
“Clinical studies” OR
“Clinical study” OR
"single blind*" OR
"double blind*" OR
"triple blind*" OR
"treble blind*" OR

"single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*

End

	Complete search query
P1	TS=((anorexia OR anorexic*) AND (Treat* OR Therap* OR "disease management" OR rehabilitation)) Indexes=SCI-EXPANDED, SSCI Timespan=2005-2016
S	TS=("Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR "single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*) Indexes=SCI-EXPANDED, SSCI Timespan=2005-2016
P2	**TOPIC:** ((Bulimia* OR bulimic*) AND (Treatment* OR Therap* OR "disease management" OR rehabilitation))
S	**TOPIC:** ("Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR "single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*)

CINAHL

P1

(anorexia OR anorexic*) AND (Treat* OR Therap* OR "disease management" OR rehabilitation)

P2

(Bulimia* OR bulimic*) AND (Treat* OR Therap* OR

"disease management" OR rehabilitation)

S

"Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR "single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*

End

	Complete search query
P1	(anorexia OR anorexic*) AND (Treatment* OR Therap* OR "disease management" OR rehabilitation)
P2	(Bulimia* OR bulimic*) AND (Treatment* OR Therap* OR "disease management" OR rehabilitation)
S	"Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR "single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*

PsychInfo

P1

(DE "Anorexia Nervosa" OR anorexia OR anorexic*) AND (Treat* OR Therap* OR "disease management" OR rehabilitation)

P2

(DE "Bulimia" OR
Bulimia* OR
bulimic*)
AND
(Treat* OR
Therap* OR
"disease management" OR
rehabilitation)

S

"Clinical trial*" OR
“Clinical studies” OR
“Clinical study” OR
"single blind*" OR
"double blind*" OR
"triple blind*" OR
"treble blind*" OR
"single mask*" OR
"double mask*" OR
"triple mask*" OR
"treble mask*" OR
“blind single” OR
“blind double” OR
"Latin square*" OR
Placebo* OR
Random*

End

	Complete search query
P1	(DE "Anorexia Nervosa" OR anorexia OR anorexic*) AND (Treatment* OR Therap* OR "disease management" OR rehabilitation)
P2	(DE "Bulimia" OR Bulimia* OR bulimic*) AND (Treatment* OR Therap* OR "disease management" OR rehabilitation)
S	"Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR "single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*

Clinical Trial Gov

http://www.clinicaltrials.gov/

P1

(anorexia OR

anorexic)
AND
(Treatment OR
Therapy OR
"disease management" OR
rehabilitation)

P2

(Bulimia OR
bulimic)
AND
(Treatment OR
Therapy OR
"disease management" OR
rehabilitation)

End

	Complete search query
P1	(anorexia OR anorexic) AND (Therapeutic OR Treatment OR Therapy OR "disease management" OR rehabilitation) AND ("11/01/2005" : MAX) [FIRST-RECEIVED-DATE]
P2	Therapeutic OR Treatment OR Therapy OR "disease management" OR rehabilitation | bulimia

Notes

The time filter is not necessary in this database for bulimia, as datasets older than 2000 do not occur in this case. For anorexia, the time filter is used as usual. As this database only contains clinical trials, filters for studies are not used.

ICTRP

http://www.who.int/ictrp/en/

P1

(anorexia OR
anorexic)
AND
(Therapeutic OR
Treatment OR
Therapy OR
disease management OR
rehabilitation)

P2

(Bulimia OR

bulimic)
AND
(Therapeutic OR
Treatment OR
Therapy OR
disease management OR
rehabilitation)

Complete search term
anorexia OR anorexic [search field condition]
AND
Therapeutic OR Treatment OR Therapy OR disease management OR rehabilitation [search field intervention]

Bulimia OR bulimic [search field condition]
AND
Therapeutic OR Treatment OR Therapy OR disease management OR rehabilitation [search field intervention]

Notes
Studies are not filtered as this database only contains clinical trials.
Due to the low number of hits, no time filter is applied.

V. Bulimia nervosa

1. Symptoms and diagnostic criteria

Jennifer Svaldi[13], Andrea Hartmann, Tanja Legenbauer, Jörn von Wietersheim, Martina de Zwaan & Brunna Tuschen-Caffier

1.1. Symptoms

A core characteristic of BN is the excessive consumption of food in the sense of recurrent episodes of binge eating. Binge eating is understood as the consumption of unusually large amounts of food in a discrete time span (e.g. within a period of 2 hours). Frequently, the foods consumed are easily available and high-calorie foods, which are mostly avoided during regular eating (e.g. candies). Moreover, BN sufferers report feeling at the mercy of the binge episodes, or having no control over how much and what they eat. Even when they feel very full, they are not able to stop eating. Nevertheless, binge eating episodes can also be actively stopped and later continued (e.g. when friends visit unannounced or flatmates return home unexpectedly). Furthermore, individuals with BN may plan binge eating episodes in a calculated manner (e.g. shop in anticipation of having sufficient food for a binge eating episode after returning from work).

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association [APA], 2013) also does not indicate a total amount of calories for the presence of a binge eating episode. Instead, diagnosticians should orient themselves to an amount of food that is substantially larger in a binge episode than the amount other people would eat in comparable situations. Accordingly, the context in which the eating takes place is important when interpreting whether or not a binge episode has occurred (e.g. meal to mark a special occasion vs. regular evening meal).

Triggers of binge eating episodes. Binge eating episodes can be triggered by various factors, e.g. feeling hungry, restrictive eating behavior or negative affect. A meta-analysis of diary studies (ecological momentary assessment) in patients with a diagnosis of BN showed that the feeling of hunger directly before a binge episode is significantly greater than the feeling of hunger that sufferers report outside of binge episodes (Haedt-Matt & Keel, 2011a). Accordingly, the perceived hunger ("ravenous appetite"), which does not necessarily have to be physically justified, appears to be a trigger for binge episodes.

A restrictive style of eating has also been found to be a trigger of binge eating: For instance, patients with BN may try to avoid high-calorie, carbohydrate-rich or fatty foods during regular meals, for example by following strict diet rules. This can contribute to a strong mental preoccupation with the topics of eating, weight and shape and lead to a considerable burden in coping with everyday life. Often, particular foods are avoided for fear of losing control over one's own eating behavior if these foods are consumed. In individuals with BN, the degree of restrictive eating can predict binge episodes on the following day (Zunker et al., 2011).

[13] With the exception of the first and last authors, the co-authors are listed alphabetically

The results of another meta-analysis of diary studies (Haedt-Matt & Keel, 2011b) also showed that negative affect was stronger before a binge episode than before regular meals. Moreover, according to the findings, the use of compensatory behaviors leads to a substantial reduction in negative affect (Haedt-Matt & Keel, 2011b). Both binge eating and the employed inappropriate compensatory behaviors are associated with a pronounced feeling of shame, which is why both behaviors mostly take place in secret. For instance, a diary study showed that feelings of shame appear to play a primary role in the maintenance of binge episodes (Berg et al., 2013).
An enduring worry about weight gain is closely linked to the described disturbances in eating behavior. Among other things, this is reflected in the focusing of thoughts on shape and weight, with sufferers' self-worth being unduly influenced by the evaluation of their own appearance (APA, 2013).
Through fear of gaining weight due to the binge eating, individuals with BN regularly employ various strategies (e.g. vomiting, excessive exercise) to control their weight, the most frequent of which is (deliberately induced) vomiting. Furthermore, methods of gastric emptying (laxatives, diuretics, enemas), a restrictive eating style, or longer fasting as well as excessive exercise are used as measures for weight control. Less common, and mostly not exclusively implemented, measures for weight control include, for example, misuse of thyroid hormones, chewing and spitting out food, or sauna visits. Additionally, some patients with BN and comorbid diabetes mellitus regulate their weight by reducing the intake of their prescribed insulin amount (so-called insulin purging) or refrain from taking insulin entirely (Pinhas-Hamiel, Hamiel, & Levy-Shraga, 2015; Pinhas-Hamiel & Levy-Shraga, 2013).

1.2. Diagnostic criteria according to DSM-5™ and ICD-10

For the diagnosis of BN according to the DSM-5™ (307.51), various criteria need to be fulfilled: regular, recurrent episodes of binge eating are an important criterion (criterion A). The consumption of an amount of food that can generally be seen as large within a particular period of time (e.g. two hours) is typical for a binge eating episode (criterion A1); a binge eating episode is accompanied by a sense of lack of control (criterion A2). To counteract the threat of weight gain, inappropriate compensatory behaviors are repeatedly employed (criterion 2). Such measures include self-induced vomiting, misuse of laxatives, diuretics or other medications (thyroid preparations, skipping insulin), fasting or excessive exercise. For the diagnosis of BN, the binge eating has to occur, on average, at least once a week over a period of three months (criterion C). Furthermore, shape and weight have to unduly influence the individual's self-evaluation (criterion D). Another criterion is that the disorder does not exclusively occur in the framework of AN (criterion E).
In the DSM-5™, the severity of BN is classified based on the number of inappropriate compensatory behaviors employed per week. Up to three episodes of inappropriate compensatory behaviors per week are defined as mild BN, four to seven as moderate, eight to 13 as severe, and 14 or more as extreme BN.
The differentiation of BN into the subtypes *purging type* and *non-purging type* was included in the DSM-IV but not in the ICD-10. Due to the controversial clinical significance, this subclassification was dropped in the currently valid version of the DSM-5.

If full criteria for BN were previously met and some but not all criteria of BN have been met for a sustained period of time, the disorder is seen as being in partial remission. If full criteria were previously met and none of the criteria have been met for a sustained period of time, the disorder is seen as being in full remission.

In order to diagnose BN according to the *International Classification of Mental and Behavioral Disorders* (ICD-10; Dilling, Mombour, & Schmidt, 2013) (F 50.2), episodes of binge eating must occur; similarly to the DSM-5™, binge eating episodes are defined as the consumption of an amount of food that can be generally seen as large within a short time span (criterion 1). Furthermore, the sufferer attempts to counteract weight gain through one or more compensatory behaviors (criterion 2). BN sufferers perceive themselves as "too fat" and have a morbid dread of fatness (criterion 3). Moreover, it is emphasized in criterion 3 that individuals set sharply defined weight thresholds for themselves which are well below the premorbid weight that constitutes a healthy weight according to the physician. In contrast to the DSM-5™, the ICD-10 does not provide operational criteria regarding the frequency and duration of binge eating episodes and compensatory behaviors. Moreover, the ICD-10 does not define levels of severity for BN. However, the category of Atypical Bulimia nervosa (ICD-10 F 50.3) is considered, in which one or several criteria of BN are not fulfilled. A subtyping of BN (purging vs. non-purging type) is not implemented in the ICD-10.

1.3. Comorbidity

Comorbid mental disorders and personality disorders are very frequent in BN. In a representative face-to-face survey in the USA, 94.5% of individuals with BN fulfilled the criteria for at least one of the DSM-IV core diagnoses (lifetime) (Hudson, Hiripi, Pope, & Kessler, 2007). The greatest proportion of these were anxiety disorders (mainly specific and social phobia), followed by affective disorders (mainly major depression). Currently, the association between attention-deficit/hyperactivity disorder (ADHD) and BN is being examined. A recent meta-analysis showed that patients with eating disorders had a twofold increased risk of fulfilling symptoms of ADHD, and patients with ADHD had a three-fold increased risk of suffering from an eating disorder, with a – non-significant – trend for an increased risk of comorbid BN (Nazar et al., 2016). A shared developmental pathway is suspected, for instance through dysfunctions in the dopaminergic neurotransmitter and reward system. The risk of comorbid ADHD in adults with BN is 5.71 (95%; CI: 3.56–9.16; Nazar et al., 2016).

With respect to the comorbidity of BN with personality disorders, a high prevalence is found for emotionally unstable personality disorder, followed by dependent, histrionic and anxious-avoidant personality disorder (Preti et al., 2009).

1.4. Differential diagnosis

From a differential diagnostic perspective, BN is delineated in particular from the other eating disorders, depressive disorders, as well as borderline personality disorder (BPD).

BN versus AN. Here, weight is a main, important differential diagnostic criterion. If a patient shows binge eating episodes and inappropriate compensatory behaviors and at the same time

has a significantly low body weight, then a diagnosis of AN should be made (subtype: binge-eating/purging type [bulimic form of AN]); an additional diagnosis of BN is not made in this case.

BN versus BED. BN is distinguished from BED through the regular use of inappropriate compensatory behaviors, which occur less systematically or not at all in BED. BN patients are generally of normal weight to slightly overweight, while patients with BED are generally overweight to obese. However, weight status is not a diagnostic criterion of either BN or BED.

BN versus Major Depression. Increased appetite (also including binge eating) is both a classification criterion of a major depressive episode and one of the atypical features of depressive disorders. In contrast to BN, however, individuals with depressive disorder do not employ inappropriate compensatory behaviors. Moreover, the overvaluation of shape and weight with respect to self-esteem, as is typical for BN, is lacking in depressive disorders. If the criteria for both diagnoses are fulfilled, both should be made.

BN versus BPD. Binge eating can also occur in the framework of impulsive behaviors in potentially demanding areas in individuals with BPD. However, primarily typical for BPD is a pronounced instability in interpersonal relationships, in self-image and in the area of affect. By contrast, substantial body image problems, which are typical for BN, do not constitute core symptoms of BPD.

BN versus Kleine-Levin syndrome. Binge eating can also occur within Kleine-Levin syndrome, although except the inappropriate compensatory behaviors typical for BN and the overvaluation of shape and weight with respect to self-esteem.

Besides the differential diagnostic clarification of BN and the associated general eating-related psychopathology, further comorbid disorders should also be systematically assessed (e.g. using guidelines or structured interviews). If comorbid mental disorders are present, it needs to be clarified whether of the presented disorders takes precedence concerning treatment or whether both have to be treated simultaneously due to of the respective disorders being maintained by the symptoms of the other. For instance, current substance abuse within outpatient treatment may first require inpatient detoxification. On the other hand, if, for example, the confrontation with certain situations (or their avoidance) as well as the occurrence of intrusive thoughts in a patient with BN and comorbid PTSD causes and perpetuates bulimic eating behavior and a negative body image, a simultaneous treatment of both disorders is useful. In this respect, the patient's general stability also needs to be taken into account.

1.5. Etiology and maintenance

A series of biological, social and psychological factors are involved in the development and maintenance of BN. For instance, family and twin studies point to the influence of *genetic factors*, although their influence varies between 28 % and 83 % (for an overview see Bulik, Sullivan, Wade, & Kendler, 2000; Bulik & Tozzi, 2004).

Retrospective findings suggest that *obesity in childhood* and *family (parental) obesity* are relevant predictors for BN (Fairburn, Cooper, Doll, & Welch, 1999; C. G. Fairburn et al., 1998; C. G. Fairburn, Welch, Doll, Davies, & O'Connor, 1997; Hilbert et al., 2014; Sullivan, Bulik, Carter, & Joyce, 1996).

Prospective studies show that the *internalization of an extreme thinness ideal* leads to increased body dissatisfaction, which in turn promotes bulimic eating behavior via restrictive eating and negative affect (Stice, 2001; Stice, Shaw, & Nemeroff, 1998).

Several studies have demonstrated that *restrictive eating behavior* fosters the occurrence of binge eating (Mauler, Hamm, Weike, & Tuschen-Caffier, 2006), with the likelihood of a binge eating episode rising with the duration of attempted *dietary restriction* (Holmes, Fuller-Tyszkiewicz, Skouteris, & Broadbent, 2014). Field studies in individuals with a diagnosis of BN have meta-analytically shown that restrictive eating behavior appears to precede binge eating (Haedt-Matt & Keel, 2011a). On the neuronal level, studies have suggested that dietary restriction is accompanied by an increased activation of cortical areas which are related to attention, reward and motivation (Stice, Burger, & Yokum, 2013).

In cross-sectional studies, individuals with BN report significantly lower self-esteem (for an overview see Cagar-Nazai et al., 2014). However, from most of the studies, it remains unclear to what extent the reported self-esteem problems constitute an expression or consequence of comorbid depressive symptoms. Most prospective studies did not find a causal relation between negative self-esteem and the development of eating disorder symptoms (for a review see Stice, 2016).

The *overvaluation of shape and weight* with respect to self-esteem is relevant not only for the development of BN (Stice, 2016), but also for the maintenance of the disorder. For instance, a prospective study showed that body dissatisfaction – as an emotional correlate of body image disorder – at the beginning of the study predicted a chronic course of eating disorder symptoms after 5 years in women with BN (Fairburn et al., 2003). Furthermore, treatment studies showed an unfavorable therapeutic course in BN patients who reported strongly pronounced body dissatisfaction at the start of therapy (Fichter, Quadflieg, & Hedlund, 2008; Wagner et al., 2015). High body dissatisfaction at the end of therapy was also positively correlated with the relapse rate of BN (Keel, Dorer, Franko, Jackson, & Herzog, 2005).

Stressful events (stressors) are linked to bulimic eating behavior. A more recent field study showed that an increase in negative affect mediated the relation of various stressors, and the appraisal thereof, with bulimic eating behavior (Goldschmidt et al., 2014). Interpersonal stressors, daily hassles, and the way of stress appraisal were especially important in this regard.

Several studies have demonstrated that *negative affect* triggers and/or maintains bulimic eating behavior. For instance, a meta-analysis of various field studies (Haedt-Matt & Keel, 2011b) showed that individuals with BN are in a more negative mood preceding a binge eating episode as compared to their general mood and their mood preceding a regular meal. Furthermore, the maintaining role of negative emotions (e.g. depressive mood) in BN was also apparent in the treatment context: The reduction of depressive symptoms at treatment start (i.e. within the first four weeks of treatment) was associated with symptom remission of bulimic symptoms (Thompson-Brenner, Shingleton, Sauer-Zavala, Richards, & Pratt, 2015).

Prospective data (Nolen-Hoeksema, Stice, Wade, & Bohon, 2007) indicate that *dysfunctional emotion regulation* increases the risk of bulimic symptoms. Experimental findings have demonstrated a rise in the desire to binge following induction of sadness and encouragement of a ruminative emotion regulation style in patients with BN (Naumann, Tuschen-Caffier, Voderholzer, Caffier, & Svaldi, 2015). These findings support the assumption that the influence

of negative affect in individuals with BN is mediated by dysfunctional strategies when dealing with negative feelings.

1.6. Course

Natural course. Results of longitudinal studies show a fluctuating natural course in individuals with BN (Fairburn, Cooper, Doll, Norman, & O'Connor, 2000). In a naturalistic longitudinal study, 72% of women originally diagnosed with BN were completely remitted at the 20-year follow-up (Keel, Gravener, Joiner, & Haedt, 2010).

In terms of mortality risk, patients with BN also show an increased mortality rate and a higher suicide rate compared to the normal population. A meta-analysis of 12 studies (Arcelus, Mitchell, Wales, & Nielsen, 2011) showed a weighted mortality rate (i.e. deaths per 1000 person-years) of 1.74 in individuals with BN; for exclusively female BN samples, the weighted mortality rate was at 2.22 per 1000 person-years, and was thus substantially lower than the weighted mortality ratio for AN (5.39). The standardized mortality ratio (i.e. the number of observed deaths compared to the number of expected deaths in the normal population) was at 1.93. The risk of suicide is also increased in individuals with BN, with a meta-analysis of 16 studies (Preti, Rocchi, Sisti, Camboni, & Miotto, 2011) reporting a suicide rate of 0.3 per 1000 person-years. Accordingly, around one in five deaths in individuals with BN is a consequence of suicide.

Course post therapy. If one considers the complete remission rates (recovery) across various studies, it becomes apparent that the proportion of completely remitted patients after treatment increases with the duration of the follow-up.

A recent study showed rates of complete remission over a 4-month follow-up between 22.5% (enhanced cognitive-behavioral therapy) and 32.5 % (integrative cognitive-affective therapy; Wonderlich et al., 2014). Studies with a one-year follow-up after completed treatment have reported remission rates of 14.6 to 22.5% (depending on the treatment arm; Bailer et al., 2004) or up to 27.8 % (Schmidt et al., 2008). In a study with BN patients who had received treatment, 32.5% of participants who received outpatient treatment were symptom-free over a 4-year period (Bogh, Rokkedal, & Valbak, 2005). Castellini and colleagues (2011) found a complete recovery in 49.6 % in patients treated with cognitive-behavioral therapy at a 6-year follow-up. In this study, recovery was defined as the absence of an eating disorder according to both the DSM-IV and DSM-5 criteria (not including EDNOS). In the observed time period (i.e. from baseline assessment to 6-year follow-up) according to the diagnostic criteria of the DSM-5, 9.2% of the BN patients had transitioned to AN and 8.4% had transitioned to BED. The relapse rate in BN patients who were in full remission by the end of treatment was 17.7%. Moreover, 18.1% of the patients who relapsed developed AN or BED. The results of a longitudinal study conducted over 12 years revealed a complete remission rate of 70.1% following inpatient therapy (at the 12-year follow-up; Fichter & Quadflieg, 2004). Many of the patients who were still symptomatic continued to fulfill the diagnostic criteria (DSM-IV) of BN (17.7%); only a small number fulfilled the criteria for a diagnosis of AN (1.8%) or BED (1.8%), while most fulfilled the diagnostic criteria for EDNOS. Four BN patients had died by the time of the 12-year follow-up.

Predictors of course. With regard to the natural (i.e. untreated) course of BN, a prospective study (Keski-Rahkonen et al., 2013) identified a strong drive for thinness as a negative predictor for the natural course of BN. In another prospective study over a 5-year period (Fairburn et al., 2003), duration of pathological eating behavior, stronger level of overvaluation of shape and weight, overweight in childhood, a lower social adaptability as well as enduring inappropriate compensatory behavior were prognostically unfavorable factors with regard to binge eating. By contrast, ongoing binge eating episodes were the only predictor of the continuation of inappropriate compensatory behaviors. Moreover, in contrast to treatment-seeking samples, the frequency of binge eating episodes and compensatory behaviors was not predictive of the course.

With regard to treatment-seeking patients with BN, in a study by Bulik and colleagues (1999), a lower frequency of binge eating and a lower frequency of inappropriate compensatory behaviors at baseline were predictors of a prognostically favorable treatment course. Past history of overweight (Bulik, Sullivan, Joyce, Carter, & McIntosh, 1998; Fichter & Quadflieg, 2004) and alcohol abuse in the family history (Bogh et al., 2005), by contrast, constitute negative predictors of treatment course. Other studies indicate that a rapid reduction in the frequency of inappropriate compensatory behaviors and in restrictive eating behavior in the first four weeks of treatment are prognostically favorable predictors of the short- and long-term course (Agras et al., 2000; Fairburn, Agras, Walsh, Wilson, & Stice, 2004; Olmsted, Kaplan, Rockert, & Jacobsen, 1996; Wilson, Fairburn, Agras, Walsh, & Kraemer, 2002). Furthermore, a recent study showed that a rapid reduction (rapid response) in the severity of depression is prognostically favorable for treatment course in BN (Thompson-Brenner et al., 2015). In this study, 70% of the patients who had achieved a 25% reduction in depression severity within the first four sessions were completely remitted, while 30% of the patients who achieved an at least 25% reduction in depression severitywere still symptomatic at the end of therapy. By contrast, of those patients who did not achieve a 25% reduction in depression severity within the first four sessions, only 15% achieved complete remission, while 85% continued to be symptomatic. Interestingly, in this study, the rapid reduction in terms of depression severity was a better predictor of treatment course than the reduction in the frequency of compensatory behaviors, although the latter was also a significant predictor of a favorable course. In the longitudinal study by Fichter and Quadflieg (2004), by contrast, comorbidity with other mental disorders was the most stable predictor of a prognostically unfavorable therapy course.

1.7. Bulimia nervosa in childhood and adolescence

Comorbidity. Regarding the comorbidity of adolescent BN with other mental disorders, a representative face-to-face survey of American adolescents (Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011) showed a lifetime comorbid prevalence that was comparable to an adult sample: 88.0% of adolescents with BN showed at least one further comorbid mental disorder, and 27% fulfilled the criteria for three or more comorbid disorders. The most frequent comorbid disorders were anxiety disorders (especially specific and social phobia), followed by affective disorders (major depression) and behavioral disorders (especially conduct disorder and oppositional-defiant disorders). High comorbidity rates, above all those of depressive disorders and ADHD, followed by somatoform and anxiety disorders, are also shown in

German samples of children and adolescents with BN who are in outpatient treatment (Jaite, Hoffmann, Glaeske, & Bachmann, 2013). A recent meta-analysis (Nazar et al., 2016) showed that in pediatric samples, above all, associations between ADHD and so-called *loss of control eating* exist, while the risk of full-blown BN was lower than in adult populations. This may possibly be attributed to the later age of onset for BN relative to AN. An increased suicidality among adolescents with BN compared to other eating disorder diagnoses is notable: Approximately half of adults with BN appeared to have suicidal thoughts and around a third reported suicide attempts (Swanson et al., 2011). Personality disorders are less common in adolescent samples of patients with BN than in adult samples. In a study by Magallon-Neri and colleagues (2014), the prevalence of BPD in adolescent patients with BN was 23.5% (firm diagnosis). In a further 17.6%, the diagnosis of BPD according to the DSM-IV was seen as likely. In a study conducted within the German-speaking area (Bottin et al., 2010), in a sample of 99 consecutively included outpatients or inpatients with an eating disorder, 48% of the patients with BN showed a personality disorder. In terms of the distribution of diagnoses, the most frequent personality disorder diagnoses were avoidant and depressive personality disorder, and BPD.

Course. In terms of the untreated course, population-based prospective studies in adolescent samples show high remission rates of 91% within one year for subclinical forms and full-blown BN (Stice, Marti, Shaw, & Jaconis, 2009). These remission rates are substantially higher than findings on complete recovery in treatment-seeking populations. It can be thus be assumed that treatment-seeking individuals with BN show substantially more severe eating pathology (Fichter & Quadflieg, 2007; Herzog et al., 1999). However, in the study by Stice and colleagues, the relapse rates were very high in the adolescent sample, with 41% for subclinical and full BN (Stice et al., 2009). In a more recent prospective population-based study (Allen, Byrne, Oddy, & Crosby, 2013) over a period of six years (age 14-20), 56.2% of the adolescents with BN were in complete remission by the age of 20, while 37.6% continued to fulfill the criteria for a subclinical eating disorder or full-blown BN. Importantly, in this study, 47.1% of the 14-year-old adolescents with BED fulfilled the criteria for a diagnosis of BN at the age of 17 years; at the age of 20 years, this figure was still at 17.6%. The prospective study by Nagl and colleagues (2016) also provides information about the course of BN, and shows that of the individuals suffering from BN at baseline, 24% still show symptoms of eating disorders almost 10 years later.

Course after therapy. Compared to adult patients with BN, data on the course of BN following therapy in adolescent patients with BN are much less clear. Family therapy-oriented treatments, including programs with a cognitive behavioral basis, as well as individual CBT have proven to be effective in randomized controlled trials. In studies with a 6-month to one-year follow-up after completion of treatment, abstinence rates for bingeing and compensatory behaviors combined range from 29% to 39% (family therapy) up to 41% (guided [CBT-oriented] self-management interventions (Le Grange, Crosby, Rathouz, & Leventhal, 2007; Schmidt et al., 2007). A recent study (Le Grange, Lock, Agras, Bryson, & Jo, 2015) reported rates of complete remission from 20% (cognitive-behavioral therapy) to 39% (family-based therapy) at the end of treatment. At the 12-month follow-up, no significant differences depending on treatment arm were found; 32% (cognitive-behavioral therapy) to 48.5% (family-based therapy) of the patients were in complete remission. A Danish study which examined the therapy course

following outpatient treatment in a specialized eating disorder outpatient clinic with an integrative approach (CBT, psychoeducation, nutrition management, interpersonal therapy and additional family therapy) showed an average treatment duration until partial remission (diagnostic criteria are no longer fulfilled) of 16 months (range 12-22) and an average treatment duration until complete recovery of 26 months for adolescent BN patients (Helverskov et al., 2010).

Predictors of treatment course. So far, there are few studies examining the predictors of treatment course in adolescent patients with BN. However, there are indications that factors which predict therapy course are influenced by age: For instance, in the framework of secondary analyses of various therapy studies, Lock and colleagues (2013) showed that in adult patients with BN, especially the *frequency of compensatory behaviors* at the end of treatment (< 2x per week) positively predicted the further course, while in adolescent patients with BN, the best predictors were (a.) *abstinence from compensatory behaviors* and (b.) *reduction in the extent of restraint eating*. Moreover, a further study investigating adolescent patients with BN showed, that lower engagement in an internet-based vs. cognitive-behavioral treatment (randomized controlled design) was associated with a higher BMI and lower expectation of success. Treatment dropout was especially likely to occur if patients reported having a low social status, showed higher values in inquisitive behavior, already had experience of CBT, or had been randomized into their non-preferred treatment arm. Another randomized controlled trial compared family-based treatment (FBT) with counseling (supportive therapy, SPT) and showed that older adolescents' self-esteem improved more quickly than that of younger adolescents ($p = 0.03$) and that adolescents with medication achieved a quicker reduction in eating-related concerns compared to those without medication ($p = 0.02$). Furthermore, it was found that age and severity of compensatory behaviors at baseline moderated the relation between intervention and reduction in the area of eating-related concerns: Younger adolescents and individuals with greater severity of compensatory behaviors showed a stronger improvement in FBT than in SPT (Ciao, Accurso, Fitzsimmons-Craft, & Le Grange, 2015). A similar study in adolescent patients with BN who took part in FBT as compared to SPT (Le Grange, Crosby, & Lock, 2008) showed that, in particular, lower levels of eating-related concerns at the beginning of therapy were associated with abstinence from bingeing and purging at the end of therapy (OR = 0.47), independent of the type of treatment, while patients with an overall lower eating disorder pathology (Eating Disorder Examination Total score) benefited especially from FBT (OR = 0.44).

2. Therapy

2.1. Treatment aims

The treatment of BN is based on the following treatment aims:

- Reduction in symptoms of BN, i.e. reduction of binge eating episodes, of compensatory behaviors (e.g. vomiting, laxative use), and of the importance of weight for self-evaluation (body image problems).

- Treatment of psychological problems (e.g. self-esteem problems, perfectionism, impulsivity, problems with affect regulation) and background conflicts associated with the BN.
- Treatment of comorbid mental disorders (e.g. depression, social anxiety).
- Prevention and/or relapse prevention.

2.2. Treatment approaches

The foundation of the treatment recommendations of the AWMF-S3-guideline (2010) was a meta-analysis on the efficacy of different treatment forms for BN, described in the guidelines for the diagnosis and treatment of eating disorders, with which effect sizes on post-scores from intervention groups and untreated control groups were calculated and compared (Jacobi et al., 2011). A prerequisite for the inclusion of a treatment approach in the (old) meta-analysis was the existence of at least one randomized controlled trial (RCT). The prerequisite for evidence level 1a was seen as fulfilled if at least three RCTs could be included in the meta-analysis; otherwise, evidence level 1b was assigned. If, for a form of intervention, no RCTs with untreated control groups were available, but rather only non-controlled studies or RCTs with an exclusively treated control group, the effect sizes of the meta-analysis were based on the comparison of the pre- and post-scores of the respective intervention groups (evidence 2a for at least three RCTs with pre-post comparison; evidence level 2b with fewer than three RCTs with pre-post comparison). If the number of primary studies did not allow for either of the two described meta-analytic integration forms, individual studies were used for the recommendations for the respective treatment form (evidence levels 2c to 4). When interpreting the results, it should be noted that effect sizes based on the comparison of post-scores from intervention and control conditions, and those based on a comparison of pre- and post-scores for one intervention condition, are not directly comparable with one another with regard to their size.
In the first version of the treatment recommendations, the procedure for determining levels of evidence was following the guidelines of the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009). This schema was also the basis for determining the levels of evidence in the revision of the recommendations for the currently conducted meta-analysis (Svaldi et al., 2019). Inclusion criteria for the meta-analysis (Svaldi et al., 2019) are as follows:

1. Included studies had to have considered a follow-up period of at least one week.
2. Only methodologically high-quality studies in the sense of randomized controlled trials (RCTs) for adolescent and adult populations were considered.
3. A formal diagnosis of BN (according to ICD or DSM) needed to be present.
4. Sufficient data for calculating effect sizes needed to be available.
5. In RCTs which included patients with different eating disorder diagnoses, separate analyses for BN needed to be available.

The exclusion criteria were as follows: (1) unpublished studies, (2) dual publications of the same RCTs and (3) RCTs with a sample size < 10.
Of the 4515 potentially relevant articles identified in the various databases, after exclusion of duplicates (n=2148), 2367 articles were viewed. Of these, 2247 articles were excluded for the following reasons: no RCTs, no BN-relevant outcome variables, no separate analyses for the BN sample, studies that did not refer to the treatment of BN, unpublished articles, as well as studies that were not published in either the German or the English language. In total, the full texts of 120 articles were read, of which a further 36 had to be excluded: 28 of these did not use an interview for diagnosis, and a further 8 only provided information on BN subgroups.
Of the remaining 84 studies, effect sizes could not be determined for five studies. Therefore, 79 studies were included in the quantitative meta-analysis (see Table 9) with a total of 143 active treatment arms.

As a primary evidence source, randomized control group comparisons (evidence level 1a) were targeted, in which it was possible to estimate the efficacy of one specific therapy compared to a control group without an effective intervention. However, a large number of studies did not contain any untreated control groups; instead, various potentially effective interventions were compared with one another. In other studies, there was no explicit information about non-active control groups, meaning that it was not possible to conduct group comparisons. Therefore, as a further source of evidence, pre-post comparisons within the active arms were conducted (evidence level 2b). If the respective information was available, the sustainability of the intervention at a follow-up time point > 1 month after the end of therapy was tested.
As central dependent variables, the probabilities (relative frequencies) of the absence of diagnostic criteria for BN or the absence of separate constitutive criteria for binge eating episodes and compensatory behavior (purging behavior) at post-test were evaluated. For content-based reasons, it was not possible to transform the variables into one joint dependent variable, meaning that these three categorical variables had to be separately evaluated. If possible, for the categorical variables (abstinence from binge eating episodes, compensatory behavior, absence of diagnosis) of the therapy outcome, odds ratios (OR) were calculated into order to detect possible differences between intervention group and control group. While in classical works on meta-analytically determined OR, values over 1.0 were interpreted as small and values over 3.0 as large effects (Haddock, Rindskopf, & Shadish, 1998), in more recent works (e.g. Chen, Cohen, & Chen, 2010) higher thresholds are suggested, namely of 1.6, 3.47 and 6.71 as small, medium, and large effects, analogous to standardized mean differences for continuous variables. If no sufficient data were available for control groups, simple relations to the post-test within the active arm were indicated. Moreover, a series of continuous variables were evaluated, which enabled the examination of the reduction in symptom severity (binges, vomiting, laxative use), as well as in self-reported eating disorder pathology and depressive symptoms. For these continuous variables, standardized mean differences were calculated using the effect size measure Hedges' g. A Hedges' g of 0.2, 0.5, 0.8 and 1.2 was evaluated as low, medium, large and very large, respectively (Sawilowsky, 2009).

2.2.1. Cognitive-behavioral therapy

Post-control group (CG) comparison. For this intervention, data in an RCT design were available for a total of 10 arms from 8 RCTs with their respective control groups and a total number of N=320 persons. Three RCTs report statistics on the absence of binge eating post-treatment, from which a small improvement in the treatment group relative to the control group could be determined (log OR=1.66; CI: 0.47, 2.84). Five RCTs report post-treatment absence of purging, and show a moderate improvement (log OR=1.94; CI: 0.92, 2.96) relative to the control group. Five RCTs report statistics for a reduction of binge eating episodes in the intervention group relative to the control group, corresponding to a large effect (g=0.97; CI: 0.44, 1.50). With regard to a reduction in compensatory behavior, eight RCTs show a strong improvement (g=0.82; CI: 0.58, 1.05). One study (Griffiths, Hadzi-Pavlovic, & Channon-Little, 1994) reports a very strong reduction in self-reported eating pathology (g = 1.49; CI: 0.94, 2.05). Two studies reveal a very strong reduction of depressive symptoms relative to control groups (g = 1.20; CI: 0.60, 1.78).

Pre-post. Data from 49 arms of 35 studies with a total number of N=1425 persons at baseline and N=1087 persons at posttest could be considered for pre-post analyses. 22 study arms report an absence of binge eating episodes in 51% of cases at post, 22 study arms an absence of purging in 45% of cases and 16 study arms report an improvement in absence of a BN diagnosis in 39% of cases. Overall, 38 study arms report a strong reduction in binge eating (g = 0.89; CI: 0.77, 1.00), 40 study arms a medium reduction in compensatory behavior (g = 0.69; CI: 0.61, 0.77), 18 study arms a very strong reduction in self-reported eating pathology (g = 1.43; CI: 1.24, 1.63) and 24 study arms a strong reduction in depressive symptoms (g = 0.90; CI: 0.75, 1.05).

Pre-follow-up. Data from follow-up assessments were available from 34 arms of 24 studies with a total of N=646 persons (range: 1 month to 2 years). In four study arms, an absence of binge eating is reported in 62% of cases, in four study arms an absence of purging in 54% of cases and in 14 studies the absence of a diagnosis in 38% of cases. In 28 arms, a strong reduction in binge eating episodes is reported (g = 0.86; CI: 0.71, 1.01), in 25 arms a medium to strong reduction in compensatory behavior (g = 0.69; CI: 0.56, 0.81), in 12 arms a very strong reduction in self-reported eating pathology (g = 1.59; CI: 1.33, 1.80) and in 14 arms a strong reduction in depressive symptoms (g = 0.96; CI: 0.77, 1.16).

The efficacy of behavior therapy could be assessed for all central disorder variables in several well-conducted RCTs, meaning that in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), behavior therapy can be assigned with evidence level 1a. Additionally, the findings from the other analyses confirm the efficacy and sustainability of the intervention.

