Developmental Concerns in Psychopharmacological Treatment of Children and Adolescents with Eating Disorders

Jennifer O. Hagman and Guido K.W. Frank

Abstract

This chapter reviews the limited studies relevant to psychopharmacology in children and adolescents with eating disorders and discusses approaches to treating comorbid diagnoses. Promising research in neuroscience is presented and future directions that may lead to more effective interventions are discussed. No randomized controlled trials demonstrate efficacy for any psychotropic medication for children or adolescents with eating disorders. All medications used in children and adolescents specifically for treatment of an eating disorder are considered “off-label” as there are no medications approved by the U.S. Food and Drug Administration (FDA) for this use in this population. Severe food restriction and emaciation, or binge eating and purging during periods of critical brain development may alter brain function permanently and make recovery challenging. There is insufficient evidence at this time to support prescribing selective serotonin reuptake inhibitors (SSRIs) or atypical neuroleptics for the treatment of anorexia nervosa, and evidence for efficacy of SSRIs for bulimia nervosa exists only for adults.

Keywords: Psychopharmacology, eating disorders, child and adolescent, comorbid diagnoses, anorexia nervosa, bulimia nervosa, neuroimaging, genetics

Despite decades of research, the pathophysiology of anorexia nervosa (AN) and bulimia nervosa (BN) remains elusive. Efforts to identify psychopharmacologic approaches for any psychiatric illness occurring in childhood and adolescence are quite limited, with high placebo response rates and research suggesting that psychological treatment, at least for depression and anxiety disorders, are as effective as medications or contribute substantially to improvement in response to treatment with medications. Furthermore, parents are often reluctant to provide consent for their child to participate in medication studies, which creates challenges in enrolling adequate numbers of subjects. Advances in defining psychopharmacologic approaches to the treatment of eating disorders are challenged by primary age of onset in adolescence; changes in brain development through childhood and adolescence; low prevalence in comparison to other more common childhood-onset illnesses such as attention deficit-hyperactivity disorder (ADHD), depression, and anxiety disorders; and parental resistance to participation in medication studies.

Eating disorders most often begin during adolescence, a sensitive period for physical and emotional development. Puberty is both biologically and socially an active and at times stressful period, during which structural and neurochemical cerebral changes take place. Although neurobiological underpinnings for eating disorders have been suggested (Klump, Bulik, Kaye, Treasure, & Tyson, 2009), most experts agree that environmental, cultural, and personality factors contribute to the development of these illnesses (Treasure, Claudino, & Zucker, 2010). The common onset of eating disorders during adolescence and the high predominance of
females suggest developmental neurobiological and genetic factors as contributing to AN and BN pathophysiology, in addition to well-known psychological and environmental factors (Bulik, 2005; Frank & Kaye, 2005). Genetic factors may thus set the stage for altered emotional processing and response to stress and, when coupled with the challenges of adolescence and body dissatisfaction, the adolescent may experience eating disordered behaviors as helping him or her to have an increased sense of control and thus feel better (Frank & Kaye, 2009). Altered eating patterns, such as severe food restriction and emaciation or binge eating and purging during periods of critical brain development may lead to brain changes that are difficult to overcome and reverse and make recovery from these disorders difficult (Drew et al., 2007; Kellendonk et al., 2006). The impact of such changes on brain chemistry and body physiology seem to worsen the cognitive processes that maintain the illness. Because eating disorders typically begin to develop during the adolescent years, it is conceivable that specific developmental insults on the developing brain neurotransmitter systems could put some at risk for long-term behavioral effects. Research in rhesus monkeys suggests that an initial overproduction of central dopamine (DA D₁, DA D₂), serotonin (5HT₁, and 5HT₂), and adrenergic (α₁, α₂, and β) receptors (Lidow & Rakic, 1992) in the first few months of life is followed by a gradual decrease during childhood up to puberty. Thus, food restriction, exposure to toxins, genetic translational and transcriptional factors, etc. could profoundly affect the functionality and interactions of those systems.

This type of understanding of the etiology of eating disorders lays the foundation for a developmental neuroscience perspective in eating disorder research and may inform the development of more effective treatments, including pharmacologic interventions.

