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REVIEW

An update on current clinical management of eating disorders

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ABSTRACT

INTRODUCTION: Eating disorders (ED) are severe conditions featuring abnormal eating patterns and pervasive and distressing concerns with one's body image. ED are relatively common and have considerable high mortality rate and costs for Public Health. The aim of this paper was to review recent findings in the field of treatment strategies in ED, including psychotherapeutic, pharmacological and non-pharmacological novel approaches.

EVIDENCE ACQUISITION: A review of all recently published randomized controlled clinical trials (RCTs) on treatment of ED was undertaken and reported, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations. The bibliographic search yielded 444 records. After screening, 62 articles were finally included: 22 concerned patients with anorexia nervosa (AN), 9 with bulimia nervosa (BN), 19 with binge-eating disorders (BED) and 12 with mixed ED.

EVIDENCE SYNTHESIS: There have been substantial developments in psychological therapies for ED within the last few years, with evidence conforming the importance of multidisciplinary team approaches and expanding indications of cognitive behavioral and family based interventions. Pharmacological treatment of ED remains poorly evidence-based, while the involvement of carers in treatment programs are increasingly being given importance.

CONCLUSIONS: Further research efforts are needed for elucidating the effectiveness and differential indications of stepped care approaches involving different settings, psychotherapy models, age and type of ED.

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Key words: Anorexia nervosa - Bulimia nervosa - Binge-eating disorder - Feeding and eating disorders.

Introduction

Eating disorders (ED) are severe, long-lasting psychopathological conditions featuring abnormal eating patterns and pervasive, distressing concerns about one's body image. ED are relatively frequent in the general population. A recent review reported the following prevalence rates in Europe: anorexia nervosa (AN) <1-4%, bulimia nervosa (BN) <1-2%, binge-eating disorder (BED) <1-4%, subthreshold ED 2.2% of women and 0.7% of men. ED affected 0.3% of men. While incidence of AN is stable, that of BN may be declining.[1] Most mortality studies in ED focused on inpatients with AN, with few studies on patients with BN and BED. ED show one of the highest mortality rates among all psychiatric disorders: crude mortality rates — deaths per 1000 person-years — are 5.1 for AN, 1.7 for BN and 2.9 for BED.[2] Average treatment-related costs associated with ED are estimated to be € 500 per day for inpatients and € 400 per day for outpatient: also including addition-

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al costs related to family therapy, primary and private care, costs may reach around € 10,000 per patient per year.[3] Psychotropic medications are widely prescribed to ED patients. A retrospective study on patients with AN and BN outlined that at least one medication was prescribed to a high proportion of patients in both groups.[4] In a survey on an ED population, nearly half of the sample was taking an antidepressant (AD), most often a serotonin selective reuptake inhibitor (SSRI), but a significant minority were also taking anti-anxiety drugs, mood stabilizers, and antipsychotics (AP), despite the limited evidence of effectiveness, potential risks and contraindications. Just over half of the sample was receiving cognitive behavior therapy (CBT) and/or, for AN patients, family therapy, which is consistent with guidelines and existing evidence. Several other psychological therapies were used, with minimal evidence of effectiveness for ED.[5]

Considering the high clinical impact of ED and the growing body of research, the aim of this paper was to review recent findings in the field of treatment strategies in ED, including psychotherapeutic, pharmacological and other non-pharmacological emerging approaches.

Evidence acquisition

A review of the recent scientific literature on treatment of ED was undertaken and reported, according to the PRISMA statement recommendations. PubMed was searched on papers published from November 2011 to November 2016 with the following key words: "eating disorder OR anorexia nervosa OR bulimia nervosa OR binge eating AND treatment." The search was restricted to articles published in English and to Clinical Trials in humans.

Inclusion criteria for trials were: that patients met the diagnostic criteria for AN, BN, BED or an eating disorder not otherwise specified (EDNOS) according to the DSM IV-TR [6] or DSM 5;[7] and that they compared treatments, including no treatment or treatment as usual (TAU). TAU was defined as the care that the patient would normally receive if he/she had not been included in the research trial. No restrictions were made as to the duration of interventions or follow-up.

"Treatments" were considered in their broader meaning, including nutritional, pharmacological, psychotherapeutic and psychological interventions. Similarly, no limitation was posed as to the clinical setting of the intervention: inpatient, outpatient, day clinic and even virtual (telemedicine).

Selected outcome measures were both psycho-social or psychopathological outcomes (*e.g.* severity of psychopathology, functioning, quality of life, self-perception, therapeutic alliance, etc.) and anthropometric endpoints (*e.g.* BMI).

Exclusion criteria were: off-topic papers (*e.g.* organic conditions leading to weight variation, treatments of comorbidities associated with weight gain or loss); works on ED in patients with comorbidities (physical or psychiatric, *e.g.* acute mania, psychosis or severe depression); studies focused on prevention, or not reporting clinical outcomes, or with a sample size smaller than 30 patients, or not RCTs. Furthermore, no pilot studies or research protocols were included. Titles and abstracts were screened according to these exclusion criteria, retrieving full texts for potentially eligible works.