2.2.1.1. Dialectical behavior therapy (DBT)

Post-CG comparison. Data from an RCT design are available for 2 arms from 2 RCTs with their respective control groups and a total of N=61 persons. In one study (Safer, Telch, & Agras, 2001) the absence of a diagnosis shows a medium improvement in the treatment group relative to the control group (log OR = 2.73; CI: -0.31; 5.77). Compensatory behavior improved

moderately (g = 0.36; CI: -0.36, 1.09). In the other study (Hill, Craighead, & Safer, 2011), after the first half of the treatment, when a control group comparison was still available, the self-reported eating pathology improved very strongly (g = 1.18; CI: 0.47, 1.88). Both studies attest to an improvement in depressive symptoms, with a medium effect size (g = 0.64; CI: 0.14, 1.13).

Pre-post. For pre-post analyses within arms of this category, two study arms from two studies with a total of N=32 persons at pretest and N=28 persons at posttest were available. One study (Safer et al., 2001) reports an absence of diagnosis post-treatment of 29 %. This study also reports a strong reduction in binge eating (g = 0.82; CI: 0.17, 1.47) and a moderate reduction in compensatory behavior (g = 0.29; CI: -0.24, 0.81). The other study (Hill et al., 2011) reports a strong reduction in self-reported eating pathology (g = 0.93; CI: 0,46, 1.40) and both studies report a strong reduction of depressive symptoms (g = 0.78; CI: 0.41, 1.14).

Pre-follow-up. For one arm from one study (Hill et al., 2011) with N=22 persons at posttest, results for a follow-up measurement time point are reported. However, this follow-up measurement time point is dated at the end of treatment of the DBT arm. The post-score was defined as a 6-week period after the start of treatment, as at this time point, the control group comparison was ended and the waiting control group also received the treatment (see post-CG comparison). At this follow-up time point, a very strong reduction in self-reported eating pathology was shown (g = 1.29; CI: 0.82, 1.77).

The efficacy of DBT could be assessed for all central disorder variables in several well-conducted RCTs, such that in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), DBT can be assigned with evidence level 1b. In addition, the findings from the other analyses confirm the efficacy of the intervention. With regard to sustainability, further investigations are required.

2.2.2. Psychodynamic psychotherapy

From the area of psychodynamic therapies, there are studies on psychoanalytic and psychodynamic psychotherapy.

Post-CG comparison. For psychodynamic therapies, there are no available data with passive/placebo-controlled control groups.

Pre-post. For pre-post analyses, it was possible to analyze data from two arms of two studies with their respective control groups, with a total of N=76 persons at pretest and N=64 persons at posttest. One study on psychoanalytic psychotherapy (Poulsen et al., 2014) reports an absence of binge eating at post-treatment in 6% of cases, and the other study (psychodynamic psychotherapy; Stefini et al., 2017) an absence of diagnosis in 31% of cases. Both studies report a weak to medium reduction in binge eating (g = 0.37; CI: 0.12, 0.62), a comparable reduction in compensatory behavior (g = 0.38; CI: 0.16, 0.61) and a medium reduction in self-reported eating pathology (g = 0.59; CI: 0.37, 0.82). The study by Poulsen and colleagues (2014) shows a slight reduction in depressive symptoms (g = 0.12, CI: –0.18, 0.42).

Pre-follow-up. Follow-up were available from two arms of two studies (Poulsen et al., 2014; Stefini et al., 2017) (range: 1 to 2 years). At this time point, one study describes the absence of binge eating in 6% of participants (Poulsen et al., 2014). Both studies report a medium to strong

reduction in binge eating (g = 0.67; CI: 0.39, 0.94), Stefini and colleagues a medium reduction in compensatory behavior (g = 0.46; CI: 0.16, 0.76), and Poulsen and colleagues a very strong reduction in self-reported eating pathology (g = 1.66; CI: 1.32, 2.01) as well as a strong reduction in depressive symptoms (g = 0.82, CI: 0.46, 1.17).

The efficacy of psychodynamic psychotherapy could be confirmed for all central disorder variables in two cohort studies without control groups, meaning that in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), psychodynamic psychotherapy can be assigned with evidence level 2b. Findings on the sustainability of the intervention are mixed and require further investigation. It should be noted that both of the examined cohort studies were compared with cognitive-behavioral psychotherapy. In the study by Stefini and colleagues (2017; psychodynamic psychotherapy), no differences were found between the approaches at a mean therapy duration of 36 hours. Both were equally efficacious, with large effect sizes (d = 1.2) and a remission rate of 32% at the end of therapy. In the study by Poulsen and colleagues (2014, psychoanalytic psychotherapy), by contrast, clear differences emerged between the two therapy approaches. After five months (therapy end for CBT), 42% of the patients who were treated with CBT were completely abstinent from binges and from purging behavior, while this was the case in only 6% of patients who had received psychoanalytic treatment. Moreover, two years after the start of treatment (therapy end of the psychoanalytic arm and simultaneous follow-up in the CBT arm), 44% of patients in the CBT arm and only 15% in the psychoanalytic arm were completely remitted with regard to binge eating and purging behavior. The results of the study by Poulsen and colleagues (2014) support the superiority of CBT over psychoanalytic psychotherapy, with the former achieving better results after five months than the latter after two years. Furthermore, the results confirm the importance of distinguishing between the efficacy of different psychodynamic approaches. While according to the available study, psychodynamic psychotherapy appears to be comparable to CBT in terms of efficacy, the study on psychoanalytic psychotherapy showed clearly poorer results.

2.2.3. Interpersonal psychotherapy

Post-CG comparison. For interpersonal psychotherapy (IPT), there are no available data with a passive/placebo-controlled control group.

Pre-post. Data were available from three arms of three studies with a total number of N=166 persons. One study (Fairburn et al., 1991) reports an absence of binge eating post-treatment in 62% of cases, and two studies (Agras, Walsh, Fairburn, Wilson, & Kraemer, 2000; Mitchell et al., 2002) an absence of diagnosis in 8% of cases . The study by Mitchell and colleagues (2002), however, only included patients who had previously had no success with CBT. One study (Fairburn et al., 1991) reports a very strong reduction in binge eating (g = 1.44; CI: 0.86, 2.03) and in compensatory behavior (g = 0.58; CI: 0.19, 0.97). Two studies (Agras et al., 2000; Fairburn et al., 1991) report a very strong reduction in self-reported eating pathology (g = 1.38; CI: 1.21, 1.55).

Pre-follow-up. Data were available for three arms from three studies with a total of N=166 persons at pretest and N=108 persons at follow-up (range: 4 to 6 months). In one study (Mitchell

et al., 2002), an absence of a diagnosis is reported in 16% of cases. In another study (Fairburn et al., 1991), a very strong reduction of binge eating episodes is reported (g = 1.53; CI: 0.93, 2.14) as well as a strong reduction in compensatory behavior (g = 0.66; CI: 0.27, 1.05). Two studies (Agras et al., 2000; Fairburn et al., 1991) report a very strong reduction in self-reported eating pathology (g = 1.51; CI: 1.34, 1.68).

The efficacy of IPT could be confirmed for all central disorder variables in several cohort studies without control groups, such that in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), IPT can be assigned with evidence level 2a. The follow-up findings speak in favor of the sustainability of the intervention.

Compared to CBT (Fairburn et al., 1991, Agras et al., 2000), IPT was less effective regarding the reduction in binge eating episodes, compensatory behavior and eating pathology (pre-post). At the follow-up time points, the results for CBT were somewhat better but did not differ significantly (Agras et al., 2000).

2.2.4. Family-based therapy

The terms *family therapy* or *family-based therapy* encompass therapeutic programs which activate family resources in order to bring about an improvement in the child's eating behavior. Besides the term family therapy (Dodge, Hodes, Eisler, & Dare, 1995), the term family-based therapy is often synonymously used (Le Grange, Lock, & Dymek, 2003). In addition, cognitive-behavioral approaches which include the family also count as family-based therapy (Lock, 2005). Family-based treatments for BN predominantly target the activation of parental support in order to overcome the child's eating disorder. In this respect, in the first phase, the parents are guided to actively support their child in coping with the eating disorder and to proactively deal with the problems in eating behavior (restrictive eating, compensatory behaviors, pathological weight control behavior, etc.). Furthermore, the parents are supported in their actions by learning to externalize the eating disorder and not to equate it with their child's actions. This should foster mutual understanding and reduce the child's resistance. Once abstinence has been achieved, the control over eating is given back to the child in a step-by-step manner, and in the final treatment cycle, the family is supported in coping with the consequences of BN for the child's development (Le Grange et al., 2007).

In the few available randomized controlled trials (RCT) testing the efficacy of family-based therapy, the available manuals for family-based treatment of anorexia nervosa were transferred to the treatment of adolescents with BN, analogously to the above-described procedure (Lock, Le Grange, Agras, & Dare, 2001).

Post-CG comparison. For family-based therapies, there are no data with passive/placebo-controlled control groups.

Pre-post. Data for pre-post analyses were available for two arms from two studies (Le Grange et al., 2007; 2015) and a total of N=93 persons at pretest and N=79 persons at posttest. One study (Le Grange et al., 2007) reports an absence of binge eating post-treatment in 39% of cases. Both studies report a moderate reduction in binge eating (g = 0.39; CI: 0.16, 0.62), one study (Le Grange et al., 2007) reports a strong reduction in compensatory behavior (g = 0.94; 0.63, 1.25), both studies report a very strong reduction in self-reported eating pathology (g =

1.58; CI: 1.37, 1.78), and one study (Le Grange et al., 2007) reports a strong reduction in depressive symptoms (g = 1.08; CI: 0.72, 1.44).

Pre-follow-up. Data were available from two arms from two studies (Le Grange et al., 2007; 2015) with a total of N=93 persons at pretest and N=68 persons at follow-up (range: 3 to 6 months). Both report a medium reduction in binge eating (g = 0.43; CI: 0.20, 0.66), one (Le Grange et al., 2007) a strong reduction in compensatory behavior (g = 0.99; CI: 0.68, 1.29), both studies report a very strong reduction in self-reported eating pathology (g = 1.63; CI: 1.43, 1.84) and a strong reduction in depressive symptoms (g = 0.81; CI: 0.59, 1.02).

It should be noted that both examined cohort studies were compared with one (2007) or two (2015) active control groups. The first randomized controlled trial (LeGrange et al., 2007) included 80 patients aged from 12 to 19 years (M = 16.1, SD = 1.7 years) and compared six months of supportive therapy (SPT, 20 sessions) with family-based therapy (20 sessions). The SPT was conceived such that it did not contain any putative active therapeutic elements such a stimulus control, problem-solving techniques (implicit) support for changing eating behavior or similar, and thus there were no overlaps with cognitive-behavioral therapy, interpersonal therapy or psychodynamic interventions. With regard to categorical variables (symptom remission and partial remission), at treatment end, FBT was found to be superior to SPT (39% remitted in FBT vs. 18% in SPT; Fisher's Z = 0.049), although this was only the case by trend for partially remitted patients (41% in FBT vs. 21% in SPT; Fisher's Z = 0.06). After 6 months, 29% of the patients in the FBT group were in complete remission vs. 10% in the SPT condition; Fisher's Z= 0.05, although FBT was no longer superior regarding the rate of partial remission (49% in FBT vs. 38% in SPT; Fisher's Z=0.38). A similar pattern emerges for the dimensional scales; here, FBT was superior at posttreatment, while at follow-up, no significant differences on the scales of the EDE-Q were found. The second study by LeGrange and colleagues was conducted in 2015 and compared FBT-BN with a cognitive-behavioral therapy (CBT) as well as an unspecific treatment form (SPT; 18 sessions over 6 months). The SPT was conceived analogously to the study from 2007, CBT was based on CBT for BN in adulthood, with the additional offer of psychoeducation sessions for parents. 130 patients aged between 12 and 18 years were included and randomized to the treatment arms. Follow-up investigations took place after 6 and 12 months. Similarly to the study from 2007, FBT was found to be superior at the end of treatment (abstinence: 39% in FBT vs. 20% in CBT; p=0.040). FBT was also superior to CBT after 6 months (44% vs. 25%; p=0.030), but this effect did not remain at the 12-month follow-up (49% vs. 32%: P = 0.130).

Above all, these results demonstrate the quicker efficacy of FBT compared to unspecific but also specific approaches in terms of disorder-relevant problem areas. This may be attributable to the stronger support from the parents in coping with the eating disorder during the first, more intensive treatment phase of FBT. In the further course, the approach appears to lose its superiority. Accordingly, based on the classification of evidence levels in line with the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), the efficacy of family-based therapy can be confirmed for all central disorder variables in two cohort studies without control groups, meaning that FBT-BN can be assigned with evidence level 2b. The follow-up findings speak in favor of the sustainability of the intervention.

2.2.5. (Therapist-guided) self-management[14]

In this section, the term self-management is used rather than self-help, as the studies included in the analyses concern approaches which are based on a structured evaluated programs and are thus distinguishable from classical self-help groups. Such self-management programs for patients with BN are available in online and offline versions and range from pure self-help using a book (bibliotherapy), an app or a computer program, through programs with occasional therapist contact, to guided self-help programs. In addition to personal contact, these therapist contacts can take place within an audio and video chat program, but also in written chat or by email, with the latter enabling asynchronous communication. Fundamentally, these forms of contact take up less time than psychotherapy sessions and the contents are not psychotherapeutic in the narrower sense (Cuijpers & Schuurmans, 2007). Besides their use for bridging waiting times for therapy or in the transition from inpatient to outpatient treatment, self-management approaches can also be used in cases when there is a lack of efficacy of or a insufficient access to state-of-the-art therapy (Beintner & Jacobi, 2017).

Post-CG comparison. Data are available for three arms from three RCTs (Banasiak, Paxton, & Hay, 2005; Carter et al., 2003; Treasure et al., 1994) with their respective control groups, with a total of N=248 persons. In two studies (Banasiak et al., 2005; Treasure et al., 1994) statistics are reported for the absence of binge eating post-treatment, which corresponds to a moderate improvement in the treatment group compared to controls (log OR = 1.72; CI: 0.86, 2.58). Likewise, both studies provide evidence of a weak improvement regarding the absence of compensatory behavior (log OR = 1.44; CI: 0.53, 2.36) and a weak effect on the absence of diagnostic criteria according to DSM (log OR = 1.22; CI: 0.31, 2.13). Both studies report a medium to strong reduction in binge eating (g = 0.66; CI: 0.28, 1.03) and a medium to strong reduction in compensatory behavior (g = 0.71; CI: 0.42, 1.00). One study (Banasiak et al., 2005) shows a strong reduction in self-reported eating pathology (g = 1.76; CI: 1.38, 2.14). Two studies (Banasiak et al., 2005; Carter et al., 2003) report a slight decline in depressive symptoms (g = 0.14; CI: -0.43, 0.71).

Pre-post. For pre-post analyses, data are available from 10 arms from 9 studies with a total of N=451 persons at pretest and N=277 persons at posttest. In four study arms, at post-treatment, an absence of binges is reported in 43% of cases, two studies report an absence of purging in 27% of cases and four studies an absence of diagnosis in 26% of cases. Nine study arms show a moderate reduction in binge eating (g = 0.51; CI: 0.34, 0.67), ten study arms show a moderate reduction in compensatory behavior (g = 0.41; CI: 0.27, 0.54), five study arms a strong reduction in self-reported eating pathology (g = 0.95; CI: 0.52, 1.38) and five study arms a medium reduction in depressive symptoms (g = 0.45; CI: 0.20, 0.71).

Pre-follow-up. Data are available from seven arms from six studies with a total of N=344 persons at pretest and N=194 persons at follow-up (range: 3 to18 months). One study (Banasiak et al., 2005) reports the absence of binge eating in 46% of cases, absence of purging in 26% of cases, and two studies report the absence of a BN diagnosis in 25% of cases. Seven studies report a medium-sized reduction in binge eating (g = 0.63; CI: 0.33, 0.92) as well as a moderate reduction in compensatory behavior (g = 0.56; CI: 0.29, 0.83). In two studies, a strong reduction

[14] Described in chapters IV. (Anorexia nervosa) and VI. (Binge Eating Disorder) as self-help.

in self-reported eating pathology is reported (g = 1.11; CI: 0.87, 1.36). Furthermore, three studies show a strong reduction in depressive symptoms (g = 0.79; CI: 0.49, 1.09).
The efficacy of self-management could be ensured for all central disorder variables in several well-conducted RCTs. Thus, in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), self-management can be assigned with evidence level 1a. In addition, the results from the other analyses confirm the efficacy and sustainability of the intervention.
Nevertheless, it should be noted that among the self-management programs of the nine studies which are described under post-CG and pre-post comparisons, six followed a CBT-based concept (this remains unclear for two, one did not follow a CBT concept). With the exception of two of the nine studies, all used a therapist-guided design, i.e. contact to a therapist with a different professional background took place at different time periods. Furthermore, it needs to be emphasized that only one arm of one study describes an online-based self-management approach, and this did not differ from traditional guided self-management applied in the same study in terms of the results. Moreover, it is not possible to make any clear recommendations regarding which patients are most likely to benefit from (guided) self-management. For instance, the samples of the studies entered into the analysis vary in terms of symptom severity, from mild to severe. In sum, it can be stated that guided self-management can be indicated when there is a lack of efficacy of or lack of access to conventional CBT. Nevertheless, it should be noted that only a small number of validated disseminated manuals are available for this approach (Fairburn, 2008; Schmidt, Treasure, & Alexander, 2016) and guidance from a therapist is essential.

2.2.6. Other non-pharmacological interventions

Interventions with a focus on dietary change

Post-CG comparison. One arm of one study (Sundgot-Borgen, Rosenvinge, Bahr, & Schneider, 2002) with its control group with a total of N=17 participants was assigned to this category. However, information in a between-group design was not provided for any of the examined variables.

Pre-post. For pre-post analyses, three arms from three studies with a total of N=67 persons at pretest and N=36 persons at posttest were considered. One study arm (Laessle et al., 1991) reports an absence of binge eating at post-treatment in 41% of cases, as well as an absence of purging in 30% of cases, and one study (Hsu et al., 2001) reports the absence of a diagnosis in 17% of cases. Two study arms (Laessle et al., 1991; Hsu et al., 2001) report a moderate reduction in binge eating (g = 0.76; CI: 0.42, 1.09) and a strong reduction in compensatory behavior (g = 0.84; CI: 0.56, 1.12), one study (Laessle et al., 1991) reports a very strong reduction in self-reported eating pathology (g = 1.20; CI: 0.82, 1.59) and one study a moderate reduction in depressive symptoms (g = 0.79; CI: 0.39, 1.18).

Pre-follow-up. For follow-up analyses (range 6 to 12 months), data were available from two arms of two studies (Laessle et al., 1991; Sundgot-Borgen et al., 2002) with a total of N = 44 persons at pretest and N = 20 persons at follow-up. In one study (Laessle et al., 1991) a reduction in binge eating of g = 0.93 is reported. Both studies report a medium to strong reduction in

compensatory behavior (g = 0.73; CI: 0.43, 1.03). Furthermore, one study (Laessle et al., 1991) reports a strong reduction in depressive symptoms (g = 0.86; CI: 0.45, 1.27).
The efficacy of interventions that aim to bring about a change in nutritional habits and thus in the associated psychological factors was confirmed for all central disorder variables in several cohort studies without control groups. Similarly to comprehensive cognitive-behavioral approaches, which tackle further areas of psychopathology in addition to the focus on nutrition, it is thus also apparent that interventions that directly target a change in eating pathology are also effective for BN. Thus, in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), nutrition-based interventions can be assigned with evidence level 2b. The follow-up findings also generally speak in favor of the sustainability of such interventions, although the small sample sizes limit the meaningfulness of the findings.

Other interventions

The residual category of other non-pharmacological interventions includes those which cannot be clearly or exclusively assigned to a particular therapy orientation or school or those which were not bulimia-specific. These comprised a behavioral therapy-oriented stress-management with a focus on cross-disorder aspects of psychopathology (e.g. communication and problem-solving deficits; Laessle et al., 1991), pyschoeducation (R. Davis & McVey, 1999), exercise-based interventions (Sundgot-Borgen et al., 2002), "Guided Imagery Therapy" (Esplen, Garfinkel, Olmsted, Gallop, & Kennedy, 1998), "Cognitive Orientation Training" (Bachar, Latzer, Kreitler, & Berry, 1999) as well as "Self-Psychological Treatment" (Bachar et al., 1999).

Post-CG comparison. For the aforementioned interventions, there are no available data with a passive/placebo-controlled control group.

Pre-post. Overall, data were available from six study arms from five studies with a total of N = 111 persons at pretest and N= 99 persons at posttest. Two studies (Davis et al., 1999; Laessle et al., 1991) report at post-treatment an absence of binge eating in 36% of cases, an absence of purging in 23% of cases and one study (Esplen et al., 1998) an absence of diagnosis in 21% of cases. Three studies (Davis et al., 1999; Esplen et al., 1998; Laessle et al., 1991) report a strong reduction in binge eating (g = 0.87; CI: 0.59, 1.16) and a strong reduction in compensatory behavior (g = 0.78; CI: 0.55, 1.01). Four study arms (Bachar et al., 1999 [2 arms]; Davis et al., 1999; Laessle et al., 1991) report a very strong reduction in self-reported eating pathology (g = 1.10; CI: 0.58, 1.62) and one study (Laessle et al., 1991) a very strong reduction in depressive symptoms (g = 1.15; CI: 0.70, 1.59).

Pre-follow-up. Data were available from three arms from two studies (Davis et al., 1999; Laessle et al., 1991) with a total of N = 62 persons at pretest and N = 39 persons at follow-up test (range: 4 to 12 months). One study (Davis et al., 1999) reports the absence of binge eating in 26% of cases, the absence of purging in 21% of cases and the absence of a diagnosis in 16% of cases. Two studies (Davis et al., 1999; Laessle et al., 1991) report a strong reduction in binges (g = 0.92; CI: 0.55, 1.28). One study (Laessle et al., 1991) reports a strong reduction in compensatory behavior (g = 0.95; CI: 0.58, 1.32), while the other study (Davis et al., 1999) reports a very strong reduction in self-reported eating pathology (g = 1.24; CI: 0.79, 1.70).

Laessle et al. (1991) in turn report a very strong reduction in depressive symptoms (g = 1.56; CI: 1.03, 2.08).
The efficacy of the aforementioned interventions was confirmed for all central disorder variables in at least one cohort study without control group per type of intervention. Thus, in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al, 1998-2009), the aforementioned interventions can be assigned with evidence level 2b. The follow-up findings for stress management and psychoeducation, moreover, suggest a certain sustainability of the respective interventions, although the sample sizes are small, thus limiting the meaningfulness of the findings.

2.2.7. Psychotherapeutically oriented combination therapies

The residual category of psychotherapeutically oriented combination therapies includes those studies which, in the framework of their RCTs, combined integrative approaches and thus interventions from different therapeutic orientations and schools. These comprised (a) an integrative inpatient and day-clinic treatment (eclectic treatment with a combination of psychodynamic therapy, systemic and cognitive-behavioral therapy elements; Zeeck et al., 2009 [2 arms]), (b) a hypnobehavioral therapy (combination of behavioral therapy elements and hypnotherapy; Griffiths et al., 1994), (c) a combination therapy consisting of CBT elements and elements of IPT (Durand & King, 2003), as well as (d) an "Emotional and Social Mind Training" (combination of IPT, mindfulness-based therapy and CBT; Lavendar et al., 2012).
Post-CG comparison. Data are available from one arm from one RCT study (Griffiths et al., 1994) with its control group with a sample of N=55 persons. This reports a medium effect for the post-treatment absence of binge eating (log OR = 2.95; CI: 0.77, 5.13) and a small to medium effect for the absence of purging (log OR = 2.56; CI: 0.37, 4.75). Moreover, in a between-group comparison, the study reveals a medium reduction in binge eating (g = 0.59; CI: –0.02, 1.20), a medium to strong reduction in compensatory behavior (g = 0.67; CI: 0.14, 1.20) and a very strong reduction in self-reported eating pathology (g = 2.12; CI: 1.59, 2.66).
Pre-post. For pre-post analyses, data were available from five arms from all four studies with a total of N=153 persons at pretest and N=122 persons at posttest. In one study (Griffiths et al., 1994), a post-treatment absence of binges is reported in 48% of cases and an absence of purging in 38% of cases, while two study arms (Zeeck et al., 2009 [2 arms]) indicate the absence of a diagnosis in 85% of cases. Four study arms (Durand & King, 2003; Griffiths et al., 1994; Zeeck et al., 2009 [2 arms]) report a reduction in binge eating with a medium to strong effect (g = 0.68; CI: 043, 094) and two studies (Durand et al., 2003; Griffiths et al., 1994) a medium reduction in compensatory behavior (g = 0.62; CI: 0.37, 0.87) and a strong reduction in self-reported eating pathology (g = 1.07; CI: 0.82, 1.33) and one study (Durand & King, 2003) reports a small to medium effect in the reduction of depressive symptoms (g = 0.30; CI: –0.01, 0.61).
Pre-follow-up. Data on a follow-up measurement time point (range 3 to 6 months) were found in four arms of three studies (Durand & King, 2003; Griffiths et al., 1994; Zeeck et al., 2009 [2 arms]) with a total of N=116 persons at pretest and N=90 persons at follow-up test. In one study (Griffiths et al., 1994) an absence of a diagnosis was reported in 41% of cases. Four study arms

(Durand & King, 2003; Griffiths et al., 1994; Zeeck et al., 2009 [2 arms]) report a medium to strong reduction in binge eating (g = 0.70; CI: 0.36, 1.03), one study (Durand & King, 2003) reports a moderate medium reduction in compensatory behavior (g = 0.50; CI: 0.16, 0.84), a strong reduction in self-reported eating pathology (g = 0.85; CI: 0.52, 1.19) and a moderate reduction in depressive symptoms (g = 0.54; CI: 0.21, 0.87).

The efficacy of psychotherapeutically oriented combination therapies could only be confirmed for hypnobehavioral therapy in one well conducted RCT study. Thus, in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), hypnobehavioral therapy can be assigned with evidence level 1b. Nevertheless, it should be noted that it is difficult to clearly delineate the hypnobehavioral therapy conducted in this study from CBT: The first half of the 8-week treatment in the hypnobehavioral arm contained all essential components of CBT according to Fairburn (1991). Only in the second half of treatment were the cognitive treatment elements of CBT replaced by hypnotherapeutic suggestions in terms of retaining the normalized food intake, increasing self-control and on relapse prevention, while the behavioral therapeutic elements were retained. Accordingly, there were also no differences in central BN outcome measures between the CBT arm and the hypnobehavioral therapy.

For all other intervention studies with an eclectic treatment approach ([a] Zeeck et al., 2009: eclectic treatment with a combination of psychodynamic therapy, systemic and cognitive-behavioral therapy elements; [b] Durand et al., 2003: eclectic treatment with a combination of CBT elements and elements of IPT; [c] Lavender et al., 2012: “emotional and social mind training” [eclectic treatment with a combination of IPT, mindfulness-based therapy and CBT]), there is at least one cohort study without control group, resulting in evidence level 2b. With one follow-up for each respective intervention, the sustainability is also shown for the eclectic treatment approach according to Zeeck and colleagues (2009), Durand and King (2003) and for hypnobehavioral therapy.

2.2.8. Pharmacotherapy

Regarding the medical treatment of BN, a multitude of different medications have been tested in controlled studies (Aigner, Treasure, Kaye, Kasper, & Disorders, 2011; Mitchell, Roerig, & Steffen, 2013): TCAs (amitriptyline, imipramine, desipramine, nomifensine), non-tricyclic antidepressants (mianserin, trazodone, bupropion), monoamine oxidase inhibitors (MAOIs; phenelzine, isocarboxazid, tranylcypromine, brofaromine, moclobemide), SSRIs (fluoxetine, sertraline, fluvoxamine, citalopram), appetite suppressants (d-fenfluramine), tryptophan, antiepileptics (carbamazepine, phenytoin, topiramate), lithium, ondansetron and opioid antagonists (naloxone, naltrexone).

It should be noted that fluoxetine is the only SSRI which is approved for the treatment of BN in Germany (and in many other countries), albeit only in conjunction with psychotherapeutic measures. If other medications are used for the treatment of BN, the concern is with off-label use and the patient needs to be informed of such.

To date, meaningful data are primarily available for substances from the group of antidepressants, with the greatest evidence of low side effect rates being found for SSRIs (H.

Davis & Attia, 2017). Antidepressants not only have a positive effect on binge eating and compensatory behavior, but also reduce eating disorder-specific psychopathological features such as dysfunctional attitudes to body and weight. Many studies have also observed a reduction in depressive and anxiety symptoms (Fluoxetine Bulimia Nervosa Collaborative Study Group [FBNCSG], 1992; Kanerva, Rissanen, & Sarna, 1995). Several studies explicitly excluded patients with depressive symptoms and found that the response to antidepressants appears to be independent of mood (H. Davis & Attia, 2017). Therefore, a direct anti-bulimic effect of antidepressant substances in assumed. An onset of effect is frequently already observed after the first week. A treatment attempt should be undertaken for a minimum of 4 weeks. However, an increase in restrictive eating behavior has also been observed in patients taking fluoxetine. This might appear to be counter-therapeutic but an essential first step in the treatment of BN is to build up regulated eating behavior and reduce the fear of weight gain. Restrictive eating behavior, by contrast, can increase the risk of renewed binge eating in the sense of a vicious cycle.

In the case of treatment with medications, dropout rates can be considerable (Mitchell et al., 2013). Moreover, even if medication proves to significantly superior in statistical terms, the clinical effect is not substantial in many patients. For instance, remission rates after short-term treatment lie between 0 and 63%, and around 24% on average, (Bacaltchuk & Hay, 2003). If qualified psychotherapy is not available, fluoxetine can be recommended as an initial treatment. Antidepressants can prove to be helpful in patients with significant comorbid symptoms such as depression, anxiety, obsessiveness and impulse control disorders, or for patients who have responded suboptimally to an appropriate psychotherapy.

To achieve an optimal effect, it may be necessary to employ different antidepressants sequentially (Mitchell et al., 2013). In the case of insufficient response to medication, it should be checked whether the medication is being taken close in time to self-induced vomiting. If serum levels for a medication are available, it can be checked whether an effective level has been reached.

Bupropion should be specifically mentioned here: Although it has shown significantly better results than placebo, it is contraindicated for BN because it was found to lead to generalized seizures more frequently than would be expected by chance (Horne et al., 1988).

Recently, an association between BN and ADHD in childhood and adolescence has been reported. Therefore, in the case of this comorbidity, treatment with stimulants should be considered with caution. In the case of a firm diagnosis of ADHD, a treatment with stimulants (methylphenidate) or atomoxetine can, of course, be considered. As an appetite reduction occurs especially with methylphenidate, the risk of a potential misuse needs to be monitored (Nazar et al., 2016; Svedlund, Norring, Ginsberg, & von Hausswolff-Juhlin, 2017); moreover, weight loss can be contraindicated in patients with BN.

Tricyclic antidepressants (TCA)

Post-CG comparison. For this intervention, data are available from 10 arms from 9 RCTS with their respective control groups, comprising a total of N=438 persons. For the absence of binge eating episodes post-treatment, four studies report a weak effect (log OR = 1,10; CI: 0.01, 2.18). One study reports a small improvement regarding the absence of purging (log OR = 1.35; CI: -0.12, 3.82). Five studies provide information on binge eating episodes, yielding a strong

reduction (g = 0.95; CI: 0.58, 131). Three studies (Agras et al., 1987; Strasser et al., 1992; Walsh et al., 1991) report a medium-sized reduction in compensatory behavior (g = 0.66; CI: -0.33, 1.65), a very strong reduction in self-reported eating pathology (g = 1.31; CI: 0.50, 2.12), and two studies report a small to moderate reduction in depressive symptoms (g = 0.35; CI: -0.21, 0.90).

Pre-post. For pre-post analyses, data were available from 15 study arms from 13 studies with a total of N=305 persons at pretest and N=200 persons at posttest. In four study arms, information was provided on the absence of binge eating episodes post-treatment, in 13% of cases, while two studies report an absence of purging in 47 % of cases. Five study arms report a strong reduction regarding binge eating (g = 0.95; CI: 0.68, 1.22), four study arms report a medium-sized to strong reduction in compensatory behavior (g = 0.45; CI: 0.00, 0.90), three study arms report a medium-sized to strong reduction in self-reported eating pathology (g = 0.77; CI: 0.30, 1.25] and three study arms report a medium-sized reduction in depressive symptoms (g = 0.50; CI: 0.06, 0.95).

Pre-follow-up. Data are available for one arm from one study with a total of N=62 persons at pretest and N=18 persons at a follow-up time point (range: 1 to 6 months). One study arm (Leitenberg, et al., 1994) shows a medium-sized reduction in compensatory behavior (g = 0.50; CI: -0.25, 1.25).

The short-term efficacy of tricyclic antidepressants could be confirmed for all central disorder variables in several well-conducted RCT studies. Thus, in accordance with the classification of evidence levels of the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), tricyclic antidepressants can be assigned with evidence level 1a. In addition, the findings from the other analyses confirm the efficacy of the intervention. Based on the available study findings, it is not possible to make any definitive statements regarding maintenance treatment and the progression following discontinuation of treatment.

Monoamine oxidase inhibitors (MAOI)

Post-CG comparison. Data are available from four arms from four RCTs with their respective control groups and a total of N=175 persons. With regard to the absence of binge eating posttreatment, one study reports an improvement in the intervention group of log OR=2.63 (CI: 0.46, 4.80). Three studies report a weak reduction in binge eating (g = 0,11; CI: -0,65, 0.87). Two studies (Carruba et al., 2000; Kennedy et al., 1993) report a medium-sized reduction in compensatory behavior (g = 0.51; CI: 0.01, 1.01) and a very strong reduction in self-reported eating pathology (g = 1.20; CI: 0.47, 1.93). Moreover, one study (Walsh et al., 1988) reports a medium-sized reduction in depressive symptoms (g = 0.61; CI: 0.15, 1.08)

Pre-post. Data are available from t study arms from three studies with a total of N=88 persons at pretest and N=66 persons at posttest. In one study, an absence of binge eating at posttreatment is reported in 35% of cases. Three studies report a medium-sized to strong reduction in binge eating episodes (g = 0.70; CI: 0.20, 1.19), two studies a weak reduction in compensatory behavior (g = 0.23; CI: -0.03, 0.49) and a medium-sized reduction in self-reported eating pathology (g = 0.52; CI: 0.26, 0.78) and one study a medium-sized reduction in depressive symptoms (g = 0.58; CI: 0.23, 0.92).

Pre-follow-up. No follow-up data are available for this intervention. The short-term efficacy of monoamine oxidase inhibitors was confirmed for all central disorder variables in several well-

conducted RCT studies. Therefore, in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), monoamine oxidase inhibitors can be assigned with evidence level 1a. In addition, the findings from the other analyses confirm the efficacy of the intervention. There are no available data on the sustainability of the intervention.

Summary on TCA and MAOI

TCAs and MAOIs have rarely been used in patients with BN, and despite partial proof of efficacy, cannot be recommended, and particularly not as the sole form of treatment in patients with BN. Most of the studies were conducted in the 1980s and 1990s. Clinical trials for TCAs and MAOIs are not available, and a treatment of patients with BN with TCAs or MAOIs is always off label. Only one study has examined the efficacy of maintenance treatment over four months in patients who achieved a 50% reduction in frequency of binge eating after eight weeks of desipramine. The dropout rate during this maintenance phase lay at 29% and desipramine was not found to be superior to placebo as a maintenance treatment. There are no longer follow-up investigations after discontinuation of the medication. The high dropout rates are partially attributable to the side effects of these substance classes. Tiredness, dizziness, mouth dryness, constipation, increased heart rate, low blood pressure and above all weight gain are especially difficult to tolerate for patients with BN. The toxicity and potential lethality in the case of overdose warrant extreme caution in suicidal patients. When taking MAOIs, in the case of very chaotic eating behavior (CAVE tyramine-containing foods), the danger of hypertonic crises is not inconsiderable.

Selective serotonin reuptake inhibitors (SSRI)

Post-CG comparison. Overall, data are available from 10 arms from seven RCTs and their respective control groups with a total of N=955 persons. For the absence of binge eating, two studies report a weak effect (log OR = 0.39; CI: -0.13, 0.91). Two studies report a small effect for the absence of purging (log OR 0.67; CI: 0.11, 1.24). One study (Schmidt et al., 2004) reports a weak to medium-sized effect for the absence of diagnosis (log OR = 0.06; CI: –1.20, 1.33). Five study arms report data for the frequency of binge eating episodes and point to a weak effect (g =0.10; CI: -0.08, 0.29). Four studs arms demonstrate a medium-sized to strong reduction in compensatory behavior (g = 0.56; CI: 0.40, 0.73). Three studies report a strong reduction in self-reported eating pathology (g = 1.00; CI: 0.84, 1.17). One study reports a medium-sized reduction in depressive symptoms (g = 0.58; CI: -0.24, 1.39).

Pre-post. For pre-post analyses, data are available from 18 arms from 13 studies with a total of N=788 persons at pretest and N=424 persons at posttest. Six study arms report a mean absence of binge eating episodes posttreatment in 20% of cases and an absence of purging in 17% of cases and five study arms an absence of diagnosis in 16 % of cases. Eleven study arms show a strong reduction in binge eating episodes (g = 0.81; CI: 0.70, 0.92), 12 study arms show a medium-sized reduction in compensatory behavior (g = 0.47; CI: 0.31, 0.64), six study arms show a strong reduction in self-reported eating pathology (g = 1.00; CI: 0.32, 1.67) and six study arms a medium-sized reduction in depressive symptoms (g = 0.48; CI: 0.24, 0.71).

Pre-follow-up. For three arms from three studies with a sample size of N = 36 persons, data are reported for one follow-up measurement (range: 1 to 6 months). The studies showed a medium-

sized reduction in binge eating episodes (g = 0.53; CI: 0.17, 0.89), while compensatory behavior slightly improved (g = 0.28; CI: -0.26, 0.81).
The efficacy of SSRIs was confirmed for all central disorder variables in several well-conducted RCT studies. Therefore, in line with the classification of levels of evidence according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), SSRIs can be assigned level of evidence 1a. Additionally, the findings from other analyses confirm the efficacy of the intervention. However, the findings on the sustainability of the intervention are still sparse and differ depending on outcome measure, and thus require further investigation.