### Psychopharmacology of Eating Disorders in Children and Adolescents

To date, no randomized controlled trials (RCTs) demonstrate efficacy for any category of psychotropic medication for children or adolescents with AN, BN, or eating disorder not otherwise specified (EDNOS). All medications used in children and adolescents specifically for treatment of an eating disorder are considered “off-label” as there are no medications approved by the U.S. Food and Drug Administration (FDA) for this use in this population. This situation is not uncommon in the practice of child psychiatry, as most psychotropic medications are studied first in adults and prescribing them extended off-label to other populations once the drug has FDA approval for use (Zito et al., 2008). This results in younger populations often being exposed to medications before efficacy has been established in their age group. Selective serotonin reuptake inhibitors (SSRIs), anxiolytics, and antipsychotics can have significant side-effect profiles, and the impact on the developing brain is still not well understood. Several authors have provided comprehensive reviews of the state of psychopharmacology and lack of evidence supporting medication use in patients with eating disorders (Couturier & Lock, 2007; Crow, Mitchell, Roerig, & Steffen, 2009; Martiadis, Castaldo, Monteleone & Maj, 2007).

Crow and colleagues (2009) reviewed all existing studies, including controlled, case series and open trials, of medications used for treatment of AN (Table 16.1) and concluded that “at present, there is no convincing evidence for any drug treatment for AN, in either the acute or chronic phase of the illness” (Crow et al., 2009, p. 1).

Couturier and Lock reviewed studies of medications in children and adolescents with eating disorders and concluded that “Further medication trials are needed in order to delineate which, if any, pharmacological treatments are efficacious for children...”

### Table 16.1 Medications studied previously for anorexia nervosa treatment

<table>
<thead>
<tr>
<th>Controlled Trials</th>
<th>References</th>
<th>Case Series/ Open Trials</th>
<th>References</th>
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<tbody>
<tr>
<td>Fluoxetine</td>
<td>Walsh et al., 2006; Halmi et al., 2005; Barbarich et al., 2004b; Attia et al., 1998; Brambilla et al., 1995; Kaye et al., 2001</td>
<td>Quetiapine</td>
<td>18</td>
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<tr>
<td>Sulpiride</td>
<td>Vandereycken, 1984</td>
<td>Haloperidol</td>
<td>Cassano et al., 2003</td>
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<tr>
<td>Controlled Trials</td>
<td>References</td>
<td>Case Series/Open Trials</td>
<td>References</td>
</tr>
<tr>
<td>Cispride</td>
<td>Stacher et al., 1987; Szmukler et al., 1995</td>
<td>Olanzapine</td>
<td>Boachie et al., 2003; Brambilla et al., 2007; Dennis et al., 2006; Ercan et al., 2003; Hansen, 1999; La VIA et al., 2000; Mehler et al., 2001; Mondrany et al., 2005; Malina et al., 2003</td>
</tr>
<tr>
<td>Zinc</td>
<td>Birmingham et al., 1994</td>
<td>Paroxetine</td>
<td>Heiden et al., 1998; Strober et al., 2004</td>
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<tr>
<td>Amitriptyline</td>
<td>Halmi et al., 1986; Biederman et al., 1985</td>
<td>Fluoxetine</td>
<td>Corwin et al., 1995; Ferguson, 1987; Gwirtsman et al., 1990; Holtkamp et al., 2005; Kaye et al., 1991; Ricca et al., 1999; Ruggiero et al., 2001; Strober et al., 1997; Strober et al., 1999</td>
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<tr>
<td>Ciproheptadine</td>
<td>Halmi et al., 1986</td>
<td>Fluvoxamine</td>
<td>Holtkamp et al., 2005; Rey Sanchez et al., 1993</td>
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<tr>
<td>Pimozide</td>
<td>Vandereycken &amp; Pierloot, 1982</td>
<td>Sertraline</td>
<td>Holtkamp et al., 2005; Frank et al., 2001; Santonastaso et al., 2001</td>
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<tr>
<td>Clonidine</td>
<td>Casper et al., 1987</td>
<td>Tramadol</td>
<td>Mendelson, 2001</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Brambilla et al., 1995</td>
<td>Amisulpride</td>
<td>Ruggiero et al., 2001</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Lacey &amp; Crisp, 1980</td>
<td>Clomipramine</td>
<td>Strober et al., 2004; Ruggiero et al., 2001</td>
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<tr>
<td>Lithium</td>
<td>Gross et al., 1981</td>
<td>Citalopram</td>
<td>Bergh et al., 1996; Calandra et al., 1999; Fassino et al., 2002</td>
</tr>
<tr>
<td>Tetrahydrocannabinol</td>
<td>Gross et al., 1983</td>
<td>Venlafaxine</td>
<td>Ricca et al., 1999</td>
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<tr>
<td>Olanzapine</td>
<td>Powers et al., 2007</td>
<td>Growth hormone</td>
<td>Hill et al., 2001</td>
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<td>Testosterone</td>
<td>Miller et al., 2005</td>
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<td>Ethylloicosapentenoate</td>
<td>Ayton et al., 2004</td>
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<tr>
<td>Risperidone</td>
<td>Fisman et al., 1996; Newman-Tozier, 2000</td>
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<tr>
<td>Isocarboxazid</td>
<td>Kennedy et al., 1985</td>
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<tr>
<td>Imipramine</td>
<td>Mumford et al., 1984</td>
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<tr>
<td>Lithium</td>
<td>Hudson et al., 1985</td>
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<tr>
<td>Carbamazepine</td>
<td>Hudson et al., 1985</td>
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<td>Dexamethasone</td>
<td>Gordon et al., 2000</td>
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<tr>
<td>Amitriptyline</td>
<td>Moore, 1977</td>
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<td>Nandrolone</td>
<td>Tec, 1974</td>
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<tr>
<td>Naltrexone</td>
<td>Luby et al., 1987</td>
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<tr>
<td>L-Dopa</td>
<td>Johanson &amp; Knott, 1977</td>
<td></td>
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<tr>
<td>Glycerol</td>
<td>Caplin et al., 1973</td>
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and adolescents with eating disorders” (Couturier & Lock, 2007, p. 176). A publication by Treasure et al. (2010) provided a review and summary of all treatments for eating disorders and the strength of their empirical support (Table 16.2), and similar to other authors, concluded that for AN: “No strong evidence lends support to drug treatment either in the acute or maintenance phase of the illness.” (Treasure et al., 2010, p. 588)

