Clinical psychopharmacology of eating disorders: a research update

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Abstract

The paper presents a critical review (with search date 2010) of the major psychotropic medications assessed in eating disorders, namely antipsychotics, antidepressants, mood-stabilizing medications, anxiolytic and other agents. The evidence of efficacy of drug treatments is mostly weak or moderate. In addition, attrition rates are usually higher than for psychotherapies. However, there is support for use of antidepressants, particularly high-dose fluoxetine in bulimia nervosa, and anticonvulsants (topiramate) for binge-eating disorder. Low-dose antipsychotic medication may be clinically useful as adjunct treatment in acute anorexia, particularly where there is high anxiety and obsessive eating-related ruminations and failure to engage, but more trials are needed. Drug therapies such as topiramate and anti-obesity medication may aid weight loss in obese or overweight patients with binge-eating disorder; however, common or potentially serious adverse effects limit their use.

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Key words: Anorexia nervosa, binge eating, bulimia nervosa, treatments.

Introduction

Eating disorders comprise anorexia nervosa, bulimia nervosa, binge-eating disorder (BED) and eating disorder not otherwise specified (EDNOS) (APA, 2000). Lifetime prevalence estimates in the community are 0.6% for anorexia nervosa, 1.0% for bulimia nervosa, and 2.8% for BED (Hudson et al. 2007). Both birth-cohort estimates (Hudson et al. 2007) and sequential population surveys (Hay et al. 2008) suggest an increase in disorders of recurrent binge eating in recent years. Eating disorders are characterized by disordered eating behaviours together with cognitive schema of self-view being unduly influenced by body image or weight and shape concerns and extreme preoccupation with thoughts of food and eating (APA, 2000). Disordered eating behaviours include binge eating (uncontrolled eating of inappropriately large amounts of food), subjective binging on smaller food quantities, severe dietary restriction, and weight control behaviours such as vomiting, use of diuretics or laxatives and driven exercise. The latter behaviours are also used as compensation for the recurrent binge eating typical of bulimia nervosa. In BED there is similar recurrent overeating without compensation. All eating disorders have known physical as well as psychological morbidity. People with anorexia nervosa are distinct in being underweight and hence in a starvation state. In the clinic obesity is extremely common in patients with BED and in community surveys (e.g. Hudson et al. 2007) over 40% with BED are obese with body mass index (BMI) > 30. Those with BED may also be at increased risk of metabolic syndrome over and above risk due to obesity alone (Hudson et al. 2010). Other non-specific psychiatric features such as anxiety or mood disturbance, obsessional and impulsivity are also common. Treatments are thereby multi-dimensional comprising psychotherapy, nutritional rehabilitation, sometimes medical resuscitation and the judicious use of psychotropic and other medication (Treasure et al. 2010).

The present paper reviews the use of psychopharmacological agents in eating disorders. The focus of research (and hence this review) has been on the
three well-described diagnostic groups of anorexia nervosa, bulimia nervosa and BED, as efficacy for pharmacotherapy for EDNOS is largely unknown. It is also acknowledged that the treatment of anorexia nervosa is particularly poorly studied with rigorous systematic reviews consistently concluding there is little evidence for any therapy (e.g. Lock & Fitzpatrick, 2009). The major groups of antipsychotic, antidepressant, mood-stabilizing and anxiolytic agents are presented first, followed by less commonly used agents and a discussion of issues in the management of comorbid weight disorder. Comprehensive information on medications used in the treatment of complications of starvation and poor nutrition is found in the text by Birmingham & Treasure (2010). Literature for the present review was sourced from recent extensive searches conducted by either or both authors for the purposes of Cochrane Library and Clinical Evidence and other reviews (Claudino et al. 2006; Hay & Claudino, 2010a,b; Treasure et al. 2010; search date 2009) and updated to June 2010 for this report with a Pubmed search using the terms ‘anorexia nervosa or bulimia nervosa or BED and therapy or treatment’. Also searched were reference lists of the following systematic reviews: Brownley et al. 2007; Bulik et al. 2007 and Shapiro et al. 2007. Studies were selected for inclusion, first, if they met a level of evidence that minimized risk of bias as in the above reviews, i.e. were randomized controlled trials (RCTs) with completion rates at least 50%, or a systematic review of RCTs. Second, we included studies of case series or case reports or non-randomized trials where there were no RCTs of an agent or where they were of relevance in presaging RCTs. It should be noted that these latter studies are at high risk of bias and should be read as indicative of putative effects and not as substantive evidence of efficacy.