Summary SSRIs
Following two multicenter outpatient studies with large numbers of participants, fluoxetine is the only SSRI which is approved for the treatment of BN in Germany and in many other countries, albeit only in conjunction with psychotherapeutic measures. In the interim, several controlled studies are available (Beumont et al., 1997; Fichter et al., 1991; Goldstein, Wilson, Thompson, Potvin, & Rampey, 1995; FBNCSG, 1992; Kanerva et al., 1995; Levine, 1992; Romano, Halmi, Sarkar, Koke, & Lee, 2002). In the treatment of BN, a higher fluoxetine dosage of 60mg/day appears to be more effective than the dosage of 20mg/day which is recommended for the treatment of depression. Generally, it is advised to increase the dosage in a step-by-step manner, although there have also been some good experiences with the immediate administration of the full dosage of 60mg/day, once, in the morning. Fluoxetine has also proven to be beneficial for patients who achieved low to no improvement in bulimic symptoms through psychotherapy (Walsh et al., 2000).
For the treatment with SSRIs, the available meta-analysis (Svaldi et al 2019) yielded only weak effects regarding the reduction in frequency of binge eating episodes (level of evidence 1a).
In the large multicenter studies with fluoxetine, sexual side effects were frequent, and with a dosage of 60mg/day, sleep disturbances, nausea and asthenia occurred in 25-33% of patients (Levine, 1992). The results of an open study suggest that fluoxetine at 60mg/day is also effective in adolescents with BN. However, with this indication, no medication is approved for children and adolescents and the use is only possible in the framework of an "individual curative attempt" according to § 41 of the German Medicinal Products Act (Couturier & Lock, 2007; Kotler, Devlin, Davies, & Walsh, 2003). Smaller controlled studies are available for sertraline (Leombruni et al., 2006), citalopram (Leombruni et al., 2006) and fluvoxamine (Fichter, Kruger, Rief, Holland, & Dohne, 1996; Milano, Siano, Putrella, & Capasso, 2005), although it should be critically mentioned that there could also be a publication bias in medication studies in the case of BN. There are at list two unpublished studies of negative, multicenter and multinational placebo-controlled studies with fluvoxamine, which were unable to demonstrate a superiority of the medication (Flament, Bissada, & Spettigue, 2012).

However, findings on the sustainability of the intervention are still sparse and differ depending on the outcome measure, and thus require further investigation. Only two studies have tested the efficacy of SSRIs as a maintenance treatment. Fichter et al. (1996) employed fluvoxamine as relapse prevention following inpatient treatment compared to placebo. Fluvoxamine was better able to prevent relapses in the treatment period of three months after discharge compared to placebo. However, the dropout rate in the fluvoxamine arm lay at 51%. Romano and

colleagues (2002) conducted the largest study on maintenance therapy to date, in this case with fluoxetine. Patients with BN, who had achieved a 50% reduction in frequency of vomiting with 60mg fluoxetine, were treated further with fluoxetine as maintenance treatment or placebo over a period of one year. The results are difficult to interpret, as the dropout rate lay at 83% in the fluoxetine group and 92% in the placebo group.
Although respective data are lacking, in the case of a good response, a treatment duration of 9-12 months is generally recommended. An increase in dosage or the administration of a second medication might be useful in the case of relapses under maintenance treatment. However, so far, there are only open investigations which support this.

Other antidepressants and other medications

Post-CG comparison. Data are available from 13 arms from 11 studies with their respective control groups with a total of N=378 persons. Two studies (Horne et al. 1988; Pope et al., 1989) report a strong reduction in binges (log OR = 2.11; CI: -0.01, 4.23), one study (Horne et al. 1988) a strong reduction in compensatory behavior (log OR = 2.38; CI: -0.53, 5.29), and one study (Hedges/Hoopes et al., 2003) reports a moderate improvement in the intervention group regarding the absence of a diagnosis posttreatment (OR = 1.51; CI: -0.15, 3,17). Eight study arms (flutamide, lithium, topiramate, ondansetron, naltrexone) report a medium-sized to strong reduction in binge eating (g = 1.00; CI: 0.43, 1.58) and seven study arms a strong reduction in compensatory behavior (g = 0.89; CI: 0.48, 1.30). One study (Hedges/Hoopes et al., 2003) reveals a strong reduction in self-reported eating pathology (g = 0.85; CI: 0.38, 1.33).
Pre-post. For pre-post analyses, data are available from 13 arms from 11 studies with a total of N=199 persons at pretest and N=159 persons at posttest. Two studies (Horne et al. 1988; Pope et al., 1989) report the absence of binges in 22% of cases, one study (Horne et al. 1988) the absence of compensatory behavior in 30% of cases, and two studies (Hedges/ Hoopes et al., 2003; Mitchell et al., 2002) report an absence of diagnosis in 15% of cases at posttreatment. In total, eight study arms report a strong reduction in binge eating episodes (g = 1.04; CI: 0.73, 1.36), eight study arms (flutamide, lithium, topiramate, ondansetron, naltrexone) a medium-sized reduction in compensatory behavior (g = 0.57; CI: 0.25, 0.90), one study on topiramate (Hedges / Hoopes et al., 2003) a medium-sized reduction in self-reported eating pathology (g = 0.53; CI: 0.20, 1.08) and one study (naltrexone) a medium-sized reduction in depressive symptoms (g = 0.46; CI: -0.16, 1.08).
Pre-follow-up. No follow-up data are available for this intervention.
The efficacy of topiramate was confirmed for all central disorder variables in one conducted RCT study (Nickel et al., 2005). Therefore, in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), topiramate can be assigned with evidence level 1b. In addition, the findings from the other analyses confirm the efficacy of topiramate. Due to the numerous side effects (cognitive disturbances, difficulty findings words, paresthesias), however, the medication should only be used if other medicinal treatment attempts have proven to ineffective. Accordingly, the dosage should be increased slowly. Moreover, the weight-reducing effect of topiramate further restricts its use in normal-weight and underweight patients (Hoopes et al., 2003). No data are available on the sustainability of topiramate (maintenance treatment, progression following discontinuation).

The efficacy of flutamide, lithium, naltrexone and ondansetron can be assigned with evidence level 1b. Additionally, the findings from other the analyses confirm the efficacy of these substances. However, there are no findings on sustainability. In the treatment of BN, lithium harbors the danger of overdosing due to fluid shifts, particularly in the case of frequent vomiting (L. K. Hsu, Clement, Santhouse, & Ju, 1991). For patients with BN and a bipolar disorder, therefore, the toxicity risk is increased under lithium treatment. Both lithium and valproic acids can lead to considerable weight gain, which reduces the acceptance of these medications. In the case of comorbid bipolar disorder, an alternative mood stabilizer should thus be considered. Flutamide (an anti-androgen used for example in the treatment of prostate cancer), ondansetron (a 5-HT_3 antagonist used in the treatment of nausea and vomiting, e.g. with chemotherapy) and naltrexone (an opioid antagonist, which is approved, for example, for relapse prevention in alcohol dependence), are not recommended for the routine treatment of patients with BN. Furthermore, naltrexone was used in high doses (200 to 300 mg) and at these doses led to a significant increase in liver transaminases.

2.2.9. Combination treatment with pharmacotherapy and psychotherapy

Pharmacotherapy does not necessarily have an additive effect to a psychotherapeutic approach in BN (ceiling effect). In several studies, the combination of CBT and an antidepressant showed the highest remission rates. In other investigations, the administration of antidepressant medication in addition to CBT only showed moderate to no additional effects in terms of bulimic symptoms. However, a superiority of the combination treatment was reported for the reduction of depression and anxiety. Therefore, combination therapy can initially be recommended, especially if a qualified CBT is simultaneously offered (Bacaltchuk et al., 2000). Sequential treatment studies examine the efficacy of a second-line treatment when the patient has not responded to first-line treatment (Mitchell et al., 2013). If CBT alone has not led to a clear symptom reduction after 10 sessions, the additional administration of fluoxetine is recommended. Relapse prevention after the end of psychotherapy can be discussed as a further possible indication.

Post-CG comparison. For this intervention, no data with passive/placebo-controlled control group are available.

Post-CG comparison psychotherapy and placebo vs. psychotherapy and pharmacotherapy. For these analyses, data were available from six studies, each with one arm of combination therapy (SSRI and CBT) with a corresponding comparison arm (CBT only). In total, N=239 persons took part at pretest and N=163 at posttest (Agras et al., 1992 [two arms]; Fichter et al., 1991; Goldbloom et al., 1997; Jacobi et al., 2002; Leitenberg et al., 1994; Walsh et al., 1997). In four study arms, the combination therapy slightly outperformes the simple therapies in terms of absence of binges (log OR = 0.58; CI: -0.13, 1.30). Five study arms show a slight superiority regarding the absence of compensatory behavior (log OR = 0.59; CI: -0.73, 1.91), and two study arms regarding the absence of a diagnosis (log OR = 0.11; CI; -0.80, 1.03). Six study arms show moderately higher reductions in the frequency of binge eating episodes (g = 0.30; CI: -0.03, 0.63), six studies showed slightly stronger reductions in compensatory behavior (g = 0.19; CI: -0.09, 0.46), one study showed a stronger reduction in self-reported eating pathology with a

medium effect size (g = 0.56; CI: -0.02, 1.15) and three study arms showed a slightly stronger reduction in depressive symptoms (g = 0.15; CI: -0.32, 0.62).

Pre-post. For pre-post analyses on the individual combination studies (CBT or BT combined with SSRIs or D-fenfluramine [one study arm]; self-management in the sense of a stepped-care approach followed by SSRI and possibly CBT), 14 arms from 9 studies with a total of N=499 persons at pretest and N=387 persons at posttest were available. In four study arms (CBT/BT plus SSRIs), an absence of binge eating episodes posttreatment was reported in 48% of cases, in five study arms the absence of purging in 43% of cases and in two studies (Goldbloom et al., 1997; Walsh et al., 1997) the absence of a diagnosis in 31% of cases. In seven study arms, a very strong reduction in binge eating episodes for BT/CBT in combination with SSRI or D-fenfluramine (g = 1.25; CI: 0.73, 1.76) was reported, in seven study arms a strong reduction in compensatory behavior for BT/CBT in combination with SSRI or D-fenfluramine (g = 1.15; CI: 0.75, 1.55). Five study arms report a very strong reduction in self-reported eating pathology for BT/CBT in combination with SSRI or D-fenfluramine as well as stepped care (g = 2.49; CI: 0.64, 4.34) and five studies report a medium-sized reduction in depressive symptoms for BT/CBT in combination with SSRI or D-fenfluramine as well as stepped care (g = 0.54; CI: 0.43, 0.65).

Pre-follow-up. Data are available for seven arms from five studies (CBT plus SSRI or D-fenfluramine) with a total of N=362 persons at pretest and N= 37 individuals at follow-up (range: 1 to 12 months). In four study arms, a very strong reduction in binge eating (g = 1.37; CI: 0.68, 2.06) is reported. Five study arms report a very strong reduction in compensatory behavior (g = 1.28; CI: 0.82, 1.74), two study arms a very strong reduction in self-reported eating pathology (g = 1.04; CI: 0.92, 1.15) and a medium-sized reduction in depressive symptoms (g = 0.50; CI: 0.39, 0.61).

The efficacy of combination therapies consisting of BT or CBT combined with SSRIs or D-fenfluramine was confirmed for all central disorder variables in several cohort studies without control groups. In line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), the combination of CBT or BT with SSRIs can be assigned with evidence level 2a; the combination of CBT or BT with D-fenfluramine as well as the stepped-care approach can be assigned with evidence level 2b. Additionally, the findings from the other analyses confirm the efficacy of these substances. The follow-up findings speak in favor of the sustainability of the mentioned combination therapies. In the comparison of combination therapies (SSRI and CBT) with simple psychotherapy (CBT), the combination therapies only performed slightly better. As the confidence intervals for the group comparison included zero in each case, it was not possible to confirm a significant superiority of the combination therapies.

2.2.10. Other combination therapies

In the residual category of other combination therapies, the following RCTs were included: one study arm with a nutrition-based intervention combined with SSRI, three arms with CBT or

cognitive therapy with a nutrition-based intervention, one self-management study arm combined with SSRI, and one study arm with supportive therapy combined with SSRI.

Post-CG comparison. Allocated to this category was one arm from one study (combination of self-management [CBT-based manual, not therapist-led] plus SSRI; Mitchell et al., 2001) including its control group with N = 43 individuals at pretest and N = 37 individuals at posttest. This study reports a strong reduction in binge eating (g = 0.85; CI: 0.08, 1.61) and a very strong reduction in compensatory behavior (g = 1.54; CI: 0.94, 2.14).

Post-CG comparison psychotherapy and placebo vs. psychotherapy and pharmacotherapy. For these analyses, data were available from four study arms with their respective comparison groups with a total of N=207 individuals at pretest and N=167 individuals at posttest. In two study arms, a slightly higher absence of binge eating is determined in the combination therapy (log OR = 0.21; CI: -0.62, 1.04), in one study a slightly higher absence of compensatory behavior can be seen (log OR = 0.46) and in three study arms a slightly higher absence of diagnoses becomes apparent (log OR = 0.46; CI: -0.33, 1.25). In the combination therapies, four study arms showed a marginally stronger reduction in binge eating episodes (g = 0.16; CI: -0.19, 0.51) and a slightly stronger reduction in compensatory behavior (g = 0.24; CI: -0.03, 0.51). One study showed a marginally stronger reduction in eating pathology (g = 0.16) and in depressive symptoms (g = 0.30).

Pre-post. For pre-post analyses, six arms from five studies with a total of N=144 individuals at pretest and N=119 individuals at posttest were considered. In two study arms, an absence of binge eating post treatment was reported in 52% of cases, in one study arm an absence of purging was apparent in 14% of cases, and in three study arms the absence of a diagnosis in could be seen in 29% of cases . Six study arms report a strong reduction in binge eating (g = 0.88; CI: 0.65, 1.11), six study arms report a strong reduction in compensatory behavior (g = 0.92; CI: 0.73, 1.10), one study arm reports a very strong reduction in self-reported eating pathology (g = 1.23; CI: 0.80; 1.65) and one study reports a moderate to large reduction of depressive symptoms (g = 0.74; CI: 0.31, 1.17).

Pre-follow-up. For one arm (Beumont et al., 1997) with a total of N=34 individuals at pretest and N=17 individuals at posttest, follow-up data (after one month) are available. The study shows a medium-sized to strong reduction in binge eating (g = 0.76; CI: 0.35, 1.17), and a strong reduction in compensatory behavior (g = 0.83; CI: 0.49, 1.17).

The efficacy of combination therapy consisting of CBT-based, non-therapist-led self-management manual and SSRI was confirmed for all central disorder variables in one well-conducted RCT study. Therefore, in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), this combination can be assigned with evidence level 1b. Furthermore, it is apparent that the combination of the two interventions has a better effect than the respective individual interventions alone.

For the other combinations, there are several cohort studies without control groups, meaning that for CBT/BT plus nutrition-based therapy, evidence level 2a can be assigned. For the combination of nutrition-based intervention plus SSRI as well as supportive therapy and SSRI, evidence level 2b can be assigned.

When comparing the other combination therapies with simple psychotherapy, the combination therapies only performed marginally better. Here too, the confidence intervals included zero, meaning that no significant effect could be determined.

3. Treatment settings

For BN, there are essentially three possible treatment settings in Germany just as well: inpatient, partial inpatient/day-clinic, and outpatient. The majority of patients with BN can be treated in the outpatient setting. In this respect, in the framework of the directives for psychotherapy, patients are treated by medical or psychological psychotherapists or child and adolescent psychotherapists.
If the following indication criteria are present, an inpatient or day-clinic treatment can be indicated:

- Insufficient change from outpatient treatment,
- Failure of outpatient or day-clinic treatment,
- Substantial mental and physical comorbidity (e.g. self-harm, Diabetes mellitus Type I), which necessitates close medical supervision,
- Illness severity (e.g. very severe symptoms, very chaotic eating behavior),
- Social or familial influencing factors which strongly hinder the recovery process (e.g. social isolation, problematic family situation, insufficient social support),
- Suicidality,
- Necessity for treatment by a multiprofessional team with treatment methods typical for hospitals (inpatient intensive therapy).

In the case of inpatient or day-clinic treatment, transitions often occur (e.g. inpatient-outpatient). In this respect, good coordination and cooperation between the treatment providers involved is necessary. This also applies for the combination of psychotherapeutic and psychopharmacological treatments, if they are not carried out by one person. For children and adolescents who are well integrated with their same-aged peers, caution is particularly advised when considering inpatient treatment. Fundamentally, a treatment against a minor's express will should only ensue in exceptional cases. In order to prepare patients and their parents for treatment and to ensure insight into the illness and motivation for change, clinical experience has shown that intensive preliminary discussions are helpful.

The few findings comparing inpatient and day-clinic treatment of BN available so far indicate that the two treatment settings do not differ a great deal (Zeeck, Weber, Sandholz, Joos, & Hartmann, 2011; Zeeck, Weber, Sandholz, Wetzler-Burmeister, Wirsching, & Hartmann, 2009; Zeeck, Weber, Sandholz, Wetzler-Burmeister, Wirsching, Scheidt, et al., 2009). At 3- and 12-month follow-up, the success of the day-clinic patients was somewhat better than that of the inpatients. An uncontrolled study compared outpatient and inpatient treatment on the basis of cognitive-behavioral therapy. Patients treated in the inpatient setting were more strongly impaired regarding eating disorder and psychopathology. Both treatment settings were effective, but the inpatient treatment led to quicker changes and a more obvious improvement in mental comorbidities (Williamson et al., 1989).
Studies on the efficacy of inpatient treatments within the German care system were presented by Fischer and Quadflieg (1997), von Wietersheim, Kordy, Kächele, and MZ-Ess (2004) and Zeeck and colleagues (2007). Depending on the success criterion, a large proportion of patients

show a clear improvement in symptoms during the inpatient treatment, and the remission rates at the time of discharge were around 50%. Generally speaking, the inpatient stay was followed by outpatient psychotherapy.

Recommendations

Diagnosis

- Patients with BN should be offered treatment as early as possible to avoid the disorder becoming chronic (GCP).
- Some patients with BN are ambivalent towards changing their eating disorder; therefor, patients should be offered intervention actively motivating for treatment (GCP)
- Comorbid disorders should be diagnosed systematically (GCP).

Treatment setting

- There are indications that it can be justified to treat patients with BN in the outpatient, day-clinic and inpatient setting (GCP).
- For patients with BN a treatment in an outpatient setting should be considered (B, evidence level 1a).
- If certain indication criteria are present (see below), type of treatment (inpatient or day-clinic treatment) should be offered in dependence of the level of severity (GCP).
- The criteria for inpatient or day-clinic treatment are as follows (GCP):
  - mental or physical comorbidity which constitutes an indication for inpatient or day-clinic treatment (e.g. suicidality, inadequately controlled diabetes mellitus, severe self-harm, drug or alcohol dependency)
  - pronounced bulimic symptoms (including derailed eating behavior, electrolyte shift)
  - pregnancy complications due to eating disorder
  - insufficient efficacy of outpatient treatment
  - circumstances in the patient's environment which hinder treatment
- Outpatient, inpatient and day-clinic treatments should take place in institutions or with therapists which possess expertise in the treatment of patients with eating disorders (GCP).

Treatment form

- Psychotherapy should be offered as first-line treatment approach in adults (A, level of evidence 1a)
- Psychotherapy should be offered as first-line treatment approach in adolescents with BN (A, level of evidence 2a).
- CBT (including its further developments such as dialectical behavior therapy) is the most researched psychotherapy approach with the highest evidence level; therefore, CBT should be considered as first-line treatment in patients with BN (B, evidence level 1a).
- Other psychotherapeutic approaches or methods are available; these should be considered if CBT proves to be ineffective or is not desired in individual cases (B, evidence level 2b).
- Interpersonal psychotherapy (IPT) should be considered as an alternative to CBT (B, evidence level 2a). [However, in the German directives for psychotherapy, IPT is not an approved method]. Alternatively, psychodynamic psychotherapy can be recommended (O, evidence level 2b).

- In the treatment of children and adolescents, CBT should be considered as first-choice psychotherapeutic treatment (B, 2a[15]); treatment should be provided according to the individual state of development (GCP).
- In children and adolescents, family-based therapy can also be recommended (O, evidence level 2b).
- For some patients with BN, participation in an evidence-based self-management program which is therapist-guided ("guided self-help") and is based on elements of cognitive behavioral therapy can be recommended (O, evidence level 1a).
- Pharmacotherapy must not be offered as a sole treatment (A, evidence level 1a).
- If pharmacotherapy is offered, fluoxetine should be considered as treatment (B, evidence level 1a). A treatment of BN with a dose of 60mg fluoxetine is more effective than a treatment with a dose of 20mg fluoxetine (evidence level 1b). This is the only active substance which is approved in Germany for the BN treatment of adults in combination with psychotherapy.
- A treatment attempt using fluoxetine should be undertaken for a minimum of four weeks; a longer treatment duration can be assumed for treatment success (GCP).
- If medications other than fluoxetine are used for the treatment of BN, patients must be informed that the treatment is off-label (GCP).
- Bupropion is contraindicated for the treatment of patients with BN (2b).
- If comorbid disorders are present, the treatment disorder-specific elements should be offered (GCP).

[15] The evidence level corresponds to an extrapolation from evidence from studies in adulthood, which partially included adolescents with BN, who were offered a treatment that was comparable to the treatments for adults with BN.

Table 1: Overview of all studies entered into the current meta-analysis

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
1	Agras et al. (1987)	PHARMA	TCA	10	0	100	30.3	1	0	1	1	1	0	1	Self-report	16	PP	No intake of antidepressants to treat BN in the past (inclusion criterion)
		PHARMA	PL	10	0	100	31.5	1										
2	Agras et al. (1989)	actCONT	SM + ND	19	3	100	29.2	1	1	0	9	1	0	0	Self-report	16	PP; FU (6 months)	No additional treatment at start of study (inclusion criterion); no further info on FU period
		PT	CBT	22	5	100	29.2	1										
		PT	CBT-ERP	17	1	100	29.2	1										
		CONT	WL	19	1	100	29.2	1										
3	Agras et al. (1992)	PHARMA	SSRI16w	12	2	100	29.6	1	0	1	1	1	0	1	Self-report	16	PP; FU (1 month)	No psychotropic drugs at start of study (inclusion criterion); duration of intake of psychotropic drugs during study 16 or 24 weeks; duration CBT 24 weeks; 4 patients received additional treatment during FU period (1 patient from each arm except CBT+SSRI24)
		PHARMA	SSRI24w	12	2	100	29.6	1										
		COMBI (PT+PH)	CBT+SSRI16w	12	2	100	29.6	1										
		COMBI (PT+PH)	CBT+SSRI24w	12	2	100	29.6	1										
		PT	CBT	23	1	100	29.6	1										
4	Agras et al. (2000)	PT	CBT	110	32	100	28.1	1	1	0	9	1	1	1	Inter view	20	PP; FU (4 months)	No additional treatment at start of study (inclusion criterion); no further info for FU period
		PT	IPT	110	26	100	28.1	1										
5	Bachar et al. (1999)	OTH	Self-PT	10	2	100	24.1	1	0	0	9	1	0	0	Self-report	52	PP	No treatment-specific inclusion criteria
		OTH	COT	11	1	100	24.1	1										
		actCONT	NU	10	3	100	24.1	1										

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
6	Bailer et al. (2004)	SM	GSM	40	10	100	23.3	1	0	0	9	1	1	0	Self-report	18	PP; FU (12 months)	Stable intake of psychotropic drugs for BN treatment during the study possible; additional treatment during FU period possible (no sig. differences between groups)
		PT	CBT	41	15	100	24.2	1										
7	Banasiak et al. (2005)	SM	GSM	54	18	100	29.5	1	1	0	9	1	1	1	Inter view	17	PP; FU (3 months)	No additional treatment at start of study (inclusion criterion); No further info for FU period
		CONT	WL	55	16	100	28.3	1										
8	Barlow et al. (1988)	PHARMA	TCA	47	23	Not specified	27.2	1	0	1	1	1	1	1	Self-report	15	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	47	23	Not specified	27.2	1										
9	Beumont et al. (1997)	COMBI (OTH+PH)	NU + SSRI	34	11	100	24.2	1	0	1	1	1	1	1	Self-report	8	PP; FU (1 month)	No intake of psychotropic drugs at start of study (inclusion criterion); Duration of intake of psychotropic drugs during the study for 8 weeks
		COMBI (OTH+PH)	NU + PL	33	7	100	25.1	1										
10	Blouin et al. (1988)	PHARMA	SSRI	17	7	100	25.5	1	0	1	1	1	1	1	Self-report	6	PP	No intake of psychotropic drugs at start of study (inclusion criterion) as well as during the course of the study
		PHARMA	SSRI	19	7	100	25.3	1										
		CONT	PL	17	7	100	25.5	1										
		CONT	PL	19	7	100	25.3	1										
11	Bulik et al. (1998)	PT	CBT + ERP-B	37	2	100	26.1	1	0	0	9	1	1	0	Inter view	12	PP; FU (6 months)	No intake of psychotropic drugs at start of study (inclusion criterion);
		PT	CBT + ERP-P	35	2	100	26.1	1										

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
		PT	CBT + RELAX	39	1	100	26.1	1										no further info for FU period
12	Carruba et al. (2000)	PHARMA	MOCL	38	10	100	25.7	1	0	1	1	1	0	1	Self-report	6	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	39	15	100	25.2	1										
13	Carter et al. (2003)	SM	SM-CBT	28	5	100	27.0	1	0	1	9	1	1	1	Inter view	8	PP	No current or past eating disorder-specific treatment (inclusion criterion); Stable intake of antidepressants during the study possible
		actCONT	SM-NS	28	7	100	27.0	1										
		CONT	WL	29	8	100	27.0	1										
14	Chen et al. (2003)	PT	CBT-indv	30	8	100	25.8	1	1	0	9	0	1	0	Inter view	19	PP; FU (3 months)	No additional treatment at start of study (inclusion criterion); no further info on follow-up period
		PT	CBT-group	30	8	100	25.8	1										
15	Cooper et al. (1995)	PT	CBT	15	2	100	23.8	2	0	0	9	1	1	1	Inter view	18	PP; FU (12 months)	No treatment-specific inclusion criteria; No additional treatment during the FU period
		PT	ERP	16	2	100	23.8	2										
16	Davis et al. (1999)	PT	EDU + CBT	39	1	100	27.1	1	0	0	9	0	1	1	Inter view	22	PP; FU (4 months)	No additional treatment at start of study (inclusion criterion) as well as during the course of the study
		OTH	EDU	19	0	100	27.1	1										
17	Durand et al. (2003)	SM	GSM-CBT	34	12	100	28.3	1	1	0	9	1	1	0	Inter view	24	PP; FU (3 months)	No treatment-specific inclusion criteria; additional treatment during the FU period possible
		COMBI	CBT + IPT	34	6	100	24.5	2										
18	Esplen et al. (1998)	OTH	GIT	28	4	98	26.6	1	0	1	0	1	0	1	Self-report	6	PP	No psychotherapeutic treatment at start of

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
		actCONT	act CONT	30	4	98	26.6	1										study (inclusion criterion)
19	Fahy et al. (1993)	COMBI (PT + PH)	CBT + d-Fenfluramine	20	0	100	23.0	1	0	1	1	1	1	0	Self-report	16	PP (8 weeks [end CBT]); FU (16 weeks; [end PHARMA])	No intake of psychotropic drugs at start of study (inclusion criterion); no further info for FU period
		COMBI (PT + PH)	CBT + PL	23	4	100	23.0	1										
20	Fairburn et al. (1986)	PT	CBT	12	1	100	22.9	1	0	0	9	1	1	1	Inter view	18	PP; FU (4 months)	No additional treatment at start of study (inclusion criterion) as well as over the course of the study
		actCONT	SFT	12	1	100	22.9	1										
21	Fairburn et al. (1991)	PT	CBT	25	4	100	24.2	1	1	1	0	1	1	1	Inter view	18	PP; FU (4 months [Fairburn et al. (1993)])	No additional treatment during the study; 7 patients received an additional treatment during the FU period and were thus excluded
		PT	BT	25	7	100	24.2	1										
		PT	IPT	25	4	100	24.2	1										
22	Faris et al. (2000)	PHARMA	ODA	14	1	100	29.1	1	0	1	1	0	1	1	Self-report	6	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	12	0	100	29.1	1										
23	FBNC Study Group (1992)	PHARMA	SSRI60	129	40	100	26.4	1	0	1	1	1	1	0	Self-report	8	PP	No additional treatment at start of study (inclusion criterion)
		PHARMA	SSRI20	129	31	100	27.4	1										
		CONT	PL	129	50	100	27.7	1										
24	Fichter et al. (1991)	COMBI (PT+PH)	BT + SSRI	20	1	98	26.5	2	0	1	1	1	1	1	Self-report	7	PP	Both groups additionally received the same inpatient treatment components during the study
		COMBI (PT+PH)	BT + PL	20	0	98	24.6	2										

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
25	Garner et al. (1993)	PT	CBT	30	5	100	23.7	1	0	0	9	1	1	1	Inter view	19	PP	No info on treatment-specific inclusion criteria
		actCONT	SET	30	5	100	24.6	1										
26	Ghaderi et al. (2006)	PT	CBT	26	2	Not specified	27.2	1	0	0	9	1	1	1	Inter view	19	PP; FU (6 months)	No additional treatment at start of study (inclusion criterion); no further info for FU period
		PT	CBT-INDV	24	2	Not specified	27.2	1										
27	Goldbloom et al. (1997)	PT	CBT	24	10	100	25.8	1	0	0	9	1	1	1	Inter view	16	PP	No additional treatment at start of study (inclusion criterion)
		PHARMA	SSRI	23	11	100	25.8	1										
		COMBI (PT+PH)	CBT + SSRI	29	15	100	25.8	1										
28	Griffiths et al. (1994)	PT	CBT	23	4	100	24.4	1	0	0	9	1	1	1	Self-report	8	PP; FU (6 months)	No additional treatment at start of study (inclusion criterion); additional treatment during FU period possible (concretely mentioned in the paper)
		COMBI (PT+PT)	HBT	27	6	100	24.4	1										
		CONT	WL	28	6	100	27.1	1										
29	Hedges et al. (2003)/ Hoopes et al. (2003)	PHARMA	TOP	35	4	97	29.6	1	0	1	1	1	0	0	Self-report	10	PP	No intake of psychotropic drugs at start of study (inclusion criterion); continuation but not beginning of psychotherapy during the study possible
		CONT	PL	31	1	100	29.6	1										
30	Hill et al. (2011)	PT	DBT	18	2	100	22.7	1	0	1	9	1	1	1	Inter view	6	PP (6 weeks); FU (12 weeks [end DBT])	No eating disorder-specific treatment at start of study
		CONT	WL	14	2	100	21.1	1										

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
31	Horne et al. (1988)	PHARMA	BUPR	55	18	100	26.1	1	0	1	1	0	1	1	Self-report	8	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	26	14	100	26.9	1										
32	Hsu et al. (1991)	PHARMA	LI	17	6	100	25.4	1	1	0	1	1	1	1	Self-report	8	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		PHARMA	LI	30	3	100	25.4	1										
		PL	PL	11	6	100	25.4	1										
		PL	PL	27	8	100	25.4	1										
33	Hsu et al. (2001)	PT	CT	26	4	100	24.2	1	0	1	9	1	1	1	Inter view	14	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		NUTRI	NU	23	9	100	23.3	1										
		COMBI (PT+OTH)	CT + NU	27	3	100	24.1	1										
		actCONT	SM-group	24	11	100	26.5	1										
34	Hughes et al. (1986)	PHARMA	TCA	10		100	25.4	1	0	1	1	1	0	1	Self-report	6	PP	No treatment-specific inclusion criteria
		CONT	PL	12		100	25.4	1										
35	Husemann et al. (1990)	PHARMA	NALT	10	1	100	26.0	1	0	1	1	0	0	1	Self-report	10	PP	No treatment-specific inclusion criteria
		CONT	PL	10	1	100	26.0	1										
36	Jacobi et al. (2002)	PT	CBT	19	8	100	26.0	1	0	0	9	1	0	1	Self-report	16	PP; FU (6 months)	No additional treatment at start of study (inclusion criterion); no further info for FU period
		PHARMA	SSRI	16	4	100	26.0	1										
		COMBI (PT+OTH)	CBT + SSRI	18	6	100	26.0	1										
37	Kanerva et al. (1994)	PHARMA	SSRI	24	2	100	25.2	1	0	1	1	1	1	1	Self-report	8	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	26	2	100	25.2	1										
38	Kennedy et al. (1993)	PHARMA	MAO	19	4	100	27.6	1	1	1	1	1	1	1	Self-report	8	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	17	4	100	25.9	1										

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
39	Laessle et al. (1987)	PT	GT	8	0	100	23.5	2	0	0	9	1	0	0	Self-report	16	PP; FU (3 months)	No treatment-specific inclusion criteria; No further info for FU period
		CONT	WL	9	0	100	23.3	2										
40	Laessle et al. (1991)	NUTRI	NM	27	5	100	28.8	1	0	1	9	1	1	1	Self-report	12	PP; FU (6 months)	No additional treatment at start of study (inclusion criterion); additional treatment during FU period possible
		OTH	Stress-M	28	2	100	28.8	1										
41	Lavender et al. (2012)	COMBI (PT+PT)	ESM-group	37	2	98	27.7	1	1	1	9	1	1	1	Inter view	16	PP	No treatment-specific inclusion criteria
		PT	CBT-group	35	2	88	27.7	1										
42	Le Grange et al. (2007)	PT	FBT	41	5	98	16.0	1	1	0	9	1	1	1	Inter view	24	PP; FU (6 months)	No psychotherapeutic treatment at start of study; psychotropic drugs possible (inclusion criterion): no further info for FU period
		actCONT	SPT	39	4	97	16.1	1										
43	Le Grange et al. (2015)	PT	FBT	52	9	92	15.9	1	1	1	9	1	1	1	Inter view	24	PP; FU (3 months)	No psychotherapeutic treatment at start of study (inclusion criterion); stable intake of antidepressants possible; additional psychotherapeutic treatment during the FU period possible
		PT	CBT	58	15	95	15.7	1										
		actCONT	SPT	20	1	97	15.1	1										

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
44	Lee & Rush (1986)	PT	CBT	15	1	100	27.7	1	0	0	9	1	0	0	Self-report	6	PP; FU (4 months)	No additional treatment at start of study (inclusion criterion); additional treatment during FU period possible
		CONT	WL	15	1	100	27.7	1										
45	Leitenberg et al. (1994)	PT	CBT	7	1	100	26.7	1	0	0	9	1	1	1	Self-report	20	PP; FU (6 months)	No additional treatment at start of study (inclusion criterion); no further info for FU period
		PHARMA	TCA	7	4	100	26.7	1										
		COMBI (PT+PH)	CBT + TCA	7	2	100	26.7	1										
46	Leombruni et al. (2006)	PHARMA	SSRI (CL)	19	5	100	28.7	1	0	1	9	1	1	1	Inter view	12	PP	No intake of antidepressants to treat ED in the past (inclusion criterion)
		PHARMA	SSRI (FL)	18	4	100	26.6	1										
47	McCann et al. (1990)	PHARMA	TCA	15	5	100	n.a.	1	0	1	1	1	1	1	Self-report	12	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	15	2	100	n.a.	1										
48	Mitchell et al. (1989)	PHARMA	NALT	9	0	100	23.7	1	0	1	1	1	0	0	Self-report	3	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	9	2	100	23.7	1										
49	Mitchell et al. (1993)	PT	HI/HE	33	4	100	25.8	1	0	0	9	1	0	0	Self-report	12	PP	No additional treatment at start of study (inclusion criterion)
		PT	HI/LE	41	5	100	25.6	1										
		PT	LI/LE	34	6	100	25.7	1										
		PT	LI/HE	35	5	100	26.4	1										
50	Mitchell et al. (2001)	PHARMA	SSRI	26	1	100	26.6	1	0	0	9	1	0	0	Self-report	16	PP	No additional treatment at start of study (inclusion criterion)
		COMBI (OTH+PH)	SM-CBT+PL	22	1	100	26.8	1										
		COMBI (OTH+PH)	SM-CBT+SSRI	21	2	100	29.3	1										

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
		CONT	PL	22	4	100	35.8	1										
51	Mitchell et al. (2011)	PT	CBT	147	34	n.a.	29.5	1	1	1	9	1	1	1	Inter view	18	PP; FU (12 months)	No psychotherapeutic eating disorder-specific treatment at start of study (inclusion criterion); no further info for FU period
		COMBI (OTH+PT+PH)	stepped care	146	42	n.a.	29.8	1										
52	Mitchell et al. (2002)	PT	IPT	31	10	100	28	1	0	0	9	1	1	1	Inter view	16	PP; FU (6 months)	Sample consists of CBT non-responders (see Agras et al. 2000); no additional treatment at start of study (inclusion criterion); additional treatment during FU period possible
		PHARMA	SSRI/TCA	31	15	100	27.1	1										
53	Nickel et al. (2005)	PHARMA	TOP	30	5	100	21.5	1	1	1	1	0	0	1	Self-report	10	PP	No treatment-specific inclusion criteria
		CONT	PL	30	6	100	21.5	1										
54	Ordman et al. (1985)	PT	CBT	10	0	100	19.8	1	0	0	9	1	0	0	Self-report	20	PP	No treatment-specific inclusion criteria
		CONT	WL	10	0	100	19.8	1										
55	Pope et al. (1983)	PHARMA	TCA	11	2	100	27.9	1	0	1	1	1	0	1	Self-report	6	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	11	1	100	27.6	1										
56	Pope et al. (1989)	PHARMA	TRAZO	23	3	100	25.7	1	0	1	1	1	0	1	Self-report	6	PP	No additional treatment at start of study (inclusion criterion)
		CONT	PL	23	1	100	26.2	1										
57	Poulsen et al. (2014)	PT	PA	34	5	100	25.8	1	0	1	9	1	0	1	Inter view	104	PP (5 months [end CBT]); FU (2 years [end PA])	No psychotherapeutic treatment at start of study (inclusion criterion); during FU period: *for PA:* additional