As such, this chapter will review the limited number of studies relevant to children and adolescents with eating disorders, and focus on consideration of psychopharmacology approaches in eating disorders in children and adolescents, promising research that may lead to more effective interventions, psychopharmacologic and otherwise, and finally, a discussion of future directions.

Emotional and behavioral symptoms in children and adolescents with eating disorders can be dramatic and severe, including dysphoria, severe anxiety, impulsivity, self-harm behaviors, and suicidal ideation. Furthermore, some symptoms do not always improve sufficiently with weight restoration or stabilization of eating behaviors. Patients with eating disorders have the highest risk of completed suicide of any mental illness (Holm-Denoma et al., 2008). It is thus not difficult to understand why physicians often feel compelled to try medications, despite a medicati-

<table>
<thead>
<tr>
<th>Pharmacological Treatment</th>
<th>Anorexia Nervosa</th>
<th>Bulimia Nervosa</th>
<th>Binge Eating Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants (acute phase)</td>
<td>Weak –</td>
<td>Strong +</td>
<td>Moderate +</td>
</tr>
<tr>
<td>Antidepressants (relapse prevention)</td>
<td>Weak –</td>
<td>Strong* +</td>
<td>Moderate –/+</td>
</tr>
<tr>
<td>Antipsychotic: olanzapine</td>
<td>Weak* –</td>
<td>Weak +</td>
<td>Weak +</td>
</tr>
<tr>
<td>Zinc</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Drugs for osteoporosis/osteopenia</td>
<td>Weak –/+</td>
<td>Weak –/+</td>
<td>N/A</td>
</tr>
<tr>
<td>Anticonvulsant: topiramate</td>
<td>Weak –/+</td>
<td>Weak –/+</td>
<td>N/A</td>
</tr>
<tr>
<td>Appetite suppressor: sibutramine</td>
<td>Weak –/+</td>
<td>Weak –/+</td>
<td>N/A</td>
</tr>
<tr>
<td>Obesity drug: orlistat</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Behavioral Treatment</th>
<th>Evidence Effect</th>
<th>Evidence Effect</th>
<th>Evidence Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive-behavioural therapy</td>
<td>Weak* –</td>
<td>Strong* ++</td>
<td>Moderate +++</td>
</tr>
<tr>
<td>Interpersonal psychotherapy</td>
<td>Weak* +</td>
<td>Moderate +</td>
<td>Weak ++</td>
</tr>
<tr>
<td>Cognitive analytical therapy</td>
<td>Weak +</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Dialectical behavioural therapy</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Psychodynamic therapies</td>
<td>Weak +</td>
<td>Weak –/+</td>
<td>N/A</td>
</tr>
<tr>
<td>Behavioural therapies</td>
<td>Weak –/+</td>
<td>Weak* +</td>
<td>N/A</td>
</tr>
<tr>
<td>Family-based therapy (Maudsley)</td>
<td>Moderate* ++</td>
<td>Weak –/+</td>
<td>N/A</td>
</tr>
<tr>
<td>Specialist clinical management</td>
<td>Weak* –</td>
<td>Weak –/+</td>
<td>N/A</td>
</tr>
<tr>
<td>Nutritional counseling (alone)</td>
<td>N/A</td>
<td>Weak –/+</td>
<td>N/A</td>
</tr>
<tr>
<td>Behavioural weight loss therapy</td>
<td>N/A</td>
<td>Weak* +</td>
<td>Weak +</td>
</tr>
<tr>
<td>Self-help interventions (GSH/PSH)</td>
<td>N/A</td>
<td>Weak –/+</td>
<td>Weak +</td>
</tr>
<tr>
<td>Mobile/Internet/telemedicine</td>
<td>N/A</td>
<td>Weak –/+</td>
<td>Weak +</td>
</tr>
</tbody>
</table>