**Antipsychotic medications**

Antipsychotic medication use is largely confined to people with anorexia nervosa. It is thought antipsychotics act by targeting dopaminergic and/or serotonergic dysfunction (Connnan & Stanley, 2003; Kaye et al. 1999). Clinically, antipsychotics are used to reduce extremal beliefs regarding body image and eating-related disturbed thoughts such as intense ruminations about food, pseudo-hallucinations as well as the hyper-arousal and agitation found when people are confronted with weight gain (Powers & Santana, 2004; Taylor & McAskill, 2000). Paradoxically, in anorexia nervosa, they may not consistently promote weight gain (McKnight & Park, 2010), despite this being a common side-effect in normal weight people with other psychiatric illnesses such as schizophrenia (e.g. Chwastiak et al. 2009).

First-generation antipsychotics such as chlorpromazine were found to cause severe adverse effects such as convulsions and Parkinsonism. In addition as summarized in Table 1, there was inconsistent evidence from RCTs regarding the efficacy of tested agents such as pimozide and sulpiride, in placebo-controlled trials (Vandereycken, 1984; Vandereycken & Pierloot, 1982). However, there have been a number of promising trials of the second-generation antipsychotics olanzapine and quetiapine, following case-series reports in all age groups by Bosanac et al. (2005), Court et al. (2010), Duncan & del Dotto (2007),

<table>
<thead>
<tr>
<th>Medication</th>
<th>Clinical effects</th>
<th>RCT (n)</th>
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</thead>
<tbody>
<tr>
<td><strong>Antipsychotic</strong></td>
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<tr>
<td>First generation</td>
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<td></td>
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<tr>
<td>Pimozide</td>
<td>Inconsistent vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>Inconsistent vs. placebo</td>
<td>1</td>
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<tr>
<td>Second generation</td>
<td></td>
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<tr>
<td>Amisulpride</td>
<td>Greater weight gain vs. antidepressants</td>
<td>1</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Greater reduction in ruminations vs. chlorpromazine</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Greater weight gain and reduction psychological distress vs. placebo</td>
<td>2</td>
</tr>
<tr>
<td><strong>Antidepressant</strong></td>
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<td></td>
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<tr>
<td>Amitriptyline</td>
<td>Inconsistent greater weight gain vs. placebo</td>
<td>2</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>No significant effects vs. placebo</td>
<td>1</td>
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<tr>
<td>Fluoxetine</td>
<td>Reduced relapse after weight gain vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No reduced relapse after weight gain when added to cognitive behaviour therapy vs. cognitive behaviour therapy</td>
<td>1</td>
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</table>
Leggero et al. (2010) and Powers et al. (2007). In these studies low doses (e.g. 1–5 mg/d olanzapine, 100–400 mg/d quetiapine) were commonly used. There is also one case report supporting the use of aripiprazole in three patients with bulimia nervosa as well as eight with anorexia nervosa (Trunko et al. 2010). In this series, the three patients with bulimia nervosa had or previously had low weight. However, there are few RCTs.

One RCT compared low-dose (50 mg/d) amisulpride (a D₂ and D₃ receptor antagonist at higher doses, pre-synaptic antagonism at lower doses) to fluoxetine (mean dose 28 mg/d) and to clomipramine (mean dose 57.69 mg/d) in 35 in-patients with anorexia nervosa attending a weight restoration programme for 12 wk. Those given amisulpride had significantly greater weight gain but other illness features did not differ between groups (Ruggiero et al. 2001).

A systematic review (search date 2009) reported on three RCTs testing olanzapine, a 5-HTᵢ/₃ receptor antagonist, vs. placebo or other antipsychotic for anorexia nervosa (McKnight & Park, 2010). The first RCT compared it to chlorpromazine added to standard care in 15 anorexia nervosa patients (Mondratty et al. 2005). In this trial (which was not blinded), olanzapine (mean dose 10 mg/d) showed greater efficacy in reducing ‘anorexic ruminations’ compared to 50 mg/d chlorpromazine. Brambilla et al. (2007) compared olanzapine (2.5 mg for 1 month, 5 mg for 2 months) to placebo as an adjunctive treatment with cognitive behaviour psychotherapy (CBT) in 30 anorexia nervosa outpatients. Olanzapine was reported to increase weight gain, and reduce depressive symptoms and aggressiveness compared to placebo, but only for patients of the binge-purge type. Finally, Bissada et al. (2008) compared olanzapine combined with a day-hospital treatment for 10 wk to placebo in 34 anorexia nervosa participants. Those taking olanzapine showed a greater rate of increase in weight (achieving target BMI earlier) and improvement of obsessive symptoms. While completion rates were high (82%), 55% of eligible patients declined to be randomized, indicating a potential problem of low acceptance of olanzapine by people with anorexia nervosa.

