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Psychopharmacologic Treatment of Eating Disorders: Emerging Findings

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Abstract Psychopharmacologic treatment is playing a greater role in the management of patients with eating disorders. In this paper, we review randomized, placebo-controlled trials (RCTs) conducted in anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and other eating disorders over the past 3 years. Fluoxetine remains the only medication approved for an eating disorder, that being BN. RCTs of antipsychotics in AN have had mixed results; the only agent with some evidence of efficacy is olanzapine. One study suggests dronabinol may induce weight gain in AN. Preliminary studies suggest lack of efficacy of alprazolam, dehydroepiandrosterone, or physiologic estrogen replacement in AN; erythromycin in BN; and the opioid antagonist ALKS-33 in BED. In BED with obesity or overweight, bupropion may cause mild weight loss without seizures, and chromium may improve glucose regulation. Also in BED, three RCTs suggest the stimulant prodrug lisdexamfetamine may reduce binge eating episodes, and another RCT suggests intranasal naloxone may decrease time spent binge eating. There remains a disconnection between the size of eating disorders as a public health problem and the lack of pharmacotherapy research of these conditions.

Keywords Pharmacotherapy · Anorexia nervosa · Bulimia · Binge eating

At time of publication, lisdexamfetamine had recently received approval by the FDA for the treatment of moderare to severe BED in adults.

This article is part of the Topical Collection on *Eating Disorders*

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Introduction

The past 5 years have seen a refinement of the nosology of eating disorders. Thus, the DSM-5 Feeding and Eating Disorders category includes pica, rumination disorder, avoidant/restrictive food intake disorder (ARFID), anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and a residual category that includes subthreshold AN, BN, and BED, purging disorder, and night eating syndrome (NES) [1]. Parallel with advances in the nosology of eating disorders, the past 5 years has also seen increased research into the psychopharmacologic treatment of these conditions [2–5]. In 2011, the World Federation of Societies of Bipolar Disorder (WFSBP) reviewed the extant pharmacotherapy literature for AN, BN, and BED and provided preliminary guidelines [3]. In this paper, we review the WFSBP guidelines and the literature on the pharmacotherapy of eating disorders published since then with a focus on randomized, placebo-controlled trials (RCTs). Of note, there have been a number of recent excellent reviews [3, 4]; this paper is focusing on emerging findings.

Methods

We searched PubMed for placebo-controlled trials of AN, BN, and BED from 2011 through January 20, 2015 using the term "placebo" matched with "anorexia nervosa," "bulimia," and "binge eating." We also searched the Cochrane data base, using the same three terms. Additionally, we searched ClinicalTrials.gov for any ongoing randomized, placebo-controlled studies of AN, BN, and BED. Finally, as the WFSBP did not evaluate pharmacotherapy of other eating disorders, we also searched for RCTs of pica, rumination disorder, ARFID, purging disorder, and NES.

Anorexia Nervosa (AN)

Based on 20 RCTs, the WFSBP concluded there was limited positive evidence from controlled studies for zinc supplementation and olanzapine for weight gain in AN; and limited positive evidence from uncontrolled studies or case reports for other second-generation antipsychotics (SGAs). It was also concluded that there was no evidence of usefulness of tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) for weight restoration or relapse prevention in AN, but that antidepressants might improve co-occurring depressive and obsessive-compulsive symptomatology [6]. Data from small studies of lithium, naltrexone, and growth hormone were mixed. Small studies of D-cycloserine and tetrahydrocannabinol (THC) were negative. Studies of treatment of AN-associated osteopenia were not reviewed and will not be reviewed in this paper.

We located nine published RCTs in patients with AN since publication of the WFSBP guidelines: four of the studies were with SGAs [7••, 8, 9••, 10], one with dronabinol [11, 12], one with intranasal oxytocin [13, 14], one with alprazolam [15], and two with hormonal agents [16, 17]. On ClinicalTrials.gov, we found ongoing studies of aripiprazole (NCT01082848), olanzapine (NCT01170117), growth hormone (NCT01626833), cycloserine (NCT01996644), lactobacillus reuteri (NCT02004288), omega-3 fatty acids (NCT01761942), and RM-131 (NCT01642550) in patients with AN. No preliminary results were posted.