*At least one trial included adolescents (<18 years). SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; SNRIs, serotonin-norepinephrine reuptake inhibitors; GSH, guided self-help; PSH, pure self-help. Evidence grades: N/A, nonexistent or not applicable; grades weak/moderate/strong. Beneficial Effect (reduction of symptoms or behaviors or maintenance of improvements); N/A, no randomized or controlled trial available; –, no beneficial effect; –/+ mixed results or still inconsistent results (possible beneficial effect); +, slight beneficial effect, ++, moderate beneficial effect; ++++, strong beneficial effect. Reprinted with permission from Treasure, J., Glaudino, A. M., & Zucker, N. (2010). Eating disorders. Lancet, 375, 583–593.
Despite a lack of evidence supporting psychotropic medications in eating disorders in children and adolescents. In addition to dysregulated eating patterns, drive for thinness, body dissatisfaction, and body image distortion, patients with AN and BN often suffer from anxiety symptoms, depression, obsessional thinking, and compulsive behaviors within the context of the eating disorder. Early efforts to intervene with fluoxetine were based on the concept that it was helpful in adults with primary depression or anxiety disorders, including obsessive compulsive disorder (OCD), and such symptoms in eating disordered patients might be similarly responsive. Antidepressants, specifically SSRIs, are the most common category of medication prescribed for patients with eating disorders, including children and adolescents. Target symptoms include body image distortion, depression, anxiety, and obsessional thinking—although it remains unclear if such symptoms improve in response to medications during the course of an active eating disorder. A retrospective study of SSRI use in adolescents with AN (mean age 14.5 years) during inpatient treatment and at 6-month follow-up found no difference between the two groups with respect to course of illness and weight restoration (Holtkamp et al., 2005). The authors concluded by recommending that clinicians should be more cautious when prescribing SSRIs in this populations.

Another study examined the adjunctive use of fluoxetine during the 24 month post-hospital period in a young adult sample with AN (mean age 17.6 years) and similarly found no differences (Strober, Freeman, DeAntonio, Lampert, & Diamond, 1997). Another study found no differences between fluoxetine and placebo when used to augment inpatient treatment of AN in a sample that included adolescents (age range 16–45, average age 26); and symptoms specific to the eating disorder, such as drive for thinness and body dissatisfaction, did not improve with fluoxetine use (Attia, Haiman, Walsh, & Flater, 1998). The authors did not report any correlations between age and response.

Studies of fluoxetine for BN in adults, in the late 1980s demonstrated benefit of this medication for this disorder leading to FDA approval for individuals over age 18 (Fichter et al., 1991; Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldstein, Wilson, Thompson, Potvin, & Ramphey, 1995). There are no double-blind studies of fluoxetine in adolescents with BN, and only one open-label study of fluoxetine in adolescents with BN, which reported a significant decrease in binge eating and purging (Kotler, Devlin, Davies, & Walsh, 2003). Based on the positive studies, and FDA approval for adults, it is common clinical practice for fluoxetine or similar SSRIs to be prescribed for adolescents with BN, primarily when symptoms do not improve with behavior and psychotherapeutic interventions.

Turning to the use of medications in the context of psychological treatments for adolescent AN, the only intervention with a solid evidence base for treatment of AN is family-based therapy (FBT) for adolescents with AN (Couturier, Iserlin, & Lock, 2010; Le Grange, Lock, Loeb, & Nicholls, 2010; Lock, Agras, Bryson, & Kraemer, 2005; Lock, Couturier, & Agras, 2006; Loeb et al., 2007). Family-based therapy is a psychotherapeutic intervention focused on empowering the parents to successfully manage eating disorder symptoms and to provide the supervision and support necessary to stabilize eating patterns and weight. In the original FBT study, 14% of subjects were on psychotropic medications for anxiety or depression at baseline, and 52% had been on a psychotropic medication at follow-up (average 3.96 years after treatment). Of those treated with medication, 69% were prescribed medication for psychiatric diagnoses other than AN. Medication use during FBT and in the subsequent follow-up period was not a significant moderator of outcome (Lock et al., 2006). Family-based therapy has also been studied in adolescents with BN with favorable results (Le Grange, Crosby, & Lock, 2008; Le Grange, Crosby, Rathouz, & Leventhal, 2007; Le Grange, Doyle, Crosby, & Chen, 2008). Medication use for comorbid conditions was allowed during the BN-FBT study, and 32.5% of the adolescents were on antidepressants. Medication status did not impact remission. Although the published FBT studies allowed use of medications for comorbid diagnoses during FBT, there are no studies designed to evaluate the use of medication in the course of FBT.