These few RCTs suggest a role for low-dose second-generation antipsychotics in reducing psychological distress particularly in the re-feeding phase of anorexia nervosa treatment. However, there may be problems with patient acceptance. Larger trials of efficacy are needed, particularly of quetiapine and aripiprazole which may be less sedating and better tolerated as they are putatively less likely to cause severe weight gain feared by patients. At present there are no trials of efficacy in other eating disorders and thus no specific indication for their use in recognized guidelines (APA, 2006; NICE, 2004; RANZCP, 2004).

Antidepressants and like medications

In both anorexia nervosa and bulimia nervosa there is putative rationale for the use of antidepressants. In anorexia nervosa shared inheritance with depression (Strober et al. 2000; Wade et al. 2000), neurobiological, most notably serotonin dysfunction (Kaye et al. 1998, 2005) and concurrent depressive and obsessional psychopathology (Godart et al. 2007; Kaye et al. 2004) have suggested a role for antidepressant treatment. In addition a recent meta-analysis (Lee & Lin, 2010) has supported there being a specific genetic variant of the serotonin transporter gene promoter found in people with anorexia nervosa (but not bulimia nervosa). Similarly, there are high rates, up to 50%, of lifetime comorbid depression and bulimia nervosa (Hudson et al. 2007). However, the efficacy of antidepressant treatment in bulimia nervosa appears independent of effects on mood and is more likely related to augmentation of satiety mechanisms and subsequent reduction in binge eating (see below) (Goldstein et al. 1999; Walsh et al. 2000).

Calduno et al. (2006) conducted a systematic review of efficacy of antidepressants in acute phase anorexia nervosa. Only four small RCTs were identified, three of the tricyclic antidepressants (TCAs) amitriptyline (Biederman, et al. 1985; Halmi, et al. 1986) and clomipramine (Lacey & Crisp, 1980), and one of the selective serotonin reuptake inhibitor (SSRI) fluoxetine (Attia et al. 1998). Halmi et al. (1986) randomized 72 in-patients to amitriptyline, cyproheptadine or placebo treatment groups. They reported a small statistically significant effect in decreasing the time to achieve target weight for both drug groups. The three other acute-phase trials found no significant differences in symptom response or weight gain between active and placebo groups. In addition, cardiovascular risk with tricyclic drugs limits their use in this patient group (Biederman et al. 1985; Halmi et al. 1986). While the doses of antidepressant used in these trials were low and the duration of treatment was short, the consistency of negative findings does not provide support for their use. There is little evidence for other classes of antidepressants, although a case report for mirtazapine (which has noradrenergic and serotonergic activity) is promising. In this report mirtazapine aided weight gain and mood in a 50-yr-old woman with a
history of food restriction since her adolescence (Safer et al. 2011).

It has been postulated that the lack of efficacy of serotonergic drugs in the acute phase of anorexia nervosa may be related to low levels of serotonin metabolites in cerebrospinal fluid (e.g. as found by Jimerson et al. 1992) due to poor dietary intake of the serotonin precursor tryptophan. However, a small RCT that compared fluoxetine + nutritional supplements with fluoxetine + ‘placebo nutritional supplements’ found that the former did not improve the physiological effects of chronic under-nutrition or appear to enhance the efficacy of drugs (Barbarich et al. 2003). More recent findings using positron emission tomography (PET) imaging by Baier et al. (2007) suggest that there may be a better response to medication for those with restricting type anorexia vs. those with bulimic type because of a differential serotonin receptor-binding activity. A body of work summarized in Kaye (2008) now supports the view that there is a poor response to antidepressants because of adverse effects of starvation in the 5-HTT receptor and in extracellular 5-HT concentrations.

Two double-blind RCTs have tested fluoxetine for patients following acute treatment weight restoration (Kaye et al. 2001; Walsh et al. 2006). The first small trial (n=35) found significantly more patients on fluoxetine had reduced relapse, namely, they maintained an adequate weight and symptom reduction during the 1-yr follow-up after hospital discharge compared to the control group. However, attrition was very high in the placebo group (84% vs. 37% in the treatment group), and for most the decision to terminate the study was based on symptoms indicating a relapse. A second larger trial of 93 patients (Walsh et al. 2006) did not find adding fluoxetine to CBT helped prevent relapse (defined as BMI falling to ≤16.5 kg/m² and/or worsening of anorexic symptoms, development of major clinical problems or suicidal ideation). In addition a well-designed RCT (n=122 randomized; Halmi et al. 2005) was inconclusive as there was an unacceptably high rate of attrition (73%) in participants randomized to a fluoxetine (60 mg/d) arm compared to CBT arm (57% attrition) or combination arm (59%). Thus, antidepressant use is supported neither in the acute nor maintenance phases of anorexia nervosa treatment.