The articles thus selected were listed in a chart according to the following headings: title, first author, year of publication, journal, sample size, interventions (psychotherapy, psycho-pharmacotherapy, others), outcomes, follow-up duration and conclusions. This chart is available on request from the corresponding author.

Evidence synthesis

The bibliographic search yielded 444 records, whose titles and abstracts were screened. Of these: 241 were off-topic, 30 were not RCTs, 38 were pilot trials or protocols, 4 involved patients with physical or psychiatric comorbidities, 35 did not report on clinical outcomes, 17 papers concerned prevention programs and 16 were excluded because sample size was smaller than 30 subjects.

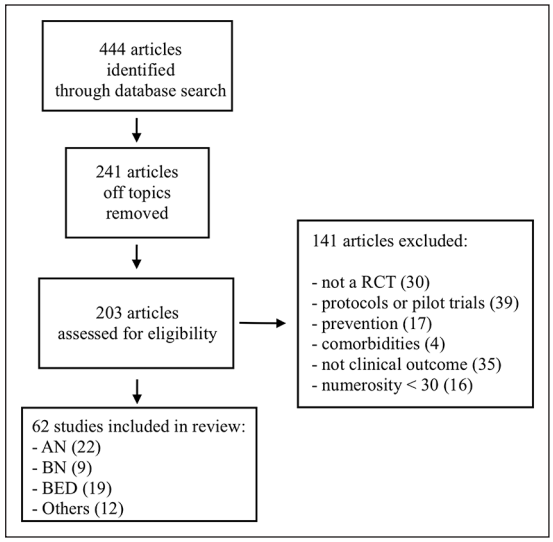

Figure 1.—Flow chart of the paper selection process for the present review.

Consequently, 62 articles were found eligible to be included: 22 concerned patients with AN, 9 with BN, 19 with BED and 12 with different combinations of ED. Figure 1 depicts the section process followed for this review.

What follows is a summary of findings and recommendations derived from the included studies. Findings were categorized according to different options of intervention.

Treatment recommendations based on severity of illness

ED are complex disorders leading to severe medical, psychiatric and psychosocial dysfunctions if left untreated. Malnutrition and long-time starvation can negatively affect almost every organ in the body, with a potentially lethal impact.[8] Early diagnosis and appropriate treatment are crucial, and are associated with a higher rate of recovery.[9]

There is consensus that treatment of different stages of the disorders must be individualized and that a multidisciplinary team-based approach is needed, also involving primary care. The team commonly includes a psychotherapist, a psychiatrist, a dietitian, an ED specialist and other professionals (*e.g*. the school personnel).[10]

In uncomplicated and less severe cases, primary care can provide an optimal setting to deliver both medical and psychosocial interventions. Moreover, screening by means of short tools such as the Eating Disorders Screen for Primary Care (ESP) can be used in primary care, to support basic assessment.[11]

Nutritional interventions are a fundamental element of the multidisciplinary team approach. The nutritionist's role is to assess the current and past patterns of dietary intake, including timing of meals, portion size, and food or body related rituals/practices. The nutritional intervention addresses nutrition recovery, balanced body weight, normalized eating patterns and perception of hunger and satiety, and correction of malnutrition.[12] In less severe cases, the oral refeeding plan, with a strict behavioral protocol, is the treatment of choice. The dietary goal is usually to move from the reduced calories-oriented approach to a balanced nutritional program with adequate calories to balance energy expenditures and nutritional needs appropriate to the patient's developmental stage.[13]

When severity of cases indicates hospital admission, assessment of medical instability indicators usually has the priority (BMI, physical examination, other biological indicators, *i.e*. low sodium, low potassium, raised transaminases, hypoglycemia, raised urea and creatinine), to confirm that hospital care is really necessary.[10] Research shows that inpatient care for AN is not a predictor of better outcomes than treatment in less intensive (and cheaper) settings, suggesting that its use should be limited to patients with severe disorders and intensive medical needs (*e.g*., preliminary weight gain/refeeding, medical stabilization). An RCT comparing the effectiveness of different inpatient treatments in medically unstable adolescents with AN prior to outpatient family-based treatment (FBT), evaluated the numbers of hospital days in the acute phase and in follow-up after remission. The authors concluded that outcomes were similar, and that cost savings would result from combining shorter length of stay in hospital with FBT.[14] A systematic review by the same author focused on the com-

parison of 5 trials in order to test which setting (outpatient or inpatient) leads to better outcomes for adults and adolescents with AN: no significant differences were found. The comparison, however, supported partial hospitalization (*i.e*. day hospital patient treatment after short inpatient care) as more cost-effective than continued inpatient care, which should be reserved for medically unstable cases or in the presence of other risk issues.[15]