Atypical Neuroleptics

Another category of medications that have been prescribed and studied in AN with increasing frequency are the atypical neuroleptics. When the atypical neuroleptics were first introduced in the mid-1990s, they gradually began to be prescribed off-label for a range of diagnoses beyond schizophrenia. In the late 1990s, atypical neuroleptics, specifically olanzapine and risperidone, began to be prescribed in AN, targeting body image distortion, fear of weight gain, and anxiety. Case reports were
published in the 1990s, some of which included child and adolescent cases (Boachie, Goldfield, & Spettigue, 2003; Dennis, Le Grange, & Bremer, 2006; Ercan, Copkunol, Cykoethulu, & Varan, 2003; La Vea, Gray, & Kaye, 2000; Mehler et al., 2001; Newman-Toker, 2000). These early case reports suggested that atypical antipsychotics were generally well tolerated by subjects and were associated with improvement in psychological factors (e.g., anxiety, obsessiveness) that made it easier to treat such patients. An open-label trial of olanzapine included subjects aged 14 to 56 years (Powers, Santana, & Bannon, 2002). Six of the 18 subjects were between 14 and 18 years of age. Although results were not reported by age, the study found clinically significant weight gain over the 10-week study period in the 14 subjects who completed the study (Powers et al., 2002). A second open-label trial of olanzapine included 17 subjects aged 15-25, of which 12 subjects completed 6 weeks of open-label olanzapine (Barbarich et al., 2004a); again, results were not reported by age. The authors reported a significant reduction in anxiety, depression, core eating disorder symptoms, and increase in weight. An RCT of olanzapine in 34 adult women over 13 weeks reported that subjects on olanzapine had an increased rate of weight gain and a reduction in obsession scores (Bissada, Tasca, Barber, & Bradwejn, 2008). A second RCT of olanzapine and cognitive-behavioral therapy (CBT), over 3 months, in 30 adult females with AN reported no significant differences in body mass index (BMI), but did find improvement in compulsivity, depression, and aggressiveness with CBT and olanzapine (Brambilla et al., 2007).

There is only one RCT of an atypical neuroleptic (risperidone) in an adolescent population (Hagman et al., 2011). Forty subjects (age range 12-21, mean age 16) were randomized in a double-blind, placebo-controlled exploratory pilot study. Average length of time on medication was 9 weeks. Although there was a significant decrease in the risperidone subjects on the drive for thinness and interpersonal distrust subscales of the Eating Disorders Inventory (EDI-2), there were no other significant differences from placebo with respect to time to reaching target weight, length of time in treatment, measures of anxiety, body dissatisfaction, body image distortion, and other EDI subscales (Hagman et al., 2011). There was a significant increase in prolactin levels in the risperidone group, but no other significant differences in other laboratory measurements, electrocardiograms, resting energy expenditure, or vital signs (Hagman et al., 2011). Forty-two percent of subjects enrolled in the study were on an antidepressant prior to enrollment and during the study, and randomization was stratified by antidepressant status equally between risperidone and placebo. The authors concluded that "this exploratory pilot study does not demonstrate a clear benefit from the addition of risperidone in the course of active treatment and weight restoration in adolescents with AN." (Hagman et al., 2011)

In summary, there is insufficient evidence at this time to support the prescription of SSRIs or atypical neuroleptics for the treatment of AN. Studies indicate that SSRIs are unlikely to show efficacy in AN, although they may play a role in the treatment of adolescent BN, studies are lacking. Further research is needed to clarify if atypical neuroleptics provide any significant benefit in AN.

One of the main challenges in studying pharmacologic interventions in eating disorders involves patient willingness to consider participation in a double-blind study. Studies of medications in children, adolescents, and adults with eating disorders have been significantly limited by challenges in enrollment. Spettigue and colleagues opened a protocol for an RCT evaluating the safety and efficacy of olanzapine in adolescent females (Spettigue et al., 2008), but were unable to enroll sufficient subjects to complete the study (Norris, Spettigue, Buchholz, Henderson, & Obeid, 2010). A study of challenges in participant recruitment for an AN treatment study suggested that recruitment from many sites in a short period may be more effective than at a few sites over a long period (McDermott et al., 2004). In an editorial on the "perplexities of conducting randomized double-blind, placebo controlled treatment trials in AN", Halmi (2008, p. 1228) concluded that "It is unlikely that predictably effective treatment for AN will be available until we decipher the reinforcing neurobiological mechanisms sustaining the disorder."

