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Treatment of Eating Disorders: a systematic meta-review of meta-analyses and network meta-analyses

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1 Introduction

Eating Disorders (EDs) have a peak age at onset during key developmental adolescent years (Solmi et al., 2021), and have severe mental and physical health impacts (Voderholzer et al., 2020). The treatment of EDs is complex and typically involves several health care disciplines (Monteleone et al., 2019). However, the efficacy of treatment is modest (Treasure et al., 2020), with remission ranging from 40% to 60% in anorexia nervosa (AN), bulimia nervosa (BN) and binge-eating disorder (BED) (Eddy et al., 2017; Linardon, 2018a; Slade et al., 2018; Steinhausen, 2002; Steinhausen and Weber, 2009; Zipfel et al., 2015). The variability of remission also reflects the heterogeneous definition of remission (Bardone-Cone et al., 2018), which should ideally encompass psychological, cognitive, physical (i.e., body mass index, BMI) and behavioural (i.e., binge eating or purging behaviours) criteria (Lilienfeld, 2019). Relapse frequently occurs in EDs, especially after discharge from inpatient treatment (Gregertsen et al., 2019; Marzola et al., 2021b).

International guidelines (e.g., the National Institute for Health and Care Excellence, NICE, National Guideline Alliance, 2017) recommend psychological interventions as first-line treatment for individuals with AN. Across psychotherapies, manualised family-based therapy (FBT) is suggested for adolescents with AN, while individual psychotherapies (i.e., cognitive-behavioural therapy for eating disorders (CBT-ED), focal psychodynamic psychotherapy (FPT), Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA), or Specialist Supportive Clinical Management (SSCM)) are recommended for adults with AN. With the exception of FPT among these therapies, some have been superior to 'treatment as usual' conditions, but none has been found to be superior to another manualised specialist therapy (Byrne et al., 2017; Schmidt et al., 2016; van den Berg et al., 2019; Zeeck et al., 2018; Zipfel et al., 2014). International guidelines concur that medications should not be used as the sole or primary treatment for those with AN (Hilbert et al., 2017). For BN, NICE (2017) guidelines recommend individual psychological interventions as first-line treatment, namely FBT for adolescents or CBT-ED (in both the guided self-care and therapist-delivered forms) for adults. This latter intervention is also considered the treatment of choice for BED in adults, yet no

evidence-based recommendation is available for adolescents. Antidepressants, and selective serotonin reuptake inhibitors (SSRI) in particular, have been proposed as an adjunctive treatment to psychotherapy for people within binge-eating spectrum disorders although only lisdexamfetamine has been approved in the US for BED (Hilbert et al., 2019; Slade et al., 2018; Treasure et al., 2020). There is currently no approved medication for EDs in Europe except the fluoxetine for bulimia nervosa (Tortorella et al., 2014).

However, notable differences exist among the current guidelines (Hilbert et al., 2017). These inconsistent recommendations reflect methodological limitations. For instance, a network meta-analysis (NMA) by Zeeck et al. (2018) only considered body weight as the primary outcome and found more rapid weight gain in adolescents than in adults and no superiority of a specific psychological approach for adults with AN. A meta-analysis (MA) by Murray et al. (2019) considered both physical and psychological outcomes, and found that specialized psychological treatments outperformed control interventions on weight outcomes, but not on psychological outcomes, and no differences emerged between adolescents and adults with AN. Finally, a recent NMA (Solmi et al., 2021) only based on standalone outpatient treatment of adults with AN concluded that no reliable evidence supports the clear superiority or inferiority of any treatment recommended by the NICE guidelines.

A previous umbrella review summarized meta-analytic evidence on the efficacy and acceptability of interventions for any mental disorders including EDs (Correll et al., 2021). However, that umbrella review only focused on children and adolescents, and only considered a pre-selected range of outcomes. A comprehensive umbrella review is needed to summarize the findings and to grade the quality of previous meta-analyses of RCTs in EDs, without restricting studies to specific age groups or specific outcomes, and providing a synopsis of efficacy, safety, acceptability and tolerability of treatments for ED. Also, currently there is no umbrella review accounting for effect modifiers and confounding factors, and conducting analyses by age group, type of intervention, setting, control condition, ED diagnosis (i.e. AN, BN, BED, EDNOS), and mode of treatment delivery. The present

work aims to fill this gap, distilling clinically relevant information from a vast body of data to inform clinical care, clinical guidelines, and research directions.