Second-Generation Antipsychotics (SGAs)

Randomized, placebo-controlled trials of SGAs in AN, including those published before 2011, are summarized in Table 1 [7••, 8, 9••, 10, 18, 19]. As noted, four of these studies were published since the WFSBP Guidelines. Attia et al. [7••] evaluated olanzapine or placebo in 23 patients with AN ≥16 years of age. Study drug was administered with medication management sessions that enhanced compliance. Seventeen (74 %) patients completed the trial. End-of-treatment body mass index (BMI), with initial BMI as covariate, was significantly greater in patients receiving olanzapine. Psychological symptoms improved in both groups with no significant differences. Olanzapine was well tolerated with no adverse metabolic effects; sedation was the most common side effect.

Kafantaris et al. [8] conducted a 10-week study of olanzapine versus placebo in 20 adolescent females with AN receiving comprehensive eating disorder treatment. Fifteen patients completed the study. Mean olanzapine dose was 8.5 mg/day at week 10. Change in percent median body weight improved similarly in both treatment groups at midpoint and endpoint. Olanzapine and placebo also produced similar improvements in eating pathology, psychological functioning, and resting energy expenditure. Olanzapine was associated with a trend of increasing fasting insulin and glucose levels at 10 weeks.

Hagman et al. [9••] compared risperidone with placebo for 11 weeks in 40 female AN patients 12 to 21 years of age who were receiving treatment in a specialized eating disorder program. Patients had to be actively engaged in the specialized eating disorder treatment program to be enrolled in the study. Risperidone (mean dose 2.5 mg/day) was associated with a significantly greater reduction of drive for thinness on the Eating Disorder Inventory-2 (EDI-2) [20] over the first 7 weeks, but this difference was not sustained at week 11. Risperidone was also associated with a significantly greater

Table 1 Randomized, placebo-controlled trials of second-generation antipsychotics in anorexia nervosa

Study	Drug (mg/day)	*N*	Population setting	Duration (weeks)	Result
Brambilla et al. 2007 [18]	OLZ (2.5–5)	30	Adult AN outpatients receiving CBT	16	OLZ>PBO for psychological symptoms but not weight gain
Bissada et al. 2008 [19]	OLZ (2.5–10)	34	Adult AN patients in day treatment	10	OLZ>PBO for weight gain and obsessive-compulsive symptoms
Attia et al. 2011 [7••]	OLZ (2.5–10)	23	Adult AN outpatients r eceiving compliance-enhancing medication management sessions	8	OLZ>PBO for weight gain but not psychological symptoms
Kafantaris et al. 2011 [8]	OLZ (2.5–10)	20	Restricting AN patients, ages 12–22 years, receiving comprehensive eating disorder treatment	10	OLZ=PBO for weight gain and psychological symptoms
Hagman et al. 2011 [9••]	RIS (0.5–4)	40	AN patients, ages 12–21 years, receiving specialized eating disorder treatment	11	RIS>PBO for interpersonal distrust but RIS=PBO for weight gain and other psychological symptoms
Powers et al. 2012 [10]	QTP (177.7)	15	Adults with AN[a]	8	QTP=PBO for weight gain and psychological symptoms

AN anorexia nervosa, *CBT* cognitive behavioral therapy, *OLZ* olanzapine, *PBO* placebo, *QTP* quetiapine, *RIS* risperidone

[a] Clinical setting and adjunctive treatment, if any, not reported

decrease on the EDI-2 Interpersonal Distrust Subscale. There were no drug-placebo differences on any other measure of psychological symptoms. There were no changes between risperidone and placebo for change in ideal body weight or BMI: 33 % of risperidone patients and 45 % of placebo patients reached target weight and maintained it for 4 weeks. Side effects of risperidone were fatigue and dizziness. Prolactin levels were significantly increased in risperidone-treated patients at weeks 7 and 11.