**Treatment of Comorbid Diagnoses in Eating Disorders**

There are no studies on the efficacy or outcome of treating comorbid diagnoses while the individual has an active eating disorder. Although comorbid diagnoses are quite common in eating disorders (Hanzug, Nussbaum, & Marmor, 1996; Treasure et al., 2010), research exploring the outcome of treatment with medications for comorbid OCD, major depression, or anxiety disorders in the context of active AN or BN does not exist. In the treatment of eating disorders, common clinical practice is to identify comorbid diagnoses through thorough history taking to identify present before the onset, as well as to clarify duration of symptoms accompanying body dissatisfaction and of eating scales and pay assist with identifying anxiety.

Preexisting anxiety is followed by depression (Fear, & Joyce, 1997; C & Jeammet, 2002; Steiner, & Diamond, 2007; Wade, 2000). It is not unusual to often lorazepam, to be the anxiety that often after eating; however, the efficacy of this practice.

Medication interventions are often initiated a have been interrupted. Clinical stability has been under way. A least been, most ciliation until the individual body weight (IBW); inpatients believe that once reaching 85% of

When using psychosomatic diagnosis in order, the provider’s approaches whenever plus CBT for the tre (March et al., 2009; line plus CBT for the et al., 2010; Walkup et al., 2003; Pelit et al., 2004). A patients with eating, ADHD, stimulants caution in patients their potential importance weight loss and pot approaches to the treatment of eating disorders show. Medications other than prescribed in eating, indications for psychosomatic populations.

**Neurobiologic Drug Development**

Neurobiologic situation in eating dis...
history taking to identify any symptoms that were present before the onset of the eating disorder, as well as to clarify duration and intensity of symptoms accompanying the eating disorder beyond body dissatisfaction and drive for thinness. The use of rating scales and psychological testing can also assist with identifying comorbid diagnoses.

Preexisting anxiety disorders are most common, followed by depression and OCD (Bulik, Sullivan, Fear, & Joyce, 1997; Godart, Flament, Perdereau, & Jeanmet, 2002; Strober, Freeman, Lampert, & Diamond, 2007; Wade, Bulik, Neale, & Kendler, 2000). It is not unusual for benzodiazepines, most often lorazepam, to be used before meals to decrease the anxiety that often builds before, during, and after eating; however, there are no studies related to efficacy of this practice either.

Medication interventions for comorbid diagnoses are often initiated after eating disorder behaviors have been interrupted and, in the case of AN, medical stability has been achieved and weight restoration is under way. Although this practice has not been studied, most clinicians delay starting a medication until the individual has reached 85% of ideal body weight (IBW; in the case of AN). Many physicians believe that medication may be more effective once reaching 85% or higher of IBW.

When using psychopharmacology to target a comorbid diagnosis in the context of an eating disorder, the provider should rely on evidence-based approaches whenever possible, such as fluoxetine plus CBT for the treatment of comorbid depression (March et al., 2009; March et al., 2007), or sertraline plus CBT for the treatment of anxiety (Compton et al., 2010; Walkup et al., 2008) or OCD (Geller et al., 2003; Pediatric OCD Treatment Study [POTS], 2004). Although it is uncommon for patients with eating disorders to have comorbid ADHD, stimulants should be prescribed with great caution in patients with eating disorders due to their potential impact on appetite suppression and weight loss and potential for misuse. Nonstimulant approaches to the treatment of comorbid ADHD in eating disorders should be utilized whenever possible. Medications other than stimulants that are sometimes prescribed in eating disorders and have FDA-approved indications for psychiatric diagnoses in child and adolescent populations are listed in Table 16.3.

### Neurobiologic Perspectives for Novel Drug Development

Neurobiologic studies have implicated genetic variation in eating disorders, and neuroimaging studies have found serotonin and dopamine alterations that could be related to eating disorder psychopathology and potentially become a target for specific pharmacologic treatment. Childhood and adolescence are transition periods during which structural and neurochemical cerebral changes take place. Food restriction may influence neurotransmitter expression and could modify neurotransmitter receptor function. It is not clear if abnormalities in receptor functioning and neurotransmitters are premorbid or are altered during the course of illness. Abnormally high brain serotonin could be a trait marker perhaps related to anxiety (Naughton, Mulrooney, & Leonard, 2000), and eating disordered behavior might be a means to reduce serotonin (SHT) transmission. Whether individuals with restricting AN have intrinsically lower dopamine (DA) remains uncertain. A key question here is how over- or underfeeding shapes the brain DA neurotransmitter system, if such alterations are state dependent only, or whether they persist into and beyond recovery.
Various medications (e.g., haloperidol, risperidone, and olanzapine) block, for instance, DA D₄ receptors, while others (e.g., aripiprazole) are likely partial agonists that promote DA transmission in the prefrontal cortex, but block DA D₄ in the basal ganglia. However, neuroscience-based studies are needed to investigate the interplay between neurotransmitter receptor availability and sensitivity in relation to behavior, in order to systematically better identify targets that effectively improve eating as well as cognitive and emotional problems in eating disorders.