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
		PT	CBT	36	3	97	25.7	1								20		pharmacological treatment possible (n = 2); *for CBT*: additional psychotherapeutic (n = 11) and pharmacological treatment possible (n = 0)
58	Romano et al. (2002)	PHARMA	SSRI/PL	74	68	99	30.0	1	0	1	1	1	0	1	Self-report	52	PP	No psychotherapeutic treatment at start of study (inclusion criterion)
		PHARMA	SSRI/SSRI	76	63	97	29.5	1										
59	Russel et al. (1988)	PHARMA	d-Fenfluramine	21	8	100	24.3	2	0	1	1	1	1	1	Self-report	12	PP	No treatment-specific inclusion criteria; all patients received supportive psychotherapy in course of study
		CONT	PL	21	9	100	24.3	2										
60	Safer et al. (2001)	PT	DBT	14	2	100	34.0	1	0	0	9	0	1	0	Inter view	20	PP	No additional treatment at start of study (inclusion criterion)
		CONT	WL	15	1	100	34.0	1										
61	Schmidt et al. (2004)	PHARMA	SSRI/SSRI	83	61	100	16.0	1	1	1	1	1	0	1	Inter view	52	PP	No additional treatment at start of study (inclusion criterion)
		PHARMA	SSRI/PL	46	26	100	16.0	1										
		CONT	PL	43	26	100	16.0	1										
62	Schuetzmann et al. (2010)	actCONT	SPT	29	4	100	24.0	1	0	0	9	1	1	1	Inter view	52	PP; FU (12 months)	No psychotherapeutic treatment at start of study (inclusion criterion); no further info for FU period
		SM	GSM-CBT	30	5	100	23.6	1										
63	Stefini et al. (2017)	PT	CBT	39	15	100	18.8	1	1	1	9	1	1	1	Inter view	52	PP; FU (12 months)	No additional treatment at start of study (inclusion

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
		PT	PD	42	9	100	18.6	1										criterion); no additional treatment during FU period
64	Strasser et al. (1992)	PHARMA	TCA	9		100	27.8	1	0	1	1	1	1	1	Self-report	6	PP	No treatment-specific inclusion criteria
		CONT	PL	9		100	24.1	1										
65	Sundblad et al. (2005)	PHARMA	FLUT	12	3	100	29.0	1	0	1	1	1	0	1	Self-report	12	PP	No treatment-specific inclusion criteria; all patients received a minimum of supportive/psychoeducation therapy
		PHARMA	SSRI	18	3	100	26.0	1										
		PHARMA	FLUT+SSRI	12	2	100	25.0	1										
		CONT	PL	14		100	28.0	1										
66	Sundgot-Borgen et al. (2002)	OTH	SPORT	15	3	100	23.0	1	0	0	9	1	1	1	Self-report	16	PP; FU (6 months)	No additional treatment at start of study (inclusion criterion)
		PT	CBT	16	2	100	22.0	1										
		NUTRI	NU	17	0	100	22.0	1										
		CONT	WL	16	1	100	23.0	1										
67	Thackwray et al. (1993)	PT	CBT	16	3	100	31.3	1	0	0	9	1	0	0	Self-report	8	PP; FU (6 months)	No psychotherapeutic treatment at start and one year before study (inclusion criterion): additional treatment after FU assessment offered
		PT	BT	16	3	100	31.3	1										
		actCONT	SPT	16	3	100	31.3	1										
68	Thiels et al. (1998)	SM	GSM-CBT	31	9	n.a.	27.5	1	0	0	9	1	1	1	Inter view	16	PP; FU (6 months - 2 years)	No treatment-specific inclusion criteria; additional treatment during FU period possible
		PT	CBT	31	4	n.a.	28.7	1										
69	Treasure et al. (1994)	SM	SM	55	14	100	25.7	1	0	0	9	1	0	1	Self-report	8	PP	No treatment-specific inclusion criteria
		PT	CBT	28	7	100	26.0	1										
		CONT	WL	27	8	100	26.0	1										

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
70	Ventura et al. (1999)	COMBI (PT+OTH)	CBT+PNR	20	1	100	24.1	1	0	0	9	1	0	0	Self-report	24	PP	No info on treatment-specific inclusion criteria
		COMBI (PT+OTH)	CBT+TNR	20	2	100	24.0	1										
71	Wagner et al. (2013)	SM	WEB-GSM-CBT	83	35	100	24.2	1	0	0	9	1	1	0	Self-report	22	PP; FU (18 Monate)	No behavior therapy treatment at start of study (inclusion criterion); additional treatment during FU period possible
		SM	GSM-CBT	72	43	100	25	1										
72	Walsh et al. (1988)	PHARMA	MAO	31	8	100	26.9	1	0	1	1	1	1	1	Self-report	8	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	31	4	100	27.1	1										
73	Walsh et al. (1991)	PHARMA	TCA	40	9	100	25.7	1	0	1	1	1	1	1	Self-report	6	PP	No intake of psychotropic drugs at start of study (inclusion criterion)
		CONT	PL	38	6	100	24.8	1										
74	Walsh et al. (1997)	COMBI (PT+PH)	CBT-SSRI	23	8	100	26.1	1	0	1	1	1	1	0	Self-report	16	PP	No treatment-specific inclusion criteria
		COMBI (PT+PH)	CBT-PL	25	9	100	25.8	1										
		COMBI (OTH+PH)	SPT-SSRI	22	6	100	28.0	1										
		COMBI (OTH+PH)	SPT-PL	22	6	100	26.9	1										
		PHARMA	SSRI	28	12	100	24.3	1										
75	Walsh et al. (2000)	PHARMA	SSRI	13	0	100	32.0	1	0	1	1	1	1	0	Inter view	8	PP	Sample consists of CBT/IPT non-responders (see Agras et al., 2000); no additional treatment at start of study (inclusion criterion)
		CONT	PL	9	0	100	27.8	1										
76	Wilson et al. (1986)	PT	CR-EP	9	2	100	21.9	1	0	0	9	1	1	0	Self-report	16	PP; FU (6 months)	No treatment-specific inclusion criteria; patients without improvement in the CR

No.	Study	Main category	Sub-category	n	Drop-Out	Gender (%female)	Age	Setting	Q_power	Q_blind1	Q_blind2	Qdim_op	Qdim_met	Q_rosent	Instru-ment	Time pre post	Measurement time point	Notes
		PT	CR	8	2	100	19.2	1										condition received CR-EP before the FU period
77	Wolf et al. (1992)	PT	BT	15	0	100	26.5	1	0	0	9	1	0	0	Self-report	8	PP; FU (1 month)	No treatment-specific inclusion criteria; 1 patient was excluded due to another therapy during the study
		PT	CBT	15	0	100	25.1	1										
		CONT	WL	12	1	100	27.8	1										
78	Zeeck et al. (2009)	COMBI (PT+PT)	CBT + PD (IP)	27	9	91	24.0	2	1	0	9	1	1	0	Inter view	12	PP; FU (3 months)	No treatment-specific inclusion criteria; additional treatment during FU period possible
		COMBI (PT+PT)	CBT + PD(DC)	28	10	96	26.2	3										
79	Zerwas et al. (2016)	PT	WEB-CBT	98	38	98	28.5	5	1	1	9	1	1	1	Inter view	20	PP; FU (12 months)	No psychotherapeutic treatment at start of study, stabile intake of antidepressants possible (inclusion criterion); additional treatment during FU period possible)
		PT	CBT	98	26	98	27.5	1										

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Method report bulimia nervosa

Literature search and study selection

The aim of the guideline revision from 2010 was to check the existing recommendations for the treatment of bulimia nervosa (BN) on the basis of a meta-analysis of randomized controlled trials on the efficacy of psychotherapeutic and pharmacological interventions in adolescent and adult patients with a diagnosis of BN. Therefore, in addition to a manual search in reference lists, viewing recent reviews and meta-analyses together with the anorexia nervosa guideline subgroup, the University Library of Heidelberg was tasked with conducting a systematic literature search for primary literature, initially encompassing the timeframe of all BN publications up to 31.01.2016. Due to a delay in the work on the guidelines, at the end of March 2017, the search was updated to 03.03.2017. The meta-analysis was preregistered in PROSPERO (Svaldi, Schmitz, Tuschen-Caffier, Bauer, & Thaler, 2017).

For coding the studies, the following predetermined inclusion and exclusion criteria were defined. Predefined inclusion criteria for entry in the meta-analysis were (1) randomized controlled trials (RCTs) of adolescent and adult populations, (2) studies in patients with a formal diagnosis of BN, (3) studies with an assessment period of eating disorder pathology as outcome measure of at least one week, (4) studies with sufficient data to calculate effect sizes and (5) studies with multiple patient groups for which separate data are available for patients with BN. The following studies were excluded: (1) unpublished studies, dual publications of the same trials and (3) RCTS with a sample size < 10.

The studies were first roughly viewed with regard to the determined inclusion and exclusion criteria by two independent raters (two psychologists with an MSc and experience in the area of eating disorder research). Subsequently, a total of 79 RCTs with 185 arms (55 psychotherapeutic interventions, 41 pharmacological interventions, 21 combination interventions [pharmacotherapy and psychotherapy], 10 self-help interventions, 3 nutrition-specific interventions, 9 other non-pharmacological interventions, 46 non-active control groups (waitlist/placebo) were coded and evaluated by the two raters. Study coding and evaluation of study quality were undertaken on the basis of the coding scheme used in the first edition in a slightly modified form. The modification referred to the specification of information about abstinence (abstinence from compensatory behaviors, abstinence from binge eating, abstinence from DSM criteria, abstinence time period) and the introduction of a general "purging" variable if no specific information about the individual compensatory behaviors (vomiting, laxative abuse etc.) was provided. Furthermore, the follow-up effects of the interventions were coded according to the same scheme as the post-effects and included in the analysis. In the case of discrepancies between the raters, consensus was reached following discussion. Prior to the coding procedure, the two raters underwent intensive training in handling the coding scheme. In total, 32 studies (41%) were coded by both raters. The inter-rater reliability was determined using Cohen's Kappa (κ) for categorical variables and intra-class correlations (ICC) for continuous variables. The calculated coefficients amount to a mean of κ/ICC = .763 and ICC = .997 (95% confidence interval .996 - .997; $p<.001$). Discrepant codings were resolved by consensus. Due to the good inter-rater reliability, the remaining 47 studies (59%) could be coded by only one of the two respective raters.

The 79 studies were assigned to 15 categories. Psychotherapies were differentiated into (cognitive) behavioral therapy, dialectical behavior therapy, psychodynamic therapies, interpersonal therapy and family-based therapy. Moreover, there was a category for self-help and a category for "other non-pharmacological interventions". The latter encompasses nutrition-based interventions as an independent subgroup as well as a residual category "other interventions" containing those RCTs which could not be allocated to one particular therapy direction or school. Furthermore, there was the category "psychotherapeutically oriented combination therapies", subsuming RCTs which examined integrative approaches in terms of their efficacy.

With regard to pharmacotherapy, a distinction was made between tricyclic antidepressants (TCA), monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitors (SSRI) and a category "other antidepressants and other medications". Furthermore, there was a category containing combination therapy (combination of pharmacotherapy and psychotherapy) as well as a residual category "other combination therapies". The latter subsumes combination therapies consisting of in part non-psychotherapeutic interventions and stepped-care approaches combined with pharmacotherapy.

Primary outcome measures for the meta-analysis were the absence of diagnostic criteria after completing the intervention, thus the absence of binge eating, the absence of purging behavior and the absence of all diagnostic criteria of the DSM/ICD. Furthermore, the severity of illness was assessed in continuous variables, thus the frequency of binge eating episodes, of vomiting and of laxative consumption. For the evaluation as standardized effect sizes, the two compensatory measures were integrated into one variable "compensatory behavior". Secondary outcome measures were general eating pathology and depression. All available self-reported data on eating pathology (EDE, EDI, EAT total scores) were summarized into one variable in order to obtain an integrated measure and to be able to compare more studies. For depressive symptoms, data on the BDI total score were used.

When determining meta-analytic effect sizes, the main focus was on pre-post changes, and wherever possible in a control group comparison. Additionally, the sustainability of the interventions was examined with respect to the described dependent variables using follow-up data (> month after the end of therapy).

If possible, intervention effects were evaluated using a pre-post between-group design. In the absence of data for the pre-time point or invariance (generally 100% prevalence of diagnostic criteria at the start), between-group comparisons at the post time point were used. If there were no data from non-active control groups, pre-post change effects for the examined cohort were calculated. The same approach was used to determine sustainability using follow-up data. Generally speaking, from three analyzable studies onwards, mixed models with random effects were calculated; in the case of two studies, models with fixed effects were calculated. If there was a sufficient number of studies, funnel plots were constructed and influence statistics calculated in order to estimate publication bias and/or be able to identify extreme values. If indicated, leave-one-out re-analyses were conducted to estimate the robustness of effects. If only one study was available, the findings of this study were mentioned and the database was explicitly pointed out. The presentation of the meta-analytic results is structured into post-control-group (CG) comparison, pre-post and follow-up findings, in order to facilitate the determination of evidence levels and sustainability.

In the revised version of the guidelines, the text and the evidence tables were revised and recommendations were checked regarding whether – in relation to evidence levels among other factors – they can remain unchanged or whether changes need to be undertaken. Recommendations were made based on the results of the meta-analysis. In the case of a lack of empirical evidence, good clinical practice was developed following discussion in the expert group. Upon consensus in the expert group, some of these (GCP) recommendations were formulated as "We recommend" or "We suggest" recommendations due to their high clinical relevance.
The individual chapters were revised by members of the working group. Represented in the working group were experts from the area of inpatient and outpatient treatment for children, adolescents and adults. Text, evidence evaluation and recommendations were discussed and approved within telephone conferences and meetings on the basis of previously sent documents. For the evaluation of the meta-analysis, a methodologist was included.

Joint systematic literature search for the chapters Bulimia nervosa (and Anorexia nervosa): Conducted by: Mr Maurizio Grilli M.A.L.I.S. Library for the Medical Faculty of Mannheim, University of Heidelberg; maurizio.grilli@medma.uni-heidelberg.de

Initial literature search up to 1.11.2016, then supplementary search up to end of February 2017.

Determination of the relevant aspects of the theme

P_1	Anorexia Nervosa
P_2	Bulimia Nervosa
S	Filter document type

Strategy

1	P	Keywords (with subheadings in PubMed)
2	S	
3	P AND S	
4	4 AND time filter	Anorexia from November 2005 For the bulimia search, it is very easy to filter out the publications before 2000 by ordering the hits according to publication year in EndNote in the central area (mouse-click on "Year" in the column of the same name).

Notes
P1 and P2 were separately combined with S. The respective results were also, as desired, saved in separate EndNote libraries.

For the anorexia nervosa search, a limitation from 01.11.2005 was always undertaken. If the filter function does not allow day and month to be entered, the whole year of 2005 was set as filter.
The respective number of hits refers to the number before deduplification in EndNote.

Queried databases

- PubMed
- Cochrane Library
- Web of Science Core Collection
- Cinahl
- PsychInfo
- ClinicalTrial.gov (study register)
- ICTRP (WHO study register)

PubMed
P1

"Anorexia/diet therapy"[Mesh] OR "Anorexia/drug therapy"[Mesh] OR "Anorexia/rehabilitation"[Mesh] OR "Anorexia/therapy"[Mesh] OR
"Anorexia Nervosa/diet therapy"[Mesh] OR "Anorexia Nervosa/drug therapy"[Mesh] OR "Anorexia Nervosa/rehabilitation"[Mesh] OR "Anorexia Nervosa/therapy"[Mesh]

OR

(anorexia[tiab] OR anorexic*[tiab]) AND (Treat*[tiab] OR Therap*[tiab] OR "disease management"[tiab] OR rehabilitation[tiab])

P2

"Bulimia/diet therapy"[Mesh] OR "Bulimia/drug therapy"[Mesh] OR "Bulimia/rehabilitation"[Mesh] OR "Bulimia/therapy"[Mesh] OR
"Bulimia Nervosa/diet therapy"[Mesh] OR "Bulimia Nervosa/drug therapy"[Mesh] OR "Bulimia Nervosa/rehabilitation"[Mesh] OR

"Bulimia Nervosa/therapy"[Mesh]

OR

(Bulimia*[tiab] OR
bulimic*[tiab])
AND
(Treat*[tiab] OR
Therap*[tiab] OR
"disease management"[tiab] OR
rehabilitation[tiab])

S

"Randomized Controlled Trials as Topic"[Mesh] OR
"Randomized Controlled Trial" [Publication Type] OR
"Controlled Clinical Trials as Topic"[Mesh] OR
"Controlled Clinical Trial" [Publication Type] OR
"Clinical Trials as Topic"[Mesh] OR
"Clinical Trial" [Publication Type] OR
Clinical trial*[tiab] OR
“Clinical studies”[tiab] OR
“Clinical study”[tiab] OR
"Randomized Controlled Trials as Topic"[Mesh] OR
"Randomized Controlled Trial" [Publication Type] OR
"Random Allocation"[Mesh] OR
"Double-Blind Method"[Mesh] OR
"Single-Blind Method"[Mesh] OR
single blind*[tiab] OR
double blind*[tiab] OR
triple blind*[tiab] OR
treble blind*[tiab] OR
single mask*[tiab] OR
double mask*[tiab] OR
triple mask*[tiab] OR
treble mask*[tiab] OR
“blind single”[tiab] OR
“blind double”[tiab] OR
Latin square*[tiab] OR
"Placebos"[Mesh] OR
Placebo*[tiab] OR
Random*[tiab] OR
"Research Design"[Mesh] OR
"Comparative Study" [Publication Type] OR
"Evaluation Studies" [Publication Type] OR
"Evaluation Studies as Topic"[Mesh] OR
"Follow-Up Studies"[Mesh] OR

"Prospective Studies"[Mesh] OR "Cross-Over Studies"[Mesh]

End

	Complete search query
P1	((("Anorexia/diet therapy"[Mesh] OR "Anorexia/drug therapy"[Mesh] OR "Anorexia/rehabilitation"[Mesh] OR "Anorexia/therapy"[Mesh] OR "Anorexia Nervosa/diet therapy"[Mesh] OR "Anorexia Nervosa/drug therapy"[Mesh] OR "Anorexia Nervosa/rehabilitation"[Mesh] OR "Anorexia Nervosa/therapy"[Mesh]))) OR (((anorexia[tiab] OR anorexic*[tiab]) AND (Treat*[tiab] OR Therap*[tiab] OR "disease management"[tiab] OR rehabilitation[tiab])))
P2	((("Bulimia/diet therapy"[Mesh] OR "Bulimia/drug therapy"[Mesh] OR "Bulimia/rehabilitation"[Mesh] OR "Bulimia/therapy"[Mesh] OR "Bulimia Nervosa/diet therapy"[Mesh] OR "Bulimia Nervosa/drug therapy"[Mesh] OR "Bulimia Nervosa/rehabilitation"[Mesh] OR "Bulimia Nervosa/therapy"[Mesh]))) OR (((Bulimia*[tiab] OR bulimic*[tiab]) AND (Treat*[tiab] OR Therap*[tiab] OR "disease management"[tiab] OR rehabilitation[tiab])))
S	("Randomized Controlled Trials as Topic"[Mesh] OR "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [Publication Type] OR Clinical trial*[tiab] OR “Clinical studies”[tiab] OR “Clinical study”[tiab] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Randomized Controlled Trial" [Publication Type] OR "Random Allocation"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR single blind*[tiab] OR double blind*[tiab] OR triple blind*[tiab] OR treble blind*[tiab] OR single mask*[tiab] OR double mask*[tiab] OR triple mask*[tiab] OR treble mask*[tiab] OR “blind single”[tiab] OR “blind double”[tiab] OR Latin square*[tiab] OR "Placebos"[Mesh] OR Placebo*[tiab] OR Random*[tiab] OR "Research Design"[Mesh] OR "Comparative Study" [Publication Type] OR "Evaluation Studies" [Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Cross-Over Studies"[Mesh])

Cochrane Library

P1

[mh "Anorexia"/DH] OR [mh "Anorexia"/DT] OR [mh "Anorexia"/RH] OR [mh "Anorexia"/TH] OR
[mh "Anorexia Nervosa"/DH] OR [mh "Anorexia nervosa"/DT] OR [mh "Anorexia nervosa"/RH] OR [mh "Anorexia nervosa"/TH]

OR

(anorexia OR anorexic*):ti,ab,kw AND (Treat* OR Therap* OR "disease management" OR rehabilitation):ti,ab,kw

P2

[mh "Bulimia"/DH] OR [mh "Bulimia"/DT] OR [mh "Bulimia"/RH] OR [mh "Bulimia"/TH] OR
[mh "Bulimia Nervosa"/DH] OR [mh "Bulimia nervosa"/DT] OR [mh "Bulimia nervosa"/RH] OR [mh "Bulimia nervosa"/TH]

OR

(Bulimia* OR bulimic*):ti,ab,kw AND (Treat* OR Therap* OR "disease management" OR rehabilitation):ti,ab,kw

End

	Complete search query
P1	[mh Anorexia/DH] or [mh Anorexia/DT] or [mh Anorexia/RH] or [mh Anorexia/TH] or [mh "Anorexia Nervosa"/DH] or [mh "Anorexia nervosa"/DT] or [mh "Anorexia nervosa"/RH] or [mh "Anorexia nervosa"/TH] OR (anorexia or anorexic*):ti,ab,kw and (Treat* or Therap* or "disease management" or rehabilitation):ti,ab,kw
P2	[mh Bulimia/DH] or [mh Bulimia/DT] or [mh Bulimia/RH] or [mh Bulimia/TH] or [mh "Bulimia Nervosa"/DH] or [mh "Bulimia nervosa"/DT] or [mh "Bulimia nervosa"/RH] or [mh "Bulimia nervosa"/TH] OR (Bulimia* or bulimic*):ti,ab,kw and (Treat* or Therap* or "disease management" or rehabilitation):ti,ab,kw

Notes

In this database, the study filter is not necessary. In the Cochrane Library, only systematic literature reviews and clinical studies are included.

Web of Science Core Collection

P1

(anorexia OR anorexic*) AND (Treat* OR Therap* OR "disease management" OR rehabilitation)

P2

(Bulimia* OR bulimic*) AND (Treat* OR Therap* OR "disease management" OR rehabilitation)

S

"Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR "single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*

End

	Complete search query
P1	TS=((anorexia OR anorexic*) AND (Treat* OR Therap* OR "disease management" OR rehabilitation))

	Indexes=SCI-EXPANDED, SSCI Timespan=2005-2016
S	TS=("Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR "single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*) Indexes=SCI-EXPANDED, SSCI Timespan=2005-2016
P2	**TOPIC:** ((Bulimia* OR bulimic*) AND (Treatment* OR Therap* OR "disease management" OR rehabilitation))
S	**TOPIC:** ("Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR "single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*)

CINAHL

P1

(anorexia OR
anorexic*)
AND
(Treat* OR
Therap* OR
"disease management" OR
rehabilitation)

P2

(Bulimia* OR
bulimic*)
AND
(Treat* OR
Therap* OR
"disease management" OR
rehabilitation)

S

"Clinical trial*" OR
“Clinical studies” OR
“Clinical study” OR
"single blind*" OR
"double blind*" OR
"triple blind*" OR
"treble blind*" OR
"single mask*" OR
"double mask*" OR
"triple mask*" OR
"treble mask*" OR
“blind single” OR

“blind double” OR "Latin square*" OR Placebo* OR Random*

End

	Complete search query
P1	(anorexia OR anorexic*) AND (Treatment* OR Therap* OR "disease management" OR rehabilitation)
P2	(Bulimia* OR bulimic*) AND (Treatment* OR Therap* OR "disease management" OR rehabilitation)
S	"Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR "single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*

PsychInfo
P1

(DE "Anorexia Nervosa" OR anorexia OR anorexic*) AND (Treat* OR Therap* OR "disease management" OR rehabilitation)

P2

(DE "Bulimia" OR Bulimia* OR bulimic*) AND (Treat* OR Therap* OR "disease management" OR rehabilitation)

S

"Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR

"single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*

End

	Complete search query
P1	(DE "Anorexia Nervosa" OR anorexia OR anorexic*) AND (Treatment* OR Therap* OR "disease management" OR rehabilitation)
P2	(DE "Bulimia" OR Bulimia* OR bulimic*) AND (Treatment* OR Therap* OR "disease management" OR rehabilitation)
S	"Clinical trial*" OR “Clinical studies” OR “Clinical study” OR "single blind*" OR "double blind*" OR "triple blind*" OR "treble blind*" OR "single mask*" OR "double mask*" OR "triple mask*" OR "treble mask*" OR “blind single” OR “blind double” OR "Latin square*" OR Placebo* OR Random*

Clinical Trial Gov

http://www.clinicaltrials.gov/

P1

(anorexia OR anorexic) AND (Treatment OR Therapy OR "disease management" OR rehabilitation)

P2

(Bulimia OR bulimic) AND (Treatment OR Therapy OR "disease management" OR rehabilitation)

End

	Complete search query
P1	(anorexia OR anorexic) AND (Therapeutic OR Treatment OR Therapy OR "disease management" OR rehabilitation) AND ("11/01/2005" : MAX) [FIRST-RECEIVED-DATE]
P2	Therapeutic OR Treatment OR Therapy OR "disease management" OR rehabilitation | bulimia

Notes

The time filter is not necessary in this database for bulimia, as datasets older than 2000 do not occur in this case. For anorexia, the time filter is used as usual. As this database only contains clinical trials, filters for studies are not used.

ICTRP

http://www.who.int/ictrp/en/

P1

(anorexia OR
anorexic)
AND
(Therapeutic OR
Treatment OR
Therapy OR
disease management OR
rehabilitation)

P2

(Bulimia OR
bulimic)
AND
(Therapeutic OR
Treatment OR
Therapy OR
disease management OR
rehabilitation)

End

Complete search query

anorexia OR anorexic [search field condition]
AND
Therapeutic OR Treatment OR Therapy OR disease management OR rehabilitation [search field intervention]

Bulimia OR bulimic [search field condition]

AND
Therapeutic OR Treatment OR Therapy OR disease management OR rehabilitation [search field intervention]

Notes
Studies are not filtered as this database only contains clinical trials.
Due to the low number of hits, no time filter is applied.

VI. Binge-Eating Disorder

Anja Hilbert, Stephan Herpertz, Anette Kersting, Reinhard Pietrowsky, Brunna Tuschen-Caffier, Silja Vocks[16]

1. Clinical presentation

1.1. Symptoms of binge-eating disorder

Persons with a diagnosis of binge-eating disorder (BED) suffer from regularly occurring binge-eating episodes. Characteristic for such an episode is to eat a considerably larger amount of food than most people would eat under similar circumstances, and within a discrete period of time (e.g. within two hours) (American Psychiatric Association, APA, 2013). To decide, in a concrete case, whether or not a binge-eating episode is present, the context within which eating occurs is recommended to be considered. For instance, most people eat substantially more at a party buffet than at regular mealtimes. Thus, according to the DSM-5 criteria, the amount of food eaten may be evaluated as objectively large in one context (e.g. during a regular mealtime), while this does not apply in a different context (e.g. at a party buffet).

Binge-eating episodes can be triggered by negative affect; this has been meta-analytically shown in various diary studies ("ecological momentary assessment") (Haedt-Matt & Keel, 2011a). However, affect can also be more negative after a binge-eating episode than prior to the episode (Haedt-Matt & Keel, 2011a). In the sense of the "trade-off" theory, this can be explained such that the function of a binge-eating episode may lie in swapping one particular emotion for another (possibly also negative) emotion (Kenardy, Arnow & Agras, 1996). This theory has been supported, among others, by field studies showing that guilt, anger, fear and sadness are reduced over the course of a binge-eating episode (Berg et al., 2013). Another meta-analysis indicated that persons with BED estimate their feeling of hunger directly before a binge-eating episode as significantly greater than outside of binge-eating episodes (Haedt-Matt & Keel, 2011b).

1.2. Associated psychological problems

Negative body image. Empirical findings suggest that persons with BED show an overvaluation of shape and weight as well as clinically relevant shape and weight concerns, or dissatisfaction with shape and weight, which can be relevant to self-esteem and can precede binge-eating episodes (Ahrberg, Trojca, Nasrawi & Vocks, 2011; Grilo, Masheb & White, 2010; Goldschmidt, Wall, Loth, Bucchianeri & Neumark-Sztainer, 2014; Stein et al., 2007). The overvaluation of shape and weight is further associated with a more pronounced eating disorder

[16] Ulrich Hagenah and Harriet Salbach-Andrae were coauthors of a previous version of this chapter.

psychopathology and psychological burden, and is negatively related to treatment outcome (Grilo, 2013).

Restrictive eating behavior. Several diary studies have shown that restrictive eating behavior ("dietary restraint") promotes the occurrence of binge-eating episodes (Haedt-Matt & Keel, 2011b). In this regard, the likelihood of a binge-eating episode increases with the duration of attempted dietary restriction (Holmes, Fuller-Tyszkiewicz, Skouteris & Broadbent, 2014). On the neural level, food deprivation may be accompanied by an increased activation of cortical areas associated with attention, reward and motivation (Stice, Burger & Yokum, 2013).

Low self-esteem. BED is frequently associated with low self-esteem. For instance, it was shown that persons with overweight and BED have lower implicit and explicit self-esteem than normal-weight persons without a diagnosis of a mental disorder (Brauhardt, Rudolph & Hilbert, 2014). Moreover, low self-esteem in persons with BED is also related to a pronounced overvaluation of shape and weight (Grilo, White & Masheb, 2012). However, a recent review (Stice, 2016) showed that most prospective studies did not find a causal relationship between negative self-esteem and the development of eating disorder symptoms.

Interpersonal problems. Furthermore, interpersonal problems are characteristic for BED and are associated with greater symptomatology (Blomquist, Ansell, White, Masheb & Grilo, 2012; Ivanova et al., 2015). Interpersonal problems are also linked to an earlier onset of the disorder (Blomquist et al., 2012). Moreover, a higher degree of interpersonal problems is associated with a lower response to psychotherapy (Hilbert et al., 2007).

Dysfunctional emotion regulation. On the basis of self-reports, it was found that persons with a diagnosis of BED, like persons with a diagnosis of another mental disorder, more frequently use dysfunctional strategies and more rarely use functional strategies in dealing with negative feelings (e.g. Svaldi, Griepenstroh, Tuschen-Caffier & Ehring, 2012). Experimental studies have also confirmed that dysfunctional emotion regulation in persons with BED is associated with eating disorder symptoms (e.g. increased eating) (e.g. Svaldi, Tuschen-Caffier, Trentowska, Caffier & Naumann, 2014). Recent findings show that in persons with BED who show a high degree of dysfunctional emotion regulation strategies, the overvaluation of shape and weight is also strongly pronounced (Harrison, Mitchison, Rieger, Rodgers & Mond, 2016).

1.3. Diagnostic criteria

BED is still a relatively new diagnostic category, which was initially introduced as a research diagnosis in the Diagnostic and Statistical Manual of Mental Disorders DSM-IV (APA, 1994). Research findings have shown that BED is a clinically significant mental disorder which is delimitable from other eating disorders, e.g. bulimia nervosa (BN), which justifies a separate clinical diagnosis (Wonderlich, Gordon, Mitchell, Crosby & Engel, 2009). Therefore, in the current version of the DSM, BED has been included as a clinical diagnosis (307.51 in the DSM-

5, APA, 2013; 50.8 in the International Classification of Diseases, ICD-10, World Health Organization, WHO, 1992).

To diagnose BED according to the DSM-5 (APA, 2013), the following criteria need to be fulfilled:

A. Recurrent episodes of binge eating, accompanied by a sense of lack of control over eating
B. Association of binge-eating episodes with at least three of five behavioral characteristics (eating more rapidly than normal; eating until feeling uncomfortably full; eating large amounts of food when not being hungry; eating alone because of feeling embarrassed; feeling disgusted with oneself, guilty or depressed after a binge-eating episode)
C. Marked distress regarding binge eating
D. Frequency of binge eating: at least once a week for three months
E. Binge-eating episodes are not followed by regular use of inappropriate compensatory behavior and do not occur exclusively in the context of BN or anorexia nervosa (AN).

The minimum severity of BED is determined based on the frequency of binge-eating episodes. The level of severity may be considered to be higher to reflect other symptoms and the degree of functional disability (mild: 1-3 episodes per week; moderate: 4-7 episodes per week; severe: 8-13 episodes per week; extreme: 14 or more episodes per week).

Partial remission vs. full remission. If the number of binge-eating episodes previously met the diagnostic criterion (at least one binge-eating episode per week for three months) but fewer episodes currently occur, the DSM-5 speaks of partial remission. If all diagnostic criteria were previously met and are no longer present, BED is seen as being in full remission.

Other classifications of eating disorder symptoms. If a person fulfills some but not all criteria of BED, classification can be made through the category Other Specified Feeding or Eating Disorders (307.59 and F50.8) by indicating the disorder concerned, for example BED with low frequency and/or limited duration. If insufficient information is available for a more precise diagnosis or the clinician does not wish to record this, the category Unspecified Feeding or Eating Disorder (307.50 and F50.8) can be used in the classification.

In the still current version of the classification system of the World Health Organization (ICD-10), BED is only classified within the general category of other eating disorders (F50.8) (WHO, 1992). In the revised version which is currently in preparation (ICD-11), it is highly likely that BED will also be included as its own diagnosis.

1.4. Etiology and maintenance

The etiology of BED is not yet sufficiently understood. However, it is a complex mental disorder which is presumably multifactorial in nature, and various mechanisms are involved in its development, triggering and maintenance.

Predisposing factors. A greater prevalence of BED within families can be interpreted as suggesting that genetic factors are involved in the development of BED. Recent molecular genetic studies in BED point to changes in dopaminergic and opioid neurotransmitter networks, which are associated with binge-eating episodes (Kessler, Hutson, Herman & Potenza, 2016). However, overweight or obesity in childhood also appears to be a relevant predictor for BED (Fairburn et al., 1998; Hilbert et al., 2014). The psychosocial risk factors include general vulnerability factors such as critical life events (e.g. separation of parents), neglect, stress at school, depressiveness or shyness as well as eating disorder-specific factors such as restrictive eating behavior, emotional eating, restrictive parental feeding practices, a higher body weight, dissatisfaction with one's shape as well as a pronounced thinness ideal and shape- and weight-related criticism (Fairburn et al., 1998; Hartmann, Czaja, Rief & Hilbert, 2012; Hilbert et al., 2014). Furthermore, compared to persons without a mental disorder diagnosis, persons with a diagnosis of BED more frequently report experiences of sexual and physical abuse (Fairburn et al., 1998; Hilbert et al., 2014). With regard to these findings, it should be kept in mind that despite the systematic interview methods used for these investigations, retrospective reports were gathered, which can be subject to memory and reporting biases. Further individual factors which might be involved in the etiology of BED and which have been neuropsychologically or neurophysiologically examined are problems in the area of executive functions, which affect decision-making behavior, impulse control and action planning, against the background of an altered function in the prefrontal and orbitofrontal cortex as well as in the insula and striatum (Kessler et al., 2016; Kittel, Brauhardt & Hilbert, 2015). Also for these studies, causality has not been clearly established.

Triggering factors. Study findings suggest that the onset of BED is preceded by a series of stressors, which might represent triggering factors for the development of the disorder (Hartmann, Czaja et al., 2012; Pike et al., 2006). In this regard, concerns about shape and weight seem to be especially relevant for the development of eating disorders. In a prospective longitudinal study, girls with a high degree of dissatisfaction with their body had a much higher risk of developing an eating disorder, including BED, over the course of eight years compared to girls with a low level of body dissatisfaction (Stice, Marti & Durant, 2011).

Maintaining factors. For the direct triggering of binge eating in BED, negative mood has been shown to be a preceding factor; binge-eating episodes can contribute to an improvement in mood (Haedt-Matt & Keel, 2011b). In addition, the exposure to food is also important for eliciting binge eating. For instance, experimental studies have shown that persons with overweight and BED ate significantly more when a larger amount of food was available. Neurophysiological findings point to an increased appetitive value of foods for persons with BED (Schienle, Schäfer, Hermann & Vaitl, 2009). Problems in the area of executive functions can also be relevant for the maintenance of BED. For instance, binge eating is more likely when persons with BED favor a reward-oriented decision-making behavior, show a tendency for impulsive behavior and generate fewer effective and specific problem-solving strategies (Kittel et al., 2015). Moreover, the environmental factors that may maintain BED include stressors

such as interpersonal conflicts or exposure to weight and shape (Hilbert & Tuschen-Caffier, 2007; Stein et al., 2007).

1.5. Differential diagnosis

Like BED, BN and AN of the binge-eating/purging type are characterized by binge-eating episodes. According to the DSM-5 (APA, 2013), in the differential diagnosis of BED and these two other eating disorders, it should be taken into account that the compensatory strategies that are anchored in the diagnostic criteria for BN and AN binge-eating/purging type (e.g. self-induced vomiting, intake of laxatives and diuretics, use of enemas as well as excessive exercise) do not regularly occur in BED. Furthermore, in contrast to AN and BN, BED is associated with a less severe and enduring restrictive eating behavior employed for the purpose of weight loss (APA, 2013). Additionally, BED needs to be differentiated from affective disorders such as major depression or bipolar disorder, as an increased appetite and increased food consumption, including binge eating with a sense of loss of control over eating, can also occur in these disorders. Likewise, BED needs to be delineated from personality disorders, especially borderline personality disorder, as these can also be accompanied – among others – by impulsive behavior including binge eating. According to the DSM-5, if the diagnostic criteria for affective disorders and borderline personality disorder are fulfilled, these disorders can also be diagnosed in addition to BED, as they are not mutually exclusive (in contrast to the eating disorder diagnoses). Disordered eating behavior can also occur in certain neurological or other medical diseases (e.g. Prader-Willi syndrome, Kleine-Levin syndrome etc.); however, in these cases, the other features of the BED diagnostic criteria are lacking.