2 Methods

2.1 Search, inclusion and exclusion criteria

This umbrella review followed an *a priori* PRISMA 2020-compliant (Page et al., 2021) protocol (https://osf.io/wg5de/?view_only=177c444c41514fadb386ef1d57dee99d) (Figure 1, supplementary Tables 1-2). We conducted a systematic search in PubMed, PsycINFO, and Cochrane database up to December 15th, 2020, using the search key "(anorexia or bulimia or eating disorder) AND (meta-analy*)". We also manually searched references of included MAs and other relevant reviews. Two independent (FP, MC) authors conducted title/abstract screening, full-text assessment, and data extraction into a pre-defined Excel spreadsheet. A third author (MS) resolved any conflicts.

Included were: a) MAs or NMAs, b) of RCTs testing any intervention in comparison to an active or inactive control condition, c) in any age group and setting, d) in participants with a DSM/ICD diagnosis of an eating disorder (AN, BN, BED, eating disorder not otherwise specified or unspecified feeding or eating disorder (EDNOS or OS/UFED), e) reporting on comparative estimates of efficacy, and discontinuation due to any cause (acceptability) or due to adverse events (tolerability). Exclusion criteria were: a) systematic reviews without MA, b) pooling studies other than RCTs, c) including participants without an ED diagnosis, d) MA reporting on pre-post changes of a given set of interventions.

Whenever two NMAs/MAs reported on the same combination of disorders, interventions, comparisons and/or outcomes, we prioritized NMA over MA, or MA with more RCTs. NMAs have been prioritized over pairwise MAs previously, as they are deemed the highest level of evidence in treatment guidelines (Leucht et al., 2016). To avoid relying on completely indirect estimates, we only extracted effect sizes from NMAs that were based on at least one direct comparison for the outcome of interest.

2.2 Participants, interventions, comparison, outcomes, setting operationalization

Participants were diagnosed with AN, BN, BED, EDNOS/OSFED, or combined ED. Their age group could be adolescents (<18 years only), adults (≥ 18 years old only) or mixed.

We categorized interventions as follows: behavioural therapy (including behavioral weight loss therapy) (BT), CBT-ED, family therapy (FAM) (separating specific family-based therapy, FBT), interpersonal psychotherapy (IPT), Maudsley Model of Anorexia Nervosa Treatment for Adults, mixed or unspecified psychotherapy (PT), multidisciplinary care (including SSCM) (MULTI), psychodynamic-oriented (PSD-O), psychoeducation (EDU), physical exercise, and pharmacological treatments. Pharmacological treatments were subdivided by class (antidepressants, anticonvulsants, antipsychotics, stimulants, anti-obesity). Treatment format was individual (-i), group (-g), self-help (-s), or their combinations.

Comparators were specific drug or psychological intervention (active), treatment as usual (TAU), placebo (PBO), waiting list or no treatment (WL/NT), mixed TAU and WL/NT, mixed active and WL/NT.

Outcomes were ED-specific behaviours (BEHAVIOURAL, i.e. binge-eating and/or purging episodes remission or frequency, compensatory behaviours), neuropsychological functioning (COGNITION, i.e. central coherence, emotion recognition), eating disorder-specific psychopathology (EDP, i.e. body dissatisfaction, drive for thinness, shape/weight concern); functioning and quality of life (F-QOL); general psychiatric symptoms (GENERAL, i.e. depressive/anxiety/obsessive-compulsive); global course of the disease (GLOBAL, i.e. response/remission/relapse/clinical improvement/abstinence from binge eating/abstinence from purging/all outcomes); weight or body mass index (WEIGHT/BODY). Whenever possible, we extracted outcomes both at end of treatment and at follow up (any time point). Acceptability (inferred from drop out due to any cause) and safety (adverse effects of medications) were also extracted.

The setting in which the intervention was delivered was inpatient only, outpatient only, or mixed.

2.3 Quality of evidence

The quality of MAs and NMAs was measured using A Measurement Tool for the Assessment of Multiple Systematic Reviews (AMSTAR-PLUS) (Correll et al., 2017) to quantify both the methodological quality of MAs and NMAs with the first 11 items (AMSTAR) (Shea et al., 2007), and of included RCTs with six additional items (AMSTAR-Content (Correll et al., 2017), for each MA/NMA primary outcome).

Methodological quality was categorized as low (<4), medium (4-7), and high (>7). Content quality was categorized as low (<4), medium (4-6), and high (>6), as done previously (Correll et al., 2021; Solmi et al., 2020). Quality assessment was done by two independent reviewers. Full details on the quality assessment are available elsewhere (Correll et al., 2021; Solmi et al., 2020) .