Genetic Studies
The mechanism through which genetic code abnormalities influence AN behaviors is not known. However, abnormalities in serotonin and opioid receptor function could be a risk factor for emotional problems, sensitivity to stress, and negative self-evaluation, which could subsequently then become a vulnerability for developing AN-specific cognitions and behaviors (Herbeth et al., 2005; Nacmias et al., 1999; Ricca et al., 2004). Environmental factors might then activate such genetic predispositions.

Anorexia nervosa and BN share common genetic vulnerabilities, based on familial cross-transmission (Bulik, Sullivan, Wade, & Kendler, 2000). These heritability estimates are similar to those found in schizophrenia and bipolar disorder, suggesting that AN and BN may be highly genetically influenced. Various studies have linked specific chromosomes or genes with eating disorders, and the 5-HT2A/1438G/A receptor, the serotonin HTR1D receptor, the 5HT transporter, and the opioid OPRD1 receptor gene variants seem to be the best candidates for potential genetic contributors to eating disorder pathophysiology (Bergen et al., 2003; Brown & Harris, 2006; Lee & Lin, 2009; Nacmias et al., 1999; Ricca et al., 2004). Thus, those neurotransmitter receptor types could become targets for pharmacologic agonist or antagonist action.

Functional Neuroimaging
Most functional task activation and neurotransmitter-receptor studies in eating disorders have been conducted with adults, but those results may shed light on underlying pathophysiologic processes in eating disorders at any age. In AN, using positron emission tomography (PET), 5HT₁₆ receptor binding has been found to be elevated across most brain regions in ill restricting and ill and recovered binge-purging type AN subjects compared to healthy controls (Bailer et al., 2005). In contrast, recovered restricting-type AN patients show normal brain 5HT₁₆ binding (Bailer et al., 2005). For the 5HT₁₆ receptor type, one group, using single proton emission computed tomography (SPECT) found reduced binding in symptomatic AN patients (Audenaert et al., 2003), but a study that controlled for brain volume loss found normal 5HT₂A receptor availability in symptomatic restricting and binge eating–purging type AN (Bailer et al., 2007). After recovery, both restricting and binge eating–purging type AN had reduced 5HT₂A binding (Bailer et al., 2004; Frank et al., 2002). The restricting-type AN group also presented with significantly reduced 5HT₂A binding. In summary, in the ill state, 5HT₁₆ receptor binding is elevated, suggesting a compensatory up-regulation, possibly in response to low brain serotonin levels. After recovery, 5HT₁₆ receptor binding seems to differentiate AN subtypes, with restricting AN showing normal binding, whereas binge-purge AN continues to show elevated binding. In contrast, 5HT₂A receptor binding is reduced in both restricting and binge eating–purging AN in various brain regions.

There is reduced DA release when fasting (Kaye, Ebert, Raleigh, & Lake, 1984), which reduces DA receptor stimulation. Conversely, fasting increases DA receptor availability at the same time (Carr, Tsimberg, Berman, & Yamamoto, 2003). One study found increased DA D₁/D₅ receptor binding ([11C]raclopride, PET) in the anteroverentral striatum of a group of recovered restricting and binge eating–purging type AN patients (G. K. Frank et al., 2005). This receptor increase could be consistent with reduced cerebrospinal fluid (CSF) DA metabolites found in the past (Kaye, Frank, & McConaha, 1999) and may suggest low brain DA associated with increased DA receptors in AN, which may have implications for pharmacologic interventions.

In a PET study of recovered adults with BN, Kaye (W.H. Kaye et al., 2001) found orbitofrontal 5HT₂A receptor binding was reduced, possibly in response to increased brain serotonin (W. Kaye, Gendall, & Stober, 1998). Orbitofrontal alterations may contribute to behavioral disturbances associated with BN, such as impulsivity and altered emotional processing (Steiger et al., 2001). Another 5HT receptor is the 5HT transporter that removes 5HT from the synapse. Symptomatic BN patients were found to show reduced 5HT transporter binding in the thalamus and hypothalamus (Taushcer et al., 2001), but increased 5HT₁₂ receptor binding (Tiilhonen et al., 2004), most prominently in the medial prefrontal or angular gyrus of the brain. The between 5HT transporter and 5HT receptor are well known to increase up-regulation to low 5HT (Meyer, dynamic 5HT tran adjust to hypotheso 2006). The SSRIs, 5HT in the brain, the treatment of e demonstrated efficacy lack of improve This indicates that the serotonin system remains to be und

Future Directions
Although research in eating disorders is critical to understanding the factors maintenance of necessary to devise and apply regard it will be sychosocial as quite variable in gies for measures as it relates to be inform approaches also important associated with psychiatric disorder. Thus, future research should develop better information to further eating disorder fear of fat sb the development. Research orders may include treatment approaches focused on younger children. Typically, the sample here understand lenges with
medial prefrontal cortex, posterior cingulate, and angular gyrus of the parietal cortex. The dynamics between 5-HT transporter expression and synapticle 5HT are not well understood. Two explanatory hypotheses can be entertained: Either 5-HT transporter up-regulation (negative feedback) in response to low 5HT (Meyer et al., 2004), or adaptive, dynamic 5HT transporter reduction in order to adjust to hypothesized low 5HT (Parsey et al., 2006). The SSRIs, which enhance availability of 5HT in the brain, result in differential responses in the treatment of eating disorders. The SSRIs have demonstrated efficacy in BN, but show apparent lack of improvement in the course of illness in AN. This indicates that the impact of abnormalities in the serotonin system in patients with AN and BN remains to be understood.

**Future Directions**

Although research can be challenging in the field of eating disorders in children and adolescents, it is critical that efforts continue so that we may understand the factors that contribute to the onset and maintenance of these illnesses. Further research is necessary to develop a disease-specific model for AN and BN and to clarify the EDNOS category. In this regard it will be important to stress a range of biopsychosocial factors. Treatment interventions are quite variable in part because of inconsistent strategies for measuring eating disorder psychopathology as it relates to both diagnosis and outcome. To better inform approaches to treating eating disorders, it is also important to distinguish between symptoms associated with AN or BN and common co-morbid psychiatric disorders (e.g., anxiety and depression). Thus, future research should focus on the impact of behavioral or pharmacological interventions in the developmental context of an active eating disorder to better inform clinical approaches to treatment. Efforts to further characterize cognitive processes in eating disorders beyond body dissatisfaction and fear of fat should continue, and should emphasize the developmental spectrum.

Research on age-related differences in eating disorders may further inform differential approaches to treatment, including medications and nonmedication approaches. Most research in eating disorders is focused on females age 16 and older. Males and younger children should be included in studies. Typically, they have been excluded to minimize sample heterogeneity, but this further limits our understanding of these subgroups. Given the challenges with adequate enrollment in clinical trials, multisite studies should likely be pursued to improve subject numbers and allow for more conclusive data analysis.

Research related to the role of changes in diet and exercise in the development and maintenance of eating disorders may improve our ability to address and improve symptoms and outcomes through nonpharmacologic interventions related to nutrition and activity. Perhaps most promising is research to better understand the underlying biological factors, including use of brain imaging techniques and receptor and genetic studies, which may allow for more effective efforts at primary prevention of these devastating illnesses. Specifically, we need to identify neurobiological targets, such as specific neurotransmitter systems, and investigate those in a translational fashion—that is, across animal and human studies—to assess the plasticity of those systems and the effects of pharmacologic or behavioral interventions.

**Conclusion**

The typical age of onset during adolescence and their skewed gender distribution suggest a strong role for developmental factors in the etiology of eating disorders. Although there appear to be alterations in serotonin, opiate, and dopamine transmission in the brain in eating disorders, the psychopharmacological interventions currently available do not significantly impact the course of illness for patients with AN. Based on current research, the treatment of eating disorders in children and adolescents should rely on family-based interventions, emphasizing the use of FBT (Le Grange et al., 2010). There are no medications with approval for use in this population specifically for an eating disorder diagnosis, and caution should be used when doing so. Careful identification of comorbid conditions that may warrant symptom-specific treatment with evidence-based approaches may improve outcome, although more research is needed in this area. Identifying neurobiologic mechanisms that contribute to eating disorder development using genetic and neuroimaging methods should help identify targets for pharmacologic intervention.

**References**


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Gordon, C. M., Emants, S. J., Ed

Endocannabinoid and pharmacological amethasone in anorexia nervosa. *Psychopharmacology, 175–182.

Gross, H., Ebert, M. H., Faden, V. blind trial of delta 9-tetrahydro
motivation and interval timing. Journal of Neuroscience, 27(29), 7731–7739.