Powers et al. [10] randomized 15 participants with AN to quetiapine (N=6) or placebo (N=9) for 8 weeks. Ten patients completed the study. Quetiapine (mean daily dose 177.7 mg) was not superior to placebo in reducing core eating disorder, depressive, or obsessional symptoms. Additionally, there was no difference in change in BMI between study groups.

Similar to earlier studies [18, 19], these trials [7••, 8, 9••, 10] are all limited by small sample size and, hence, inadequate power to detect potential clinically significant differences. Negative trials [8, 9••, 10] could therefore represent failed trials. Some negative trials are further limited by requiring participants to be receiving comprehensive psychosocial treatment [8, 9••]; with small sample sizes, it may be difficult to show medication effects beyond those of psychosocial treatment. Indeed, the mixed findings have led to different conclusions on the usefulness of antipsychotics in AN. Three groups, conducting meta-analyses of RCTs of antipsychotics in AN, have concluded that antipsychotics are not efficacious for weight gain or psychological symptoms in AN [21–23]. Other experts, however, have argued that olanzapine in particular may be efficacious, especially if it has to be administered alone without adjunctive psychosocial treatment [24]. Indeed, authors of negative trials have qualified their findings by reporting that some AN patients do respond well to SGAs [10]. Finally, it has been repeatedly noted that pharmacotherapy studies of AN are extraordinarily difficult to conduct in a large part due to patients' lack of insight and fear of weight gain [25]. Thus, patients studied represent only a small subset of AN patients in general. It might thus be possible that certain subsets of AN may be responsive to SGAs, including, for example, those with prominent anxiety, obsessive-compulsive symptoms, impaired insight, or hyperactivity, or those with SGA-responsive comorbid conditions, such as bipolar disorder. Ongoing studies of SGAs in AN will hopefully clarify some of these issues.

Dronabinol

Dronabinol is a synthetic cannabinoid used for treating nausea and vomiting due to cancer chemotherapy and for AIDS-associated anorexia and wasting syndrome. In one small crossover study in 24 patients with enduring AN, adjunctive dronabinol, given at 2.5 mg BID for 4 weeks, was superior to placebo, also given for 4 weeks, for weight gain [11, 12]. Specifically, participants gained 0.73 kg (p<0.01) during dronabinol treatment above that gained during placebo treatment. Also, during dronabinol treatment, physical activity intensity increased by 20 % (p=0.01), resulting in an increased energy expenditure of 68.2 kcal/day above placebo (p=0.01). Changes in EDI-2 scores during treatment with dronabinol or placebo were minimal, and there were no statistically significant differences on EDI-2 scores between treatment periods. The drug was well tolerated without adverse psychiatric effects.

Oxytocin

The study exploring intranasal oxytocin in 64 patients with AN was a single dose, within-subject crossover trial conducted in a laboratory setting [13, 14]. Patients with AN showed significant reductions in attentional biases toward eating-related stimuli and negative shape stimuli, and the effect of oxytocin was correlated with autistic spectrum traits. However, oxytocin had no effect on amount of juice consumed.

Alprazolam

In a randomized, placebo-controlled, crossover study, one dose of alprazolam 0.75 mg was administered to 17 in patients with AN [15]. Within-subject comparisons showed that alprazolam did not increase caloric intake during a laboratory test meal or reduce anxiety as compared to placebo, but did increase fatigue. The authors concluded that short-acting benzodiazepines may have a limited therapeutic role in AN.

Hormonal Agents

Dehydroepiandrosterone (DHEA), a hormone produced by the adrenal gland and brain that enhances production of androgens and estrogens, may have antidepressant properties. Bloch et al. [16] randomized 26 premenopausal female patients with AN to DHEA 50 mg BID or placebo in a 3:2 ratio for 6 months. All patients continued to receive psychotherapy, weekly nutritional assessments, and daily calcium carbonate 600 mg and vitamin D_3 200 IU. BMI in DHEA-treated patients was significantly increased at 4 months compared with placebo-treated patients. However, the difference in BMI increase was not statistically significantly different across the 6 months of the study. Additionally, there were no drug-placebo differences in depressive symptoms, bone mineral density, or bone mineral content. DHEA was well tolerated without significant adverse experiences.

Seventy-two adolescent girls with AN were randomized to transdermal estradiol (100 mcg twice weekly) with cyclic progesterone or placebo patches and pills for 18 months [17]. Thirty-seven completed the 18 months of treatment. Outcome was assessed with the Spielberger's State-Trait Anxiety

Inventory for Children (STAIC) [26], the EDI-2, and the Body Shape Questionnaire (BSQ-34) [27]. Estrogen replacement produced a decrease in STAIC trait anxiety scores but had no effect on STAIC state anxiety, EDI-2, or BSQ-34 scores. BMI changes did not differ between groups, and estrogen's effect on STAIC trait anxiety scores persisted after controlling for BMI changes. The authors concluded that physiologic estrogen replacement improved trait anxiety in adolescent girls with AN, but had no effect on state anxiety, eating attitudes, or body shape perception.

Bulimia Nervosa (BN)

Based on 36 RCTs, the WFSBP guidelines concluded there was evidence for efficacy of tricyclics, SSRIs, and topiramate for reducing binge eating and purging in BN [2]. It was also concluded that ondansetron was efficacious, lithium was not, and results for opioid antagonists were mixed.

Since the 2011 WFSBP guidelines, we found only one published RCT of a medication in BN and that was with a prokinetic agent [28]. Twenty-nine patients with BN were randomized to receive erythromycin up to 500 mg three times daily or placebo for 6 weeks. Thirteen patients in each group completed the trial. Treatment with erythromycin showed no beneficial clinical effect: patients receiving erythromycin had weekly binge/vomit frequencies of 11.4±10.7/11.3±10.9, while those receiving placebo had weekly binge/vomit frequencies of 7.2±4.1/7.6±4.4.

We found no ongoing pharmacotherapy studies in BN on ClinicalTrials.gov. A study of cholecystokinin for reducing binge eating in BN had been terminated due to inability to recruit patients (NCT00308776).

Binge Eating Disorder (BED)

Based on 26 RCTs, the WFSBP guidelines concluded there was evidence for efficacy of sertraline and topiramate in BED [2]. Since then, we located nine published RCTs of medications in BED: two with antidepressants [29, 30•], three with anti-obesity agents [31–33], one with an opioid antagonist [34]; one with a GABAergic agent [35], one with an essential nutrient [36], and one with a psychostimulant [37••]. ClinicalTrials.gov identified seven additional recently completed or ongoing trials in BED: five with psychostimulants (NCT01090713, NCT01718483, NCT01718509, NCT02009163, and NCT01921582), one with intranasal naloxone (NCT01567670), and one with the alerting agent armodafinil (NCT01010789).

Antidepressants

As noted, we found two small RCTs of antidepressants in BED that were published since the 2011 WFSBP guidelines [29, 30•]. In the first, 40 patients with BED and a co-occurring depressive disorder received the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine or placebo for 12 weeks [29]. Duloxetine (mean dose 78.7 mg/day) was superior to placebo in reducing weekly frequency of binge eating days and binge eating episodes, global severity of BED symptoms, global severity of depressive symptoms, and body weight.

In the second RCT, 61 overweight or obese patients with BED received the weak norepinephrine dopamine reuptake inhibitor bupropion (300 mg/day) or placebo for 8 weeks [30•]. Bupropion was similar to placebo in reducing binge eating frequency but produced greater weight loss. Also, it was well tolerated and there were no seizures.

Anti-obesity Medications

One RCT each of orlistat (a lipase inhibitor) [31], sibutramine (an SNRI) [32], and rimonabant (an endocannabinoid receptor antagonist) [33] have been published since 2011. Of note, the latter two drugs have been removed from the market for safety concerns (cardiovascular events for sibutramine and psychiatric adverse events for rimonabant), but all three trials will be reviewed for completeness.

In the orlistat study, 79 obese Spanish-speaking-only Latino/as with BED (N=40) or without BED (N=39) at a community mental health center were randomly assigned to 4 weeks of orlistat (120 mg TID) plus behavioral weight loss therapy (BWL) or placebo plus BWL [31]. Seventy-eight percent of patients completed the trial. Among BED patients, remission of binge eating did not differ between orlistat (60 %) and placebo (70 %). Also, there was no difference in improvement in eating psychopathology, BMI, or depressive symptoms. Orlistat plus BWL produced greater weight loss than placebo plus BWL in patients with obesity alone, but not in patients with BED. These findings are inconsistent with two earlier RCTs finding that orlistat may reduce body weight in patients with BED [38, 39]. However, they are consistent with the finding that orlistat may not reduce binge eating behavior [39].

In the sibutramine study, 104 patients with BED were randomized to one of four 16-week treatment periods: sibutramine alone, placebo alone, sibutramine plus self-help cognitive behavior therapy (shCBT), or placebo plus shCBT [32]. There were two primary treatment outcomes: remission of binge eating for the previous 28 days and weight loss. At post-treatment, remission rates did not differ across treatment groups (24–38.5 %). Percent weight loss was statistically significantly greater for patients receiving sibutramine, consistent with earlier RCTs of sibutramine in BED [40–42]. Weight regain occurred after medication discontinuation.

In the rimonabant study, 289 obese subjects with BED were randomized to active drug or placebo for 6 months [33]. All patients were also prescribed a mild hypocaloric diet.

Rimonabant-treated patients showed a greater change in body weight (the primary outcome) compared with placebo-treated patients: patients receiving rimonabant lost 4.7 % of their initial body weight, while patients receiving placebo lost 0.4 %. Rimonabant recipients also showed significant reductions in Binge Eating Scale (BES) [43] scores. No significant differences were observed for dietary restraint, disinhibition, or hunger as measured by the Three Factor Eating Questionnaire [44]. A major limitation of this study is that the presence of BED was determined with the Questionnaire of Eating Related Patterns, a self-report screening measure that may overestimate presence of BED [45].

Opioid Antagonists

Sixty-two patients with BED from six sites were randomized to the novel opioid antagonist ALKS-33 (N=26) or placebo (N=36) for 6 weeks [34]. Both drug and placebo produced similar large reductions in binge eating episode frequency, raising the possibility of a failed rather than negative trial. However, there were also no differences between drug and placebo in other measures of binge eating, eating pathology, or body weight.

A phase II placebo-controlled study of intranasal naloxone spray has been reported in abstract form but not yet published [46]. Sponsored by Lightlake Therapeutics Inc., 127 participants with BED were randomized to intranasal naloxone spray or intranasal placebo spray for 24 weeks. Naloxone 2 mg was administered before each binge eating episode up to a maximum of 4 mg/day; 81 % of participants completed the trial. Naloxone produced a significantly greater reduction than placebo in time spent binge eating. Additionally, among naloxone recipients, but not placebo recipients, BMI decreased significantly from week 12 to week 24. There were no serious adverse events. Of note, on ClinicalTrials.gov, the primary outcome is listed as "change in frequency of binge eating" and not time spent binge eating (NCT01567670).

Baclofen

Baclofen is a gamma-aminobutyric acid (GABA) B agonist used for spasticity that may also be effective in substance use disorders. In one small crossover RCT in 12 individuals with binge eating, participants were randomized to receive baclofen (titrated to 60 mg/day) for 48 days followed by placebo for 48 days, or the reverse [35]. Relative to the placebo phase, baclofen produced a slight but statistically significant reduction in binge eating frequency. BES severity and food craving were decreased similarly during baclofen and placebo phases. By contrast, baclofen produced a small but statistically significant increase in depressive symptoms. The most commonly reported side effects were tiredness, fatigue, and upset stomach.

Chromium

Chromium is an essential nutrient that may improve mood, appetite, and glucose regulation. In one small RCT, 24 overweight or obese patients with BED were randomized to one of three treatments for 6 months each: high dose (1000 mcg/day) chromium (N=8), moderate dose (600 mcg/day) chromium (N=9), or placebo (N=7) [36]. Numerically greater reductions in binge frequency, body weight, and depressive symptoms were observed in chromium recipients compared with placebo recipients, but reductions were not statistically significant. Fasting glucose was significantly reduced in both chromium groups, with larger effects noticed with high-dose chromium. Chromium was well tolerated.

Stimulants

Over the past 4 years, Shire has sponsored a development program for lisdexamfetamine (LDX) for the treatment of BED. LDX is a prodrug of D-amphetamine that is approved for treatment of children and adults with attention deficit hyperactivity disorder (ADHD). One phase II study of LDX in the treatment of BED has been published [37••] and two phase III studies have been completed and presented in abstract form [47]. All three studies found LDX superior to placebo for reducing binge eating episodes and inducing 4-week binge eating cessation rates. The phase II study found that 50 and 70 mg/day, but not 30 mg/day, were efficacious for reducing binge eating [37••]. The phase III studies both found that LDX, titrated to 50 or 70 mg/day, was efficacious for reducing binge eating [47]. The tolerability and safety profile of LDX was consistent with previous findings in adults with ADHD. A long-term maintenance study of LDX in BED is ongoing (NCT02009163).

Regarding RCTs of other ADHD medications in BED, one small positive study of atomoxetine has been published [48] and a comparison of extended release methylphenidate with CBT is ongoing (NCT01921582).

Other Eating Disorders

We found no published or ongoing RCTs of medications for pica, rumination disorder, ARFID, or purging disorder. We located two small RCTs of SSRIs in night eating syndrome: a positive study of sertraline [49] and a negative study of escitalopram [50]. We also found a positive pilot study of low-dose pramipexole in sleep-related eating disorder [51].

Conclusion

Perhaps the most important finding regarding the pharmacotherapy of eating disorders is the paucity of appropriately sized RCTs. Fluoxetine remains the only compound indicated

for an eating disorder, that being BN. Though antidepressants may be moderately helpful for BED, including for associated depressive symptoms, they do not appear to be efficacious for core AN symptoms. Bupropion may induce weight loss in BED associated with obesity without causing seizures. Mixed results from small RCTs have led to varying conclusions about the usefulness of SGAs in AN, though results have been more positive for olanzapine than other SGAs. One preliminary study suggests dronabinol may induce weight gain in AN, but needs replication. Physiologic estrogen replacement may improve trait anxiety in AN, but does not promote weight gain. A recent phase II study found lisdexamfetamine, at 50 and 70 mg/day, was efficacious for decreasing binge eating in BED. Small studies suggest baclofen may decrease binge eating, and chromium may have beneficial effects on glucose metabolism in BED associated with overweight or obesity. Regarding BED studies presented only in abstract form, two RCTs found lisdexamfetamine reduces binge eating episodes, and one RCT suggests intranasal naloxone may reduce time spent binge eating. Small studies of alprazolam in AN, DHEA in AN, erythromycin in BN, and the opioid antagonist ALKS-33 in BED were negative. Other studies of SGAs in AN and a maintenance study of lisdexamfetamine in BED are ongoing. In short, a further study of pharmacotherapy agents in eating disorders is greatly needed.

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Compliance with Ethics Guidelines

Conflict of Interest Anna I. Guerdjikova and Nicole Mori declare that they have no conflict of interest.

Susan L. McElroy is a consultant to, or member of the scientific advisory boards, and/or a principal or co-investigator on research studies sponsored by Agency for Healthcare Research & Quality (AHRQ), Alkermes, Bracket, Cephalon, F. Hoffman-La Roche Ltd., Forrest Laboratories, Marriott Foundation, MedAvante, National Institutes of Mental Health, Naurex, Novo Nordisk, Orexigen Therapeutics, Shire, Sunovion, and Takeda Pharmaceutical Company.

She is also the inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and, along with the patient's assignee, University of Cincinnati, Cincinnati, OH, has received payment from Johnson & Johnson Pharmaceutical Research & Development, L.L.C., which has exclusive rights under the patent. Filed February 18, 2000; approved November 27, 2001.

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He is also the inventor on United States Patent No. 6,387,956: Shapira NA, Goldsmith TD, Keck, PE Jr. (University of Cincinnati) Methods of treating obsessive-compulsive spectrum disorder comprises the step of administering an effective amount of tramadol to an individual. Filed March 25, 1999; approved Mary 14, 2002.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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