2.4 Statistical analysis

We did not recalculate all NMAs or MAs, and just reported what the original authors had done. However, in order to provide results on the same scale in Figure 2, where possible, we standardized and harmonized effect sizes. For instance, where mean difference was reported, we transformed it into standardized mean difference (SMD). Also, we harmonized outcome reporting, so that SMD>0 and odds ratio/risk ratio (OR/RR) >1 favor intervention for all outcomes. For instance, if a MA reported ED psychopathology improvement as SMD<0, we inverted the mathematical sign and 95% confidence interval. For AN, weight gain was reported as SMD>0, whilst for BED weight loss was reported with SMD>0, so that the statistical direction matched the clinical direction of the finding.

3 Results

The search flow is reported in Figure 1. Out of 884 articles, 55 MAs and 4 NMAs were included (Albano et al., 2019; Bacaltchuk et al., 1999; Josue Bacaltchuk et al., 2000; Josué Bacaltchuk et al., 2000; Bacaltchuk and Hay, 2003; Barakat et al., 2019; Berkman et al., 2015; Brownley et al., 2016;

Cassioli et al., 2020; Claudino et al., 2006; Couturier et al., 2013; Cuijpers et al., 2016; de Vos et al., 2014; Dold et al., 2015; Fisher et al., 2018, 2010; Fornaro et al., 2016; Ghaderi et al., 2018; Ghaderi and Andersson, 1999; Grenon et al., 2018a; Hagan et al., 2020; Hasselbalch et al., 2020; Hay et al., 2019, 2015, 2004, 2001, 2009; Hilbert et al., 2019; Kishi et al., 2012; Lebow et al., 2013; Linardon, 2018b; Linardon et al., 2020, 2019, 2017a, 2017b, 2017c; Loucas et al., 2014; Low et al., 2021; Machado and Ferreira, 2014; Murray et al., 2019; Nakash-Eisikovits et al., 2002; Ng et al., 2013; Nourredine et al., 2020; Palavras et al., 2017; Peat et al., 2017; Perkins et al., 2006; Polnay et al., 2014; Reas and Grilo, 2008; Eric Slade et al., 2018; M Solmi et al., 2021; Stefano et al., 2008, 2006; Svaldi et al., 2019; Swift et al., 2017; Thompson-Brenner et al., 2003; Traviss-Turner et al., 2017; van den Berg et al., 2019; Vocks et al., 2010; Zeeck et al., 2018). Publications excluded after full-text assessment, with reason for exclusion are available in supplementary table 3. MAs and NMAs included in the umbrella review are reported in table 1. Among included (N)MAs, 33 (55.9%) assessed non-pharmacological interventions only, 16 (27.1%) pharmacological interventions only, while 10 (17%) assessed both (AN: 65%/35%/0%; BN: 60%/20%/20%; BED: 47.4%/26.3%/26.3%; combined ED: 94.1%/0%/5.9%). Overall, 33 different non-pharmacological interventions and 19 different (combinations of) medications have been identified. Regarding age groups, 19 (57.6%) (N)MAs reported on adults, five (15.2%) on adolescents, and the remaining nine (27.3%) reported on mixed or unspecified age. Only one MA (1.7%) reported on inpatients, and in AN only; eight (13.6%) reported on outpatients; and the others on any or unspecified settings.

The number of trials for a specific outcome ranged from 2-35 (median=4, interquartile range=2-7).

Quality of included studies is reported in supplementary table 4. Overall AMSTAR/AMSTAR-Content mean scores were 7.9±1.7 and 2.7±1.5. Thirty-five (59.3%) (N)MAs had an AMSTAR >7, one (1.7%) had the maximum score (11), whilst none had an AMSTAR-Content score >6. The main reasons for lower quality rating had to do with the quality of the meta-analyzed RCTs included in (N)MAs, and namely no “double-blind” design in most of the studies (81%), primary outcome result

not confirmed in at least one large study with approximately 100 patients per arm (74%), and the presence of publication bias regarding the primary outcome result (78%).

Below, effect sizes versus WL/NT, PBO, TAU and Active are reported by disorder (see tables 2-3). We left results from MAs mixing TAU with active or inactive controls in supplementary tables only, as those comparisons inappropriately mixed different control groups (see supplementary tables 5-6). In the paragraphs below, results are reported with number of RCTs (k), number of subjects (n), effect size with 95% confidence interval, quality score, and quality category (L/low, M/medium, H/high).

3.1 Anorexia nervosa

AN was investigated in two NMAs and 18 MAs; four (20.0%) reported data on adolescents, seven (35.0%) on adult patients.