In the UK, observing that a number of patients with severe AN were being admitted to general medical units and sometimes deteriorating and dying on those units because of psychiatric problems, such as non-adherence to nutritional treatment, and medical complications, such as re-feeding syndrome, the Royal Colleges of Psychiatrists, Physicians and Pathologists developed joint guidelines, the MARSIPAN.[16] These guidelines apply to patients with severe AN (BMI<15 kg/m^2) and AN patients admitted to medical wards or to specialist ED units. Criteria for medical admission in specialist ED units (SEDUs) should be the need for treatments not normally available on a psychiatric ward. The inpatient medical team should be supported by a senior psychiatrist with specific competence in ED and should include a physician and a dietitian with specialist knowledge in ED, preferably within a nutrition support team. The key tasks of the inpatient medical team should be to safely refeed the patient, obtaining clinical stabilization of the patient and the restoration of weight, taking into account the wide range of physiological, psychological and familial problems that are encountered, with the specific aim to reduce the number of avoidable deaths of patients with severe AN.

Compulsory nutrition

In case of persistent failure to gain weight with other standard dietary therapies, or life-threatening weight loss, or worsening of psychological state despite standard treatments, or behavioral problems (*e.g*. sabotaging nutrition), the inpatients medical team should also take into consideration, with the help of mental health professionals, alternative modes of weight restoration other than oral refeeding.[13] These may include compulsory feeding tube and high caloric intravenous nutrition as the only last resort viable lifesaving treatment strategy.

Compulsory inpatient refeeding of patients with severe AN has been the subject of considerable controversy, both on clinical and ethical grounds. Moreover, effectiveness of such intervention on longer-term outcome has not been studied properly,[8] with most of the available studies being retrospective analyses.

A recent review by Elzakkers *et al.*[17] showed that, in the short term, compulsory refeeding in AN appears to be beneficial. In a recent retrospective study, 68 AN patients were enrolled in a percutaneous refeeding program based in a psychiatric intensive care unit (PICU) for patients with extreme AN. Patients were able to participate in more structured psychotherapeutic programs soon afterwards, thanks to the restoration of cognitive functions after the normalization of normal weight.[8]

The long-term effects and prognosis of refeeding nutrition, on the contrary, remain uncertain. More research is needed in this area to better understand and optimize caloric intakes and refeeding practices for individuals recovering from AN, and to develop detailed and reliable guidelines for clinicians and providers about this important topic.[18]

Nutrition, even when forced, should fulfill standards, referring particularly to balanced intensity of refeeding procedures, to avoid both re-feeding syndrome (caused by too rapid refeeding) and underfeeding syndrome (caused by too cautious rates of re-feeding). The restoration of both nutrient status and weight should start slowly and gradually accelerate as tolerated, constantly monitoring glucose and electrolytes levels.[18]

Psychological interventions for AN, BN, BED

Anorexia nervosa

In a sample of women with broadly defined AN, no difference was found in the long-term

effectiveness (6.7 years follow-up on average) of three different psychotherapy approaches: CBT, interpersonal psychotherapy (IPT) and a control intervention.[19] Day hospital was found to be a safe and less costly alternative to an inpatient setting for adolescents with non-chronic AN. The intervention consisted in a multimodal multidisciplinary treatment program based on weight restoration, nutritional counselling, CBT and family therapy. After a short period of inpatient care, day hospital was no less effective than inpatient treatment for weight restoration and maintenance during the first year after admission.[20] BMI at discharge was the best predictor of full recovery for long-term AN patients receiving residential treatment based on a combination of group therapy modalities, nutrition education, meal support, mindfulness training and psychotherapeutic support.[21]

Family-based treatments.—Even if FBT for adolescents with AN is considered to be an effective treatment, so far it has been difficult to define which aspect of the treatment underpins the process of change.[22] FBT focuses on facilitating weight gain, whereas systemic family therapy (SyFT) addresses general family processes. In a group of adolescents with AN receiving FBT *vs*. SyFT, there were no statistically significant differences in percentage of ideal body weight (based on age, sex and height) gained and remission rate, however FBT led to significantly faster weight gain early in treatment, significantly fewer days in hospital, and lower treatment costs. SyFT, on the other hand, led to greater weight gain than FBT for participants with more severe obsessive-compulsive symptoms. FBT may be more cost-effective.[23]

In an 18-month follow-up study on girls with severe AN, family therapy sessions focusing on the dynamics of the family as a whole — and not addressing eating behaviors directly — were included in a multidimensional treatment program and led to improvement in treatment effectiveness.[24] In a multi-centric RCT on adolescents receiving FBT or individual adolescent focused therapy, FBT was found to be more effective on subjects with higher scores on eating-related obsessionality and eating disorder specific psychopathology.[25] FBT also contributed to clinical and cost-effectiveness of hospitalization in medically unstable adolescents, particularly with the intention of achieving medical stability rather than weight restoration.[14]