1.6. Comorbidity

Comorbidity with mental disorders. Compared to the general population, persons with BED suffer from a higher rate of diagnosed mental disorders in addition to BED. Overall, more than 70% of persons with BED show at least one comorbid mental disorder (Keski-Rahkonen & Mustelin, 2016). This predominantly includes affective disorders such as major depression and bipolar disorder as well as the various anxiety disorders (e.g. generalized anxiety disorder, panic disorder and diverse phobias). Further, although evidently more rarely occurring, comorbid disorders are substance abuse disorder, posttraumatic stress disorder, body dysmorphic disorder and the various personality disorders (Kessler et al., 2013). Moreover, there are indications that persons with BED show increased suicidality, even after controlling for the presence of depressive symptoms (Welch et al., 2016). In this respect, an increased impulsivity is discussed a possible factor underlying both BED and increased suicidality. The psychological problems and/or comorbid disorders occur more frequently in persons with BED than in persons without BED but with a comparable body weight, meaning that the increased rate of further mental disorders, besides possible comorbid overweight or obesity, also appears to be associated with higher severity of BED (e.g. Welch et al., 2016).

Comorbidity with obesity. Obesity is a condition characterized by an excessive accumulation of fatty tissue in the body; it does not reveal anything about etiology, for instance in the sense of an eating disorder. According to the guidelines of the German Obesity Society (DAG; 2014), body mass index (BMI) is the foundation for weight classification. BMI is the ratio of weight to the square of height (kg/m²). Overweight is defined as a BMI of 25 – 29.9 kg/m^2, obesity as a BMI ≥ 30 kg/m^2. Within the overall population of persons with obesity, especially in clinical practice, a subgroup of persons can be discerned in whom psychological problems and disorders lead to a change in eating and exercise behavior, the consequence of which is a sustained positive energy balance (Herpertz, 2008).

In persons with obesity who seek a behavioral weight loss treatment (clinical populations), the prevalence of BED is estimated at 20 to 30% (de Zwaan, 2002; Treasure, Claudino & Zucker, 2010), and the likelihood for the presence of BED appears to increase with the level of the BMI (Hay, 1998; Telch, Agras & Rossiter, 1988). The prevalence of BED in persons with obesity prior to bariatric surgery lies at around 15 to 30% (Dawes et al., 2016; de Zwaan et al., 2002; Engel, Mitchell, de Zwaan & Steffen, 2012; Herpertz & de Zwaan, 2015). Studies on the prevalence of obesity in samples of persons with BED have found prevalence rates between 65% and 70% (Grucza, Przybeck & Cloninger, 2007; Striegel-Moore et al., 2001; Villarejo et al., 2012). According to a study by Kessler et al. (2013) in over 23,000 persons, 32.8% to 41.7% of persons with BED were classified as obese, while approx. 16% of persons without BED were classified as obese. Thus, there appears to be a close link between obesity and BED, although it is not yet clear whether BED is a cause or a consequence of overweight and obesity (Tanofsky-Kraff et al., 2013). The assumption of a monocausal pathogenesis of obesity in persons with BED, namely that weight gain, culminating in overweight and obesity, is the sole consequence of hypercaloric eating behavior during binge-eating episodes, has not been empirically proven.

The observation that in BN and subgroups of AN, binge-eating episodes are almost always preceded by hypocaloric eating behavior (e.g. fasting), led to the hypothesis of restrictive eating behavior as an important pathomechanism in the genesis of eating disorder symptoms (Andrés & Saldana, 2014; Fairburn, Cooper, Doll & Davies, 2005; Fairburn & Harrison, 2003; Jacobi, Hayward, de Zwaan, Kraemer & Agras, 2004), although restrictive eating behavior appears to be less pronounced in BED than in BN (Roberto, Grilo, Masheb & White, 2010). In contrast to persons with obesity without BED, the food and energy intake in persons with obesity and BED appears to be greater, both in general and specifically on days without binge-eating episodes (Dingemans, Bruna & van Furth, 2002). The degree of psychopathology is more strongly associated with the severity of the eating disorder than with BMI (Fairburn et al., 1998).

Since the inclusion of BED within the research criteria in the DSM-IV (APA, 1994), numerous studies have found differences between persons with obesity with and without BED not only on the behavioral level (eating behavior, binge-eating episodes), but also with regard to comorbidity with Axis I and II mental disorders, dysfunctional cognitions regarding shape and weight etc. (Mitchell, Devlin, de Zwaan, Crow & Peterson, 2008; Schag, Schönleber, Teufel, Zipfel & Giel, 2012). Latner and Clyne (2008) as well as Tanofsky-Kraff and colleagues (2013)

describe that compared to persons with obesity without BED, persons with obesity and BED show a greater dissatisfaction with their own body, lower self-esteem, and lower quality of life.

Depressive disorders, anxiety disorders and phobic disorders, as well as a harmful use of alcohol and alcohol addiction are frequent comorbid disorders in persons with obesity and BED (Bulik, Sullivan & Kendler, 2002; Fandiño et al., 2010; Reichborn-Kjennerud, Bulik, Sullivan, Tambs & Harris, 2004). Moreover, persons with obesity and BED suffer more frequently from a comorbid personality disorder, with reported prevalence rates ranging between 7.5% and 30% (Gerlach, Loeber & Herpertz, 2016). According to Picot and Lilenfeld (2003), comorbid personality disorders act as predictors for the frequency of binge-eating episodes; however, from the majority of the studies, it is not possible to deduce an influence of comorbid personality disorders on the treatment outcome of BED (Gerlach et al., 2016).

In the long term, persons with obesity and BED appear to show a lower weight loss in behavioral weight loss programs than persons with obesity without BED (Wilson, Wilfley, Agras & Bryson, 2010). The assumption that an improvement in psychological symptoms as well as eating disorder symptoms is associated with weight loss has not been confirmed in the majority of studies (Brownley et al., 2016; Vocks et al., 2010). In the long term, the successful treatment of BED shows only marginal effects with regard to weight trajectory (Dingemans, Bruna & van Furth, 2002; Vocks et al., 2010), meaning that it is likely that other factors, such as hypercaloric eating behavior, also between the binge-eating episodes, have a decisive influence on weight (see section 2.1 “Treatment goals”).

For persons with obesity class III (BMI $\geq$ 40 kg/m^2) and class II (BMI 35 – 39.9 kg/m^2) with chronic somatic diseases, obesity surgery is the method of choice (DAG, 2014). Persons with BED prior to surgery carry a greater risk of problematic eating behavior post-surgery (Niego, Kofman, Weiss & Geliebter, 2007; Opozda, Chur-Hansen & Wittert, 2016), which is in turn associated with a lower weight loss or greater weight gain. Not least due to the changed anatomical, but also frequent neurohormonal changes following the operation, the number of binge-eating episodes decreases substantially. Persons generally no longer consume objectively large amounts of food, meaning that a binge-eating episode rarely occurs. Pre-operative binge-eating episodes often lead to “grazing” (i.e. consumption of small amounts of food distributed over the day without feelings of hunger; Colles, Dixon & O'Brien, 2008). After the operation, some persons continue to feel a loss of control over eating subjectively (or also objectively) large amounts of food, which is termed “loss of control eating” (Colles et al., 2008; Niego et al., 2007; Opozda et al., 2016). In a minority of persons, the loss of control eating occurs for the first time after the operation. Those with loss of control eating and grazing show a lower weight loss post-operatively and report more psychological stress than those without disordered eating behavior. When considering the relation of pre- and post-operative eating behavior in their predictive function for postoperative weight course, the postoperative eating behavior is substantially more meaningful (Opozda et al., 2016). The question of which persons will re-develop binge eating and in which persons binge eating will remain absent in the long term is difficult to answer from a pre-operative perspective (Herpertz & de Zwaan, 2015). Following an initial weight loss, in the majority of persons, a weight increase is observed one to two years

after the operation, which generally reaches a weight plateau. Not uncommonly, the affected persons perceive this weight gain with great anxiety. The consequence is often a consciously restrictive eating behavior, which in the case of respective vulnerability can foster the re-occurrence of binge eating.

1.7. Course

Natural course. Based on retrospective studies, the course of untreated BED is considered as chronic and persistent (de Zwaan, Mitchell, Raymond & Spitzer, 1994; Spitzer et al., 1993). The findings of a longitudinal study by Cachelin et al. (1999) on the natural course of BED over a period of six months, however, pointed to a variable course, which can include virtually disorder-free phases as well as phases with strong symptoms. In the largest prospective study on the course of eating disorders conducted to date, it was shown – similarly to retrospective studies – that the majority (64%) of persons with BED continued to fulfill all or almost all of the BED criteria at one-year follow-up; only in 7% of the sample was an eating disorder no longer diagnosed (Crow, Agras, Halmi, Mitchell & Kraemer, 2002). By contrast, there are also findings to suggest a relatively high remission rate for BED (Fairburn et al., 2000). The inconsistent findings may be due to the fact that the samples are not comparable across the different studies (e.g. regarding the duration of symptoms). In summary, it must be emphasized that so far, the state of research on the natural course of BED is relatively weak and conclusions are not sufficiently empirically supported.

Clinical course. There are now numerous studies demonstrating a sustained treatment success following psychotherapy (Brownley et al., 2016; Fichter, Quadflieg & Hedlund, 2008; Fischer, Meyer, Dremmel, Schlup & Munsch, 2014; Hilbert et al., 2012; Schlup, Munsch, Meyer, Margraf & Wilhelm, 2009; Wilfley et al., 2002; Wilson et al., 2010). In a study on a sample of 64 persons with BED, who had received inpatient treatment in a clinic with a predominantly behavioral therapy orientation, 67% of the sample had no eating disorder diagnosis at 12-year follow-up, around 13% had an eating disorder diagnosis from the residual category of EDNOS, 8% still had a diagnosis of BED, and 9% had a diagnosis of BN (purging type); 3% of the sample were deceased (Fichter & Quadflieg, 2004). The disorder-specific and general psychopathology showed stable reductions over the different follow-up periods (e.g. posttreatment, 2-3-year follow-up, 6- and 12-year follow-up (Fichter & Quadflieg, 2004; Fichter, Quadflieg & Hedlund, 2006, 2008). The results indicate that about two thirds of treated persons were able to successfully overcome their eating disorder. A long-term stable treatment outcome has also been documented in persons treated in the outpatient setting (Hilbert et al., 2012). In this study comprising a sample of 90 persons, half were randomized to cognitive-behavioral therapy (CBT) and half to interpersonal psychotherapy (IPT). Four years after the end of therapy, stable treatment outcome was shown for the core symptoms of BED. At this time point, 52% of those who had received CBT still no longer fulfilled criteria for BED, while this figure lay at 77% for those who had received IPT. While the persons treated with IPT continued to show symptom improvements over the follow-up period, persons treated with CBT showed a slight reduction in their treatment outcome. In a total of 12% of the CBT sample and

9% of the IPT sample, BED was diagnosed again four years after the end of treatment. General psychopathological features (e.g. depressiveness) did not reduce during the follow-up period. A short-term CBT (eight group sessions and five booster sessions, the latter distributed over one year), was also found to lead to long-term stable treatment outcome over a four-year follow-up period in 41 persons with BED (Fischer et al., 2014). Overall, 67% of the treated persons did not show BED at the follow-up, and the number of binge-eating episodes (over the last 28 days) decreased on average to 0.7. Moreover, both measures continued to improve substantially between end of therapy and four-year follow-up.

In sum, it can be stated that psychotherapy in BED leads to clear and stable treatment effects, both with respect to the common primary outcome measures (diagnosis of BED, binge-eating episodes) and with respect to secondary outcome measures such as eating disorder psychopathology, but less so with regard to other psychopathologies. Moreover, body weight appears to barely decrease over the duration of treatment. The long-term course of body weight is unclear, although there are some indications that BMI reduces over long-term follow-up (Fischer et al., 2014; Munsch, Meyer & Biedert, 2012). In addition to CBT, particularly IPT appears to show substantial effects.

Following pharmacological treatment, consistent but rather weak symptom improvements in BED were shown (Brownley et al., 2016). These were generally inferior to the combined treatment with psychotherapy (Grilo, Crosby, Wilson & Masheb, 2012). In terms of pharmacological treatments, the administration of second-generation antidepressants, anticonvulsant medications (e.g. topiramate) and stimulants (lisdexamfetamine) has proven to be successful in reducing binge eating and/or the rates of BED diagnosis, although less so in reducing eating disorder psychopathology (Brownley et al., 2016). By contrast, lisdexamfetamine and topiramate had substantial effects on weight loss (Brownley et al., 2016). Follow-up studies also show a stable but rather weak effect of purely pharmacological treatment (Grilo, Crosby et al., 2012). The involvement of psychological factors in pharmacological treatment is also supported by findings demonstrating a high rate of placebo response to medication treatment. For instance, Carter et al. (2003) reported a mean placebo response of 33% for the various pharmacological active substances, which was also confirmed by Jacobs-Pilipski et al. (2007) for an appetite suppressant (sibutramine). However, in this study, persons who showed a placebo response were found to have a more unfavorable spontaneous course. Hence, these findings reflect the aforementioned variability in the course of illness, as well as the importance of unspecific (psychological) factors in the pharmacotherapy of BED.

Predictors of treatment outcome. Above all, disorder-related features (e.g. the level of eating disorder psychopathology) predict the long-term course of (treated) persons with BED, while general psychopathological features are less predictive (Fairburn et al., 2003; Fichter, Quadflieg & Rehm, 2003; Grilo, Masheb & Crosby, 2012; Vall & Wade, 2015). This applies to levels of these measures not only at pretreatment, but also at the end of treatment. For instance, a pronounced eating disorder psychopathology and binge eating at the end of treatment represented negative prognostic indicators of long-term treatment outcome (i.e. over a four-year follow-up period) (Fischer et al., 2014). The most important predictor of treatment

outcome, though, appears to be the rapid response to treatment, and this seems to be the case both for psychotherapeutic treatment and to a lesser degree also for an adjuvant pharmacotherapeutic treatment (Grilo, White, Wilson, Guerguieva & Masheb, 2012; Linardon, Brennan & de la Piedad Garcia, 2016; Nazar et al., 2017; Vall & Wade, 2015). Compared to AN and BN, the prognosis for BED is more favorable, not only with respect to eating disorder symptoms but also regarding other psychological parameters (Fichter et al., 2008; Nazar et al., 2017). Nevertheless, the long-term treatment outcome is less favorable if disorder-specific features are not already clearly reduced during therapy.

1.8. BED in childhood and adolescence

Symptoms and associated psychological problems. The symptoms of BED can already occur in childhood and adolescence. For instance, children from the age of six years report recurrent overeating with a sense of loss of control over eating (Tanofsky-Kraff et al., 2004). Due to an often limited access to food, children are especially likely to eat amounts of food which are often not excessively large (Hilbert & Czaja, 2009; Schlüter, Schmidt, Kittel, Tetzlaff & Hilbert, 2016; Tanofsky-Kraff et al., 2004). Therefore, in children and adolescents, the subjective sense of loss of control during a binge-eating episode is seen as more psychopathologically relevant than the amount of food consumed (Shomaker et al., 2010). Therefore, in children and adolescents, subjective binge eating (i.e. loss of control over eating a subjectively large amount of food) and objective binge eating (i.e. loss of control over eating an objectively large amount of food, in line with the DSM-5) are considered, both described as "loss of control eating" (see chapter VII. "Atypical eating disorders and eating disorders not otherwise specified"). Such binge-eating episodes can take place alone or in the presence of other persons and at any time of day, but especially in the afternoon and evening (Kass et al., 2017; Tanofsky-Kraff et al., 2009).

Also in childhood, BED is associated with an increased eating disorder-specific (e.g. shape and weight concerns) and general psychopathology (e.g. internalizing behavior problems, low self-esteem, suicidality) as well as impairments in psychosocial adjustment (Hilbert & Czaja, 2009; Matherne et al., 2015; Schlüter et al., 2016; Swanson, Crow, Le Grange, Swendsen & Merikangas, 2011; Tanofsky-Kraff et al., 2004). Children and adolescents with BED are more frequently affected by overweight and obesity than children and adolescents without BED (ibid.). Cognitive-emotional dysfunctions have been reported, including deficits in inhibition, increased impulsivity, a visual attentional bias for food stimuli as well as difficulties in emotion regulation (Czaja, Rief & Hilbert, 2009; Kittel, Schmidt & Hilbert, 2017; Schmidt, Lüthold, Kittel, Tetzlaff & Hilbert, 2016). While BED in middle childhood is rarely accompanied by physical functional impairments, there are indications that in adolescents, BED is already linked to symptoms of type 2 diabetes mellitus or cardiovascular diseases associated with overweight and obesity (Radin et al., 2015).

Diagnostic criteria. Due to developmental particularities, age-adapted diagnostic criteria have been suggested for BED in children and adolescents (Hilbert & Czaja, 2009; Marcus &

Kalarchian, 2003; Tanofsky-Kraff, Marcus, Yanovski & Yanovski, 2008). Accordingly, for a diagnosis of BED in childhood and adolescence, not only objective binge eating but also subjective binge eating, i.e. loss of control eating, needs to be considered (DSM-5, criterion A). In general, binge-eating episodes are less frequent than in adults (Hilbert & Czaja, 2009; Stice, Marti, Shaw & Jaconis, 2009; Tanofsky-Kraff et al., 2004), leading to the suggestion that the diagnostic frequency criterion should be decreased, for instance, to two episodes per month (criterion D) (Tanofsky-Kraff et al., 2008). Likewise, the distress due to binge eating is often weaker in BED in childhood and adolescence (criterion C) (Hilbert & Czaja, 2009). Age-adapted behavioral features have also been suggested (e.g. feelings of numbness during binge-eating episodes; criterion B; Tanofsky-Kraff et al., 2009). However, the diagnosis of BED in childhood and adolescence requires further empirical validation (Matherne et al., 2015), and specific age-adapted criteria for BED are found neither in the DSM-5 nor in the ICD-10. The symptoms of BED in childhood and adolescence can be subsumed under the category *Unspecified Feeding or Eating Disorders* in the DSM-5 and ICD-10 (307.50 and F50.9).

Comorbidity. Approximately 83.5% of children and adolescents with BED show at least one comorbid mental disorder (e.g. affective disorder, anxiety disorder, substance abuse or dependence; Swanson et al., 2011). Moreover, the symptoms of BED often occur comorbidly with attention-deficit/hyperactivity disorder (Hartmann, Rief & Hilbert, 2012; Reinblatt et al., 2015), and both disorders are longitudinally associated with obesity (Nigg et al., 2016; Tanofsky-Kraff et al., 2009, 2011). Already in childhood and adolescence, BED is linked to overweight and obesity and their sequelae such as type 2 diabetes mellitus or cardiovascular diseases as well as chronic inflammation (Shank, Tanofsky-Kraff et al., 2017; Tanofsky-Kraff et al., 2012).

Etiology and maintenance. A risk factor for BED in adolescence is a persistent loss of control eating in middle childhood (Hilbert & Brauhardt, 2014; Hilbert, Hartmann, Czaja & Schoebi, 2013; Tanofsky-Kraff et al., 2011). Retrospective and prospective studies show that the symptoms of BED are predicted by a higher body weight, critical life events (e.g. separation of parents), stress at school, depressiveness, emotional eating, restrictive eating behavior, restrictive parental feeding practices, dissatisfaction with one's shape as well as shape- and weight-related criticism (Allen, Byrne, Oddy & Crosby, 2013; Goldschmidt, Wall, Zhang, Loth & Neumark-Sztainer, 2016; Hartmann, Czaja et al., 2012). Similarly to adults with BED, maintaining factors include negative mood and difficulties in emotion regulation, stress, a restrictive eating style, the consumption of "forbidden foods", negative self-esteem and negative body image, and interpersonal problems, for instance, within the family (Hilbert, Tuschen-Caffier & Czaja, 2010; Ranzenhofer et al., 2016; Schmidt, Tetzlaff & Hilbert, 2015; Shank, Crosby et al., 2017; Tanofsky-Kraff et al., 2009; Tetzlaff, Schmidt, Brauhardt & Hilbert, 2016; Vannucci et al., 2014).

Course. Regarding the natural course, BED in childhood and adolescence shows a moderate stability with a clear tendency for spontaneous remission and relapse (Allen et al., 2013; Goldschmidt et al., 2016; Stice et al., 2009). To date, there are few findings specifically for BED regarding the course after treatment. Treatability was suggested by a randomized

controlled pilot study in 12-18-year-old youth with recurrent binge eating. Compared to a waitlist control condition, CBT proved to be efficacious regarding the remission of binge eating up to three months after treatment (DeBar et al., 2013). Further initial evidence is available for IPT in the prevention of overweight and obesity in adolescent girls in a randomized controlled pilot study (Tanofsky-Kraff et al., 2014). Compared to health-related psychoeducation, IPT was shown to be significantly more efficacious in reducing binge-eating episodes at one-year follow-up.

2. Therapy

2.1. Treatment goals

In light of the multifactorial etiology of BED (see section 1.4 "Etiology and maintenance") and a symptomatology arising in psychological, physical and social areas, different treatment goals should be considered in the individual treatment planning.

Essentially, the treatment goals encompass the following aspects:

- Treatment of the symptoms of BED (e.g. binge eating, eating disorder-specific psychopathology)
- Treatment of further psychological complaints (e.g. problems with self-esteem and shame, affect regulation)
- Treatment of comorbid mental disorders (e.g. depression, social anxiety)
- Relapse prevention (e.g. imparting meta-knowledge).
- If indicated, treatment of obesity (see S3-guideline Diagnosis and Prevention of Obesity; DAG, 2014)

Of course, the above-mentioned treatment goals are neither mutually exclusive nor independent from one another. If several treatment goals are pursued, it is necessary to determine priorities and temporal sequencing in treatment (de Zwaan, 2002).

Often, persons with BED aim to lose weight. This concern needs to be addressed with the patient as part of the treatment planning, considering in how far a too strong focus on weight loss can hinder the primary treatment goal for BED: the reduction of binge eating.

2.2. Treatment approaches

In the following, recommendations for individual treatment forms are made. These are mostly based on the results of a comprehensive meta-analysis by Hilbert et al. (2017, 2019, in press) on the efficacy of different treatment approaches for BED (see "Binge eating disorder – Methods report"). If a sufficient number of randomized controlled trials were available for a particular treatment approach, a meta-analysis was conducted for this approach, into which the effect sizes (ES) for the quantification of differences between pre-post values from intervention

groups and untreated control groups were entered. Evidence levels were classified following the recommendations of the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009): Evidence level Ia was assigned if at least three randomized controlled trials could be included in the meta-analysis; otherwise, evidence level Ib was assigned. If no randomized controlled trials with an untreated control group were available for a treatment approach, but rather exclusively non-randomized controlled studies, uncontrolled studies or randomized controlled trials with a treated control group, the ES of the meta-analysis are based on the comparisons of the pre- and the post-values of the respective intervention groups (evidence level IIa). When interpreting the results, it should be noted that ES which are based on the comparison of pre-post values from intervention and control conditions, and those which are based on a comparison of pre- and post-values for one intervention condition, are not directly comparable with one another in terms of their size; generally speaking, the ES turn out to be smaller for the integration of randomized controlled trials. For this reason, the classification according to Cohen (1988) in the proper sense is solely applicable to the ES for the integration of randomized controlled trials. Besides ES, in meta-analysis on the basis of randomized controlled trials odds ratios were calculated as indicators of symptom remission, and in the meta-analysis based on pre-post comparisons alternatively the abstinence rates. Pre-follow-up effects were meta-analytically evaluated if data were available. If the number of primary studies did not allow for either of the two described meta-analytic comparisons, the individual studies for the respective treatment approach were used for deriving recommendations (evidence levels IIb to IV).

2.2.1. Psychotherapy

In the current meta-analysis (Hilbert et al., 2019, in press), 46 treatment conditions were included in the evaluations on the psychotherapy of BED, encompassing a total of 1,915 persons. In 40 of the treatment conditions, psychotherapy took place in group setting, while in six of the conditions, psychotherapy was carried out in individual format. Of the treatment conditions, 36 study arms contained CBT, two study arms contained IPT and three study arms contained psychodynamic therapy, one study arm humanistic therapy and four study arms other forms of psychotherapy. With regard to study quality, the psychotherapy studies predominantly showed a high risk of bias.

When solely analyzing the randomized controlled trials, it was possible to include 32 treatment conditions with a total of 1,278 persons. Here, 27 study arms comprised CBT, two IPT, and one study arm each for psychodynamic therapy, humanistic therapy and another form of psychotherapy. The meta-analytic ES referred to the comparison of the pre-post data in psychotherapy versus an untreated control condition. For psychotherapy in general, a large effect was found for binge-eating episodes (ES = 1.22). Compared to persons in the untreated control conditions, the persons who had been treated with psychotherapy had a 12-fold increased likelihood of being abstinent from binge eating at the end of treatment. With regard to the group difference in eating disorder psychopathology, a medium effect (ES = 0.50) was

found, and for depressive symptoms a small effect (ES = 0.45). By contrast, no significant effect emerged with regard to BMI (ES = 0.04).

Moreover, it needs to be noted that in a comparison of psychotherapy with other treatment approaches (e.g. structured self-help treatment, pharmacotherapy, behavioral, pharmacological and surgical weight loss treatment, combination treatment) evaluated in randomized controlled trials with an untreated control group, psychotherapy was significantly superior with respect to abstinence from binge eating, but not with respect to the number of binge-eating episodes at the end of treatment. If, in addition to the randomized controlled trials, non-randomized controlled and uncontrolled studies were included, the uncontrolled pre-post comparison yielded effects in the high range for the number of binge-eating episodes (ES = 1.36). Overall, 53% of the persons treated with psychotherapy achieved an abstinence from binge eating at the end of treatment. In terms of the reduction of eating disorder psychopathology and depressive symptoms, medium effects emerged (ES = 0.52 and 0.67, respectively). A small effect was found with regard to the reduction of BMI (ES = 0.29).

With regard to follow-up, relatively stable effects were found for psychotherapy up to 6- to 12-month follow-up after the end of therapy. For instance, in the pre-follow-up comparison, large effects emerged for the reduction of the number of binge-eating episodes (ES = 0.84), eating disorder psychopathology (ES = 0.85) and depressive symptoms (ES = 0.73) and a small effect regarding the reduction of BMI (ES = 0.27). The follow-up evaluations were based on four to ten study arms with 159 to 540 persons.

A moderator analysis on the comparison of the efficacy of specific psychotherapy forms was not possible due to a lack of data on forms of therapy other than CBT. However, if specific therapy forms were additionally meta-analytically evaluated or evaluated on an individual study basis regarding their effect on eating disorder symptoms, randomized controlled trials showed a large effect size regarding the reduction of binge-eating episodes for CBT in comparison with untreated control groups (ES = 1.22; 5 study arms, 285 persons) and an 11-fold greater likelihood of being abstinent from binge eating at the end of treatment (6 study arms, 326 persons).

When considering the randomized controlled trials by Wilfley et al. (2002) and Wilson et al. (2010) for IPT, a large pre-post effect emerged with regard to the reduction of days with binge eating (ES = 1.89; 156 persons) and an abstinence rate of 70% (155 persons) with an average or small confidence interval. In terms of study quality, both studies showed an unclear risk of bias.

For psychodynamic therapy, three studies with a high risk of bias were available. The randomized controlled trial by Tasca et al. (2006) and the uncontrolled study by Tasca et al. (2013) showed large pre-post effects with regard to the reduction of days with binge eating (ES = 1.29, 150 persons) and abstinence rates of 33% (139 persons). The confidence intervals lay in the small (Tasca et al., 2013) to medium range (Tasca et al., 2006). The pooled abstinence rate was below-average, which was predominantly attributable to the randomized controlled

trial by Tasca et al. (2013), which reported an abstinence rate of 15%, The non-randomized controlled study by Ciano, Rocco, Angarano, Biasin and Balestrieri (2002) reported a remission of BED in 83% of the six treated persons post-treatment, and a total of 67% of the treated persons no longer showed an eating disorder.

For humanistic therapy, one randomized controlled trial was available, which employed this therapy as an active control condition (Safer, Robinson & Jo, 2010). In the pre-post comparison, with a small to medium confidence interval, a below-average abstinence rate of 33% (51 persons) was found. The study had an unclear risk of bias.

These results broadly correspond to those of the previous meta-analysis by Vocks et al. (2010). In line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), psychotherapy in general as well as CBT in particular are assigned with evidence level Ia. IPT, with two randomized controlled trials with a small confidence interval and an unclear risk of bias, is assigned with evidence level Ib. With one randomized controlled trial with a medium confidence interval and a high risk of bias, psychodynamic therapy is assigned with evidence level IIb; humanistic therapy, with one randomized controlled trial with a small to medium confidence interval and an unclear risk of bias, and which was solely evaluated as an active control group, is assigned with evidence level IIb.

2.2.2. Structured manualized self-help treatment

The current meta-analysis (Hilbert et al., 2019, in press) on the efficacy of structured, manualized self-help treatment included 15 study conditions with 453 persons, of which eight were guided structured self-help treatments and seven were non-guided but structured self-help treatments. In five treatment conditions, group treatments were conducted and in 10 conditions individual treatments were conducted. The majority of the employed structured self-help programs had a CBT orientation (7 of 8 of the guided and 5 of 7 of the non-guided treatments). With regard to study quality, self-help studies predominantly showed a low or unclear risk of bias.

For the most part, the contents of the structured self-help treatment broadly corresponded to those of CBT. Generally, the patients receive respective work materials (e.g. in book form), which contain information on BED as well as the individual therapeutic steps for overcoming binge eating presented in a manualized form. Thus, it should be noted that the self-help interventions entered into the analysis are based on scientifically evaluated psychotherapeutic interventions and were professionally transferred into this treatment format. By contrast, they do not contain any unstructured measures or measures that are not based on psychotherapeutic evidence.

In total, twelve treatment conditions with 397 persons were evaluated in randomized controlled trials. In the meta-analytic evaluation of these randomized controlled trials, a small effect for

the number of binge-eating episodes emerged for structured self-help treatment compared to untreated control conditions at the end of treatment (ES = 0.47). Compared to the persons in untreated control conditions, those receiving structured self-help treatment had an 8-fold increased likelihood of being abstinent from binge eating at the end of treatment. The effect on eating disorder psychopathology was small (ES = 0.33), while effects on depressive symptoms (ES = 0.25) and reduction of BMI (ES = 0.05) were not found. Consistent results were found when considering only self-help programs based on CBT, likewise with a predominantly low study quality, for example, a small effect on the number of binge-eating episodes (ES = 0.45; 5 treatment conditions, 318 persons) and an 8-fold increased likelihood of achieving abstinence from binge eating at the end of treatment (5 treatment conditions, 342 persons).

In the uncontrolled pre-post comparison, a large effect emerged for the reduction of binge-eating episodes (ES = 0.91). After the end of the structured self-help treatment, 45% of the affected persons achieved an abstinence from binge eating. Like psychotherapy, structured self-help treatment showed a medium effect on the reduction of eating disorder psychopathology (ES = 0.58), but a small effect on depressive symptoms (ES = 0.34). This treatment approach did not have a significant effect on the reduction of BMI (ES = 0.07). Consistent results were found when considering only self-help programs based on CBT, for example, a large effect on the number of binge-eating episodes (ES = 0.89; 10 treatment conditions, 333 persons) and an abstinence rate of 47% at the end of treatment (11 treatment conditions, 408 persons).

With regard to follow-up, relatively stable effects were found for structured self-help treatment up to the 6-month to 12-month follow-up after the end of treatment. For instance, in the pre-follow-up comparison, medium effects were found on the reduction of binge-eating episodes (ES = 0.65) and eating disorder psychopathology (ES = 0.68). Depressive symptoms were reduced with a small effect (ES = 0.25). By contrast, no significant effect on BMI emerged (ES = 0.11). Each of the follow-up evaluations was based on three to four study arms (89 to 146 persons).

A comparison of guided versus non-guided self-help treatment showed that in the pre-post comparison, the two forms of structured self-help did not significantly differ from one another regarding the number of binge-eating episodes and the abstinence from binge eating. These analyses were based on eight and nine study arms with 251 and 317 persons, respectively.

Therefore, in line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), the psychotherapeutic intervention using structured self-help manuals in general, and specifically when based on CBT, can be classified as efficacious with regard to the reduction of binge eating (evidence level Ia). Structured, manualized self-help treatment is found to be less efficacious than psychotherapy. Compared to the previous meta-analysis (Vocks et al., 2010), the efficacy of structured, manualized self-help treatment in the present meta-analysis, with a larger evidence base, is lower.

2.2.3. Pharmacotherapy

Regarding the efficacy of pharmacotherapy, the current meta-analysis (Hilbert et al., 2019, in press) included 37 study conditions with 1,443 persons. The examined psychotropic medications were second-generation antidepressants (e.g. fluoxetine), central nervous system stimulants (e.g. lisdexamfetamine), anticonvulsants (e.g. topiramate), and other pharmaceuticals. The average duration of the medication amounted to 14 ± 6 weeks with a range from 6 to 24 weeks. With regard to study quality, the pharmacotherapy studies predominantly showed a low or unclear risk of bias.

In total, 29 treatment conditions with 1,310 persons were evaluated in randomized controlled trials. The meta-analytic evaluation of these studies yielded a small effect for the number of binge-eating episodes at the end of treatment for pharmacotherapy in comparison to placebo (ES = 0.39). Compared to untreated control conditions, persons who had received pharmacotherapeutic treatment were twice as likely to be abstinent from binge eating at the end of treatment. An improvement in eating disorder psychopathology (ES = 0.04) and depressive symptoms (ES = 0.32) was not achieved. The effect on BMI was small (ES = 0.32).

In the uncontrolled pre-post comparison, a large effect was found for the reduction of binge eating (ES = 1.27). Overall, 45% of the treated persons were abstinent from binge eating at the end of treatment. Eating disorder psychopathology was reduced with a medium effect (ES = 0.52), as were depressive symptoms (ES = 0.58). BMI was reduced with a small effect (ES = 0.44).

When only considering the randomized controlled trials, a moderator analysis on the core symptoms of BED showed that pharmacotherapy was inferior to psychotherapy with respect to the abstinence from binge eating at posttreatment in the comparison with untreated control conditions.

When compared to placebo, the type of medication had a significant effect on the abstinence from binge eating: For instance, for persons who had been treated with central nervous system stimulants compared to those who had received placebo, the likelihood of being abstinent from binge eating at the end of treatment was significantly greater than for persons who had been treated with second-generation antidepressants. If in addition to randomized controlled trials non-randomized controlled studies and uncontrolled studies were included for a pre-post comparison, it was apparent that anticonvulsants achieved significantly higher rates of abstinence from binge eating than did second-generation antidepressants, stimulants and other medications.

When the effects of individual classes of pharmaceuticals were each meta-analytically determined, in the pre-post comparison of randomized controlled trials, central nervous system stimulants showed a greater reduction of binge-eating episodes than placebo, with a medium effect (ES = 0.54; 2 study arms, 174 persons), and a 3-fold higher likelihood of being abstinent from binge eating at the end of treatment compared to placebo (5 study arms, 946 persons). By

contrast, second-generation antidepressants yielded a small effect in the reduction of binge-eating episodes (ES = 0.37, 8 study arms, 347 persons), and double the likelihood of abstinence from binge eating (10 study arms, 466 persons). Anticonvulsant drugs brought about an almost 3-fold increased likelihood of abstinence from binge eating (3 study arms, 502 persons).

Overall, it is evident that although pharmacotherapy proved to be more efficacious than placebo, the efficacy with regard to the core symptoms of BED lay only slightly above that of a placebo medication. By contrast, in terms of amount, the effect of untreated control conditions in studies on psychotherapy or on structured, manualized self-help was larger. Due to a lack of follow-up data, it was not possible to document long-term effects of pharmacotherapy. With regard to side effects, the likelihood of various complaints (e.g. increased sympathetic arousal, gastrointestinal problems, sleep disturbances, headache) was twice as high compared to placebo. The likelihood of terminating the treatment due to side effects of pharmacotherapy was double that for placebo.

In Germany, no medication is currently approved for the treatment of BED. In line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), pharmacotherapy can be rated as efficacious in the short term for the reduction of binge-eating episodes (evidence level Ia). This applies to central nervous system stimulants – primarily lisdexamfetamine has been examined in this regard – as well as second-generation antidepressants and anticonvulsants, with the former showing a higher efficacy than the other examined classes of pharmaceuticals. Evidence on the long-term efficacy and also on long-term administration is not available; the likelihood of side effects was twice as high compared to that of placebo. The efficacy of the examined pharmaceuticals was only marginally higher than that of placebo. Pharmacotherapy was less efficacious for the treatment of eating disorder symptoms compared to psychotherapy. Overall, these results suggest the use of pharmacotherapy if psychotherapy is not desired or not effective. Compared to the previous meta-analysis on this topic (Vocks et al., 2010), the efficacy of pharmacotherapy has slightly reduced in several outcomes.

2.2.4. Weight loss treatment

In the meta-analysis (Hilbert et al., 2019, in press), weight loss treatments were categorized into behavioral, pharmacological and surgical interventions. Details on the indication and implementation of these forms of weight loss treatment in obesity can be found in the S3 guideline Diagnosis and Prevention of Obesity (DAG, 2014).

2.2.4.1. Behavioral weight loss treatment

Behavioral weight loss treatment for obesity usually has a multimodal orientation and aims to change nutrition, physical activity and behavior such that a weight loss occurs through a negative energy balance (DAG, 2014). In the current meta-analysis (Hilbert et al., 2019, in press), a total of nine active study arms were included, encompassing 391 persons. Six of these

nine study arms contained a combination of interventions on nutrition, physical activity and behavior. The remaining three study arms solely contained interventions on nutrition, on physical activity, or a combination of the two. With regard to study quality, the studies on behavioral weight loss treatment predominantly showed a high risk of bias; none of the studies had a low risk of bias.