The situation is very different for use of antidepressants in bulimia nervosa where there are a number of RCTs (see Table 2), systematic reviews and meta-analyses that have consistently supported a range of classes of agents, namely TCAs, SSRIs and monoamine oxidase inhibitors (MAOIs) in reducing binge eating and vomiting and improving mood and anxiety symptoms (Bacaltchuk & Hay, 2003; Hay & Claudino, 2010a). Specific SSRIs evaluated include fluoxetine, citalopram, sertraline and fluvoxamine.

In Bacaltchuk & Hay (2003) pooled data from 24 RCTs found that bulimic behaviours had reduced by up to 70% in the short-term (mean 8 wk); however, pooled abstinence rates were less than 20% when antidepressants were used without any concurrent psychosocial intervention. Moreover, Agras et al. (1992) found that one-third of the 25% of patients who were abstinent at the end of treatment relapsed over time. In contrast, a small number of relapse-prevention studies have reported an effect of continuing pharmacotherapy (Fichter et al. 1996; Romano et al. 2002), although these findings should be viewed with caution due to high attrition (around 90% at 1 yr follow-up in Romano et al. 2002).

Attrition is also high in most trials (around 40%) of single pharmacological treatments, in part because of side-effects but also probable patient preference for non-pharmacological therapies. There does, however, appear to be better acceptability for SSRIs. This may be because of their short-term effects on reduction in appetite and weight, and the use of fluoxetine has superseded TCAs (Fichter et al. 1991; Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldstein et al. 1999; Romano et al. 2002). The SSRI antidepressant, fluoxetine, is thus the only medication recommended by leading guidelines for bulimia nervosa (APA, 2006), and it is at a high dose of 60 mg/d. Lower doses were less efficacious in this patient group (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldstein et al. 1995). Clinicians may note that further analyses of these two studies by Sysko et al. (2010) reported attaining early response (more than 60% reduction in binge eating or vomiting frequency in the first 3 wk of treatment) was strongly predictive of eventual treatment response.

Strong evidence of the efficacy of other SSRIs agents is still lacking, but in clinical practice they may be considered for patients that do not respond well to fluoxetine. There are three similar and very small randomized placebo-controlled trials of citalopram (Milano et al. 2005a), sertraline (Milano et al. 2004), and fluvoxamine (Milano et al. 2005b), which were supportive for efficacy of all three SSRIs. In addition, a small (n=27) single blinded trial comparing fluoxetine and citalopram found no differences in outcomes, but the attrition rate was moderately high (Leombruni et al. 2006). However, a later study from the same group (Giaquinto et al. 2006) compared the three SSRIs in the
treatment of bulimia nervosa and found sertraline (100 mg/d) associated with a very small reduction in binge eating and purging compared to fluvoxamine or fluoxetine. Finally, as shown on Table 2, most agents only have one RCT published and it is also likely there is publication bias (Bacaltchuk & Hay, 2003). A large (n = 300) negative trial of 150–300 mg fluvoxamine remains published only in secondary reports (Corcos et al. 1996; Freeman, 1998).

Inconclusive and lower levels of evidence are available with drugs that act on the noradrenergic system. Based on findings from earlier studies that tested drugs with noradrenergic effects, on the involvement of the noradrenergic system in the regulation of hunger and satiety, and on existing connections between serotonergic and noradrenergic pathways in the central nervous system, two small uncontrolled trials of reboxetine, a selective noradrenaline reuptake inhibitor, have reported positive findings (El-Giamal et al. 2000; Fassino et al. 2004). Two small uncontrolled studies of milnacipran, a selective serotonin and noradrenaline reuptake inhibitor, have suggested a trend towards reduction binge eating (El-Giamal et al. 2003; Noma et al. 2008).

Finally, bupropion is an antidepressant that blocks reuptake of noradrenaline and dopamine. It was