In adolescent outpatients, individual family-based therapy proved efficacious versus active control for global course of the disease at follow up (k=3, n=183, OR=2.08, 95%CI=1.07-4.03, AMSTAR/Quality=9/H), and individual family therapy in mixed settings for change in weight or body composition (k=4, n=178, SMD=0.44, 95%CI=0.14-0.74, AMSTAR/Quality 9/ H) (40.0% of interventions).

In adults, overall, 25.0% of the interventions had evidence of efficacy, but none in the outpatient setting, 33.3% in mixed settings, and only compared to TAU; specifically, individual family therapy proved beneficial for global course of the disease (k=2, n=81, RR=3.50, 95%CI=1.49-8.23, AMSTAR/Quality=9/H).

Results on mixed age groups are reported in eResults section.

3.2.1 Bulimia nervosa efficacy

BN was investigated in one NMA and 19 MAs; two (10.0%) reported data on adolescents, six (30.0%) on adults.

For adolescents, compared to active control, in outpatients individual family-based therapy improved global course of the disease at follow-up (k=2, n=37, OR=2.22, 95%CI=1.02-4.82, AMSTAR/Quality=9/H), whereas in Mixed settings cognitive behavioural therapy for eating disorders did not differ from active control.

In adults, 42.9% of the interventions proved beneficial and 7.1% had both beneficial and detrimental effects. In outpatients, only group cognitive behavioural therapy for eating disorders was covered, compared to wait list-no treatment, with efficacy regarding eating disorder behaviours (k=4, n=51, SMD=0.56, 95%CI=0.15-0.96, AMSTAR/Quality=9/H) and global course of the disease (k=2, n=31, RR=1.29, 95%CI=1.04-1.61, AMSTAR/Quality=9/H). In mixed settings, compared to wait list-no treatment, individual cognitive behavioural therapy for eating disorders and individual psychotherapy were both beneficial for eating disorder behaviours (k=9, n=323, SMD=1.01, 95%CI=0.68-1.33, AMSTAR/Quality=5/M; k=5, n=206, SMD=1.22, 95%CI=0.92-1.52, AMSTAR/Quality=5/M), general psychiatric symptoms (k=6, n=223, SMD=0.80, 95%CI=0.37-1.22, AMSTAR/Quality=5/M; k=3, n=101, SMD=0.58, 95%CI=0.18-0.98, AMSTAR/Quality=5/M) and global course of the disease (k=5, n=204, OR=1.49, 95%CI=1.28-1.72, AMSTAR/Quality=6.5/M; k=na, n=554, OR=3.89, 95%CI=1.19-14.0, AMSTAR/Quality=6.5/M; k=4, n=162, OR=1.54, 95%CI=1.30-1.82, AMSTAR/Quality=6.5/M). Global course of the disease was ameliorated also by group behavioural therapy (k=na, n=207, OR=28.7, 95%CI=3.11-455, AMSTAR/Quality=8/H), group cognitive behavioural therapy for eating disorders (k=na, n=245, OR=7.67, 95%CI=1.51-55.7, AMSTAR/Quality=8/H) and self-help cognitive behavioural therapy for eating disorders (k=na, n=302, OR=3.49, 95%CI=1.20-11.2, AMSTAR/Quality=8/H; k=na, n=392, OR=3.81, 95%CI=1.51-10.9, AMSTAR/Quality=8/H). Compared to Active control, individual cognitive behavioural therapy for eating disorders had the broadest efficacy, namely for eating disorder behaviours (k=25, n=na, g=0.23, 95%CI=0.06-0.37, AMSTAR/Quality=5/M), EDP (k=16, n=na, g=0.27, 95%CI=0.08-0.45, AMSTAR/Quality=6/M), and global course of the disease (k=7, n=484, OR=1.20, 95%CI=1.03-1.41, AMSTAR/Quality=5/M; k=14, n=na, OR=1.70, 95%CI=1.21-2.38, AMSTAR/Quality=6/M).

Individual psychotherapy was worse than control for global course of the disease (k=6, n=257, RR=0.83, 95%CI=0.69-0.98, AMSTAR/Quality=8/H). Antidepressants were beneficial for eating disorder behaviours (k=3, n=89, RR=2.08, 95%CI=1.09-25.0, AMSTAR/Quality=8/H) and general psychiatric symptoms (k=3, n=117, RR=2.13, 95%CI=1.09-100, AMSTAR/Quality=8/H).

Results on mixed age groups are reported in eResults section.

3.2.2 Bulimia Nervosa acceptability

Individual psychotherapy was more acceptable than active control (k=6, n=295, RR=1.75, 95%CI=1.14-2.63, AMSTAR/Quality=8/H).