While for behavioral weight loss treatment, seven study arms with 277 persons in randomized controlled trials with active control conditions were available, there were no randomized controlled trials with untreated control conditions. In uncontrolled pre-post comparisons, a large effect was apparent for behavioral weight loss treatment with respect to the reduction of binge-eating episodes (ES = 0.90). At the end of treatment, an abstinence rate of 48% was achieved. The reduction of eating disorder psychopathology was in the small range (ES = 0.24), while depressive symptoms were reduced with a medium effect (ES = 0.63). BMI was reduced with a large effect (ES = 1.55). Within behavioral weight loss treatment, multimodal programs containing interventions on nutrition, physical activity and behavior showed virtually identical results in the uncontrolled pre-post comparison (binge-eating episodes: ES = 0.90, 4 study arms, 167 persons; abstinence rate: 47%, 5 study arms, 159 persons). A non-randomized controlled trial with a high risk of bias was available for dietary counseling (Compare, Calugi, Marchesini, Molinari & Dalle Grave, 2013) and showed a below-average abstinence rate of 29% at the end of treatment (63 persons). Furthermore, there was one randomized controlled trial with a high risk of bias, which focused exclusively on increasing physical activity (Levine, Marcus & Moulton, 1996). This study revealed an abstinence rate of 81% at the end of treatment (44 persons).

At follow-up, overall, behavioral weight loss programs showed relatively stable effects up to the 6- to 12-month follow-up posttreatment. In the pre-follow-up comparison, large effects were observed with regard to reduction of binge eating (ES = 1.24) and depressive symptoms (ES = 0.94) as well as a medium effect regarding eating disorder psychopathology (ES = 0.77). However, no significant effect was found with regard to the reduction of BMI (ES = 0.55). Of note, the follow-up evaluations were each based on only two to three study arms (52 to 114 persons).

In line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), based on the available randomized controlled trials with an active control group, behavioral weight loss treatment can therefore be assigned with evidence level Ia. This applies equally for programs of behavioral weight loss treatment which combined interventions on nutrition, physical activity and behavior. However, it was not possible to determine the efficacy compared to an untreated control group, and it was also not possible to conclusively evaluate the long-term efficacy for BED. In comparison to Vocks et al. (2010), the efficacy of behavioral weight loss treatment was partially improved in the current meta-analysis. Dietary counseling, evaluated in a non-randomized controlled trial with a high risk of bias, with a below-average effect on binge eating symptoms, is assigned with evidence level IIc. For an exercise program which was evaluated in one randomized controlled trial with

a high risk of bias, showing potential efficacy for binge eating symptoms, evidence level IIb is assigned.

Overall, these results suggest that behavioral weight loss treatment should be employed as a subordinate treatment following psychotherapy. In this regard, there is further evidence that an abstinence from binge eating through psychotherapy improves the long-term maintenance of weight loss achieved through behavioral weight loss treatment (Agras et al., 1997). Thus, behavioral weight loss treatment might be beneficial in terms of an improved weight loss outcome following psychotherapy.

2.2.4.2. Pharmacological weight loss treatment

In terms of pharmacological weight loss treatment, which can be offered as an adjunct to behavioral weight loss treatment for obesity (DAG, 2014), six study arms were identified, comprising 242 persons (sibutramine: 5 treatment arms, d-fenfluramine: 1 treatment arm). The examined medications are currently not approved for the treatment of BED, or their approvals were withdrawn due to cardiovascular side effects. With regard to study quality, the studies on pharmacological weight loss treatment predominantly showed a high risk of bias.

For these medications for pharmacological weight loss treatment, randomized controlled trials revealed small effects in the comparison of pre-post values from the respective intervention group and untreated control group regarding the reduction of binge eating (ES = 0.47). Persons who had received pharmacological weight loss treatment were twice as likely to be abstinent from binge eating at the end of therapy. There were no significant effects on eating disorder psychopathology (ES = 0.46) or depressive symptoms (ES = 0.34). BMI reduced to a small degree (ES = 0.38)

A moderator analysis on the core symptoms of BED showed, when solely considering the randomized controlled trials, that pharmacological weight loss treatment was inferior to psychotherapy with respect to abstinence from binge eating at the end of treatment in the comparison with untreated control conditions.

In uncontrolled pre-post comparisons, large effects were found for pharmacological weight loss treatment with regard to the reduction of binge eating (ES = 1.34) and eating disorder psychopathology (ES = 0.86) and a medium effect with regard to the reduction of depressive symptoms (ES = 0.75). Overall, 56% of the treated persons were abstinent from binge eating at the end of treatment. Weight loss lay in a medium range (ES = 0.56). No follow-up data documenting the longer-term efficacy of pharmacological weight loss treatment three months posttreatment or later were available.

In line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), pharmacological weight loss treatment is therefore assigned with evidence level Ia. However, the evaluated medications sibutramine and d-

fenfluramine are not approved for the treatment of BED, and due to their cardiovascular risk profile, they are no longer marketed for obesity. The efficacy for eating disorder symptoms turned out to be lower than that of psychotherapy. Data on the long-term efficacy are not available.

2.2.4.3. Surgical weight loss treatment

The category of surgical weight loss treatment or bariatric surgery, which is used to treat severe obesity (DAG, 2014), comprised four study arms with a total of 117 persons. The operative procedures examined were Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion, and adjustable gastric band. Only non-randomized controlled and uncontrolled designs were used. With regard to study quality, the studies on surgical weight loss treatment all showed a high risk of bias.

In uncontrolled pre-post comparisons, 79% of persons treated with obesity surgery were remitted from BED, but no effects were found regarding eating disorder psychopathology (ES = 0.05). BMI was reduced with a large effect (ES = 2.95). Follow-up data for the documentation of the longer-term effectiveness of surgical weight loss treatment three months or more post-operation were not available for BED.

In line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), surgical weight loss treatment can therefore be assigned with evidence level IIc. The long-term effectiveness for BED cannot be evaluated. All included studies had a high risk of bias.

2.2.5. Combination treatment

The meta-analysis by Hilbert et al. (2019, in press) on the efficacy of combination treatment comprised 34 study conditions, which combined CBT with behavioral weight loss treatment (10 study arms), with pharmacological treatment (5 study arms), or with both treatments (5 study arms). A further five study arms contained behavioral weight loss treatment with pharmacological treatment, and nine study arms comprised other combination treatments. In 14 of the treatment conditions, group therapies were conducted; in 15 of the conditions, individual therapies; and in five treatments, group plus individual therapy were conducted. With regard to study quality, the studies on combination treatment predominantly showed a high risk of bias.

In randomized controlled trials, a total of 30 study arms with 934 persons was available. In the evaluation of the randomized controlled trials, at the posttreatment time point, a small effect for the number of binge-eating episodes for the combination treatments compared to untreated control conditions emerged (ES = 0.33). A significant effect regarding the abstinence from binge eating, however, was not found (odds ratio = 2), and likewise, eating disorder

psychopathology did not significantly improve (ES = 0.03). Small to medium effects on depressive symptoms (ES = 0.34) and body weight (ES = 0.54) were identified.

A moderator analysis on the core symptoms of BED, when solely considering the randomized controlled trials, showed that combination treatment was inferior to psychotherapy with regard to abstinence from binge eating at the end of treatment in comparison with untreated control conditions. In randomized controlled trials, it was not possible to conduct a moderator analysis or separate evaluation on subcategories of combination treatments due to a lack of data.

In the uncontrolled pre-post comparison, a large effect size emerged for the reduction of the number of binge-eating episodes (ES = 1.64). The effect of combination treatments on the reduction of eating disorder psychopathology lay in the medium range (ES = 0.52), as did the effect on depressive symptoms (ES = 0.78). The reduction in BMI showed a large effect size (ES = 0.95)

When additional analyses were conducted to separately evaluate subcategories of combination treatments regarding eating disorder symptoms in the uncontrolled pre-post comparison (a moderator analysis was not possible here due to a lack of data), at treatment end, a large effect on the reduction of binge eating was found for CBT in combination with pharmacotherapy (ES = 1.71; 5 study arms, 113 persons) and an abstinence from binge eating in 71% of persons (2 studies arms, 54 persons). For CBT in combination with behavioral weight loss treatment, a large effect emerged on the reduction of binge eating at the end of treatment (ES = 1.19; 3 study arms, 94 persons) and an abstinence rate of 50% (7 study arms, 195 persons). For the triple combination of CBT plus behavioral weight loss treatment plus pharmacological treatment, a medium-sized effect on the reduction of binge-eating episodes in a small sample was found (ES = 0.54; 2 study arms, 20 persons), and for the combination treatment comprising behavioral weight loss and pharmacological treatment, a large effect on the reduction of binge eating at posttreatment was shown (ES = 1.83; 2 study arms, 54 persons). Due to the small samples, it is not possible to clearly derive differences in efficacy among various forms of combination treatments.

With regard to follow-up, overall, relatively stable effects up to 6- to 12-month follow-up after treatment end emerged for combination treatment. For instance, the pre-follow-up comparison showed a reduction of binge-eating episodes (ES = 1.03) and eating disorder psychopathology (ES = 1.04) with a large effect. Depressive symptoms improved with a medium effect size (ES = 0.7) and BMI was reduced with a small effect size (ES = 0.28). The follow-up evaluations were each based on five to six study arms (114 to 134 persons).

In line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), combination treatments were therefore assigned with evidence level Ia. For the treatment of binge-eating symptoms, they were less effective than psychotherapy. Within the combination treatments, no firm conclusions can be drawn about differences among various treatments.

2.2.6. Inpatient treatment

The meta-analysis by Hilbert et al. (2019, in press) was comprised of eight study conditions with 239 persons which were conducted in an inpatient setting, six of them with a multimodal therapy for BED and for weight loss, and two with a multimodal weight loss treatment. Two of the treatment conditions were conducted exclusively as group therapies and six treatment conditions comprised both group and individual therapies. All included studies on inpatient treatment showed a high risk of bias.

Although six study conditions with 117 persons in randomized controlled inpatient trials were identified that contained active control conditions, no data were available for the comparison with untreated control conditions. In untreated pre-post comparisons, it emerged, albeit on the basis of data from only three study arms of one randomized controlled trial with low methodological quality, that 95% of persons achieved abstinence from binge eating, which was substantially greater than the abstinence rate in all other therapy forms. By contrast, the effect of inpatient treatment on the reduction of eating disorder psychopathology was small (ES = 0.26), while a large effect was achieved for the reduction of BMI (ES = 1.09).

With regard to follow-up, for inpatient treatment, in the pre-follow-up comparison three to six months after the end of therapy, an abstinence rate of 44% emerged. A reduction of BMI was achieved at 6- to 12-month follow-up with a large effect size (ES = 0.95). The follow-up evaluations were based on three to four study arms (44 to 81 persons).

In line with the classification of evidence levels according to the Oxford Centre of Evidence Based Medicine (Phillips et al., 1998-2009), inpatient therapies, with a high risk of bias, were thus assigned with evidence level IIb.

2.2.7. Considerations for children and adolescents

In the meta-analysis by Hilbert et al. (2019, in press), it was not possible to include any study on the treatment of BED in children and adolescents.

Recommendations

- In the diagnosis of overweight and obesity, assessment of binge-eating episodes as an important symptom of BED should be considered (GCP).
- As the first-line eating disorder treatment, psychotherapy should be offered to patients with BED (Ia, A).
- CBT shows the most comprehensive evidence in adult patients with BED; therefore, CBT should be offered to these patients (Ia, A).
- There is evidence that IPT is likewise efficacious; therefore it should be recommended as an alternative (Ib, B). However, IPT is not an approved psychotherapy in Germany.

- There is limited evidence that psychodynamic therapy can be efficacious; therefore it may be considered for patients with BED (IIb, 0).
- There is limited evidence that humanistic therapy can be efficacious; therefore it may be considered for patients with BED (IIb, 0). However, humanistic therapy is not an approved psychotherapy in Germany.
- For structured, manualized self-help treatment, especially with treatment components of CBT, there is evidence of efficacy; therefore, it should be recommended for patients with BED (Ia, B).
- Currently, no medication is approved for the treatment of BED. Pharmacotherapy with central nervous system stimulants (especially lisdexamfetamine), second-generation antidepressants, and anticonvulsants are efficacious, but lead to side effects. Therefore, they can only be considered for patients with BED if psychotherapy is refused or unsuccessful (Ia, 0). Long-term effects of pharmacotherapy have not been researched. Therefore, no recommendation for a long-term prescription of pharmacotherapy can be made.
- For behavioral weight loss treatment, especially multimodal programs consisting of a combination of interventions for nutrition, physical activity and behavior, there is evidence of short-term efficacy; therefore, it may be recommended for patients with BED and comorbid obesity (Ia, 0). Long-term effects of behavioral weight loss treatment on BED have not been sufficiently researched.
- For simultaneous combination treatments of psychotherapy and/or behavioral weight loss treatment with or without pharmacological treatment, there is evidence of efficacy in BED. However, an additional benefit compared to monotherapies has not been proven. Combination treatments may be considered for patients with BED in individual cases when monotherapies are not sufficient (Ia, 0).
- There is limited evidence for the efficacy of inpatient treatments. They may be considered for patients with BED when outpatient treatments are not sufficient (IIb, 0). The following criteria suggest inpatient treatment (GCP):
  - Pronounced somatic comorbidity
  - Pronounced psychological comorbidity
  - High disorder severity
  - Patient factors that impede therapy (e.g., a body weight that does not permit outpatient treatment)
  - Necessity for treatment by a multiprofessional team with hospital-typical treatment methods (inpatient psychiatric/psychosomatic treatment)
  - Social or family factors which strongly hinder the recovery process (e.g., social isolation, problematic family situation, insufficient social support).
- For children and adolescents with BED, a psychotherapy which includes direct caregivers (generally the parents) is recommended (GCP).

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Method report Binge-Eating Disorder

Literature search and selection

Due to increased methodological requirements for meta-analyses, including documentation of the systematic search and of an assessment of risk of bias, a new literature search was conducted for BED. In addition to determining the efficacy after the end of treatment, as in the previous meta-analysis by Vocks et al. (2010), which was based on the first version of the S3 guideline (AWMF, 2011), the aim was to examine the long-term sustainability of treatment effects.

The study protocol for the meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42016043604) and published (Hilbert et al., 2017). Compared to the meta-analysis by Vocks et al. (2010), the search was conducted using broader search terms in a larger number of electronic databases and study registers, supplemented by a manual search in all reference lists of the included and identified reviews as well as in the International Journal of Eating Disorders. The literature search was conducted up to February 2017[17], separately by two psychologists. In the case of discrepancies, agreement was reached by consensus.

The inclusion criteria were broadly congruent, although somewhat stricter in part. Included were: (1) psychological and medical treatment studies, which (2) were conducted in persons diagnosed, before the start of treatment, with BED according to the DSM-IV (APA, 1994) or DSM-5 (including BED with limited frequency and/or limited duration; APA, 2013), (3) used a randomized controlled, non-randomized controlled, or uncontrolled design, (4) assessed the core symptoms of BED (binge eating days or episodes, abstinence from binge eating and/or diagnosis of BED), (5) provided sufficient data at baseline and for at least one post- or follow-up time point in order to calculate effect sizes (e.g. *M*, *SD* and/or *n*, %), (6) reported separate data for patients with BED in studies with multiple patient groups, and (7) were published in English. Excluded were: (1) unpublished studies, (2) dual publications of the same study, and (3) case studies and studies with a sample size of $n < 10$.

The selection of studies occurred in two steps: In the first step, two psychologists separately screened all titles and abstracts regarding their fit with the inclusion criteria. Based on automatic and manual screening, duplicates were identified and removed. If it was unclear whether inclusion criteria were fulfilled, full texts were viewed. In the second step, all articles which fulfilled the inclusion criteria were checked by two psychologists for inclusion or exclusion based on the full text. If several articles in the framework of one study were found, they were aggregated and formed one analytical unit.

Of the 21,590 identified studies, 10,613 studies remained after removal of duplicates and 506 after screening of title and abstract. Of these studies, a total of 103 studies were included in the

[17] A renewed and extended search and meta-analysis was conducted for Hilbert et al. (2019, in press).

meta-analysis after full-text screening. These 103 studies contained a total of 208 study arms. Of these, 160 were active treatment conditions and 48 were inactive control conditions.

Evaluation of scientific evidence (evidence base)

In the next step, information from the 103 identified studies which was relevant for the meta-analysis was independently extracted by two psychologists. For this purpose, a standardized coding scheme with the corresponding coding handbook was used (Vocks et al., 2010), which was updated and expanded. In this, the Cochrane Collaboration's Risk of Bias Tool (Higgins & Green, 2011) and the Effective Practice and Organization of Care (EPOC) Risk of Bias Tool (EPOC) were also used in order to assess the risk of bias in randomized controlled and non-randomized controlled studies, under consideration of the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I; Sterne et al., 2016) for the assessment of risk of bias in uncontrolled studies. The inter-rater reliability, which was determined for the primary outcome variables, was almost perfect, with a 99% agreement between the raters.

The primary outcomes comprised the amount of binge eating (episodes or days), the abstinence from binge eating, and the diagnosis of BED; the secondary outcomes were eating disorder psychopathology, depressive symptoms, quality of life, body mass index (kg/m^2), body weight, side effects and dropout.

The meta-analytic evaluation was conducted using random-effects models. In this regard, in between-group analyses in randomized controlled trials, the pre-post effects in active treatment conditions were compared with the effects in inactive control conditions within each treatment form (psychotherapy, structured self-help treatment, pharmacotherapy etc.). Additionally, in within-group analyses, pre-post effects (or pre-follow-up effects) were determined in active treatment conditions of randomized controlled, non-randomized controlled and non-controlled studies. The effects were pooled as Hedges' g, odds ratios and rates. Analogously to Cohen's d, a Hedges' g is seen as small with an effect size < 0.20, medium with an effect size > 0.50 and large with an effect size > 0.80. To determine moderator effects, meta-regression analyses between and within individual treatment forms were conducted (e.g., guided vs. non-guided self-help treatment, individual pharmaceuticals).

Additionally, on the basis of the studies included in the meta-analysis, an additional meta-analytic assessment was conducted for individual therapies or subforms, if they could not be considered in the moderator analyses but were nevertheless seen as relevant for the guidelines. Moreover, in the case of randomized controlled trials with an active control group, an individual study evaluation was carried out if a higher valuation was to be expected.

Appendix

Systematic literature search

The literature search was conducted in

(1) Electronic databases (MEDLINE, PubMED, PsycINFO, EMBASE, PUBPSYCH, LILACS, CINAHL, AMED, Web of Science, DARE, ANNUAL REVIEWS, NIHR Centre for Reviews and Dissemination, CDSR, Clinical Psychology Review),
(2) Study registers (PROSPERO, CENTRAL, International Clinical Trials Registry Platform, ClincalTrials.gov, EU Clinical Trials Register, ISRCTN Trial Registry, German Clinical Trials Register) and
(3) Through a manual search in all reference lists of the included and identified reviews as well as in the International Journal of Eating Disorders from 1990 to February 2017.

Search terms

The search was conducted in titles, abstracts and keywords (or in the full text) with the search terms:
(binge eat*) AND (efficac* OR effect* OR outcome OR counsel* OR interven* OR pharmaco* OR drug OR psychoanaly* OR psychotherap* OR therap* OR treat* OR train* OR weight loss OR weight reduction OR self-help OR bariatric surg* OR weight loss surg* OR weight reduction surg* OR obesity surg*).

VII. Atypical eating disorders and eating disorders not otherwise specified

Astrid Müller, Andrea Hartmann & Martina de Zwaan

The atypical eating disorders and eating disorders not otherwise specified (EDNOS) include conditions which do not completely fulfill the criteria for a classical eating disorder (AN, BN, BED) but nevertheless show a clear fixation on weight and shape which poses a burden to sufferers, as well as long-term difficulties in dealing with foods and eating.

Epidemiological investigations on the basis of the diagnostic criteria of the ICD-10 (WHO, 1992) or DSM-IV (APA, 2000) regularly found that with consistent use of these criteria, a clear majority of disorders of therapy-seeking patients with eating disorder symptoms had to be classified as atypical or as EDNOS (Fairburn & Cooper, 2007). The revisions in the DSM-5 (APA, 2013) have changed less in this regard than was originally expected (Machado, Goncalves, & Hoek, 2013). Through the modification of the diagnostic criteria for AN and BN and the introduction of binge eating disorder (BED) as a third classical eating disorder (see guideline chapter BED), the original category of EDNOS was made substantially smaller, but nevertheless remains prevalent (Gualandi, Simoni, Manzato, & Scanelli, 2016; Keel, Brown, Holm-Denoma, & Bodell, 2011; Mustelin, Lehtokari, & Keski-Rahkonen, 2016; Vo, Accurso, Goldschmidt, & Le Grange, 2017). At the same time, the knowledge about atypical eating disorders and EDNOS is still limited.

The division of atypical or EDNOS is not handled consistently in the ICD-10 and DSM-5 (Table 10). The ICD-10 (WHO, 1992) lists atypical AN (F50.1), atypical BN (F50.3), as well as other eating disorders (F50.8) and eating disorders, unspecified (F50.9). These categories are not described in further detail and examiners are asked to formulate their own criteria. In the DSM-5 (APA, 2013), by contrast, there are the residual categories “Other specified feeding or eating disorder” (OSFED) and “Unspecified feeding or eating disorder”. While the latter is not further specified as regards content, the category “Other specified feeding or eating disorder” now mentions atypical AN, BN of low frequency and/or of limited duration and BED of low frequency and/or of limited duration. These three disorders show the same typical symptom patterns as the classical eating disorders AN, BN and BED (see guideline chapters AN, BN and BED), but not all diagnostic criteria are completely fulfilled (e.g. with regard to weight, frequency and duration of eating episodes or compensatory, weight-regulating measures). Moreover, the category “Other specified feeding or eating disorder” also includes night eating syndrome (NES) and purging disorder with diagnostic criteria.

It should be noted that the category “Feeding and Eating Disorders” of the DSM-5 (APA, 2013), besides the classical eating disorders AN, BN, and BED, additionally also includes pica, rumination disorder and avoidant/restrictive food intake disorder (ARFID). According to the ICD-11 Beta Draft, the official draft for the new 11th version of the ICD

(https://icd.who.int/dev11; October 2017), the categorization of eating disorders in the future ICD-11 will be partially oriented to the DSM-5. For instance, the future category "Feeding or Eating Disorders" will include, besides AN and BN, also BED, as well as ARFID, pica and rumination disorder as eating disorder categories in their own right. Moreover, the categories "Other specified Feeding or Eating Disorders" and "Feeding or Eating Disorders, unspecified" are also planned.

In the following, the state of research on the treatment of persons with subsyndromal eating disorders or EDNOS according to the DSM-IV (APA, 2000) will be briefly summarized. Further on, this guideline chapter is then devoted in more detail, based on the DSM-5 (APA, 2013), to the "Other specified feeding or eating disorders" night eating syndrome and purging disorder. In the subsequent chapter, "Further feeding and eating disorders listed in the DSM-5", pica, rumination disorder and ARFID will be addressed separately.

Each subchapter concludes with treatment recommendations which are oriented to the respective levels of evidence according to the Oxford Centre of Evidence Based Medicine (2001). The studies with evidence levels are summarized further below (Tables 11, 14-16). The strength of the treatment recommendation is divided into "A" (very strong recommendation), "B" (strong recommendation), "O" (weak recommendation) and "GCP" (good clinical practice).

1. Subsyndromal eating disorders and Eating Disorders Not Otherwise Specified (EDNOS)

Subsyndromal eating disorders are clinically relevant disorders which show many but not all of the typical symptom patterns of the classical eating disorders AN, BN, and BED. In the DSM-5 (APA, 2013), the subsyndromal eating disorders are characterized as follows: For atypical AN, all criteria of AN are fulfilled (see guideline chapter AN), only body weight lies within or above the normal range despite considerable weight loss. For BN of low frequency and/or of limited duration, all criteria of BN are fulfilled (see guideline chapter BN), only the frequency and duration of eating episodes and the compensatory behaviors are lower (< once per week and/or <3 months). For BED of low frequency and/or limited duration, with the exception of the frequency and duration of eating episodes, which are rarer and shorter (< once per week and/or <3 months), all criteria for BED are fulfilled (see guideline chapter BED).

In the literature, there are barely any treatment studies which included persons with subsyndromal eating disorders or which addressed these persons separately (Table 11). It is noteworthy that those treatments were generally internet-based prevention programs or interventions.

In a randomized controlled trial, the efficacy of an internet-based prevention program "Student Bodies™" – for women with symptoms of disordered eating and/or subthreshold eating disorder syndromes was reported (Jacobi, Volker, Trockel, & Taylor, 2012). The program consists of an internet-based, structured cognitive-behavioral concept with asynchronous,

moderated online groups. The participants were 126 women with very different subsyndromal eating disorders, who were allocated either to the active arm (n=64) or to the control group (n= 62). The efficacy was measured by means of pre/post comparisons and 6-month follow-up using the Eating Disorder Examination Questionnaire (EDE-Q; Hilbert & Tuschen-Caffier, 2006) as the primary endpoint. The authors reported that women in the active arm showed a reduction in eating disorder symptoms (EDE-Q total) after participating in the program (baseline-post d=0.35; baseline-follow-up d=62) (Jacobi et al., 2012).

Similarly, an earlier internet-based study with 60 female students at risk of developing an eating disorder showed that moderated chatroom sessions, as compared to a waitlist control condition, can contribute to a reduction in eating disorder symptoms and an improvement in self-esteem (Zabinski, Wilfley, Calfas, Winzelberg, & Taylor, 2004).

Findings on internet-based interventions are also available in the area of EDNOS. For instance, web-based cognitive behavioral therapy (iCBT) with asynchronous online therapist contacts was compared to a waitlist condition (ter Huurne et al., 2015). The study included women with BN (n=44), BED (n=85) and EDNOS (n=85) (randomization stratified according to diagnosis). The iCBT showed a superior outcome to the waitlist condition and the participants in the active arm reported fewer eating disorder symptoms than the control group. However, for EDNOS, no significant interaction effect of group by eating disorder symptoms emerged, which the authors attributed to the heterogeneity of this group (ter Huurne et al., 2015).

An earlier randomized controlled trial compared the efficacy of iCBT and a waitlist control group in female students with BN (n=39) or EDNOS (n=37) (Sanchez-Ortiz et al., 2011). In the iCBT group, the students took part in a CBT online program, which also provided regular email support from eating disorder experts. For both disorders, iCBT was found to be superior, although the results were unfortunately not presented separately for BN vs. EDNOS (Sanchez-Ortiz et al., 2011).

So-called loss-of-control eating occurs predominantly in children (Hilbert, Hartmann, Czaja, & Schoebi, 2013; Tanofsky-Kraff, Marcus, Yanovski, & Yanovski, 2008). In the literature, there is one non-internet-based randomized controlled intervention study devoted to this problem. The project included 113 girls aged between 12 and 17 years (BMI 75^{th}-97^{th} percentile), who were allocated either to a modified version of interpersonal psychotherapy focusing on the prevention of overweight or to health education (Tanofsky-Kraff et al., 2014). At the end of treatment, both therapy groups showed a reduction of loss-of-control eating. At the 12-month follow-up, moreover, the modified interpersonal therapy was found to be superior to health education. By contrast, there were no differences between the intervention groups regarding weight course (significant weight gain in both groups) one or three years after the end of treatment (Tanofsky-Kraff et al., 2017).

With respect to pharmacological treatments, to the best of our knowledge, there are no findings from randomized controlled trials with patients with atypical eating disorders or EDNOS. In one case report on treatment with lamotrigine (100 mg/d over 1.5 years) in a 15-year-old girl with a diagnosis of EDNOS, a reduction up to remission of eating disorder symptoms was

described (Trunko, Schwartz, Marzola, Klein, & Kaye, 2014). The patient was additionally also taking escitalopram (20 mg/d).

Recommendations

- If, after preliminary examinations, there is continued suspicion of a subsyndromal eating disorder (atypical AN, atypical BN, atypical BED), conducting a systematic classification-based diagnosis is recommended using the current diagnostic criteria of the DSM and ICD, ideally with guidelines or validated diagnostic interviews (GCP; see guideline chapter "Diagnosis")
- Internet-based cognitive-behavioral prevention or therapy programs constitute the most researched intervention and appear to contribute to the reduction of eating disorder symptoms and/or the prevention of a full-blown version of the respective eating disorder (EL 2b).
- If a subsyndromal eating disorder is present, proceeding with treatment analogously to the treatment for AN, BN or BED should be considered (GCP; see guideline chapters AN, BN, BED)

2. Night Eating Syndrome (NES)[18]

2.1. Symptoms and diagnostic criteria

2.1.1. Symptoms

The following symptoms are characteristic for NES: a shift in the day/night rhythm regarding eating behavior, with evening/nighttime eating, lack of appetite in the mornings, disturbances in sleep onset and/or maintenance and possibly loss of control over food intake (Allison, Lundgren, O'Reardon, et al., 2010; de Zwaan, 2016; Stunkard, Grace, & Wolff, 1955).

Typically, either evening eating (food intake after the evening meal) or nighttime eating (nocturnal awakening with food intake) or both are present. Large amounts of food are not consumed in either the evening or the nighttime episodes (in contrast to BED). Patients with NES consume a large proportion of their daily food intake in the late evening or at night. The definition of "large proportion" has strongly differed in previous studies on NES, ranging from 25% of the daily calorie amount (Allison, Lundgren, O'Reardon, et al., 2010) through 35% and up to 50% (Cleator, Abbott, Judd, Sutton, & Wilding, 2012; Mühlhans, Olbrich, & de Zwaan, 2009). The DSM-5 criteria (APA. 2013) assume, rather vaguely, "excessive food consumption after the evening meal". The information also varies with regard to determining the time until which the majority of daily calorie intake is "normally" consumed. In the effort to achieve clear diagnostic criteria, times between 6pm and 7pm are often suggested (Cleator et al., 2012; Mühlhans et al., 2009). However, Adami, Meneghelli and Scopinaro pointed out as early as 1997 that clear cultural differences can be found in the daily eating rhythm. In Southern countries, an evening meal after 8pm as well as a very small breakfast are not unusual and are not suggestive of disordered eating behavior. Therefore, the criterion "after the evening meal" has prevailed, in order to adapt as far as possible to differing cultural norms as well as personal (often also influenced by external conditions such as work times) habits. In several studies, a close relation between NES with evening food intake and so-called nocturnal eating (nocturnal awakening with food intake) has been found. Many patients describe anxiety before nighttime eating and consequently also anxiety before falling asleep (Allison, 2012). Although the consumed amount of food is not large, patients with NES frequently mention a feeling of limited control over evening and specifically nighttime food consumption (Cleator et al., 2012; Royal, Wnuk, Warwick, Hawa, & Sockalingam, 2015). In particular, the thought of "having to eat to be able to fall (back) asleep" is seen as a typical symptom of NES (Vinai et al., 2014).

Moreover, the symptoms also include disturbances in sleep onset and/or maintenance, although this does not necessarily have to be linked to food consumption, and lack of appetite in the

[18] With permission from the Thieme Verlag, several paragraphs have been taken directly, or slightly modified, from the review article: de Zwaan, M. (2016). Das Night-Eating-Syndrom. *PSYCH up2date, 10*, 479-490.

mornings. The latter was defined by Stunkard et al. (1995) as “lack of appetite in the morning, in which no breakfast is consumed (apart from coffee or orange juice)”. As the formulation “lack of appetite in the morning” represents the patient’s subjective evaluation, nowadays, a complete skipping of breakfast is required as a diagnostic criterion for NES (Allison, Lundgren, O'Reardon, et al., 2010).

Since the first description of NES by Albert Stunkard and colleagues (1955), various diagnostic criteria for the disorder have been postulated (Cleator et al., 2012; Mühlhans et al., 2009). Table 12 lists the diagnostic criteria suggested in 2010 by Allison, Lundgren, O'Reardon, et al.

2.1.2. Diagnostic criteria according to ICD-10 and DSM-5

While NES is not listed in the ICD-10 (WHO, 2000), diagnostic criteria for the disorder were listed for the first time in the DSM-5 (APA, 2013), in the category “Other specified feeding or eating disorder” (Table 13). The DSM-5 criteria remain rather superficial and are less detailed than the research criteria suggested by Allison et al. (2010). For instance, frequencies or levels of severity are not defined and associated symptoms such as lack of appetite in the morning or sleep disturbances are not taken into account.

2.2. Comorbidity

Patients with NES have a higher prevalence of psychiatric lifetime diagnoses. This applies to affective disorders, anxiety disorders and substance-related disorders (Faulconbridge & Bechtel, 2014) but also psychotic disorders (Palmese et al., 2013). On the other hand, NES is found more frequently in patients in the psychiatric outpatient or inpatient setting than would be expected in the general population (Kucukgoncu, Tek, Bestepe, Musket, & Guloksuz, 2014). NES occurs particularly in times of increased stress (Vander Wal, 2012).
Based on the current state of knowledge, moreover, a close relation between NES and overweight/obesity is assumed (Gallant, Lundgren, & Drapeau, 2012). The prevalence of NES in persons with obesity lies between 6 and 16%, with the frequency of NES rising with increasing weight (Colles, Dixon, & O'Brien, 2007). Higher prevalences are also found in therapy-seeking than in non-therapy-seeking persons with obesity (de Zwaan, Marschollek, & Allison, 2015; Kucukgoncu, Midura, & Tek, 2015; Vander Wal, 2012). Furthermore, cross-sectional studies indicate that persons with diabetes mellitus type 2 show a higher prevalence of NES. There are several studies on the occurrence of NE or NES in patients with diabetes mellitus type 2 (Allison et al., 2007; Hood, Reutrakul, & Crowley, 2014; Morse, Ciechanowski, Katon, & Hirsch, 2006; Schwandt, de Zwaan, & Jäger, 2012), all of which found a significant association between NES and higher depression scores, higher eating disorder scores and reduced quality of life. In all but one study (Allison et al., 2007), there was a significant association between NES and a poorer glycemic control (higher HbA1c values and higher number of diabetes-specific sequelae).

2.3. Differential diagnosis

With regard to differential diagnosis, other eating disorders (e.g. BED, sleep-related eating disorder), physical diseases, intake of diuretics, drug misuse and similar should be clarified (Allison, Lundgren, O'Reardon, et al., 2010; APA, 2013). Equally, NES should not be diagnosed in persons who show a delayed day/night rhythm due to shift work. It should be noted that the presence of these illnesses does not rule out the simultaneous presence of NES. However, it needs to be checked whether the presenting symptoms are not sufficiently explainable by another eating disorder (e.g. evening binge eating episodes in BED or BN) or a physical disease (e.g. nocturnal hypoglycemia in the case of diabetes mellitus).

In contrast to BED (cf. guideline chapter BED), in the case of NES – and especially in nighttime eating – unusually large amounts of food are not normally consumed (Birketvedt et al., 1999; de Zwaan, Roerig, Crosby, Karaz, & Mitchell, 2006). Previous studies have yielded rather small overlaps between BED and NES, ranging between 0% and 26.5% (de Zwaan, Burgard, Schenck, & Mitchell, 2003). Accordingly, two distinct disorders are assumed. The clearest differences between BED and NES lie in the motivation to eat, in the amount of food consumed per eating episode, and in the extent of dissatisfaction with weight and shape (de Zwaan et al., 2015; Vander Wal, 2012).

In the third edition of the International Classification of Sleep Disorders (ICSD-3) by the American Academy of Sleep Medicine (Medicine, 2014), an eating-related sleep disorder is described, the so-called “Sleep Related Eating Disorder” (SRED). The syndrome is listed in the DSM-5 under the NREM parasomnias together with sleepwalking and sleep terrors (Pavor nocturnus) (APA, 2013). SRED is characterized by recurrent, undesired nocturnal eating episodes, occasionally with inedible substances also being consumed. Moreover, awareness is partially or completely impaired and there is a varying degree of amnesia regarding the nocturnal eating episode. These criteria can be categorized as a sleep disorder and rather give rise to the assumption of an association with sleepwalking than with eating disorder. Above all, the lack of awareness of the nocturnal food consumption in conjunction with an impaired recollection of the nocturnal events the next morning constitutes an important distinguishing criterion. Nevertheless, a continuum of the two syndromes can be assumed, as, for example, partial awareness (“half awake, half asleep”) is also described by patients with NES (Allison, 2012).

2.4. Etiology

Compared to control persons, a dissociation between the circadian rhythm of sleep and food intake has been found in patients with NES. At the same time, the sleep rhythm seems to be unimpaired and the circadian rhythm of food intake seems to be delayed (Stunkard, Allison, Lundgren, & O'Reardon, 2009). This could contribute to a conflict between the desire to sleep and the desire to eat. Additionally, the circadian rhythm of glucose, melatonin, leptin and ghrelin, cortisol, prolactin and TSH appears to be delayed or desynchronized (Allison et al.,

2005; Birketvedt et al., 2012; Goel et al., 2009). The biobehavioral model of Vander Wal (2014) assumes that there is a genetic vulnerability to increased serotonin reuptake and that stress triggers a dysregulation of circadian rhythms and a decrease in satiety. This, in turn, might increase the risk of developing NES.

2.5. Therapy

2.5.1. Treatment aims

The aim of treatment for NES is to reduce, and ideally cease, the evening /nighttime eating episodes and achieve a normalization of the day/night rhythm of eating behavior (de Zwaan, 2016; Pinto, Silva, Bruin, & Bruin, 2016) (Table 14).

2.5.2. Treatment approaches and methods

2.5.2.1. Pharmacotherapy

Selective serotonin reuptake inhibitors (SSRIs)

There are several case reports and uncontrolled investigations with sertraline (50-200 mg) (O'Reardon, Stunkard, & Allison, 2004; Stunkard et al., 2006), paroxetine (20-30 mg), fluvoxamine (25 mg) (Miyaoka et al., 2003) and escitalopram (5-20 mg) (Allison et al., 2013), which overall report a positive effect of SSRIs on the reduction of night-eating symptoms [see also (Vander Wal, 2014)]. However, so far, only two randomized controlled trials have been published, which will be briefly described.

Sertraline, in a flexible dosage of 50 to 200 mg, was compared in 34 outpatients with NES randomized with placebo (O'Reardon et al., 2004). The treatment duration amounted to 8 weeks, sertraline was given as an evening dosage, and the average dosage at the end of the study was 126.5 mg (SD=50.4). Diagnosis was made using a structured clinical interview. The primary endpoint was the improvement rating on the Clinical Global Impression (CGI) scale. After 8 weeks of treatment, 71% of the sertraline group and 18% of the placebo group had a CGI improvement rating of 2 or lower (strongly improved). Moreover, the scores on the Nighttime Eating Symptom Scale (NESS) also showed a significantly greater reduction in the sertraline group than in the placebo group. Calorie intake following the evening meal in the sertraline group fell from 47.3% of daily calorie intake to 14.8%, and in the placebo group from 44.7% to 31.6%. The superiority of sertraline was also demonstrated with regard to weight loss and improvement in quality of life. Most of the effects already emerged after 2 weeks of treatment. The improvements in night-eating symptoms were independent of depressive symptoms. Two patients dropped out of the study due of a lack of efficacy.