### Table 2. Main classes of medication use in bulimia nervosa tested in at least one randomized controlled trial (RCT)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Clinical effects</th>
<th>RCT (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>Bulimic symptom reduction vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Less reduction binge eating vs. cognitive behaviour</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Therapy (CBT) and less reduction binge eating vs. combined CBT and imipramine</td>
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</tr>
<tr>
<td></td>
<td>and no significant difference when combined with CBT vs. CBT alone</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>Symptom reduction vs. placebo</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No significant symptom reduction vs. CBT and combined CBT and desipramine</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>and no significant difference when combined with CBT vs. CBT alone</td>
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<tr>
<td><strong>Monoamine oxidase inhibitors</strong></td>
<td></td>
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</tr>
<tr>
<td>Phenylzine</td>
<td>Bulimic symptom reduction vs. placebo</td>
<td>2</td>
</tr>
<tr>
<td>Isocarboxacid</td>
<td>Bulimic symptom reduction vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td>Brofaromine</td>
<td>Bulimic symptom reduction vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Bulimic symptom reduction vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td>Reduced bulimic symptoms at 60 (but not 20)mg/d vs. placebo</td>
<td>3</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Reduced relapse but high attrition at 60 mg/d vs. placebo</td>
<td>1</td>
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<tr>
<td></td>
<td>No significant differences in outcome vs. CBT and no</td>
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<tr>
<td></td>
<td>reduction binge eating vs. combined CBT and fluoxetine</td>
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<td></td>
<td>and no significant difference when combined with CBT vs. CBT alone</td>
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<tr>
<td></td>
<td>No differences in outcome vs. citalopram</td>
<td>1</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Reduced bulimic symptoms vs. placebo</td>
<td>1</td>
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<tr>
<td>Sertraline</td>
<td>Reduced bulimic symptoms vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Poorer reduction in symptom vs. fluvoxamine or fluoxetine</td>
<td>1</td>
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<tr>
<td>Fluvoxamine</td>
<td>Reduced bulimic symptoms vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Reduced relapse at 150 mg/d vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mianserin</td>
<td>Bulimic symptom reduction vs. placebo</td>
<td>1</td>
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<tr>
<td>Trazodone</td>
<td>Bulimic symptom reduction vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Reduced bulimic symptoms vs. placebo but high</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Seizure rates preclude its use</td>
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<tr>
<td>Topiramate</td>
<td>Reduced bulimic symptoms and greater weight loss vs. placebo</td>
<td>2</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Inconsistent reduction bulimic symptoms vs. placebo</td>
<td>2</td>
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</tbody>
</table>
found superior to placebo at reducing binge eating and purging episodes in one trial of 55 bulimia nervosa participants (Horne et al. 1988). However, it is contraindicated for people with bulimia nervosa due to the high rates (7.2%) of generalized tonic-clonic seizures found in this RCT.

There have been a number of RCTs comparing antidepressants in combination with CBT (the present first-line treatment for bulimia nervosa; APA, 2006; NICE, 2004) with inconsistent results. When pooled in meta-analyses (Bacaltchuk et al. 2001; NICE, 2004) findings suggest that (a) drug-alone treatments have consistently less efficacious binge-eating abstinence rates than when combined with CBT, and (b) dropout rates in the antidepressant arms of such trials are high (more than 50% in some studies).

Antidepressants are considered to have a role in the treatment of BED based on their efficacy in reducing binge-eating in patients with bulimia nervosa (Bacaltchuk & Hay, 2003) and on the high rate of comorbid major depressive disorder in patients with BED (Fontenelle et al. 2003; Javaras et al. 2008). As shown on Table 3, two TCAs [imipramine (Laederach-Hofmann et al. 1999) and desipramine (Agras et al. 1994)] and several SSRIs, such as fluvoxamine, sertraline, fluoxetine and citalopram (Arnold et al. 2002; Devlin et al. 2005; Grilo et al. 2005a; Hudson et al. 1998; McElroy et al. 2000, 2003a, b; Pearlstein et al. 2003) have been evaluated in RCTs of BED. These trials have been small (n = 85 or fewer), and most short-term (mean duration of 10 wk, all <20 wk) (Claudino et al. 2010). Early trials reported consistent reductions in binge-eating frequency but more recently two trials with a longer duration of 16–20 wk that compared fluoxetine to placebo (Devlin et al. 2005; Grilo et al. 2005a) found fluoxetine ineffective in reducing binge eating or weight.

Stefano et al. (2008) reported a meta-analysis of seven pooled studies (six with SSRIs and one with imipramine) involving a total of 300 patients, whereby there was greater remission of binge-eating episodes at the end of trials in the groups that received antidepressants compared to the placebo groups (40.5% vs. 22.2%). Another meta-analysis (Reas & Grilo, 2008) found SSRIs were associated with significantly increased binge-eating remission rates compared to placebo (n = 335, n = 7 studies, RR 0.81, 95% CI 0.70–0.94) indicating that non-remission rates are reduced by 19% with this class of antidepressant.

With regard to overweight problems, a common and problematic comorbidity, weight loss has been modest in most studies and no differences in weight

### Table 3. Main classes of medication use in binge-eating disorder (BED) tested in at least one randomized controlled trial (RCT)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Clinical effects</th>
<th>RCT (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>BED symptom and weight reduction combined with dietary counseling vs. placebo and dietary counselling</td>
<td>1</td>
</tr>
<tr>
<td>Desipramine</td>
<td>No greater BED symptom reduction or weight loss when combined with cognitive behaviour therapy (CBT) and behavioural weight loss (BWL)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Inconsistent reduced binge eating and improved weight control vs. placebo</td>
<td>2</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Reduced binge eating and improved weight control vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Reduced binge eating and improved weight control vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Inconsistent reduced binge eating and improved weight vs. placebo</td>
<td>2</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>No significant reduction binge eating but improved weight vs. placebo</td>
<td>1</td>
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<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>BED symptom and weight reduction vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Reduced BED symptoms and greater weight loss vs. placebo</td>
<td>2</td>
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<tr>
<td>When combined with CBT reduced BED symptoms and weight vs. CBT alone</td>
<td>1</td>
<td></td>
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<tr>
<td>Zonisamide</td>
<td>Reduced bulimic symptoms and greater weight loss vs. placebo</td>
<td>1</td>
</tr>
<tr>
<td>Orlistat</td>
<td>When combined with BWL or guided self-help CBT reduced BED symptoms and greater weight loss vs. placebo</td>
<td>2</td>
</tr>
</tbody>
</table>

*a Sibutamine has not been included here because of safety concerns and its subsequent withdrawal from the market in North America, Europe and other countries including Australia in 2010.*
loss were found in the meta-analysis of Stefano et al. (2008). Reas & Grilo (2008) reported a modest effect on weight loss with SSRIs compared to placebo in meta-analysis. One trial of sertraline was found to lead to clinically significant weight loss: 50–200 mg/d sertraline (mean loss 5.4 kg in 6 wk) (McElroy et al. 2000). Only citalopram (McElroy et al. 2003a,b) has been found to have a greater efficacy in reducing depressive symptoms than placebo in studies, but most trials have included patients with low baseline scores in depression scales (Appolinario & McElroy, 2004). More recently, escitalopram (mean dose 25.5 mg/d) in a RCT was associated with greater weight loss than in the placebo group, but effects on binge remission were weaker (Guerdjikova et al. 2008).

Venlafaxine, a selective serotonin and noradrenaline reuptake inhibitor, has been tested in only an uncontrolled open trial of 35 obese/overweight patients with BED. Results showed a significant reduction in binge-eating episodes and weight (Malhotra et al. 2002). One case study has also reported good effects for duloxetine (another combined serotonin and noradrenaline reuptake inhibitor) in a patient with treatment-refractory BED (Bernardi & Pallanti, 2010). RCTs are needed to evaluate the efficacy of these agents.

Some agents with pharmacological actions similar to antidepressants have been trialed in BED. A short, placebo-controlled RCT tested atomoxetine, a highly selective norepinephrine reuptake inhibitor with weight loss properties, in 40 obese patients with BED. Atomoxetine was associated with greater improvement in binge-eating behaviours and weight loss and was reasonably tolerated (McElroy et al. 2007a), but to date these findings have not been replicated.

Sibutramine is an anti-obesity agent that is a selective serotonin and noradrenaline inhibitor that may induce weight loss by enhancing satiety and preventing the fall in energy expenditure that usually follows weight loss. Sibutramine at a dose of 15 mg/d has been tested against placebo in two 12-wk RCTs (Appolinario et al. 2003; Milano et al. 2005c) and one 24-wk trial (Wilfley et al. 2008) of BED. In these trials and a meta-analysis (Reas & Grilo, 2008) sibutramine was associated with significantly reduced binge eating and weight loss compared to placebo. However, attrition was high (Wilfley et al. 2008), a high placebo response (also found by e.g. Pearlstein et al. 2003) was noted, and those more likely to have a placebo response had less severe symptoms at baseline (Jacobs-Pilipski et al. 2007). More importantly, safety issues related to increased cardiovascular events in obese people with high cardiovascular risk have been reported (James et al. 2010) and in 2010 sibutramine was withdrawn from the market in the USA, Europe and other countries.

RCTs of combination approaches of antidepressants with CBT have suggested little advantage over CBT alone in reducing binge eating (Agras et al. 1994; Devlin et al. 2005; Grilo et al. 2005a), but there may be positive effects for increased weight loss beyond the effects of psychotherapy (Agras et al. 1994; Laederach-Hofmann et al. 1999) or antidepressants alone (Ricca et al. 2001). Two recent combination trials, which lasted 16 wk (Grilo et al. 2005a) and 20 wk (Devlin et al. 2005), used a four-cell design to compare CBT + fluoxetine, CBT + placebo, fluoxetine, and placebo. These studies did not report any increase of treatment efficacy when fluoxetine was added to CBT. However, when eating psychopathologies were analysed, results were better in the groups treated with CBT than in the groups treated only with drugs. For example, greater binge remission (but not greater weight loss) was found in the group treated with fluoxetine and CBT than in the one treated with medication alone (Grilo et al. 2005a).

### Mood-stabilizing agents

Mood-stabilizing agents such as lithium and anticonvulsant drugs have not had a large role in the treatment of eating disorders. A very small \( (n = 16) \) placebo-controlled RCT of lithium treatment (mean plasma level 1.0±0.1 mequiv./l) in acute-phase anorexia nervosa was supportive of greater weight gain in the active group (Gross et al. 1981). However, this early study was never followed by more substantive trials. Of more contemporary interest are anticonvulsant drugs such as topiramate, which have been studied in a range of mental health conditions (Arrnone, 2005) and been considered to be possibly useful in eating disorders for their anti-impulsivity and weight-losing effects (Ben-Menachem et al. 2003; Li et al. 2005; McElroy et al. 2007b).

Following promising case series (Barbee, 2003) a double-blind, placebo-controlled RCT has supported the efficacy of topiramate (Hedges et al. 2003a; Hoopes et al. 2003b) for bulimia nervosa patients. In this trial, those treated with topiramate had significantly greater reductions in mean weekly binge and/or purge days than those on placebo (44.8% vs. 10.7% for placebo) and also greater weight loss with topiramate (1.8 kg, compared to the placebo group mean increase of 0.2 kg). Nickel et al. (2005) also found that topiramate (250 mg/d) over a 10-wk period significantly reduced binge/purge frequency, weight and improved health-related quality of life compared to a placebo condition.
in 60 participants. However, although reportedly well tolerated, many patients in the topiramate arm experienced cognitive impairment and neurological symptoms such as paresthesia. Other problems include the report of very high congenital malformation rates in women taking topiramate for epilepsy, which may limit its acceptability and use in young women with eating disorders (Hunt et al. 2008).

Two double-blind RCTs have tested topiramate against placebo in obese patients with BED. The first study enrolled 61 subjects for a 14-wk treatment (median dose 213 mg/d) (McElroy et al. 2003b). The second larger multi-centre trial (McElroy et al. 2007b) with 394 patients lasted 16 wk and used a median dose of 300 mg/d. In these two trials, topiramate reduced binge frequency, increased binge remission and weight loss, and improved psychological comorbidity. Longer-term efficacy of topiramate was tested in a 42-wk, open-label extension (McElroy et al. 2004) of the first trial with 35 patients. Patients maintained reduced binge-eating frequency and weight loss in the subsequent open phase, and patients on placebo also showed improvements when given topiramate in the open phase. However, this study had high attrition and adverse effects during the two phases, possibly because of the rapid increase of doses and the inclusion of patients with psychiatric comorbidity (McElroy et al. 2003b, 2004).

One RCT (McElroy et al. 2006) has compared another anticonvulsant zonisamide (mean endpoint dose of 436 mg/d over 16 wk) to placebo in 60 obese women with BED. Although it was more effective than placebo in reducing binge-eating frequency and weight, zonisamide had considerable side-effects and was poorly tolerated. An open trial over 1 yr of 52 patients (30 with sub-threshold disorder) also reported an advantage in binge-eating reduction and weight loss when zonisamide was added to CBT (Ricca et al. 2009). However, attrition was high (50%) in the drug-treated group. In a meta-analysis (Reas & Grilo, 2008) of results from anti-epileptic trials (n = 515) (McElroy et al. 2003a, b, 2006, 2007a, b), large effects were reported for binge remission and weight loss (RR 0.63, 95% CI 0.51-0.78; WMD -4.6 kg, 95% CI -5.36 to -3.79, respectively) with a non-remission risk reduction of 37%.

Finally a double-blind, multicentre RCT compared the effects of topiramate (mean dose of 206 mg/d) with placebo when combined with CBT in 73 patients with BED. Those in the combined drug and CBT arm had higher rates of binge-eating remission (83.8% vs. 61.1%) and weight loss (-6.8 kg vs. -0.9 kg) in the 21 wk compared to the CBT-alone arm (Claudino et al. 2007). Adverse effects were, however, more common in the topiramate group.

Anxiolytic and other agents

Anxiolytic drugs such as benzodiazepines are sometimes used in anorexia nervosa (de Zwann & Roerig, 2003) but there are no RCTs testing their use. Steinglass et al. (2007) tested D-cycloserine (a glutamate partial agonist) in a very small study of 14 patients (nine with anorexia nervosa) which was part of evaluating an exposure (to food) therapy. Results were mixed and food intake was not enhanced.

The opioid antagonist naltrexone has been trialled in eating disorders based on the premise that some eating-disorder behaviours (specially binge eating) are ‘addictive-like’ behaviours. Results of clinical trials with naltrexone in bulimia nervosa are conflicting. Mitchell et al. (1989) reported negative results in their low-dose naltrexone cross-over study with 16 normal-weight women with bulimia nervosa, whereas Marrazzi et al. (1995a) found significant reductions in binge/purge symptoms during naltrexone treatment in all patients (n = 19) with bulimic symptoms (anorexia nervosa of the bulimic subtype or bulimia nervosa) in a double-blind placebo, cross-over study. Experimental studies suggest naloxone, also an opioid antagonist, may have a role in reducing binge eating in BED (Drewnowski et al. 1995; Marrazzi et al. 1995b) but there are no RCTs as yet. Baclofen, a centrally acting γ-amino-butyric acid B (GABA-B) receptor agonist has also shown promise in reducing binge eating at 60 mg/d in a small case series (Broft et al. 2007).

Increasing evidence suggests that the ventromedial and lateral regions of the hypothalamus and the arcuate nucleus play a significant role in the regulation of appetite, and it argues high levels of glutamate may lead to appetite dysregulation through glutamate-induced neurotoxic effects mediated by N-methyl-d-aspartate (NMDA) receptors (Hermanussen & Tresguerres, 2003). Memantine is a low-to-moderate-affinity non-competitive NMDA receptor antagonist that in one open-label trial of 16 overweight BED participants (Brennan et al. 2008; flexible dose of 5–20 mg/d) decreased binge-eating frequency and obsessive features of binge eating, but not weight.

Anti-obesity agents

The high rates of comorbidity of obesity and BED has led to interest in the use of anti-obesity agents in this group. Their use is supported by two factors: their effects on the reduction of appetite or increase in
satiety, thus their possible effects on binge-eating behaviours, and their promotion of weight loss, as BED is frequently associated with obesity or overweight (Appolinario & McElroy, 2004).

Sibutramine, a selective serotonin and noradrenaline inhibitor has been discussed above. Two RCTs have tested the use of orlistat, a lipase inhibitor, against placebo, in combination with a mildly reduced-calorie diet of 24 wk (89 obese patients with BED) (Golay et al. 2005) or combined to a CBT-based guided self-help manual for 12 wk (50 patients) (Grilo et al. 2005b). After 24 wk, patients taking orlistat showed greater mean weight loss (−7.4% vs. −2.3%) as well as a greater reduction of eating-disorder symptoms, compared to those taking placebo (Golay et al. 2005). Grilo et al. (2005b) reported better results in the orlistat group for both, binge remission (64% vs. 36%) and clinically significant weight loss (>5% from baseline weight: 36% vs. 8%), although only weight loss was kept at the 3-month follow-up.

A recent meta-analysis of comparative effect sizes for treatments of BED combined results of 38 studies of RCTs and uncontrolled studies and pooled all types of pharmacotherapy, as well as psychotherapies in computing comparative effect sizes (Vocks et al. 2010). The paper supported the above findings, namely significant albeit modest effect sizes of 1.19 (95% CI 0.88–1.49, 11 studies, 212 participants) for binge-eating reduction and for weight loss 0.50 (95% CI 0.15–0.85, three studies, 77 participants) but less impact on changes in eating-disorder cognitions. Psychotherapy had larger effect sizes supporting it as ‘first-line’ treatment over pharmacotherapy. However, the analysis was problematical in that different forms of both psychotherapy and pharmacotherapy were pooled.

Conclusions
Psychotherapies such as CBT or family therapy are treatments of choice for eating disorders but pharmacotherapies have an important role in specific disorders, albeit with a moderate to weak evidence base. Strongest evidence is for antidepressants, particularly high-dose fluoxetine in bulimia nervosa, and antiobesity agents (sibutramine) for BED. In addition, attrition rates are usually higher than for psychotherapies. Low-dose antipsychotic medication may be clinically useful as adjunct treatment in acute anorexia, particularly where there is high anxiety and obsessive eating-related ruminations and failure to engage, but more trials are needed. Drug therapies such as topiramate and anti-obesity medication may aid weight loss in obese or overweight patients with BED; however, common or potentially serious adverse effects limit their use and it is thought the placebo response may be high in this disorder.

The mechanisms of effects of pharmacological therapies in eating disorders also need further study. While putative action is through modulation of dopamine and serotonin, central pathway regulation of other neurotransmitters such as noradrenaline also occurs. This is a developing field as exemplified by Kaye and colleagues (Kaye, 2008) whose work has found limbic system dopaminergic dysregulation that persists after anorexia nervosa recovery and Frieling et al. (2010) who propose a new hypothesis of dopaminergic (dys-)regulation, namely that a hyperdopaminergic state in acutely ill anorexia nervosa leads to counter-regulatory mechanisms that in recovery result in reduced dopaminergic activity. Kaye and colleagues (2008) also postulate in an inherent serotonergic dysregulation that contributes to a dysphoria which is partially relieved by food restriction, albeit that the malnourished state impedes the biological activity of serotonergic antidepressants. Studies of antidepressant use in bulimia nervosa also support specific actions on satiety separate to mood modulation, and future research elucidating mechanisms of action will help guide more rationale developments in the pharmacotherapy of these disorders.

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