Weight gain emerged as a significant predictor of improved psychological outcomes in adolescents receiving FBT (or individual adolescent supportive psychotherapy), including global ED pathology, eating concerns, and dietary restraint. However, the impact of weight restoration on symptoms diminished over the two-year treatment and follow-up period: weight and shape concerns were not influenced by weight restoration and were the least amenable to change.[26] Early weight gain was found to be a reliable indicator of effectiveness of brief hospital admissions including FBT.[27]

Though the majority of adolescents significantly improve (80%) or fully remit (50%) with family interventions, there is still a need to find other solutions for those who are not responding.[28]

Psychodynamic therapies.—In a recent update about psychodynamic psychotherapy (PDT) effectiveness, Fonagy commented that even if literature on psychodynamic treatments in ED may be sparse and sometimes methodologically weak, there is substantial evidence that psychodynamic treatments can contribute to recovery from AN.[29] Few recent RCTs investigated psychodynamic interventions but only one met the inclusion criteria for this review: the Anorexia Nervosa Treatment of Out Patients (ANTOP) study revealed that patients allocated to focal psychodynamic therapy had higher recovery rates at 12-month follow-up than those assigned to optimised TAU.[30]

Cognitive-behavioral therapies.—In recent years, classical CBT has been adapted into an ED-dedicated technique, known as CBT-E (where E stands for 'enhanced'), designed to treat all forms of ED including AN in outpatient and inpatient settings.[31] CBT significantly reduced relapse risk and increased the

likelihood of good outcomes compared to nutritional counseling based on nutritional education after inpatient weight restoration. In inpatient settings, two programs derived from CBT-E (one focused exclusively on the patients' ED features and the other focused also on mood intolerance, clinical perfectionism, core low self-esteem or interpersonal difficulties) showed no statistically significant differences.[32]

Two other studies on patients with severe and enduring (at least seven years) AN investigated the efficacy [33] and the strength and role of therapeutic alliance,[34] compared CBT and control intervention. Both groups showed significant improvement, and no differences were found between treatment groups at the end of treatment. At 6-month follow-up, CBT participants had higher scores on a scale measuring adjustment and, at 12 months, they had lower Eating Disorder Examination (EDE) scores and higher readiness for recovery compared to controls. There were no significant differences in patients' ratings of therapeutic alliance when this measure was used as an outcome predictor of ED symptomatology. With the exception of Shape Concern at follow-up, all ED and depressive symptomatology improvements assessed at end of treatment and follow-up were significant and could be predicted by late treatment therapeutic alliance. Another study focused on the outcome predictors and moderators in a same sample: lower age and shorter duration of illness predicted better outcomes in the quality of life, mental health and depressive symptoms domains, whereas unemployment and taking psychotropic medication predicted worst outcomes.[35]

Model of Treatment for Adults with Anorexia Nervosa (MANTRA).—In recent years, Shmidt *et al.* reflected on the relative lack of efficacy of treatments for adults with AN due to insufficiently tailored interventions and they focused on how the disorder is maintained. They developed a specific maintenance model and treatment approach for AN nicknamed MANTRA, which addresses four core factors that are believed to maintain AN: 1) an inflexible thinking style; 2) impairments in the socio-emotional domain; 3) pro-anorexia beliefs; 4) the response of close others, including anxiety, worry, blame, criticism, or hostility. MANTRA is empirically-based, incorporating recent neuropsychological, social cognitive and personality trait research in AN; it includes intra- and interpersonal maintaining factors, proposes strategies for addressing these, and it is modularized with a clear hierarchical procedure.[36] However, MANTRA did not show superiority in terms of clinical outcomes after 1 and 2-year follow up, though MANTRA patients rated their treatment as significantly more acceptable.[37]

Bulimia nervosa

BN is characterized by frequent episodes of binge eating followed by inappropriate compensatory behaviors, such as self-induced vomiting to avoid weight gain, and overvaluation of body shape and weight. The disorder is associated to high rates of medical complications, psychiatric co-morbidity and psychosocial impairment.

Cognitive-behavioral therapies.—CBT is the evidence-based treatment of choice for BN, but it is effective only for 40-60% of individuals. But not all patients have access to CBT, and many trials have compared CBT to other psychotherapies in order to find tailored approaches. In a long-term follow-up for residential patients, treated with CBT and other approaches such as Dialectical Behavioral Psychotherapy (DBT) and IPT, the best predictor of a good outcome for BN patients was the combination of low vomiting frequency and low bulimia subscale scores on the EDI-2 at discharge.[21] Integrative Cognitive-Affective Therapy (ICAT) is a novel psychotherapy for BN associated with considerable improvements in BN symptoms, similar to those obtained with CBT-E. Both ICAT and CBT-E were found to improve bulimic symptoms, cognitive self-discrepancy, emotional regulation and co-morbid psychi-

atric symptoms.[38] For both CBT and ICAT, three non-specific predictors of outcomes were confirmed: level of dietary restraint, weight and shape concerns and depression. Individuals with higher weight and shape concerns and higher dietary restraint had greater reductions in bulimic behavior at the end of treatment and at 4-month follow-up, respectively. Greater depression predicted fewer reductions in ED psychopathology. For individuals with higher affective lability or higher stimulus seeking, ICAT was associated with greater improvement than CBT-E. For those with lower stimulus seeking or lower affective lability, both treatments were comparable in reducing ED psychopathology, but CBT-E performed better than ICAT in reducing bulimic behaviors.[39] Therapeutic alliance may be particularly important in the treatment of BN, given that interpersonal problems in BN are associated with symptom maintenance. A strong alliance predicts greater improvements in bulimic behaviors and improved behavior further improves alliance. Patients with BN report strong and stable therapeutic alliances both with ICAT and CBT-E.[40] The change in meal and snack consumption from baseline to end-of-treatment (both in ICAT and CBT-E groups) is used to predict changes in the frequency of bulimic behaviors at 4-month follow-up. Evening meals play an important role in patient recovery in the context of treatment, in fact the increase of evening meal consumption during treatment significantly predict decreased binge eating at 4-month follow-up, and decreased mid-morning snack and lunch consumption significantly predict decreased purging behavior. Therefore, increasing regular meal consumption to disrupt the cycle of binge eating and purging behavior in BN is an integral part of treatment.[41]

A stepped-care approach (Stepped Care CBT) was devised for the care of BN, which consists in a manualized guided self-help CBT, further addition of fluoxetine for non-responders after six sessions, and further CBT for those who fail to achieve remission with self-help and medication management. This approach had no, more immediate, effect in inducing recovery (defined as no binge eating or compensatory behaviors for 28 days) or remission than CBT with or without fluoxetine, but was found to be superior in reducing binge eating and compensatory behaviors after 1-year follow-up, suggesting the opportunity to set up individualized, flexible protocols.[42] Individual CBT was compared to group CBT, with insignificant differences in effectiveness. Initial individual sessions leading to group approaches may be a cost-effective alternative to purely individual treatment.[43]

Family-based treatments.—Several case series of bulimic adolescents suggested that FBT and CBT adapted for adolescents (CBT-A) are effective treatments and lead to clinical improvements. FBT was more effective in promoting abstinence from binge eating and purging than CBT in adolescent patients at the end of treatment and at 6-month follow-up, but at 12-month follow-up there were no statistically significant differences between the two treatments.[44]

Psychodynamic therapies.—Evidence on effectiveness of PDT for BN is still doubtful, with most studies supporting superiority of CBT, though PDT was sometimes found to be similarly effective in reducing ED symptoms.[29] A core psychopathological feature of BN is the inability to regulate affective experience and bulimic symptoms may be understood as an attempt to avoid negative affect. PDT may provide patients with increased capacity to recognize and tolerate negative affects, therefore reducing the need to resort to BN behaviors. Both PDT and CBT were found to improve ED features and general psychopathology, although the improvement was greater and quicker with CBT.[45]

Binge-eating disorder

BED has been recently formally upgraded as a specific disorder in DSM-5, to remark existing core differences between BED and non-specific overeating. Indeed BED has a distinctive presentation, distribution and course. It

also appears to be more treatment responsive than AN and BN.[46]

Cognitive-behavioral therapies and interpersonal therapy.—CBT and IPT are considered treatments of choice for BED patients, particularly for those patients with high levels of specific ED psychopathology such as overvaluation of body shape and weight.[47] A long-term follow-up study documented a substantial and long-lasting efficacy of both CBT and IPT for BED, with full recovery from binge eating in 64.4% of patients, consistently with 2-year follow-up recovery rates found in other clinical trials for BED. Both CBT and IPT yielded comparable long-term rates of remission to a subclinical level of binge eating in 80.0% of patients and of clinically significant improvement in associated ED psychopathology in 58.0%.[48] In recent years, little new information for IPT has been reported, with the exception of Group Psychodynamic Interpersonal Therapy, meanwhile Grilo *et al.* studied different aspects of the efficacy of CBT in patients with BED. In an RCT of BED patients receiving either Fluoxetine or CBT, the latter showed better improvement in overvaluation of shape and weight. In the CBT group, participants' overvaluation significantly predicted binge-eating remission and they had significantly greater reductions in ED psychopathology and depression levels then those receiving fluoxetine.[49] In another trial, CBT + placebo was superior to fluoxetine-only but adding fluoxetine to CBT was not superior to adding placebo to CBT.[50] CBT was found to be superior to body weight loss (BWL) in a group of 125 obese patients in producing reductions in binge eating, while BWL produced statistically greater weight loss during treatment. Binge eating and psychopathology outcomes were sustained after treatment completion of both treatments.[51] This was also confirmed in a 6-year follow-up study where long-term effects between CBT and BWL were observed to be comparable.[52] Rapid response (defined as ≥70% reduction in binge eating by week four) as a predictor of outcome was examined in patients receiving CBT and BWL: the first group did well regardless of rapid response in terms of reduced binge eating and ED psychopathology but it did not achieve weight loss. Among the second group, those with rapid response were significantly more likely to achieve binge eating and psychopathology remission and weight loss.[53] In another sample of patients, randomly assigned to self-help CBT intervention and/or low intensity medication (sibutiramine), rapid response represented a strong prognostic indicator of clinically meaningful outcomes.[54, 52] CBT-E was suggested to be more effective than the earlier version (CBT): CBT-E also includes a module designed to address, what Fairburn terms, "mood intolerance" (problems in coping with negative affect) that could trigger binge eating and purging. The content and strategies of the mood intolerance discussed in the CBT-E module overlap with the emotional regulation and distress tolerance skills training of Linehan's DBT. Modified DBT-BED resulted in a significantly greater remission rate from binge eating at post-treatment than a group comparison treatment designed to control for nonspecific therapeutic factors such as treatment alliance and expectations.[47]

Psychodynamic therapies.—Several group treatment outcome studies have demonstrated positive outcomes in BED; Tasca *et al.* reported that both Group Psychodynamic Interpersonal Psychotherapy (GPIP) and Group CBT were equally effective in reducing binge eating, negative mood, and total interpersonal problems. Using the Inventory of Interpersonal Problems (a 64-item measure tool which rates overall distress regarding interpersonal problems on a total score and eight subscales), Tasca *et al.* compared GPIP to Group CBT focusing on Cold/Distant and Intrusive/Needy subscales. Both therapies resulted in a significant decrease in all interpersonal problem subscales except the Nonassertive subscale. GPIP resulted in a greater reduction in the Cold/Distant subscale compared to Group CBT, which suggests that GPIP may be most relevant for those patients with BED who have Cold/Distant interpersonal problems and attachment avoidance.[55]

Other psychological interventions (spurious samples)

Cognitive remediation therapy (CRT) is a therapeutic approach, originally developed to address traumatic brain injury deficits and schizophrenia, designed to improve neurocognitive abilities. It does not include a specific focus on weight, eating, or eating related psychopathology.

CRT was found to be more effective than group CBT in addressing cognitive failures of AN inpatients, though both approaches worked on BMI and EDE global score improvements.[56] CRT was also found to be superior to TAU in improving ED-related quality of life and ED psychopathology in a group of patients with mixed ED diagnoses.[57] CRT plus emotion skills training (CREST) is an adapted approach of CRT designed to address additional emotional problems, but currently there is no evidence that it is more effective than TAU for ED.[58]

Motivational Interviewing is a collaborative intervention that focuses on strengthening a person's internal motivation to change. This intervention significantly increased readiness to change and confidence in ability to control binge eating.[59]

The purpose of the Identity Intervention Program (IIP) is to alter the array of self-schemas that comprise the self-concept, by fostering the development of new distinct and separate positive self-schemas aimed at increasing involvement and investment in more diverse behavioral domains, and decrease the singular maladaptive focus on body weight and shape. In a sample of 69 patients, although both the IIP and Supporting psychotherapy approaches were equally effective in reducing ED symptoms, IIP tended to be more effective in fostering the development of positive self-schemas, with the change staying stable over 12 months.[60]

Progress feedback effects in an inpatient ED treatment program showed that clients exposed to the feedback condition met criteria for clinically significant change with greater frequency than TAU, while a greater number of TAU patients attained the lesser standard of reliable change.[61]

A body and movement oriented approach addressed anger and aggression, affective dimensions typically associated to ED subtypes, severity of ED symptoms and poorer treatment outcome. A brief intervention with a body and movement oriented approach, compared with supportive contact only, decreased anger internalization and resulted in a significantly greater reduction in ED-related psychopathology compared with supportive therapy only.[62]

Pharmacological interventions

A recent critical review by Hay and Caudino [63] on the clinical psychopharmacology of ED concluded that the evidence for efficacy of drug treatments is mostly weak or moderate, with attrition rates usually higher than for psychotherapies.

Anorexia nervosa

Taken as a whole, pharmacological treatments in AN patients appear to be ineffective, even when depressive features are present, since most depressive symptoms are explained as a consequence of the starved state and often resolve with weight gain.[4]

Nevertheless, AP may be considered as an option in treatment-resistant AN, when severe or delusional dysmorphic features are present.[64]

Low-dose AP medication may be clinically useful also as adjunct treatment in acute AN, particularly where there is high anxiety, hyper arousal, obsessive eating-related ruminations, failure to engage, extreme beliefs on body image or pseudo-hallucinations.[63, 65] Paradoxically, in AN subjects, AP may not consistently promote weight gain,[66] despite this being a common side-effect in normal weight people with other psychiatric illnesses such as schizophrenia.[67] Brambilla *et al.*[68] measured changes in neurobiological indicators in a group of 30 AN patients treated with CBT *vs*. CBT + olanzapine. Levels of plasma homovanillic acid (HVA) increased significantly in the CBT +

olanzapine group and were unchanged in the CBT group. No correlations were observed between HVA concentrations and the psychopathological parameters examined before and after therapy. While CBT significantly improved the specific psychopathology of patients, olanzapine administration seemed to act mostly on the associated comorbidities like depression, anxiety, hostility and obsessiveness-compulsivity. Evidence for the use of AP in AN was only collected for olanzapine,[69] though this positive effect seems not to be specific for the diagnosis.

A retrospective study suggested that aripiprazole may have a role as augmentation agent, to reduce eating-related preoccupations and rituals.[70]

We found few studies focused on pharmacological treatments in AN, the majority of which had an insufficient sample size to meet our criteria. Estrogen replacement decreased anxiety traits [71] and intranasal oxytocin had no effect on emotion recognition sensitivity or consuming behavior,[72] but it attenuated attentional vigilance to disgust both in patients with AN and healthy controls.[73]

Bulimia nervosa

Good evidence supports the use of AD, particularly high-dose fluoxetine, in the management of BN symptoms such as binge eating, vomiting and mood and anxiety symptoms.[74] Effectiveness of AD in BN appears independent of effects on mood and is likely related to augmentation of satiety mechanisms and subsequent reduction in binge eating.[75] Fluoxetine is the only AD medication approved by the USA Food and Drug Administration (FDA) for the treatment of BN. Patients who fail to report a 60% decrease in the frequency of binge eating or vomiting at week 3 are unlikely to respond to fluoxetine. Early response is one of the only available indicators to guide clinical management as no reliable relationships between pretreatment characteristics and eventual response to pharmacotherapy have been identified for BN.[76]

The present review did not found any RCT on pharmacological treatments conducted on patients with BN.

Binge-eating disorder

There is a good evidence that AD, especially SSRIs, can improve outcomes in patients with BED, in terms of reducing, binge-eating behaviors (at least in the short term) [74] as well as the high rate of comorbid major depressive disorder.[77]

Treatment with SSRI, and, though evidence is less strong, with TCA, can improve BED in terms of reducing binge-eating behaviors. Yet, in the last 5 years, research focused mainly on new drugs, namely: lisdexamfetamine dimesylate (LDX), a pro-drug stimulant initially marketed for ADHD; sibutramine, a SNRI structurally similar to amphetamine; armodafinil, the (R)(-) entantiomer of modafinil, a wakefulness-promoting agent; and rimonabant, an inverse agonist for the cannabinoid receptor CB1.

In a RCT studying LDX *vs*. placebo, LDX decreased global BE severity and obsessive-compulsive and impulsive features of BED in addition to binge eating days.[78] The safety profile was consistent with previous findings in ADHD adults.[79] Sibutramine was associated with significantly greater acute weight loss than placebo in a sample of obese BED patients randomized for sibutramine, placebo or each one plus self-help CBT, but after the medication was discontinued a post-treatment weight re-gain occurred in sibutramine groups, suggesting that anti-obesity medications may need to be continued for weight loss maintenance.[80] Armodafinil and placebo did not differ in terms of improvement in binge eating day frequency; however, armodafinil was associated with a, statistically significant, higher rate of decrease in binge-eating episode frequency. Armodafinil was also associated with statistically significant reductions in obsessive-compulsive features of binge eating and BMI.[81] Finally, the rimonabant group showed a greater reduction on the binge-eating scale total score and of the initial body weight *vs*. the placebo group. The incidence of treatment emergent

adverse events was comparable in both the two groups, but discontinuations due to treatment emergent adverse events occurred more often in the rimonabant-treated group.[82] According to Hay and Claudino, drug therapies such as anticonvulsants and anti-obesity medication may aid weight loss in BED patients; however, common or potentially serious adverse effects limit their use.[63]

Only one small (61 participants) RCT focused on an AD, bupriopion. Though patients taking bupropion lost significantly more weight than placebo, bupropion did not improve binge eating, food craving, or associated eating disorder features or depression relative to placebo.[83]

Adjunctive interventions and miscellaneous

In a systematic review involving 213 inpatients diagnosed with AN and BN, specific physical therapy interventions, including aerobic and strength training, massage, yoga, and basic body awareness were beneficial on different outcomes, such as BMI, body fat percentage, muscular fitness and depressive and anxiety symptoms.[84] We found a prominent interest in published research in caregivers' role specifically in AN, adjunctive technological -including virtual reality- and lifestyle interventions.

Aardoom *et al.*[85] reviewed 21 studies on internet-based treatments of ED: these were found to be more effective than face-to-face standard approaches for individuals with less comorbid psychopathology, and more binge-eating symptoms than restrictive or bulimic. Higher levels of compliance were related to greater improvements in ED symptoms. Inclusion of face-to-face assessments and therapist support seemed to enhance study compliance. Overall, the internet was concluded to be an acceptable vehicle for delivering ED treatment.

Internet-based prevention appeared to be a promising approach in reducing the risk of relapse in patients with AN: at a 9-month follow-up, patients involved in a prevention group *vs*. TAU gained significantly more weight and had better cognitive and behavioral outcomes, with no differences in terms of general psychopathology.[86]

A RCT comparing a group of patients with restricting AN who underwent a resistance training program, consisting of 50 minutes supervised training sessions over 8 weeks, following the guidelines for healthy adolescents to a control group suggested that resistance training had a positive effect on muscle mass when performed after hospitalization. Anthropometric measurements could be useful for assessing muscle status in those patients.[87]

Repetitive transcranial magnetic stimulation techniques were also tested for potential applications in the field of ED, with non-conclusive evidence so far.[88]

It is well-established that the persistence of body dissatisfaction at the end of treatment is a reliable predictor of relapse in both AN and BN: two studies addressed this issue augmenting CBT one with a virtual reality-based intervention [89] and the second with a manualized group treatment.[90] Both achieved better clinical outcomes compared to CBT only. Web-based CBT in a randomized trial *vs*. weight loss therapy proved to be effective in improving ED psychopathology and related health outcomes among patients with BED, BN and EDNOS, however the between-group effect was significant only for participants with BED.[91]

CBT-based guided self-help is recommended as a first step in the treatment of BN. In particular, it provides an acceptable treatment alternative to BN patients who are reluctant to face-to-face contact. Bibliotherapy (*e.g*. with a 15-chapter self-help manual) is the gold standard of self-help treatment, but it is also possible to choose other telemedicine delivery media (*e.g*. CD-Rs and internet-based platforms). These different media showed comparable effectiveness on both primary (improvement of binge-eating episodes and compensatory behaviors) and secondary outcomes (decrease in associated ED psychopathology) at the end of therapy and at an 18-months follow-up.[92] In Hungary, an internet-based support program was conducted on patients with BN or related EDNOS who had completed inpatient treat-

ment within the previous 12 months. The program was feasible and well accepted but did not prove to be effective.[93] A previous RCT of internet-based CBT for BN and related disorders in 76 students showed that iCBT with e-mail support was effective in students with BN and had lasting effects.[94] In a similar population of BN or related EDNOS patients, a text messaging intervention was provided. It consisted in weekly interaction between the patient and the provider for 16 weeks and it was offered immediately after inpatient treatment. This aftercare intervention was found to be effective in enhancing treatment outcome.[95]

Two studies examined lifestyle intervention in BED patients, with encouraging results. One was based on increasing physical activity and, after a 2-year follow-up, it showed that behavioral interventions addressing physical activity led to reductions in binge-eating symptoms.[96] The second examined a low energy density diet combined with CBT. Participants were randomly assigned to either a 6-month individual treatment or general nutrition counseling. The two treatments did not differ significantly in weight loss or binge remission outcomes, but the low-energy density diet group had better metabolic outcomes and more fruit and vegetable consumption. Reduction in energy density and weight loss were significantly associated, providing evidence for the specificity of the treatment effect.[97] Another study explored the effectiveness of being exposed to virtual environments presenting critical situations related to the maintaining and relapse mechanisms (*i.e*. home, supermarket, pub, etc.) and body image comparison areas. Virtual reality-based treatment, in comparison with the standard CBT approach, was found to be effective in the prevention of weight regain but not in managing binge-eating episodes.[98]

In a RCT with BED and BN patients, guided self-help showed a significant improvement of psychopathology, laxative abuse, exercise behavior and global distress when compared to a waiting list control group.[99] However, in a more recent study, self-help CBT was not more effective compared to usual care in a small RCT on obese BED patients in primary care.[54]

Finally, the role of caregivers and family members in the care of AN was explored by different studies. A study conducted on 54 triads of adolescents and parents suggested the existence of a person/dose dependence relationship between parent's accommodation (*i.e*. not challenging and turning a blind eye to unwanted behaviors) and patient's outcome: when both parents are accommodating the outcome is poor.[100] A skill training intervention addressing inpatients' caregivers showed only a modest, not statistically significant, improvement in patients' and carers' outcomes (*i.e*. quality of life).[101] A third study examined a sample of adult inpatients whose families were offered a workshop-based intervention with group educational and skills-based components; the intervention was compared to an individually focused family intervention. In both groups, there was an improvement in patients' BMI and a reduction in carers' distress, suggesting that group approaches may be a more cost-effective intervention then individually focused family intervention.[102]

Conclusions

There have been substantial developments in the field of psychological therapies for ED within the last few years, including: a consolidation of CBT for BN and BED, further evidence that FBT as the treatment of choice for younger AN cases and clearer evidence for some other adjunctive treatment approaches.[103]

Evidence still suggest that psychotropic medications should not be the primary intervention in ED. Despite this, medications are widely prescribed to ED patients in the real world, despite poor evidence of their efficacy. This may also depend on reduced availability of the most effective treatment approaches such as structured psychotherapy programs in the real world.[104]

Considering the high prevalence and severity of ED, there is an urgent need of further elucidating the effectiveness of stepped care approaches involving different settings and psychotherapy models.

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