In a bi-center randomized controlled trial, escitalopram was used in a flexible dosage of 10 to 20 mg versus placebo in 40 patients over a period of 12 weeks (Vander Wal, Gang, Griffing, &

Gadde, 2012). Again, the medication was given in the evenings. Diagnosis was made using the NESHI interview and all patients additionally had an NEQ score of 25 or higher. The primary endpoint was the change in the NEQ sum score. Secondary endpoints were a 50% reduction in the NEQ score, no longer fulfilling the diagnostic criteria for NES, and a CGI improvement score of 1 or 2, as in the study with sertraline. The two treatment groups did not differ in any of the endpoints. The NEQ sum score decreased by 13 points in the escitalopram group and by 10.6 points in the placebo group. After 12 weeks of treatment, 60% of the escitalopram group and 35% of the placebo group had a CGI improvement rating of 2 or lower (strongly improved). Compared to the study with sertraline (18%), the placebo response rate was thus substantially higher. All patients completed the study.

Overall, SSRIs appear to be somewhat efficacious for reducing symptoms in patients with NES, although the evidence is still limited. The placebo response rates are high and the treatment durations are short, which in a disorder with a fluctuating course, may have simply led to a depiction of the natural course. Moreover, longitudinal studies are lacking, both as maintenance therapy and as follow-up after discontinuing the medication.

Agomelatine

In one case study and one case series with 5 patients with NES and comorbid depression, Milano, De Rosa, Milano and Capasso (2012, 2013) found an improvement in mood, a reduction in the sum score of the NEQ, and a weight loss following administration of agomelatine up to 50 mg/day over a period of 12 weeks. As melatonin plays an essential role in the circadian rhythm, this idea stands to reason. However, the data are not sufficient to draw any recommendations.

Other medications

Case reports and case series with positive effects also exist for topiramate (75-125 mg) (Cooper-Kazaz, 2012; Tucker, Masters, & Nawar, 2004; Winkelman, 2003). Here, due to the rather unfavorable side effect profile and the selective case reports, larger studies are certainly warranted.

2.5.2.2. Psychotherapy

Cognitive-behavioral therapy (CBT)

As early as 2010, an open pilot study with 25 patients who received 10 individual sessions of psychotherapy was published (Allison, Lundgren, Moore, O'Reardon, & Stunkard, 2010). The treatment was based on a therapy manual which is available in the English language (Allison, 2012). According to the manual, the treatment consists of 10 individual sessions which are structured into 3 phases. In the first 4 sessions, besides psychoeducation, a primary focus is on self-observation of sleeping and eating behavior as well as mood and automatic thoughts linked to the nighttime eating. A structured eating behavior with regular mealtimes is recommended, and patients should refrain from diets. The authors attribute particular importance to the thought "I won't be able to go (back) to sleep if I don't eat something" in terms of the maintenance of

the disorder, and especially of nighttime eating. In phase 2, skills (including muscle relaxation) are trained and automatic thoughts are questioned. The final two sessions (phase 3) serve the purpose of relapse prevention.

In the framework of the open pilot study (Allison, Lundgren, Moore, et al., 2010), only 14 of the 25 patients took part in at least 8 of the intended 10 sessions (56%). This group was able to successfully reduce their food intake following the evening meal (35% to 24.9%), the nocturnal awakening per week (13.5 to 8.5), the nighttime food consumption per week (8.7 to 2.6) and body weight (from 82.5 to 79.4 kg). The results are comparable with those that were achieved for sertraline (see above).

Relaxation training

In a small randomized controlled trial, the effect of progressive muscle relaxation in comparison with "quietly sitting" was examined in 20 patients with NES (Pawlow, O'Neil, & Malcolm, 2003). The therapy duration was 1 week. The rationale for this study lay in the relationship between NES and high levels of stress, as already described by Stunkard et al. (1955). Progressive muscle relaxation was superior to the control group in terms of reducing stress and anxiety. Moreover, the patients reported a significant reduction in the feeling of hunger in the evening and an increased appetite in the morning. However, the actual amount of food consumed in the night and in the morning did not differ significantly between the groups.

A further small randomized controlled trial compared three groups with one another (Vander Wal, Maraldo, Vercellone, & Gagne, 2015): 1) psychoeducation (PE) alone (PE, n=14), 2) psychoeducation with progressive muscle relaxation (PMR, n=15) and 3) PE, PMR and additional exercise (PMRplus, n=15). The authors expected to find an additive effect of the three interventions. Overall, three appointments took place over a period of three weeks. 86.7% completed the study, and the overall remission rate was 32%. Evening eating episodes were reduced by 55% and nighttime eating episodes by 23%. In all three groups, there was a significant reduction in NES symptoms, and there were no differences between the groups. Only with regard to "percent of food eaten after the evening meal" did group differences emerge. The group which received PMR in addition to PE reported the clearest reduction (-30.5%) and thus differed significantly from the group that only received PE (-0.95%). Additional exercise had no effect.

Other therapeutic techniques

In two case studies, light therapy proved to be effective in patients with depression and NES (Friedman, Even, Dardennes, & Guelfi, 2002, 2004). In both cases, a remission of NES symptoms occurred following 30-minute, morning sessions with 10,000 Lux over a period of 14 days. In a further case series with 15 patients who likewise received light therapy of 10,000 Lux over 14 days, similar effects were achieved (McCune & Lundgren, 2015).

2.5.3. Treatment settings

Currently, there are no evidence-based recommendations regarding the treatment setting for NES. It can be assumed that persons with NES can fundamentally be treated in an outpatient setting (de Zwaan, 2016; Pinto et al., 2016).

Recommendations

- Knowledge on the treatment of NES is relatively limited.
- Due to potential somatic comorbidities of NES (e.g. obesity, diabetes), medical clarification should be conducted. (GCP)
- In the presence of NES, SSRIs, progressive muscle relaxation and cognitive-behavioral therapy should be considered. (0, EL 2b)

3. Purging disorder

3.1. Symptoms and diagnostic criteria

3.1.1. Symptoms

Some patients show bulimic symptoms but do not report objectively large binge eating episodes with loss of control, as required for the diagnostic criteria of BN (see guideline chapter BN). Rather, they deem even small meals to be too big and therefore regularly apply compensatory behaviors such as self-induced vomiting and abuse of laxatives, diuretics and/or thyroid medications. For these patients, the diagnostic description of purging disorder was suggested (Keel, 2007; Koch, Quadflieg, & Fichter, 2013). Sufferers have recurrent eating episodes which are characterized by the consumption of an amount of food that is not substantially large but is subjectively perceived to be large, as well as the experience of loss of control over food intake (Forney, Haedt-Matt, & Keel, 2014; Goldschmidt et al., 2016).

3.1.2. Diagnostic criteria according to ICD-10 and DSM-5

While purging disorder is not mentioned in the ICD-10 (WHO, 2000), the disorder was included in the DSM-5 (APA, 2013) as a syndrome in the category "Other specified feeding or eating disorder". The diagnosis should be made if recurrent purging behavior is undertaken in order to influence weight or shape (e.g. self-induced vomiting, abuse of laxatives, diuretics or other medications).

3.2. Comorbidity, etiology, course

The findings on differences and overlaps between purging disorder and BN, or between purging disorder and AN, are inconsistent. While some works were able to demonstrate differences, with partially small effect sizes (Brown, Keel, & Striegel, 2012; Keel, Wolfe, Gravener, & Jimerson, 2008; Tasca et al., 2012), other authors rather assume that no substantial differences exist between patients with purging disorder and BN particularly in terms of course, prognosis, extent of restrictive eating behavior, body image disturbance or psychiatric comorbidity (de Zwaan & Mühlhans, 2015; Keel & Striegel-Moore, 2009; Tasca et al., 2012). The results of a first ecological momentary assessment study with 24 women with purging disorder indicate that purging behavior serves purposes of emotion regulation (Haedt-Matt & Keel, 2015). Due to the suspected similarity with BN, reference is made here to the guideline chapter BN.

3.3. Therapy

3.3.1. Treatment aims

Treatment aims are the reduction or cessation of purging episodes, the normalization of eating behavior and accompanying eating disorder symptoms, as well as a BMI in the normal range.

3.3.2. Treatment approaches and methods

So far, only a small number of treatment studies have been published which examined patients with purging disorder separately (table 15). One exception is the study by Tasca et al. (2015), in which a total of 265 patients with eating disorders received day-clinic treatment based on the Toronto General Hospital Eating Disorders Program (Olmsted, McFarlane, Molleken, & Kaplan, 2001). The therapy offer included group therapies for the improvement of eating disorder symptoms, mood and interpersonal problems as well as nutritional counseling and dietary change, although the authors refrained from publishing a detailed description of the therapy components. The treatment sample was composed of patients with purging disorder (n=25), AN restrictive type (n=50), AN binge-eating/purging type (n=64) and BN (n=126). A randomization was not undertaken. The endpoint was a so-called "good treatment outcome", which was operationalized as follows: 1) no binge eating or purging during the last four treatment weeks, BMI≥20 kg/m^2 during the last two treatment weeks, and 3) BMI≥19 kg/m^2 during the two weeks before the last two treatment weeks. These criteria were fulfilled by 48% of the patients with purging disorder, 57% of the patients with binge-purge BN, 36% of the patients with restrictive AN and 33% of the patients with AN binge-eating/purging type. Regression analyses yielded no significant difference in the achievement of a good treatment outcome between patients with purging disorder and the other therapy groups (odds ratios n.s. when comparing the purging disorder group with each of the other groups, dependent variable "good treatment outcome" yes/no) (Tasca et al., 2012). Likewise, patients with purging disorder did not differ regarding the post-treatment remission rates.

A case report by Sysko and Hildebrandt (2011) also appears to be promising: According to this case study, a 16-year-old girl with purging disorder benefited very much from enhanced CBT modified for adolescents (Cooper & Stewart, 2008).

3.3.3. Treatment settings

It is not possible to derive empirically based specific recommendations on treatment setting in the case of purging disorder.

Recommendations

- Currently, it is not possible to derive empirically based treatment recommendations that are specific for the treatment of patients with purging disorder.
- Due to potential somatic consequences of purging disorder, medical clarification should be considered (GCP).
- If purging disorder is present, proceeding with treatment analogously to the treatment of BN should be considered (GCP).

FURTHER "FEEDING AND EATING DISORDERS" LISTED IN THE DSM-5

This subchapter focuses on eating disorders which are listed in the DSM-5 (APA. 2013) in addition to the classical eating disorders AN, BN, and BED, in the chapter "Feeding and Eating Disorders". Table 16 summarizes the treatment studies on pica, rumination disorder and avoidant/restrictive food intake disorder (ARFID).

4. Pica

4.1. Symptoms and diagnostic criteria

4.1.1. Symptoms

Prior to the 20th century, pica was not considered as a disorder in its own right, but was rather subsumed under other diagnoses (AN, BN or rumination) (Hakim-Larson et al., 1997; Parry-Jones & Parry-Jones, 1994). Pica is characterized by the ingestion of substances that are not seen as food and also possess no nutritional value. Substances include, for example, paper, hair, earth, chalk, paint and clay. In most cases, there is no fundamental aversion to normal foods. In addition to the breadth of the possible consumed substances, the associated behaviors can also differ considerably. While some sufferers experience an urge to consume the substance due to its taste or consistency, in others, for instance persons with intellectual impairments, the behavior can constitute a form of self-soothing.

The disorder appears to be especially frequent in children, persons with developmental disorders or intellectual impairments, persons in institutions, pregnant women and persons in underdeveloped regions of the world or with a low socioeconomic status (Rose, Porcerelli, & Neal, 2000). So far, the assumption is that the disorder does not present differently in children, although it can also be assumed that children are cognitively less capable of judging and

perceiving the possible medical consequences of the behavior, which can additionally complicate the treatment of the problem.

4.1.2. Diagnostic criteria according to ICD-10 and DSM-5

In the ICD-10, pica is defined as the persistent consumption of non-nutritive substances. Only if it occurs as a relatively isolated psychopathological behavior it is diagnosed under F98.3 under the disorders with onset in childhood or adolescence. Alternatively, the broader disorder is diagnosed and the behavior is subsumed therein. For adults, a diagnosis under F50.8 – other eating disorders – is used. In the DSM-5 (APA, 2013), the diagnosis is found in the category of eating disorders and can thus be applied to all age groups. Furthermore, it is specified that the consumption of the substance takes place at least once a month and is not part of a culturally supported or socially normative practice. Furthermore, the differential diagnosis is defined somewhat further and pica should only be given as an additional diagnosis in the case of another mental disorder or medical condition if it requires additional treatment.

4.2. Comorbidity

Pica is frequently associated with intellectual impairment or developmental disorders, for instance autism spectrum disorder (Clark et al., 2010). Based on individual case studies and several larger studies, it might be part of frequently occurring comorbidities in obsessive-compulsive disorder (Bhatia & Gupta, 2009), impulse control disorder (Stein, Bouwer & van Heerden, 1996), schizophrenia (Dumaguing et al., 2003) and other eating disorders (Delaney et al. 2014). Possible comorbidly occurring medical complications (caused by the pica behavior) can include intestinal perforation or obstruction, intoxication, asphyxiation and infections (Decker, 1993; Dumaguing et al., 2003; Luoba et al., 2005; Saathoff et al., 2002).

4.3. Differential diagnosis

Pica should principally be differentiated from the following five disorders: If the substance is only consumed as an alternative to normal foods in order to counteract weight gain (as part of AN, BN or BED; Delaney et al., 2014) or in order to have a substance with the desired sensory properties (smell, taste or consistency in the case of ARFID), the diagnosis should not be made (Hartmann et al., 2012). Persons who undertake self-harm with non-suicidal intention and consequently consume potentially dangerous objects should also not receive an additional diagnosis. Moreover, persons suffering from psychoses may also consume objects and substances, possibly as a consequence of a hallucination or as the function of a delusion (Fishbain & Rotondo, 1983; Foulon, 2003). Such behavior would be subsumed as part of a psychosis diagnosis. Finally, a factitious disorder can also be mentioned as a further differential diagnosis, in which objects and substances are swallowed in order to produce medical symptoms and receive medical treatment (APA, 2013).

4.4. Etiology

To date, there are no comprehensive evidence-based models to explain the etiology of all forms of pica.

4.5. Course

Longitudinal representative data regarding the onset and course of the disorder are still lacking. Nevertheless, the typical onset appears to occur in childhood, often followed by spontaneous remission. Persistence into adolescence and adulthood seems to be detected more rarely (APA, 2013). However, particularly in children with a developmental disorder or intellectual impairment, pica can persist, especially if it remains untreated (Matson et al., 2011). In part, later disorder onsets occur in certain subgroups, for instance pregnant women (APA, 2013).

4.6. Therapy

4.6.1. Treatment aims

The aim of pica treatment is to reduce, and ideally cease, the ingestion of substances that are non-food and non-nutritive.

4.6.2. Treatment approaches

One randomized controlled trial describes the treatment of pica in children using iron or multinutrient supplementations (Nchito et al., 2004). No effect was found regarding the reduction of pica behaviors. Medical reasons for the pica behavior (for example in terms of malnutrition), however, should be considered in the treatment planning. Psychotherapeutic treatment components which are mentioned in case studies belong primarily to the group of behavior modification (operant techniques): stimulus control, habit reversal and positive reinforcement with pleasant consequences (Kelly et al., 2014).

4.6.3. Treatment settings

Currently, there are no evidence-based recommendations regarding treatment setting. It can be assumed that pica can essentially be treated in the outpatient setting, except for if the preferred substance carries a strong medical risk, and if patients show little insight into the illness and thus need closer supervision for the purpose of stimulus control.

Recommendations

- Currently, it is not possible to derive empirically based treatment recommendations which are specific for the treatment of pica.
- Due to the potential risk through accompanying diseases and deficiencies (e.g. anemia), medical clarification and where necessary medical treatment should be considered (GCP).
- In the treatment of patients with pica, behavioral-therapeutic techniques should be considered. (0, EL 5).

5. Rumination disorder

5.1. Symptoms and diagnostic criteria

5.1.1. Symptoms

Rumination disorder is characterized by the regurgitation of previously swallowed and possibly partially digested food. This process occurs intentionally without physical-somatic reasons such as reflux, nausea or aversion. It is sometimes accompanied by coughing or contractions or the tongue or abdomen or the help of the fingers. The food is then chewed again and spat out or swallowed again. Moreover, infants display a characteristic arching of the back, including jerky movements (Nicholls et al., 2008).

5.1.2. Diagnostic criteria according to ICD-10 and DSM-5

In the ICD-10, rumination disorder is not listed separately, but is rather subsumed as F98.2 under 'Other feeding disorders of infancy and childhood,' and mentioned as a possible symptom. In the DSM-5, the disorder is described as a repeated regurgitation of food over a period of at least one month. The regurgitated food can either be chewed, swallowed or spat out. The repeated regurgitation should not be a consequence of a condition of the gastrointestinal tract or of another somatic disease (e.g. esophageal reflux, pyloric stenosis). Moreover, the differential diagnosis from the eating disorders and other mental disorders is specified.

5.2. Comorbidity

In the DSM-5, it is merely noted that rumination disorder can occur in the context of other disorders, such as generalized anxiety disorder, and more frequently occurs in the context of intellectual impairment. So far, systematic empirical works examining the comorbidity of rumination disorder are lacking.

5.3. Differential diagnosis

The eating disorders AN and BN can also feature regurgitation and spitting out of food in order to rid oneself of additional calories. Furthermore, gastrointestinal conditions need to be clarified from a differential diagnostic perspective.

5.4. Etiology

So far, there are no evidence-based models to explain the etiology of rumination disorder.

5.5. Course

Fundamentally, the onset of the disorder can occur at any age. If the disorder occurs for the first time in infancy, spontaneous remission often arises. Little is known about the course of the disorder in adolescence and adulthood.

5.6. Therapy

5.6.1. Treatment aims

The aim of treatment for rumination disorder is to reduce, and ideally cease, the behavior.

5.6.2. Treatment approaches

There is one randomized controlled trial in the area of rumination disorder. In an outpatient setting, 18 women and 6 men (19-79 years old), who met the ROME III criteria for rumination, were randomized to a placebo and a treatment group. Three sessions over 10 days with EMG biofeedback training targeted increased control of the abdomino-thoracic muscles and learning of abdominal breathing. This led to a reduction in rumination activity of 74% (from 29±6 to 7±2 daily activities) in the intervention group vs. 1% in the placebo group (from 21±2 to 21± 4 daily activities) ($p = 0.001$) (Barba, Accarino, Soldevilla, Malagelada & Azpiroz, 2016). Psychotherapeutic techniques which have also been mentioned in case studies are habit reversal and reinforcement with positive consequences (Tack et al., 2011).

5.6.3. Treatment settings

Currently, there are no evidence-based recommendations regarding treatment setting. It can be assumed that rumination disorder can fundamentally be treated in the outpatient setting except for when the behavior leads to a strong medical risk and the sufferer therefore requires close supervision.

Recommendations

- Currently, it is not possible to derive empirically based treatment recommendations which are specific for the treatment of patients with rumination disorder.
- In patients with rumination disorder, somatic clarification is recommended (GCP)
- In the treatment of patients with rumination disorder, EMG biofeedback training can be justified (0, EL 3)

6. Avoidant/Restrictive Food Intake Disorder

6.1. Symptoms and diagnostic criteria

6.1.1. Symptoms

Avoidant/restrictive food intake disorder (ARFID) describes a maladaptive pattern of feeding or eating which results in significant health consequences. These can be weight loss, stalled growth, deficiencies and subsequent dependency on artificial feeding or nutritional supplements. Thus, although the food restriction in ARFID is not associated with significant body image concerns, but rather mostly with concerns about the characteristics or sensory properties of food (extreme sensitivity towards external appearance, color, smell, consistency, temperature or taste), the health consequences can be reminiscent of AN (hypothermia, bradycardia, anemia, tooth decay and electrolyte disturbances; Pinhas et al., 2011).
The disorder mostly occurs for the first time in early childhood, which is why careful attention should be paid to the symptoms in this age group. Moreover, in the very young age group, the caregiver who feeds the child, as well as his/her relationship with the child, plays a very important role for diagnosis and treatment.

6.1.2. Diagnostic criteria according to ICD-10 and DSM-5

In the ICD-10, the disorder is categorized as a feeding disorder of infancy and childhood (F98.2). It comprises food refusal or extreme fadiness in the presence of an adequate food supply and a reasonably competent caregiver and the absence of organic disease. Rumination may also be present. The disorder should be distinguished from "fussiness" and should only be diagnosed if it goes clearly beyond the normal range or is qualitatively abnormal or if the child is not gaining weight or is losing weight.
In the DSM-5, the disorder is found in the category of "Feeding and eating disorders". It describes an eating or feeding disorder in the sense of a lack of interest in eating or in food, the avoidance of sensory characteristics of foods or concerns about aversive consequences of eating. The disorder manifests in an insufficient energy consumption in terms of weight loss (or insufficient weight gain or vertical growth in children), significant nutritional deficiencies, dependence on oral nutritional supplements or enteral feeding. A particular difference from the ICD-10 diagnosis is that an onset before the age of six years is not an essential criterion.

6.2. Comorbidity

Disorders which have already been described as occurring comorbidly with ARFID are anxiety and obsessive-compulsive disorders (Norris, Robinson, Obeid, Harrison, Spettigue & Henderson, 2014; Zickgraf, Franklin & Rosin, 2016), especially generalized anxiety disorder (Fisher et al., 2014) and learning and developmental disorders (Nicely, Masciulli, Hollenbeak & Ornstein, 2014), especially autism spectrum disorder (Sharp, Berry & McCracken, 2013).

6.3. Differential diagnosis

To date, systematic investigations on mental disorders and medical diseases which should be delineated from ARFID from a differential diagnostic perspective are lacking. Anorexia nervosa constitutes a particularly relevant differential diagnostic category, in which, however, food restriction is mainly based on body image-associated concerns. Further differences from anorexia nervosa lie in the often younger age, the longer duration of illness, the larger proportion of male sufferers, higher weight and a higher likelihood of comorbid medical diseases and anxiety disorder but a lower likelihood of an affective disorder (Fisher et al., 2014; Norris et al., 2014).

However, restrictive food intake (based among other things on lack of appetite) can occur unspecifically in various mental disorders. All differential diagnoses listed in the following can also be given comorbidly, as long as all diagnostic criteria are fulfilled and a separate clinical consideration is justified. They are also mentioned in the DSM-5 (APA, 2013). Besides other interactions, the feeding situation can be affected by a reactive attachment disorder. Persons with autism spectrum disorder often show rigid eating behavior and increased sensory sensitivity. Moreover, specific phobias (especially fear of choking or vomiting) and social

anxiety disorder (fear of being observed by others while eating) can lead to an ARFID-resembling avoidance. Furthermore, persons with obsessive-compulsive disorder can show food avoidance or restriction in relation to an excessive concern with respect to eating or in relation to ritualized eating behavior. Food avoidance or restriction can additionally arise in the framework of schizophrenia or delusional disorder as a reaction to delusional ideas. A factitious disorder or factitious disorder imposed on another also need to be considered. In this context, food avoidance or food restriction might be used to bring about possible medical complications in order to be able to seek medical treatment.

Besides mental disorders, above all, other physical diseases such as gastrointestinal diseases, food allergies and intolerances as well as invisible malignancies should be considered. Furthermore, neurological/neuromuscular, structural and congenital disorders can also be linked to feeding difficulties.

6.4. Etiology

To date, there are no evidence-based models to explain the etiology of ARFID.

6.5. Course

Systematic investigations on the course of ARFID are lacking. In the DSM-5, prototypical courses for the specific subforms of ARFID are described as follows: Food avoidance or restriction based on disinterest in food mostly develop in infancy or early childhood and can persist into adulthood. Avoidance due to sensory characteristics likewise mostly arises in the first decade of life and can persist, while avoidance which is based on the anticipation of aversive consequences of eating can emerge at any age. The few available longitudinal studies point to a high persistence with a comparatively high functioning in adulthood with respect to the form based on the sensory characteristics of food. Less is known about the other forms.

6.6. Therapy

6.6.1. Treatment aims

The aim of treatment for ARFID is to reduce, and ideally cease, the food restriction and thus to reduce the medical risks, especially underweight.

6.6.2. Treatment approaches

Three randomized controlled trials were found. One was characterized as a pilot trial, in which 20 children aged between 13 and 72 months with a diagnosis of ARFID were allocated to a 5-day treatment in a day-clinic setting or a waiting list (10 patients in each group) (Sharp et al.,

2016). The behavioral therapy included reinforcement techniques as well as a formalized mealtime structure (written instructions, reduced bite volume and pureed food texture). In the framework of the treatment meals, eight foods were available, two each from the groups of proteins, starch, fruit and vegetables. At each meal, the caregiver offered four foods. The bite volume was continuously increased. At the end of treatment, the treatment group showed greater improvements on all outcome measures (bite volumes, level of disruptions of feeding situation, volume of food consumed; $p = .05$; $d=1.03$-2.11) compared to the waitlist control group ($d=-1.13$-0.24). These differences remained stable over the course of one month.

The second randomized controlled trial on general feeding disorders in childhood (not diagnosed as ARFID according to DSM-5) included 64 children aged 4-36 months who participated with their primary feeders in a 7-week week-day inpatient therapy. It was shown that behavioral therapy (main focus) plus a nutritional intervention is superior to a traditional nutritional intervention alone (establishing structured plans and routines to stimulate hunger/satiety cycles) in terms of the transition from enteral to oral feeding (Benoit, Wang & Zlotkin, 2000). 4.5 months after the first clinic visit (3rd follow-up), 15 of the 32 patients in the combination group no longer required enteral feeding, compared to no patients in the nutritional intervention alone group.

In the third randomized controlled trial, 22 children aged 9-24 months who were fully tube fed were allocated to a hunger provocation program and a standard treatment program. The hunger provocation program comprised a stepwise reduction in the proportion of food administered via the tube and an increasing oral feeding initially in the absence of the parents. As soon as it was possible to remove the tube, the parents were included in the oral feeding. In the hunger provocation program group, 9 of 11 patients (81.8%) were successfully weaned from tube feeding, while only 1 of 11 patients (9%) in the control group was successfully weaned. The control group patients who were not successfully weaned subsequently received the hunger provocation program. Accordingly, at follow-up, 18 of 21 patients (86%) had been successfully treated (Hartdorff, Kennpkens, Stok-Akerboom, van Dijl-Lokkart, Engels & Kindermann (2015).

A systematic review of pediatric feeding disorders which also considered case series in addition to the aforementioned randomized controlled trials summarizes that the potentially effective psychotherapeutic treatment techniques mainly stem from behavioral interventions (positive and negative reinforcement, shaping, discrimination, fading; Lukens & Silverman, 2014). This was confirmed by a recent meta-analytic review, which in addition to the two aforementioned randomized controlled trials (Hartdorff et al., 2015; Sharp et al., 2016) also included retrospective chart reviews (Sharp, Volkert, Scahill, McCracken & McElhanon, 2017). In summary, it can be concluded that behavioral therapy interventions and the weaning from tube feeding are the main components in the treatment of ARFID. These measures led to successful weaning from tube feeding in 71% of patients (95% CI 54%-83%). The successes also remained stable following discharge (80%; 95% CI 66%-89%). Moreover, the treatment led to an increased oral food intake, improved behavior during mealtimes and reduced parental stress (Sharp et al., 2017). For young patients suffering from ARFID, modifiable parent variables can

also constitute aims of the treatment in order to change the feeding situation (McGrath Davis et al., 2010).

An adjuvant treatment with cyproheptadine, an active substance from the group of antihistamines, may potentially lead to an improvement of ARFID. This was indicated by the results of a retrospective analysis of the medical records of 127 children aged between 7 and 80 months who were treated due to a feeding disorder fulfilling the description according to the ARFID criteria (Sant'Ana et al., 2014). 82 of the 127 children not only took part in the intervention program but additionally took cyproheptadine (0.25mg/kg per day over 1-3 weeks). The majority of parents of these children (96%) reported an improvement in mealtime and feeding behavior and a weight gain was observed (Sant'Ana et al., 2014).

6.6.3. Treatment settings

Currently, there are no evidence-based recommendations regarding treatment setting. It can be assumed that ARFID can fundamentally be treated in an outpatient setting unless a strong weight loss or medical risk is present due to malnutrition.

Recommendations

- In view of the risk of malnutrition and underweight, a medical clarification in patients with ARFID should be considered (GCP).
- In the treatment of patients with ARFID, a formalized mealtime structure and behavioral therapy interventions, including the parents or guardians, should be considered (0, EL 2b).
- It can be assumed that patients with ARFID can be treated in the outpatient setting. In the case of medical risk due to malnutrition and weight loss, an inpatient treatment is recommended (GCP).
- It is recommended that the treatment of patients with ARFID should be oriented to the guidelines on mental disorders in infancy, toddlerhood and preschool ages (S2k).

Table 1: Atypical and unspecified eating disorders in the ICD-10 and DSM-5	
ICD-10 (WHO, 1992)	**DSM-5** (APA, 2013)
Atypical and other/unspecified eating disorders	***307.59:*** *Other specified feeding and eating disorders*
F50.1: Atypical anorexia nervosa	Atypical anorexia nervosa
F50.3: Atypical bulimia nervosa	Bulimia nervosa of limited frequency and/or limited duration
F50.8: Other eating disorders F50.9: Eating disorder, unspecified	Binge eating disorder of limited frequency and/or limited duration
	Purging disorder
	Night eating syndrome
F98.21: Rumination disorder of infancy	Avoidant/restrictive food intake disorder (ARFID)
	Feeding and eating disorders (except for AN, BN, BED)
F98.21: Rumination disorder of infancy	307.53: Rumination disorder
F98.3: Pica of infancy and childhood F50.8: Other eating disorders, non-organic pica in adults	307.52: Pica

Table 2: Evidence from studies on the treatment of EDNOS (DSM-IV)							
Authors	**Diagnosis**	**Age**	**Study design**	**Treatment**	**n/arm**	Measurement time points	OCEM evidence level
Jacobi et al. 2014	Subsyndromal AN/ BN / BED	22.3 ± 2.9 yrs	RCT	Internet-based prevention program "Student Bodies™„ (SB) vs. WL	64/SB™ 62/WL	Pre-Post 6-mth FU	2b
Zabinski et al. 2004	"At risk" for eating disorder	18.9 ± 2.4 yrs	RCT	Moderated chatroom sessions vs. WL	30/Chatroom 30/WL	Pre-Post 10-wk FU	2b
ter Huurne et al. 2015	EDNOS	41.9 ± 11.3 yrs	RCT	iCBT vs. WL	43/iCBT 42/WL	Pre-Post 15-wk FU	2b
Sanchez-Ortiz et al. 2011	EDNOS	23.9 ± 5.9 yrs	RCT	iCBT vs. WL	18/iCBT 19/WL	Pre-Post 3-mth FU	2b
Tanofsky-Kraff et al. 2014	LOC eating	14.5 ± 1.7 yrs	RCT	Modified IPT vs. Health Education (HE)	52/IPT 53/HE	Pre-Post 6-mth FU 12-mth FU	2b
Psychopharmacological treatment							
Trunko et al. 2014	EDNOS	15 yrs	Case study	Lamotrigine 100mg/d	1	Pre-Post	5

EDNOS = Eating Disorder Not Otherwise Specified, RCT = Randomized Controlled Trial, WL = Waitlist/Waiting control group FU = Follow-up, iCBT = Internet-based cognitive behavior therapy, LOC = Loss-of-Control, IPT = Interpersonal psychotherapy, Wk = Week, Mth = Month

Table 3: Operationalized research criteria from an expert group for night eating syndrome (Allison, Lundgren, O'Reardon, et al., 2010)
A. Excessive eating in the evening/nighttime:
- > 25 % of daily calorie intake after the evening meal and/or
- Nocturnal awakening with food intake at least 2 nights per week.
B. Recall of evening and nocturnal eating episodes
C. At least 3 of the following criteria:
- Low food consumption in the morning and/or omitting breakfast on 4 or more days per week
- Strong urge to eat between evening meal and sleep onset and/or during the night
- Sleep onset and sleep maintenance difficulties on 4 or more nights per week
- Belief that one must eat in order to initiate or return to sleep
- Frequent depressive mood and/or mood worsens in the evening
D. Significant distress and/or decline in functioning
E. Duration of at least 3 months
F. The disorder is not a consequence of substance abuse or dependence, somatic diseases, medication side effects or mental disorders. The disordered eating behavior cannot be better explained by BED.

Table 4: Criteria for Night Eating Syndrome listed in the DSM-5 (APA, 2013)	
1.	Recurrent episodes of night eating, as manifested by eating after awakening from sleep or by excessive food consumption after the evening meal.
2.	Persons are aware of the eating and are able to recall it.
3.	The night eating causes clinically significant distress and/or impairment in social, professional or other important areas of functioning.
4.	The night eating is not better explained by external influences such as changes in the individual's sleep-wake cycle or regional social norms.
5.	The disordered pattern of eating is not better explained by binge eating disorder or another mental disorder, including disorders with substance use, and is not attributable to another medical disorder or to an effect of medication.

Table 5: Evidence from studies on the treatment of Night Eating Syndrome						
Authors	**Diagnosis**	**Study design**	**Therapy arms**	**n/arm**	Measurement time points	**OCEM evidence level**
Pawlow et al. 2003	NES	RCT	Progressive muscle relaxation vs. sitting quietly	10/PMR 10/sitting quietly	Pre-post	2b
Vander Wal et al., 2015	NES	RCT	Psychoeducation (1) Psychoeducation+PMR (2) Psychoeducation+PMR+Exercise (3)	14/(1) 15/(2) 14/(3)	Pre-post	2b
Allison et al. 2010	NES	Case series	CBT	25 (14 completers)	Pre-post	3
Friedman et al. 2002, 2004	NES + Depression	Case study	Light therapy	1 each	Pre-post	4
McCune & Lundgren 2015	NES	Case series	Light therapy	15	Pre-post	4
Psychopharmacological treatment						
O'Reardon et al. 2006	NES	RCT	Sertraline 50-200 mg/d vs. Placebo	17/Med 17/Placebo	Pre-post	2b
Vander Wal et al., 2012	NES	RCT	Escitalopram 10-20 mg/d vs. Placebo	20/Med 20/Placebo	Pre-post	2b
Milano et al. 2013	NES	Case study	Agomelatine up to 50 mg/d	1	Pre-post	4
Cooper-Kazaz 2012	NES	Case study	Topiramate 75-125 mg/d	1	Pre-post	4
Tucker et al. 2004	NES+PTSD	Case study		1	Pre-post	4
Winkelmann 2003	NES	Case study		2	Pre-post	4

NES = Night Eating Syndrome, RCT = Randomized Controlled Trial, PMR = Progressive Muscle Relaxation, CBT = Cognitive Behavior Therapy, Med = Medication, PTSD = Posttraumatic stress disorder

Table 6: Evidence from studies on the treatment of purging disorder						
Study	**Diagnosis**	**Design**	**Therapy arms**	**n/arm**	**Measurement time points**	**OCEM evidence level**
Tasca et al. 2012	PD	Case series	Day-clinic psychotherapy	25	Pre-post	3
Syko & Hildebrandt 2011	PD	Case study	CBT-E	1	Pre-post	4

PD = Purging Disorder, CBT-E = Enhanced Cognitive Behavioral Therapy

Table 7: Evidence from studies on the treatment of pica, rumination disorder, and avoidant/restrictive food intake disorder (ARFID)							
Study	**Diagnosis**	**Age**	**Study design**	**Therapy arms**	**n/arm**	**Measurement time points**	**OCEM evidence level**
Pica							
Nchito et al. 2004	Geophagy	7-15 yrs	RCT	Iron supplementation (1) vs. Placebo	120/(1) 100/Placebo	Pre-post	5 (no effect regarding pica)
				Multimicronutrient supplementation (2) vs. Placebo	109/(2) 111/Placebo		

Rumination disorder							
Barba et al. 2016	RD	19-79 yrs	RCT	Biofeedback vs. Placebo	12/Biofeedback 11/Placebo	Pre-post	2b
ARFID							
Sharp et al. 2016	ARFID	23–72 mths	RCT	Day-clinic behavior therapy (BT) vs. WL	10/VT 10/WL	Pre-post 1-mth FU	2b
Benoit et al. 2000	Feeding disorder	4–36 mths	RCT	BT with nutritional intervention (1) vs. Nutritional intervention (2)	32/(1) 32/(2)	Pre-post 2 FU appointments (final 4.5 mths after pre)	2b
Hartdorff et al. 2015	Feeding (enteral feeding)	9–24 mths	RCT	Hunger provocation vs. TAU	11/Hunger prov. 11/TAU	Pre-post 6-mth FU	2b
Sant‘Anna et al. 2014	Feeding disorder	7–80 mths		Behavior modification + Cyproheptadine (1) vs. Behavior modification (2)	82/(1) 45/(2)	approx. 6 mth preMed Start of Med 3 and 6 mths during Med	2b

RCT = Randomized Controlled Trial, RD = Rumination Disorder, WL = Waitlist/Waiting control group, BT = Behavior therapy, TAU = Treatment as Usual, FU = Follow-up, mth = month, Med = Medication

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Method report atypical, unspecified and other eating disorders

Chapter VII constitutes a revision and substantial extension of the earlier chapter “Atypical and unspecified eating disorders” in order to account for the changes in the DSM-5 (APA, 2013) as well as current considerations on the categorization of eating disorders in the new, 11th revision of the ICD (see ICD-11 Beta Draft: https://icd.who.int/dev11; October 2017). The latter are largely oriented to the DSM-5.

A systematic literature search was conducted in electronic databases (MEDLINE, PubMED, PsycINFO, Web of Science). In addition, a manual search in the reference lists of the identified relevant publications was conducted.

In the following, the search terms for titles, abstracts and keywords are summarized.