3.3.1 Binge-Eating Disorder efficacy

Data for BED were extracted from one NMA and 18 MAs; none provided information on adolescents, six (31.6%) specifically on adults.

In adult outpatients, individual cognitive behavioural therapy for eating disorders outperformed active control improving eating disorder behaviours (k=4, n=323, MD=2.04, 95%CI=0.35-3.73, AMSTAR/Quality=9/H). In mixed settings, 57.1% of the interventions proved beneficial, and 28.6% had both favourable and unfavourable outcomes. Compared to wait list-no treatment, individual cognitive behavioural therapy for eating disorders proved beneficial for eating disorder behaviours (k=3, n=208, MD=2.32, 95%CI=0.09-4.56, AMSTAR/Quality=11/H) and global course of the disease (k=4, n=401, RR=4.95, 95%CI=3.06-8.00, AMSTAR/Quality=8/H). Compared to placebo, antidepressants were superior for eating disorder behaviours (k=7, n=na, MD=0.67, 95%CI=0.09-1.26, AMSTAR/Quality=8/H), eating disorder psychopathology (k=3, n=na, MD=3.84, 95%CI=1.13-6.55, AMSTAR/Quality=8/H), general psychiatric symptoms (k=3, n=na, MD=1.97, 95%CI=0.28-3.67, AMSTAR/Quality=8/H) and global course of the disease (k=8, n=548, RR=1.67, 95%CI=1.24-2.26, AMSTAR/Quality=8/H). Also, stimulants improved eating disorder behaviours (k=3, n=1033, SMD=0.56, 95%CI=0.28-0.84, AMSTAR/Quality=9/H), eating disorder

psychopathology (k=3, n=na, MD=6.50, 95%CI=4.18-8.82, AMSTAR/Quality=8/H), global course of the disease (k=3, n=1033, RR=1.58, 95%CI=1.35-1.84, AMSTAR/Quality=9/H; k=3, n=1033, RR=2.43, 95%CI=1.95-3.01, AMSTAR/Quality=9/H) and change in weight or body composition (k=3, n=1033, SMD=1.28, 95%CI=1.06-1.51, AMSTAR/Quality=9/H). Anticonvulsants improved eating disorder behaviours (k=na, n=na, MD=0.98, 95%CI 0.15-1.80, AMSTAR/Quality=5/M; k=3, n=528, MD=1.31, 95%CI=0.03-2.58, AMSTAR/Quality=5/M) and change in weight or body composition (k=3, n=528, MD=4.91, 95%CI=3.41-6.42, AMSTAR/Quality=5/M). No intervention outperformed active control.

Results on mixed age groups are reported in eResults section.

3.3.2 Binge-Eating Disorder acceptability

Antidepressants induced more adverse events (k=3, n=938, RR=0.61, 95%CI=0.42-0.88, AMSTAR/Quality=11/H; k=3, n=938, RR=0.38, 95%CI=0.23-0.61, AMSTAR/Quality=11/H) and had lower acceptability (k=3, n=1032, RR=0.46, 95%CI=0.21-0.97, AMSTAR/Quality=9/H) than placebo.

Anticonvulsivants had lower acceptability (k=3, n=528, RR=0.52, 95%CI=0.31-0.88, AMSTAR/Quality=5/M) than placebo.

4 Discussion

To our knowledge this is the first umbrella review to systematically assess efficacy and acceptability of interventions specifically for EDs from (N)MAs of RCTs, and both the quality of the (N)MAs and of the meta-analysed RCTs. This umbrella review also follows recent recommendations regarding the need to consider a wide range of outcomes in EDs (Murray et al., 2018) including treatment acceptability (Grenon et al., 2018b). Pooling data from 55 MAs and 4 NMAs, this work advances the field by filtering the enormous body of meta-analytic evidence on interventions in EDs (1,154 effect sizes), rating quality, and providing clinicians, guideline developers and researchers with an

informative synopsis of what works better than treatment as usual and/or active control, for which symptoms, at which time-points, and based on what quality of evidence.

For AN, family-based treatment was the only intervention supported by some evidence against other active treatments for both remission and weight gain. In BN, individual cognitive behavioural therapy for ED outperformed other active treatments for ED psychopathology and behaviours, as well as remission. Among pharmacological interventions, tricyclic antidepressants (TCAs) and SSRIs were the most efficacious for ED behaviours and remission. In BED, general psychotherapy (i.e., any manualised psychological therapy) was more efficacious versus active controls for ED psychopathology and drop-out, but less effective for weight reduction; while behavioural treatments (including behavioural weight loss treatment) and cognitive behavioural therapy for ED were more efficacious than active treatments for ED psychopathology and behaviours, respectively. Lisdexamfetamine and antidepressants were more efficacious than placebo for ED psychopathology, ED behaviours, and remission. Antidepressants were also more effective than placebo for general psychiatric symptoms, while lisdexamfetamine as well as anticonvulsants and sibutramine were more effective than placebo for weight reduction. All these findings refer to status at the end of treatment.

Regarding data on follow-up, a smaller body of evidence was available. In adolescent outpatients with AN and with BN, family-based therapy was more effective than active control on remission. In BN, cognitive behavioural therapy for ED outperformed other active treatments regarding ED behaviours. In BED, behavioural treatment was less effective than active control for ED behaviours and remission, whereas psychotherapy was more effective for ED psychopathology.

This distilled evidence calls for a critical analysis of current treatment guidelines for EDs. For AN, this umbrella review supports the practice guidelines that each recommend family-based therapy for younger patients (Hilbert et al., 2017), although a recent Cochrane review (Fisher et al., 2019) commented that there is a limited amount of low-quality evidence to suggest that family therapy approaches may be more effective compared to treatment as usual. In young adults (mean age: 15.2-26.2) with AN, family therapy (not family-based treatment) was more effective than treatment as

usual regarding global remission at the end of treatment (medium-large effect). This finding is novel and seems to have been neglected by guidelines, which recommend individual psychotherapy for adults with AN, especially cognitive behavioural therapy for ED (Hilbert et al., 2017). A recent NMA (M Solmi et al., 2021) found no superiority of the most recommended individual psychotherapies (e.g. CBT-ED, MANTRA, SSCM, psychodynamic therapies) versus treatment as usual in adult outpatients with AN. However, that work focused on symptoms, and not global remission as the outcome. Thus, the current findings suggest that interventions involving family might be considered in young adults with AN, although research should aim to develop good alternatives, which does not essentially shift the treatment responsibility to families, as not all adults with AN have families involved in their care. No medication was found to be effective in reducing ED behaviours/psychopathology or general symptoms or in improving weight outcome, supporting previous evidence that the use of medications cannot be recommended to improve body weight or ED-specific psychopathology in AN (Treasure et al., 2020; Zipfel et al., 2015), unless psychiatric comorbidity is present.

In BN, the most robust evidence exists for individual cognitive behavioural therapy for ED, which was more effective in reducing specific and, possibly, general symptoms compared with active treatments at the end of treatment. The positive effect on ED behaviours persisted at follow-up. Compared to wait list-no treatment, not only cognitive behavioural therapy for ED but also general psychotherapy (i.e., any manualised psychological therapy) was more efficacious. The evidence for adolescents was different, here family-based therapy outperformed other active interventions on remission at follow-up. These findings support international clinical guidelines (Hilbert et al., 2017) which recommend individual cognitive behavioural therapy for ED as the first line treatment for adults with BN and family-based therapies for younger patients. The NICE guidelines (2017) suggest the use of guided self-help cognitive behavioural therapy for ED as the first choice: however, this recommendation is not corroborated by our findings that confirm the efficacy of self-help as well as group-delivered cognitive behavioural therapy for ED only in comparison to wait list-no treatment,

where expectation effects are not controlled for. NICE includes a cost-effectiveness outcome that was not considered in the present work, which might contribute to the highlighted discrepancy. Furthermore, antidepressants (both SSRIs and the TCAs) outperformed active treatments for ED behaviours and general symptoms and were more effective than placebo for ED behaviours and remission. However, antidepressants were less acceptable than placebo, when contrasted with psychotherapy. These findings are in line with the recommendations from most guidelines (Hilbert et al., 2017), suggesting antidepressants (i.e., the SSRIs) and psychotherapy for people with BN, although there was no evidence relating to the combination of these two treatments over monotherapy. In BED, the largest evidence existed for lisdexamfetamine and antidepressants. Across psychotherapies, general psychotherapy (i.e., any manualised psychological therapy) and behavioural treatment outperformed active treatments for ED psychopathology as did cognitive behavioural therapy for ED for ED behaviours at the end of treatment. Although general psychotherapy was less efficacious than active treatments for weight reduction, it was considered more acceptable and its effect on ED psychopathology persisted at follow-up in comparison to both active treatments and wait list-no treatment. In contrast, behavioural treatment was less efficacious than active treatments at follow-up. Our findings only partially concur with guidelines (Hilbert et al., 2017) that consistently recommend the use of cognitive behavioural therapy for ED as the specific psychological intervention for BED. Indeed, other (non-CBT-ED) psychotherapies including third wave psychotherapies were efficacious when pooled with cognitive behavioural therapy for ED. However, cognitive behavioural therapy remains the psychological treatment of choice for BED with evidence for a broad set of efficacy outcomes, relatively low attrition and some evidence on low side effects, and cognitive behavioural therapy was evaluated in the largest number of RCTs in comparison with wait-list. Regarding pharmacological interventions, antidepressants (SSRIs), anticonvulsants (namely topiramate) and anti-obesity drugs (orlistat and sibutramine) are recommended in some but not all the guidelines. However, lisdexamfetamine is the only medication indicated for BED by the US Food and Drug Administration (Fornaro et al., 2016). Nevertheless, for consideration of a range of

treatment options, the present findings suggest that all guidelines may consider pharmacological treatments for BED, given the benefits on a wide range of outcomes at the end of treatment. However, there is no evidence regarding the effectiveness of medications at follow-up in people with BED, direct comparisons with psychological interventions are lacking and, compared to placebo, lisdexamfetamine was associated with more adverse events, and topiramate was considered less acceptable. This lack of evidence on sustainability at follow-up may explain why the European Medications Agency (EMA) has not approved any medication for BED, and medications can only be recommended off-label in clinical guidelines.

Remarkably, three findings emerged as transdiagnostic features of treatments for people with EDs and are worth outlining. First, except for long-term effects of family-based treatment, no treatment showed a significant and positive impact for psychopathology and/or behaviours of adolescents with AN or with BN, while for those with BED studies of family-based treatment are missing. Future studies are encouraged to assess treatment effectiveness in adolescents given that most of EDs, except BED, have onset during adolescence (Volpe et al., 2016). Second, long-term treatment effects were found only for psychotherapy interventions, while medications displayed significant effects only at the end of treatment. This finding suggests that maintenance treatment studies with medications are needed. Third, some medications showed either less acceptability or safety than placebo. This finding suggests that clinicians and patients need to be aware of and monitor if/to what degree pharmacological or psychotherapeutic interventions potentially do harm. Overall, these findings may help clinicians with decision making and suggest possible areas for future research.

Limitations of this umbrella review need to be acknowledged. First, we selected network over pairwise meta-analyses, and chose the largest (rather than the highest quality) of the meta-analyses regarding the same population, intervention, control, and outcome. Individual RCTs not pooled in previous MAs were not included. Second, we combined different active control conditions, leading to a loss of granularity regarding potential differences in the efficacy between different active treatment conditions. However, we separated TAU from active control treatments. Third, the number

of studies and participants varied across interventions, comparisons, and outcomes. However, for transparency, we also reported how large the body of evidence was for each result. Fourth, fewer data were available for long-term outcomes, which this is a limitation of treatment literature. Fifth, apart from few MAs (M Solmi et al., 2021), many MAs, and most of those with significant findings considered mixed settings of care and did not yield specific recommendations for the inpatient and outpatient levels of care. Sixth, feasibility and acceptability were poorly reported in the included (N)MAs. Seventh, the duration of follow-up data cannot be gleaned from the present findings. Finally, individual patient data meta/analyses are needed to generate fine grained insight on specific clinical subpopulations. Nevertheless, despite these limitations, to our knowledge, this is the most comprehensive and inclusive umbrella review of interventions for people with EDs that can inform clinicians, patients and their families, guideline developers and researchers.

Based in these findings, many gaps remain in the literature. For example, long-term effects and the effectiveness of combined interventions (e.g., the combination of psychotherapy and pharmacotherapy, which is an effective strategy in common mental disorders (Cuijpers et al., 2020)), has been poorly studied or there are, in people with BED (Hilbert et al., 2019), many different combination treatment arms, which prevent detailed comparison. Similarly, second order treatments for those individuals for whom first line treatments fail have been neglected. Moreover, no meta-analytic evidence was found for treatments in people with OSFED. Finally, the cost-effectiveness outcome, required by NICE, has not been largely addressed in ED treatment studies and has thus not been reported in (N)MAs, but this outcome needs to be considered in future studies.

In conclusion, this umbrella review supports the recommendations from most guidelines relating to BN, and extends support of multidimensional short-term treatment efficacy, especially for cognitive behavioural therapy for ED. Our results also confirm the absence of a differential effect across most specialized individual psychological interventions for AN, apart from family-based therapy in adolescents, and interventions involving families show some efficacy in young adults. Importantly, such interventions outperformed active control on a limited number of outcomes. Our findings are

partially consistent with current guidelines for BED, supporting the efficacy of psychotherapy (including cognitive behavioural therapy for ED). In addition, short-term efficacy of medications (especially SSRIs and the lisdexamfetamine) may be considered and long-term effects require further study.

Despite the importance of the transdiagnostic perspective in EDs (Fairburn et al., 2003) and in other mental disorders (Fusar-Poli et al., 2019), these findings highlight the importance of not viewing EDs as a monolithic diagnostic entity. Differences across the main ED diagnoses in terms of treatment response need to be considered by researchers and clinicians, while acknowledging some transdiagnostic general psychopathology (Monteleone and Cascino, 2021; Solmi et al., 2018), and risk factors (Marzola et al., 2021a). Future meta-analyses should avoid clustering different populations (namely intervention studies should have more descriptors related to the clinical presentation such as weight status or illness duration), interventions, controls, and outcomes, and novel treatments should be tested in particular for individuals with AN of all ages and for adolescents with all specific EDs.

Conflicts of interest

CMB reports: Shire (grant recipient, Scientific Advisory Board member); Idorsia (consultant); Lundbeckfonden (grant recipient); Pearson (author, royalty recipient); Equip Health Inc. (clinical advisory board).

PH receives/has received sessional fees and lecture fees from the Australian Medical Council, Therapeutic Guidelines publication, and New South Wales Institute of Psychiatry and royalties/honoraria from Hogrefe and Huber, McGraw Hill Education, and Blackwell Scientific Publications, Biomed Central and PlosMedicine and she has received research grants from the NHMRC and ARC. She is Chair of the National Eating Disorders Collaboration Steering Committee in Australia (2019-) and was Member of the ICD-11 Working Group for Eating Disorders (2012-2018) and was Chair Clinical Practice Guidelines Project Working Group (Eating Disorders) of RANZCP (2012-2015). She has prepared a report under contract for Takeda (formerly Shire) Pharmaceuticals in regards to Binge Eating Disorder (July 2017) and is a consultant to Takeda Pharmacueticals. All views in this paper are her own.

SZ is involved in editorial duties by Elsevier, Wiley, Thieme and Frontiers; he received several grants from the German Federal Ministry of Education and Research (e.g. 01GV0624)

FFA received consultancy honoraria from Novo Nordisk and editorial honoraria as EIC from Wiley, and he received several national and international Grants (FIS-ISCIII and EU-H2020).The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

AH received: royalties for books on the treatment of binge-eating disorder and obesity with Hogrefe; honoraria for workshops and lectures on binge-eating disorder and obesity and their treatment; honoraria as associate editor of the International Journal of Eating Disorders and Psychotherapeut; honoraria as a reviewer from Mercator Research Center Ruhr, Oxford University Press, and the German Society for Nutrition; and honoraria as a consultant for WeightWatchers and Zweites Deutsches Fernsehen.

CUC has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Alkermes, Allergan, Angelini, Axsome, Gedeon Richter, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Sequirus Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva and Viatris. He has provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a stock option holder of LB Pharma.

MS has received honoraria/has been a consultant for Angelini, Lundbeck, unrelated to this work.

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Authors contribution

AM and MS designed the study. All authors contributed to the interpretation of the findings. AM and MS drafted the first version of the manuscript, all authors critically revised it for important intellectual content. All authors approve the final version of the work. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Fig. 1. PRISMA 2020 study selection flow diagram.

Fig. 2. Forest plot of interventions with evidence of efficacy in eating disorders.

Results are presented as SMD (ES; CI), ordered by control condition, and by magnitude within the control condition. In forest plot, in black comparisons against Active control, in grey against TAU. Legend: 3WPT, third wave psychotherapies; A, Active control; AC, anticonvulsants; AD, mixed antidepressants; ADU, adults; BEHAV, eating disorder behaviours; BT, behavioural therapy; CBT-ED, cognitive behavioural therapy for eating disorders; CI, confidence interval; EDP, eating disorder psychopathology; ES, effect size; FAM, family therapy; FBT, family-based treatment; g, group therapy; GENSX, general psychiatric symptoms; GLOBAL, response/remission/relapse; HOR, hormones; i, individual therapy; LDX, lisdexamfetamine; MIX, mixed age group; ORL, orlistat; P, placebo; SGAD, second generation antidepressants; SMD, standardized mean difference; SSRI, selective serotonin reuptake inhibitors; T, treatment as usual; TCA, tricyclic antidepressants; TOP, topiramate; WEIGHT/BODY, change in weight or body composition