ATYPICAL AND UNSPECIFIED EATING DISORDERS

- atypical eating disorder[All Fields] OR atypical eating disorders[All Fields]
- subsyndromal[All Fields] AND ("Eat Disord"[Journal] OR ("eat"[All Fields] AND "disord"[All Fields]) OR "eat disord"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treat"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])
- EDNOS[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treat"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])
- atyp[All Fields] AND ("Eat Disord"[Journal] OR ("eat"[All Fields] AND "disord"[All Fields]) OR "eat disord"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treat"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])
- loss of control eating[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treat"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])
- night eating[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treat"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])
- night[All Fields] AND ("eating"[MeSH Terms] OR "eating"[All Fields]) AND ("syndrome"[MeSH Terms] OR "syndrome"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treat"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])
- (purging disorder[All Fields] OR purging disorders[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treat"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])

FURTHER "FEEDING OR EATING DISORDERS" LISTED IN THE DSM-5

Pica

- Search terms: pica treatment trial; additionally added MESH terms: Additional terms
- trial; therapeutics; topic; trials; pica; clinical trials as topic; therapy; treatment; picas; clinical
- arfid treatment; additionally added MESH terms: therapeutics; treatment; arfid; therapy
- Search terms: pediatric feeding disorders treatment trial

Rumination disorder

- Search terms: rumination disorder treatment trial eating additionally added MESH terms: disorder; disorders; clinical; trials; childhood; rumination disorder; ruminate; eating; ruminators; disord; therapy; feeding and eating disorders of childhood; topic; therapeutics; feedings; eat; ruminating; treatment; ruminations; childhoods; rumination; clinical trials as topic; trial; ruminative; feeding; ruminated

ARFID

- Search terms: arfid treatment; additionally added MESH terms: therapeutics; treatment; arfid; therapy

VIII. Physical sequelae of eating disorders

Ulrich Cuntz, Christiane Walter, Stephan Zipfel

1. Concomitant physical conditions

1.1. Diabetes mellitus

In young women aged between 15 and 25 years, diabetes mellitus is comparatively rare, with an assumed point prevalence of < 0.2 %. However, the clinical frequency of concurrent AN and diabetes mellitus is comparably higher, leading to the assumption of a co-occurrence greater than would be expected by chance. Nevertheless, precise epidemiological data on AN are lacking. Disordered eating behavior that does not yet meet the diagnostic criteria for AN or BN, by contrast, is significantly more common in young female type I diabetics (Colton et al., 2004). A third of young women with insulin-dependent diabetes show disturbed eating behavior, and over 10% show a substantial underdosage or skipping of insulin administration for weight control. Disordered eating behavior is linked to a poorer attitude towards diabetes (Rydall et al., 1997). A meta-analysis on the comorbidity of diabetes mellitus and eating disorders revealed an increased prevalence for bulimia nervosa but not for anorexia nervosa.
A 10-year follow-up investigation by Nielson (Nielsen et al., 2002) compared the mortality of anorexia nervosa, of type I diabetes mellitus and of a combination of both. The mortality rate for type I diabetes amounted to 2.2 per 1000 person-years, 7.3 for anorexia nervosa, and 34.6 for comorbid cases, demonstrating how drastic the consequences of this combination of diagnoses is.

1.2. Pregnancy and eating disorders

Disruption to the hypothalamic-pituitary-gonadal axis leads to a reduced likelihood of pregnancy in the course of AN (Brinch et al., 1988). By contrast, because of menstrual cycle irregularities and the disturbed absorption of oral contraceptives, women with BN have a higher risk of unwanted pregnancies (Morgan, 1999). Pregnancies have the potential to worsen the eating disorder symptoms as the affected women fear losing control over their body weight in the course of the pregnancy. However, longitudinal studies over the course of the first months of pregnancy tend to show a reduction in eating disorder symptoms (Blais et al., 2000; Rocco et al., 2005).

Pregnancies in the case of active eating disorders are not without complications. The newborns show a lower birth weight (Bulik et al., 1999; Franko et al., 2001; Micali et al., 2007). The rate of pregnancy complications is quite substantially increased in both AN and BN (Bulik et al., 1999). By contrast, patients with a history of AN who are in remission show a normal pregnancy risk (Ekeus et al., 2006). Sufferers should receive particular attention in the postpartum period, as both the eating disorder symptoms can again increase, and the risk of postpartum depression also seems to be higher (Mazzeo et al., 2006; Morgan et al., 2006; Rocco et al., 2005).

2. Eating disorders related to physical illness and pregnancy

2.1. Laboratory changes

Eating disorders are accompanied by characteristic, pathological changes in routine lab results, although these do not generally have further clinical implications. The bone marrow, particularly in patients with AN, is hypoplastic and shows gelatinous transformation (Chen et al., 2004), which can lead to both leukopenia and anemia (Abella et al., 2002; Cleary et al., 2010; Thiel et al., 2007). Both anemia and leukopenia normalize in the course of weight gain and do not generally require separate treatment. Recent work indicates a "low grade inflammation" with an IL-6 and TNF-alpha increase found in meta-analyzes (Dalton et al. 2018). The function of the lymphocytes is also impaired (Allende et al., 1998). Thus, in everyday clinical practice, one founds that anorexic patients suffer less frequently from symptoms of common viral infections, but also show fewer physical symptoms in the case of severe infections (Mustafa et al., 1997).

In the case of underweight in AN, serum cholesterol is frequently increased (Nakai et al., 2016). This is essentially due to an increase in the LDL fraction (Weinbrenner et al., 2004). The free fatty acids, by contrast, are normal. This constellation of lab findings is attributable to various causes, such as increased synthesis within hypercortisolism (Ohwada et al., 2006), a reduced clearance due to functional hypothyroidism and a reduced clearance and reduced production of bile. Hypercholesterolemia normalizes in the course of weight gain, and a specific cholesterol-lowering medication of even low-fat diets are not indicated.

Vagal overstimulation through recurrent vomiting leads in the case of BN and the bulimic forms of AN to hypertrophy of the parotid, submandular and sublingual glands (Gunther, 1988; Pyle et al., 1981). Concurrently, a hyperamylasemia is often found (Hempen et al., 1989; Kinzl et al., 1993), which correlates with the frequency of vomiting. As patients are additionally more likely to suffer from gastrointestinal conditions, this lab finding leads not uncommonly to a misdiagnosis of pancreatitis. Typically, however, the lipase is not increased.

2.2. Eating disorders and the thyroid gland

The changes in metabolism and in hormonal regulation triggered by disordered eating behavior and semi-starvation are extremely diverse. The numerous investigations in this area, however, have only little relevance for clinical practice. The following section is therefore limited to the endocrine regulation of thyroid function, as the typical consequences of AN typically give rise to misdiagnoses and incorrect treatment in this respect.

The thyroid gland releases thyroxine, which is converted in the body into the ultimately active hormone triiodothyronine. The main effects of thyroid hormones are as follows:

- Increase in basal metabolic rate and of oxygen and energy requirements of the organism.
- Increase in protein metabolism. Proteins are increasingly broken down or also produced.
- Increase in glucose supply and of gluconeogenesis.
- Increase in the rate of lipolysis.
- Increase in heart rate and blood pressure amplitude.

All of these main effects increase the energy consumption; thus, from the perspective of the existing lack of energy, it is metabolically appropriate that in the state of malnutrition, the production of thyroid hormones is down-regulated. This applies particularly to triiodothyronine, which in AN is lowered to a much greater extent than thyroxine (Bannai et al., 1988; Casper et al., 1991; Croxson & Ibbertson, 1977; Miyai et al., 1975; Onur et al., 2005; Sato et al., 1988) and is highly correlated with the reduction in the basal metabolic rate (Aschettino-Manevitz et al., 2012). Generally speaking, functional hypothyroidism is not accompanied by an increase in TSH (thyroid-stimulating hormone), which would be the case in hypothyroidism due to the underproduction of the thyroid gland; the rise in TSH following TRH administration is delayed (Kiriike et al., 1987; Kiyohara et al., 1987; Tamai et al., 1986). Occasionally, however, increased TSH values are also found, which should not be prematurely interpreted as a sign of hypothyroidism requiring treatment (Matsubayashi et al., 1988). Thyroxine increases the energy consumption and the protein metabolism, consequently has unfavorable main effects for anorexia nervosa and therefore requires a closely defined indication in the case of anorexia nervosa. If hypothyroidism is clearly presented, thyroxine should then be substituted in very low dosages.

2.3. Fluid and electrolyte balance

Within the scope of eating disorders, substantial shifts in the fluid and electrolyte balance occur. Abnormal eating habits frequently also refer to drinking behavior, with both polydipsia (in order to suppress hunger) and water restriction being observed. Recurrent vomiting leads to volume depletions, to the depletion of chloride and other electrolytes and to metabolic alkalosis. The abuse of diuretics and laxatives also leads to volume deprivation and to shifts in the electrolyte balance, in particular to hypokalemia and loss of sodium, but not to hypochloremia.

The loss of potassium initially affects the extracellular potassium concentration, while the intracellular potassium concentration is less affected. This causes an increase in the potassium stress of muscle and nerve cells and consequently an increased electrophysiological excitability of these cells. In this regard, the speed of potassium depletion is decisive for the extent of the resulting potassium stress. Chronic potassium depletions also lead to a drop in the intracellular potassium concentration and thus to a less pronounced change in potassium stress. The risk of cardiac arrhythmia is therefore less pronounced in the case of chronic potassium depletions than in the case of acute potassium depletions. The ECG changes associated with hypokalemia (Khan et al., 2007) enable an estimation of the resulting potassium stress and thus the arrhythmogenic risk.

Hypokalemia in the scope of anorexia nervosa (Sugimoto et al., 2003) or in the scope of an abuse of diuretics (Copeland, 1989) is held responsible in case studies for the severe complication of pontine myelinolysis, even though no concomitant hyponatremia emerged in these cases. Likewise, there are case reports of a rhabdomyolysis (Dive et al., 1991). Chronic hypokalemia in conjunction with lack of volume and lack of substrates are conditions for the development of hypokalemic nephropathy. This disease is marked by a tubulointerstitial fibrosis, which is clinically expressed in polyuria, metabolic alkalosis, proteinuria and consecutively progressing impairment of renal function (Lee et al., 2015; Liang & Yeh, 2011). This type of nephropathy has been experimentally induced through potassium deprivation in rats (Manzato et al., 2009). On the other hand, renal function is also endangered through the

increased incidence of nephrolithiasis (Jonat & Birmingham, 2003) and more rarely also through nephrocalcinosis (Roberts et al., 2005). Even before the manifestation of renal insufficiency, the renal function is impaired in most patients with AN, the filtration fraction is decreased and in the case of fluid deprivation, the ability to concentrate is reduced (Aperia et al., 1978).

As nutrition begins to normalize in the framework of treatment, many patients with AN and BN show a pronounced tendency to edema, marked by a disproportionate increase in the extracellular volume (Ehrlich et al., 2006a; Tey et al., 2005). The associated high initial weight gain (the weight gain caused by edema formation can amount to up to 10 kg) often unnerves patients and therapists alike and therefore has to be considered when evaluating the course of weight. Electrolyte depletions and hypokalemia are the cause of an overactivation of the renin-angiotensin-aldosterone mechanism. The rise in plasma-aldosterone upon administration of angiotensin II is significantly higher in patients with anorexia nervosa (Mizuno et al., 1992). Under the conditions of normalization of nutrition, the activation of this mechanism leads to a substantially increased water retention and a tendency for hypokalemia. In less pronounced cases, it is sufficient to inform the patient of the benign nature of the edema formation and to take a "wait-and-see" stance, as this so-called Pseudo-Bartter syndrome normalizes completely within the first few weeks. A different stance should be taken in the case of extreme edema formation, which is associated with hyperhydration and affects the cardiovascular system (Ehrlich et al., 2006b; Rigaud et al., 2010). Here, a diuretic treatment, in this case for logical reasons with aldosterone antagonists, is indicated.

Pathophysiologically, other factors are held responsible for the edema formation. In this respect, the reinstated insulin secretion, in conjunction with increased insulin sensitivity, is discussed, which then leads to a sodium retention in the distal tubule (Yucel et al., 2005). In cases with hyponatremia, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) should also be considered – SIADH is presumably also more frequent in AN (Challier & Cabrol, 1995).

2.4. Bone structure

One of the frequent and severe medical complications in patients with a long-term course of AN or the subgroup of especially underweight patients with BN (Robinson et al., 2017) is the occurrence of osteopenia (reduced bone density) or osteoporosis (reduction of bone density by more than two standard deviations according to age- and sex-adapted values). For children and adolescents the term "osteopenia" should be avoided because of its imprecise defintion. Besides a reduced bone density the definition of osteoporosis implies the presence of at least one pathological fracture (Bianchi et al. 2014). In patients with a more than two-year course and/or in AN patients with bone pain or spontaneous fractures, a bone density measurement should be carried out (NICE guidelines 2017, Treasure et al., 2015; Zipfel et al., 2015). A systematic review pointed to the following predictors for a reduced bone mineral density (BMD) in AN patients: a) young age at onset, b) long duration of illness, c) long duration of amenorrhea, and d) low weight (BMI) (Robinson et al, 2017). While lower bone density was demonstrated in the area of the spine in AN patients and in the subgroup of BN patients, only in the AN patients

was a significantly reduced bone density in the hips, the femoral neck and in the whole-body bone density demonstrated.

Loss of bone density already sets in within the first twelve months after diagnosis, with an average yearly bone density loss of 1% (Bruni et al., 2006). 25% of patients fulfilled diagnostic criteria of osteoporosis including one pathological fracture. . A longitudinal study in adult AN patients showed that the subgroup with a chronic course had an average yearly loss in bone density of 3.7%, while the group which had recovered showed a slight increase in bone density (0.7) per year. In particular, the group of AN patients with purging symptoms showed the highest yearly bone density loss (Zipfel et al., 2001). In this group, also with regard to the bone turnover, the highest markers were found for bone loss and the lowest markers for bone formation. AN patients with amenorrhea of more than six years had a seven-fold increased risk of fractures, and with a chronic long-term course of an average of eleven years, 44% of sufferers already showed osteoporotic bones. Preferentially affected are the trabecular bones in the area of the thighs and the lumbar spine. In performance athletes (e.g., ballet dancers), the illness and the significant physical demands can lead even in young years to pathological fractures and stress fractures. As a guide, it can be stated that per standard deviation in bone density, the risk of fracture doubles. Based on a recent review, AN patients therefore have a four-fold increased risk of fractures (Robinson et al., 2016). The background for these dramatic figures is that puberty and early adulthood constitute a very sensitive period for bone formation, in which within a few years after completion of vertical growth, the maximum bone mass (peak bone mass) is reached. As AN frequently begins in the course of puberty, a reduced bone formation and consequently an already reduced peak bone mass and bone density arises. At the same time, the malnutrition and malnourishment have a series of effects on neuroendocrine factors, which are directly related to bone change. The following factors are involved in this regard:

- Reduction in the release of gonatotropin-releasing hormone (GnRH) and of gonadotropins and
- consequently reduced estrogen and androgen production (Testosteron, DHEAS)
- Increase in plasma cortisol levels
- Reduction of free T3
- Reduced hepatic synthesis of growth factors (including IGF1)
- Reduced leptin levels and increased catecholomine levels (Bruni et al., 2006)
- Reduced calcium and vitamin D supply
- Metabolic acidosis due to increased lipolysis.
- Reduced Ghrelin and Oxytocin and enhanced levels fo PYY (Fazeli & Klibanski 2014, 2018

Due to this pattern, the pathomechanisms of osteoporosis in patients with eating disorders differ from those in women with postmenopausal osteoporosis. In contrast to the postmenopausal form, in which both bone reabsorption and bone growth are simultaneously increased (“high-turnover” osteoporosis), AN patients show a “low-turnover” situation with reduced bone growth and increased reabsorption. Consequently, a lack of estrogen, which is causal for postmenopausal osteoporosis, cannot solely explain the bone metabolism situation of AN patients.

As all previous studies have revealed that body weight is the most important determinant of bone density in patients with eating disorders, weight normalization and normalization of malnutrition and malnourishment is of the highest priority (Mehler & MacKenzie, 2009). Therefore, the most effective, and considering the risk/benefit profile best measure, is to achieve an early weight restitution and normalization of eating behavior. The additional supplementation of calcium and vitamin D can have a supportive effect, especially in the early phase of weight restitution (Gatti et al., 2015). Although an oral application of estrogen-gestragen preparations has long been established as a measure in postmenopausal osteoporosis, and in a series of studies, the duration of amenorrhea was found to be a predictor for bone density in patients with AN, previous intervention studies with this subgroup did not yield significant effects. Based on a study by Misra (Misra et al., 2011), a recent systematic review (Robinson et al., 2017) pointed to the option of applying transdermal 17-ß-estradiol with cyclical progesterone application. Based on the data by Misra and Klibansky a transdermal substitution of estrogene should be considered from the age of 12 years on if patients are suffering from long lasting severe AN (see also NICE Guidelines; https://pathways.nice.org.uk/pathways/eating-disorders). Estrogene deficits during this critical time window will later often be associated with a sub-normal peak-bone mass, even if a normalisation of body weight is achieved .. Bone age of patients with AN is often deviant from that of age-mateched controls and thus not very suitable as a parameter of maturity and prognostoc indicator for adult body height. (Misra et al. 2004, Modan-Moses et al. 2012). Besides a direct effect on bone, estrogenes impact on the mechanism of endogenously secreted Growth Hormone (GH)-induced effect on bone and body composition. . Several trials demonstrated that an oral, but not transdermal application affects the metabolic effects of GH in the liver. This leads to an attenuation of the hepatic ICF-1 synthesis with unfavorable consequences of the body composition. (Leung et al. 2004). Although a physiological transdermal substitution of estrogenes helps to prevent a further loss of body mass, there is no total catch-up, probably because of additional hormonal deficits with relevance for an increase of bone growth. (Misra et al. 2011). In the subgroup with a bone age below 15 years, the British guidelines recommend considering a substitution of estrogen in increasing dosage. Generally, however, such treatment should only occur in close cooperation with an endocrinologist. A regular estrogene-progesterone application should be considered in over 15-year-old patients, who suffer from more chronic forms of AN whith insufficient weight rehabilitation and who did not resume menses for more than one year. . This recommendation was taken over from the NICE guidelines (2017) (verbally: „consider transdermal ß-estrogene application“) reover, an estrogen-gestagen application should only be reserved for those AN patients in whom the menstrual period is still absent following weight restitution. In women with AN, a hypothalamic oligo-/amenorrhea may not only be transient but can also persist despite stable weight restoration, which among other things can point to infertility (Dempfle et al. 2013; Kohmura et al. 1986; Misra & Klibanski 2014). This underlines a further aspect of the necessary follow-up care and can result in an indication for hormonal stimulation and induction of ovulation.

In the past few years, further pharmacological substances have been examined, such as in particular the orally applied bisphosphonate Risedronate, which was prescribed either in a daily dosage of 5mg over 9 months or in a weekly administration of 35mg over 12 months. This substance showed, partly in combination with an additional transdermal testosterone

administration, a significant increase in bone density in adult AN patients of up to 4.9% (Miller et al. 2011). However, this approach has only been practised in the frame of clinical trials and, because of missing data. cannot be recommended yet for routine clinical practise. When prescribing this group of substances, therefore, the patient must be clearly informed and warned of the teratogenic effects. Further substances, such as teriparatide, a human parathyroid hormone which must be applied subcutaneously, have also been successfully tested in the group of adult AN patients in first clinical studies (Fazeli et al., 2014), although it is still too early to draw any treatment recommendations from individual cases.

For male AN patients, there are currently no reliable treatment recommendations. In general, male AN patients with a longer illness duration and especially those with a documented reduced bone density, should be urged to avoid sport and exercise that is associated with high weight burden, tendency for falls and thus risk of fracture (so-called high-impact physical activities).

2.5. Cardiovascular complications

Besides an increased suicide rate and the direct consequences of malnutrition (including severe infectious diseases), cardiovascular complications are also mentioned as reasons for the increased mortality in AN (Casiero & Frishman, 2006). Indeed, at least the indirectly life-threatening cardiovascular complications of AN are diverse and pronounced.
As patients with bulimia nervosa maintain a normal weight, they are seen as less susceptible to hunger-induced cardiac complications (Casiero & Frishman, 2006). Cardiovascular complications mostly arise as a consequence of induced vomiting (Forney et al., 2016).

2.5.1. Functional changes

Sinus bradycardia (heart rate <60/min) is a typical concomitant symptom in eating disorders. It occurs both in patients with full-blown AN and in patients with atypical AN who still have a normal BMI or in the disease pattern of BN (Palla & Litt, 1988; Sawyer et al., 2016; Vo et al., 2016). In contrast to training-related bradycardia in sportspersons, a reduced increase in heart rate under physical stress and a reduced physical resilience is found (Nudel et al., 1984; Peschel et al., 2016). “Normal” heart rates between 80 and 90 beats per minute are unusual, especially in severely underweight patients (Spaulding-Barclay et al., 2016); these should be evaluated as relative “tachycardia” and give rise to respective differential-diagnostic considerations.

Bradycardia is understood as the physiological adaptation to the reduced metabolism in the case of low energy intake; an increased vagal tone is suspected to be the main cause (Portilla, 2011; Spaulding-Barclay et al., 2016). Acute reduction of food intake and rapid weight loss thus have a stronger influence on the metabolic regulation of the heart rate than chronic malnutrition (DiVasta et al., 2010). Thus, in AN, the change in heart rate begins during the first year of illness and normalizes again as the illness continues (Lesinskiene et al., 2008).
These principles also hold when examining patients with BN: The vagal activity is dependent on the BMI of the patient and is inversely correlated therewith (Peschel et al., 2016).

In the framework of bradycardia or increased vagal activity, occasionally escape rhythms are also found, which revert back to a normal sinus rhythm once the heart rate accelerates (Gaudiani & Mehler, 2016; Krantz et al., 2011). Even in the case of severe bradycardia, patients generally remain symptom-free in this regard and there is no indication for pacemaker implantation.

Furthermore, the literature describes further abnormalities of the heart rhythm such as sinus arrhythmia, AV escape rhythms, increased likelihood of supraventricular but also ventricular extrasystoles and short-lasting paroxysmal supraventricular extrasystoles. More severe arrhythmias which would explain the increased mortality were not observed (DiVasta et al., 2010; Roche et al., 2005; Roche et al., 2004). The QT interval represents the myocardial repolarization. A prolonged QT interval is seen as a risk for sudden death through Torsades-de-pointes (TdP) tachycardia or ventricular fibrillation. The sole indication of the measured QT time per se is less meaningful, as the repolarization duration and thus also the measured QT duration are largely dependent on the heart rate. Therefore, in routine practice, the measured QT duration is converted to a standardized heart rate of 60 beats per minute (QTc interval). There are various correction formulae for this calculation, although the formula by the physiologist Bazett is often used. However, this corrects substantially more strongly than other formulae (Rowlands, 2012) and in comparison, is the poorest at distinguishing patients at risk and those not at risk. For such a classification, by contrast, the Hodges formula has consistently been shown to be the best and also seems to be suitable for anorexic patients; therefore, the evaluation of the QTc interval should be based on this formula (Walter et al., 2015).

In the investigation of patients with eating disorders, the overall outcome of a meta-analysis on the QTc interval in AN showed a prolongation compared to healthy controls, but no prolongation beyond a normal extent (Lesinskiene et al., 2008). Nevertheless, there are reports of a TdP in anorexia nervosa (Isner et al., 1985; Rotondi et al., 2010), meaning that an individual risk assessment should be undertaken. At particular risk are patients with purging behavior, in whom various mechanisms accumulate which increase the risk of a QT time prolongation (e.g. potassium depletion due to vomiting and abuse of laxatives or diuretics) (Forney et al., 2016; Zenker et al., 2010).

Similar findings were observed in patients with BN: As long as the electrolytes were in the normal range, the QTc intervals were longer than in a healthy control group, but on average, they did not lie above a limit of 500ms and they remained stable during an inpatient therapy (Nahshoni et al., 2010; Takimoto et al., 2004). In this respect, the length of the QTc duration appears to be related to the amount of weight lost since disorder onset as well as with psychopathological variables (tension-anxiety score and depression score on the Profile of Mood States) (Takimoto et al., 2008).

The literature reports various thresholds for assessing the individual risk. The best balance between sensitivity and specificity for detecting patients who will develop a TdP was found at a cut-off of >500ms (Chiladakis et al., 2012).

Both the QT dispersion and the QT variability are described as an independent measure for the risk of sudden cardiac death, although this has yet to be confirmed. QT dispersion is described as the difference between the maximum and minimum duration of the QT interval (Sachs et al., 2016): The QT dispersion is higher in anorexia nervosa than in healthy controls

and is negatively correlated with the resting metabolic rate. In the framework of refeeding, the QT dispersion decreases.

Spontaneous fluctuations of the QT interval, which reflect the fine temporal variations of ventricular depolarization and repolarization, are described as QT variability. In underweight AN patients, the examination showed an increased QT variability index (QT variability normalized in relation to the heart rate variability) in comparison to healthy controls (Koschke et al., 2010). After weight normalization, by contrast, no difference in the QT variability and normalized QT variability compared to controls was found (Nussinovitch et al., 2012).

2.5.2. Structural changes

Takotsubo cardiomyopathy is a rare, sudden and often severe dysfunction of the heart muscle. The symptoms resemble those of a heart attack and mostly occur directly after an extreme emotional or physical stressor. In the literature, there is a series of case reports on the occurrence of Takotsubo cardiomyopathy within (mostly severe) AN (Kawano et al., 2016; Kim et al., 2011; Ohwada et al., 2005; Rotondi et al., 2010; Shimizu et al., 2014; Volman et al., 2011). In all cases, the illness was severe and chronic and the body mass index was mostly below ≤13 kg/m^2. The episodes occurred in the framework of an anesthesia, a hypoglycemic coma or within severe hypoglycemia and after a family argument and after spatial separation from the mother (with complete change in food intake). To date, there are no case reports on the occurrence of Takotsubo syndrome in patients with BN.

In cases of severe AN, small to medium *pericardial effusions* are often found (Docx et al., 2010; Frolich et al., 2001; Inagaki et al., 2003; Kastner et al., 2012; Oflaz et al., 2013; Ramacciotti et al., 2003; Silverman & Krongrad, 1983) – this has also been described in a male patient (Shapiro et al., 2014). The pericardial effusion is normally clinically inconspicuous and disappears following normalization of weight (Kastner et al., 2012; Ramacciotti et al., 2003; Ulger et al., 2006), meaning that no specific treatment is necessary. Nevertheless, in rare cases, it can progress to a pericardial tamponade (Kircher et al., 2012; Polli et al., 2006; Shapiro et al., 2014). So far, the pathophysiology is not entirely clear, but Docx et al. suspect a relation between the decrease in pericardial fat and myocardial atrophy (Docx et al., 2010).

In *mitral valve prolapse*, one or both leaflets of the mitral valve prolapse systolically in the left atrium. It is a frequent change in the valve apparatus in patients with anorexia. Prevalence rates range from 13% (Hall et al., 1989) up to 82.6% in a Japanese cohort (Oka et al., 1987). In comparison, the prevalence in a general population sample lay at 2.4% (Freed et al., 1999). Mitral valve prolapse in AN is mostly described as mild and asymptomatic and can persist following weight normalization (Olivares et al., 2005). However, the pathological movement of the mitral valve usually normalized following weight normalization (Meyers et al., 1987). From a pathophysiological perspective, it is assumed that a valve apparatus that has become too large relative to the dystrophic heart muscle is responsible for the occurrence of a mitral prolapse (Cheng, 1989).

One study found a strong relation between *myocardial fibrosis* and AN (Oflaz et al., 2013). Myocardial fibrosis was found in 9 of 40 examined patients; the examined patients were an average of 22.3 years old and had a BMI of 15.3kg/m^2. The fibrosis was subendocardial and transmural in segments of the left ventricle. Similar findings emerged in pathological case

reports: Lamzabi et al. (2015) described the case of a 47-year-old female patient with a BMI of 10.3kg/m^2. A postmortem showed a diffuse endocardial and intestinal fibrosis with areas of myxoid material and mast cells. An endomyocardial biopsy in a 17-year-old female patient with a BMI of 17.4 kg/m^2 also showed, among other things, a moderate interstitial fibrosis (Takahashi & Mine, 2016).

Structurally, the heart is substantially smaller in patients with AN. The left ventricular mass, as can be determined with two-dimensional echocardiogram, is substantially reduced (Oflaz et al., 2013; Olivares et al., 2005; Romano et al., 2003; Ulger et al., 2006) and lies below the parameter of constitutionally thin participants (Galetta et al., 2003). Ultimately, however, the ventricular mass increases again when patients eat a sufficient amount, and following weight restitution, no longer differs from healthy persons (Olivares et al., 2005; Ulger et al., 2006).

2.5.3. Hemodynamic and peripheral vascular changes

One of the characteristic clinical concomitant symptoms of AN is *hypotonia* (Gottdiener et al., 1978). Both systolic and diastolic blood pressure are reduced (Sachs et al., 2016). Normal circadian variation is impaired (Oswiecimska et al., 2007). Patients with atypical anorexia who still have a normal BMI show higher blood pressure values than those with typical anorexia nervosa, although 10% nevertheless show an RR <90mmHg (Sawyer et al., 2016).

Acrocyanosis is clinically characterized by cold, painless lividly colored acra (often with hyperhidrosis and hypothermia. It manifests symmetrically, predominantly on the hands and feet (often also nose, cheeks and ears) and does not occur paroxysmally (Kurklinsky et al., 2011). In anorexia nervosa, the prevalence of acrocyanosis lies at 21-40% (in questionnaires up to 81%). (Bhanji & Mattingly, 1991; Hediger et al., 2000; Schulze et al., 1999; Strumia et al., 2001). Independently of the time of year, it disappears with increasing body weight (Hediger et al., 2000). In extreme cases, acrocyanosis can lead to acral necrosis (Launay et al., 2000).

2.6. Gastrointestinal complications

Binge eating episodes as part of AN, BN or BED lead to a quite significant, unphysiological mechanical stress of the upper digestive tract, which in turn can lead to considerable and severe complications. In rare cases, perforations of the esophagus or stomach ruptures can occur (Abdu et al., 1987; Evans, 1968; Saul et al., 1981). Binge eating, by contrast, can also lead to stomach dilatation (Barada et al., 2006; Brook, 1977; Evans, 1968; Gruner, 1977; Mitchell et al., 1982; Stheneur et al., 1995), which even without perforation can lead to complications such as ischemia and necroses. Stomach necroses with perforation are also described in AN without relation to binge eating (Arie et al., 2008).

Through the recurrent vomiting and the more frequent acid contact of the epithelium of the lower esophagus, reflux problems are very frequent, and in many cases, esophagitis occurs (Aframian et al., 2010; Brown & Mehler, 2013; Denholm & Jankowski, 2011). By contrast, squamous cell carcinomas, which occur based on esophagitis caused by recurrent induced vomiting, are a rarity (Dessureault et al., 2002).

Functional gastrointestinal complaints are a regular concomitant symptom of eating disorders, and are most frequent in AN. In BN, they are somewhat rarer (Hadley & Walsh, 2003; Waldholtz & Andersen, 1990) and relatively most rare in BED (Crowell et al., 1994). The most frequently mentioned complaints are postprandial feelings of fullness and epigastric pain, a bloated abdomen and constipation (Waldholtz & Andersen, 1990). The often very pronounced complaints improve with remission of the eating disorder symptoms. Frequently, however, a symptomatic medication treatment is necessary and requested by the patient.

The increased occurrence of a sometimes very severe constipation with anorexia nervosa (Chiarioni et al., 2000; Chun et al., 1997; Waldholtz & Andersen, 1990) is likely multicausal in nature. Reasons for the reduced stool frequency include the reduced stool mass, an often co-occurring hypokalemia and hypothyroid metabolic state. In view of the diverse endocrinological changes associated with a too low body weight and disordered eating behavior, however, other causes are also likely to be found.

The functional gastrointestinal complaints are associated with abnormal transit time (Kamal et al., 1991), motility (Stacher et al., 1993) and gastric electrical activity (Ogawa et al., 2004). Although such findings suggest the use of prokinetic agents such as domperidone (Russell et al., 1983), metoclopramide (Saleh & Lebwohl, 1980) or cisapride (Stacher et al., 1993) and give rise to the assumption of affecting both a reduction of the burden of gastrointestinal symptoms and a facilitation of weight gain, in practice, their use is disappointing. The effects on gastrointestinal symptoms are low and with regard to weight, no effects are found in practice.

The increase of transminases is, dependent on the level of malnutrition, a frequent accompanying symptom, especially in AN (Bridet et al., 2014; Dowman et al., 2010; Goh & Lee, 2015; Hanachi et al., 2013; Ramsoekh et al., 2014; Rautou et al., 2008; Smith et al., 2013). In the case of severe anorexia nervosa (BMI < 15) transminases are increased in the majority of cases (Rautou et al., 2008; Tsukamoto et al., 2008). (As vitamin B12 is stored in the hepatocytes, a paradoxical increase in serum vitamin B12 is normally found in such patients (Corbetta et al., 2015)). Autophagy is a cellular process which can be induced by lack of energy to contribute to the survival of the organism. Cell autophagy can be observed in plant and animal organisms in emergency situations and takes place throughout the body. The increase in transminases indicates that autophagy particularly concerns the liver cells. Liver cell biopsies in AN have no significance for further treatment. In the cases in which biopsies were conducted, no liver cell necroses were found, but an increased sinusoidal fibrosis was found. Liver cells show increases in autophagosomes (Rautou et al., 2008). In clinical terms, the process of liver autophagy can lead to hepatic insufficiency or even liver failure (Dowman et al., 2010; Rosen et al., 2017; Sakada et al., 2006; Yoshida et al., 2010).

2.7. Dental health and eating disorders

The most frequent damage to the teeth in AN and BN arises due to the effect of acid on the teeth. Through the regurgitation of the stomach contents when vomiting, the critical pH value of 5.5 is not reached, leading to damage to the tooth enamel (Milosevic & Slade, 1989). Clear clinical symptoms of tooth erosions which can be induced by frequent vomiting are only

observable after one to two years. At that point, especially on the palatinal and occlusal tooth surfaces in the upper jaw, marked loss of hard tooth structures of enamel and dentine are found, which are also described as “perimolysis” (Hellstrom, 1977). If vomiting occurs directly before going to sleep, the exposure to acids is potentiated, as the acid remains in the oral cavity for longer and salivation is minimal during sleep.

The typical erosions in eating disorders have a soft, waxy surface. These can be accompanied by exposure of dentine or pulp, strong hypersensitivities, a thinning of the incisal edges and ultimately by a decline in the vertical dimension of the jaw. The progressive loss of hard tooth substance can lead to margins of restoration rising above the tooth level.

Often, patients brush their teeth after vomiting. When brushing, the tooth surface which has been softened by the acids is removed all the more, thus additionally accelerating the loss of hard tooth substance.

Vestibular erosions on the teeth in conjunction with eating disorders are found in those patients who are additionally triggered by extrinsic factors such as one-sided nutrition with citrus fruits or glucose in order to assuage the feeling of hunger.

Patients with BN further show a higher prevalence of caries (Ohrn et al., 1999; Ohrn & ngmar-Mansson, 2000). The excessive intake of fermentable carbohydrates during eating episodes and a reduced salivation are discussed as reasons for the increased prevalence of caries. Furthermore, during fasting, the phosphate concentration in saliva is reduced, and an increased plaque formation can be observed. As such, the dimineralized enamel caused by the attack from acid appears to be more sensitive to cariogenic noxious substances.

Due to recurrent vomiting, but also due to abuse of diuretics and laxatives, the saliva production is reduced. The resulting *xerostomia*, however, is also found in severe anorexia and with the intake of antidepressants, especially those with a tricyclic structure (Montecchi et al., 2003). Moreover, patients with AN show an increased likelihood of gingivitis and periodontosis as an expression of the poor nutritional state (Touyz et al., 1993).

Through the strong vagal stimulation, in the case of recurrent vomiting, a clear enlargement of the parotid and sublingual glands is often found, which is generally pain-free (Mignogna et al., 2004; Moorthy et al., 1998). The associated visual swelling of the parotid glands is perceived as disfiguring by some patients. In most cases, this visible swelling of the salivary glands disappears once the patient has no longer vomited for a lengthy amount of time.

The optimal preventive protection against tooth erosion is to avoid contact of the teeth with erosive noxious substances such as acid-containing drinks and foods, and to cease vomiting. In many cases, this is only achieved under psychotherapeutic treatment. As long as abnormal eating behavior persists, measures should be taken to protect dental health.

After vomiting, a short-term decrease in the pH value on the tooth surfaces occurs, particularly the palatinal surfaces of the upper front teeth. Therefore, it is especially important to inform the patient that the teeth should not be brushed directly after contact with acid, and instead, the mouth should be rinsed with water. Furthermore, it is recommended to rinse the mouth with acid-neutralizing fluids such as sodium bicarbonate, baking powder or antacids, which are first dissolved in water, in order to achieve an increase in the pH value and a buffering of acids in the mouth.

The patient can achieve a further chemical protection of the teeth, for example, by chewing sugar-free, urea-containing gum, which brings about an alkalization of the acidic

saliva. Additionally, chewing gum stimulates salivation, which also increases the buffering capacity of saliva.

Through the treatment of tooth enamel with a solution or coating containing sodium fluoride, the erosion resistance of the enamel can be increased. Fluoride-containing mouth rinses or toothpastes also contribute to this. The re-hardening of erosive-softened tooth enamel can also be accelerated by the consumption of milk or cheese.

Mechanical protection can be achieved be sealing the tooth surfaces or by recommending a tooth-covering plastic brace to protect against the exposure to acids, although this recommendation is certainly difficult to realize.

In the case of more severe hard tooth substance defects, conservational or prosthetic measures to protect the teeth and restore masticatory function are indicated. An avoidance of erosive noxious substances is based on the therapeutically guided normalization of eating behavior.

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Versions-Nummer: **2.0**
version number:

Erstveröffentlichung: **12/2010**
Initial release:

Überarbeitung von: **05/2018**
Revision of:

Nächste Überprüfung geplant: **05/2023**
Review planned: