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Olanzapine for Restrictive Eating Disorder

Adjunctive low-dose olanzapine (*Zyprexa*) increased eating and weight gain in children and adolescents undergoing treatment for avoidant restrictive food intake disorder (ARFID) at an eating disorders clinic. In this uncontrolled retrospective study, olanzapine was also associated with improvement in mood, anxiety, and cognition.

Background: Unlike other eating disorders, ARFID is not driven by body-image distortion or fear of weight gain. Rather, the food restriction and avoidance tend to be based on extreme sensitivity to the sensory characteristics of food (e.g., taste, texture, smell, temperature) and/or on a conditioned response involving the expectation that a previous negative experience (e.g., choking, difficulty swallowing) will be repeated. The treatment of ARFID generally takes an approach borrowed from other eating disorders. While there is no evidence for pharmacotherapy in ARFID, low-dose olanzapine is arguably the most effective drug treatment for anorexia nervosa.

Methods: The eating disorders program admitted 8 girls and 3 boys with DSM-5 ARFID. All patients had been symptomatic for many years but had not received a formal diagnosis before admission. Of the 11 patients, 9 were given olanzapine after they did not gain ≥1 lb per week with standard treatment in a structured behavioral program, with meal behavior therapy 6 times per day (3 meals, 3 snacks). Other treatments included individual, group, and family therapies, nutrition counseling, and pharmacotherapy. Olanzapine was typically started at 0.625 mg/day, and titrated based on response and tolerability.

Results: The 9 patients (8 girls) who received olanzapine had mean age of 14 years and an average body mass index (BMI) of 15.6, below the 11th BMI percentile for age. Six were below the 5th percentile, and 5 were below the 3rd percentile. The patients who received adjunctive olanzapine were discharged after a mean of 68 days of residential, partial hospital, and intensive outpatient treatment. They received olanzapine for a mean of 53 days, and the average olanzapine dosage at discharge was 2.8 mg/day.

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Average daily weight gain while receiving adjunctive olanzapine was 0.25 lbs, and patients had gained an average of 16 lbs and 3 BMI points by discharge. The BMI-per-age percentile increased to 36 ($p \leq 0.002$, compared with baseline). All patients had a comorbid psychiatric disorder diagnosis on admission. By the time of discharge, patients and their families reported significant improvement in anxiety and depressive symptoms. Cognitive improvement was also noted by parents, therapists, and teachers, with gains in school attendance, participation, and performance. The mean Clinical Global Impression–Severity score decreased from 5.3 (markedly ill) to 3.2 (mildly ill).

Discussion: To the authors' knowledge, there have been no randomized trials of olanzapine or any other pharmacotherapies for ARFID. While the present results are positive, they require replication. The authors emphasize the importance of using low-dose therapy (frequently requiring pill-cutting) and of slow dosage titration.

Brewerton T, D'Agostino M: Adjunctive use of olanzapine in the treatment of avoidant restrictive food intake disorder in children and adolescents in an eating disorders program. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (December):920–922. From the Medical University of South Carolina, Charleston; and the University of South Carolina, Columbia. **Source of funding not stated. The authors declared no competing interests.**

Pharmacotherapy for Tourette Syndrome

About 80% of children who present with Tourette syndrome (TS) tics at age <10 years will experience a significant decrease in tic frequency and severity during adolescence, with eventual functional recovery by age 18 years. For those who require treatment, comprehensive behavioral intervention for tics (CBIT) is highly effective and should be considered as first-line therapy. Medication is recommended when CBIT is ineffective, inappropriate, or unavailable. However, patients and families should be made aware that medications typically reduce tic symptoms by about 25–50%. The present recommendations are based on published research on drug treatment and on clinical guidelines from Canada and Europe.

First-Line Pharmacotherapy. The alpha agonists clonidine and guanfacine are appropriate first-line pharmacotherapy (after CBIT). Clonidine has been used to treat TS for >30 years and has "moderate" evidence of efficacy along with a benign adverse-effect profile. Evidence supporting a moderate effect of guanfacine for tic reduction is more limited, and the extended-release formulation does not appear to be effective.

Second-Line Pharmacotherapy. The GABA-B receptor agonist baclofen, which is commonly used to treat spasticity, should be considered next-line therapy. However, the quality of its evidence base is weak. The vesicular monoamine transporter-2 inhibitor tetrabenazine (FDA approved for Huntington's chorea) showed promising effects in preliminary studies in patients with TS. Of other agents in the class, deutetrabenazine (also FDA approved for Huntington's chorea) has shown promising results in an open-label trial, and valbenazine is currently under investigation for TS.

Third-Line Pharmacotherapy. Atypical antipsychotics are considered as next-in-line pharmacotherapy in the U.S. (and older neuroleptics elsewhere), with aripiprazole and risperidone the recommended first choices. Aripiprazole is FDA approved for this indication and supported by 2 large clinical trials. Risperidone also has convincing evidence of efficacy and may be helpful in comorbid conditions such as aggression or obsessive-compulsive symptoms, but it requires monitoring for dyskinesias and metabolic effects.

Other agents are being investigated but do not yet have sufficient evidence of efficacy. Cannabinoids have shown promise in preliminary studies and appeal to patients who are seeking a "natural" plant-based treatment. The benzodiazepine clonazepam and the investi-

gational D1/D5 antagonist ecopipam also have had promising initial results. The dopamine agonist pramipexole and the antiemetic metoclopramide have been investigated in the treatment of TS, but they were found to be ineffective.

Quezada J, Coffman K: Current approaches and new developments in the pharmacological management of Tourette syndrome. *CNS Drugs* 2018; doi 10.1007/s40263–017–0486–0. From Children's Mercy Hospital, Kansas City, MO. **Funded by the hospital. One study author disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; baclofen—*Lioresal*; clonazepam—*Klonopin*; clonidine—*Catapres*; deutetrabenazine—*Austedo*; guanfacine—*Tenex*; metoclopramide—*Reglan*; pramipexole—*Mirapex*; risperidone—*Risperdal*; tetrabenazine—*Xenazine*; valbenazine—*Ingrezza

Optimal Length of Antidepressant Treatment

Treatment with antidepressants, if response is achieved, should be continued for 9–12 months in children and adolescents with depression and for 6–9 months for those with anxiety disorders, according to a review of treatment guidelines and the limited research literature. If remission does not occur with acute antidepressant treatment, whether combined with psychotherapy, a change of antidepressant should be considered.

Based on current practice guidelines, clinical trial evidence, and specific relapse-prevention strategies, short-term use of SSRIs, particularly fluoxetine (*Prozac*), combined with psychotherapy, is effective in bringing about symptomatic and functional improvement in pediatric depression and anxiety. However, the risk of relapse and recurrence remain high. In adults, evidence-based relapse-prevention strategies include continuation of acute medication, psychotherapy booster sessions, and tailored recurrence-prevention interventions. Evidence is much more limited in the pediatric population; most studies do not extend beyond 12 weeks.

Pediatric treatment guidelines generally focus on acute treatment. For depression, guidelines recommend an evidence-based psychotherapy combined with an SSRI, with dose reevaluation every 4 weeks. Symptomatic improvement should occur by 12 weeks. Recommendations for continued treatment beyond that point conflict and may not have been updated in light of recent research. A typical recommendation, from the American Academy of Child and Adolescent Psychiatry (AACAP), is to continue antidepressant medication for 6–12 months following response to acute treatment. The guideline adds that discontinuation in the summer may be preferable to during the school year and that longer treatment may benefit patients with certain risk factors. (See table.) Studies with long-term follow-up, such as the Treatment for Adolescents with Depression Study, indicate that the response rate continues to increase from treatment week 12 to 36 if accompanied by CBT. Recovery from a major depressive episode generally occurs within 1–2 years, but recurrence is common and frequently occurs 6–12 months following the end of acute treatment.

Factors associated with a lower likelihood of response or remission in long-term treatment of anxiety and depression in children and adolescents

Depression	Anxiety
More prior depressive episodes	Older Age
Residual symptoms after treatment*	Female gender
Greater family levels of expressed emotion	Minority status
Perceived family conflict	Baseline symptom severity
Non-response to acute therapy	Lower socioeconomic status
Female gender*	Social anxiety disorder
	Negative life events
	Comorbid internalizing disorders

* Based on adult data or unpublished research.

The AACAP guidelines for acute treatment of anxiety, which have not been updated in more than a decade, recommend evidence-based psychotherapy, such as CBT for mild anxiety and SSRIs for moderate-to-severe anxiety disorders. Only 1 recommendation, based on a >15-year-old expert opinion paper, addresses long-term therapy for anxiety. This report

recommends antidepressant discontinuation during a low-stress period, at least 1 year following symptomatic response. The few published clinical trials suggest antidepressant therapy for anxiety continues to be effective for up to 6–9 months. However, many clinicians choose to treat for a full year, largely based on a discontinuation study in adults.

There is no evidence suggesting harm from long-term use of SSRIs in the absence of adverse effects. Based on the limited evidence, the authors suggest that for young patients with depression or anxiety, treatment and its discontinuation should be based on individual patient's risk factors for poor prognosis.

Hathaway E, Walkup J, Strawn J: Antidepressant treatment duration in pediatric depressive and anxiety disorders: how long is long enough? *Current Problems in Pediatric and Adolescent Health Care* 2017; doi 10.1016/j.cppeds.2017.12.002. From the Indiana University School of Medicine, Indianapolis; and other institutions. **Source of funding not stated. Two of 3 study authors disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

Multisystemic Therapy for Antisocial Behavior

In a large randomized trial, multisystemic therapy (MST) showed no advantage over usual care in adolescents with antisocial behavior. Multiple studies from the U.S. have suggested MST may improve outcomes of antisocial and offending behavior in young people; but the present study, from the U.K., indicates that this result may not be generalizable. Adolescents' parents rated MST favorably at first, but these ratings were transient and not reflected in objective measures of behavior; MST had some harmful effects; and the treatment was not a cost-effective enhancement of usual care.

Methods: The study was conducted at 9 MST pilot centers in England. The centers had ≥12 months' experience with the treatment. Participants, aged 11–17 years, were referred from a variety of sources and were required to show ≥3 severity criteria for antisocial behavior, including past difficulty in several settings and any of 5 general inclusion criteria: persistent and enduring (weekly for ≥6 months), DSM-IV conduct disorder with no response to treatment, multiple warnings and ≥1 conviction, permanent expulsion from school, or risk of harm to self or others. Half of participants were randomly assigned to receive MST followed by treatment as usual. MST consisted mainly of work with the adolescent's caregiver and was provided by therapists who met with the family 3 times a week for 3–5 months. The MST intervention used techniques from cognitive behavioral therapy, behavioral therapy, and strategic and structural family therapy to improve parenting skills, enhance family relationships, increase social-network support, improve communication, encourage school attendance, and reduce the adolescent's contact with delinquent peers. The remaining patients received only treatment as usual, which was nonstandardized but generally multicomponent and no less intensive than MST. The primary study outcome was the proportion of participants placed in out-of-home care at 18 months. Study investigators were blind to participants' treatment allocation.

Results: A total of 684 families participated in the study, of whom 72% were available for assessment at 18 months. More than 80% of adolescents had a diagnosis of any conduct disorder, 65% had persistent and enduring violent and aggressive behavior, 9% had ≥1 conviction plus multiple warnings, 26% had been expelled from school, and 10% posed a danger to themselves or others.

MST had no protective effect on the rate of out-of-home placements at 18 months, which was 13% versus 11% for care as usual. MST also did not delay the time to the first criminal offense; and at 18 months, the mean number of offenses was significantly higher in the MST group. Minor improvement, compared with usual care, in self- and parent-reported antisocial

behavior and attitudes and in self-reported substance misuse were reported at 6 months, but this effect did not last. Parents in the MST group reported improvements in multiple facets of parenting behavior, but adolescents' reports did not mirror these changes. Detrimental effects of MST on out-of-home placement were strongest in patients with younger age at onset of conduct problems, low baseline levels of callous and unemotional traits, and fewer delinquent peers. The mean total service costs over 18 months were about $42,700 for treatment as usual and about $39,620 for MST.

Discussion: Overall, it appears that parents benefited more from MST than adolescents. This parental improvement may translate into long-term behavioral benefits in adolescents over a longer time frame than 18 months. It is possible that MST increased risk of illegal activity in young people initially at low risk for criminal offenses by sensitizing them to the possibility. It is also possible that the failure of this study to replicate results of the U.S. studies could be due to greater effectiveness of treatment as usual in the U.K.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Fonagy P, Butler S, Cottrell D, Scott S, et al: Multisystemic therapy versus management as usual in the treatment of adolescent antisocial behaviour (START): a pragmatic, randomised controlled, superiority trial. *Lancet Psychiatry* 2018;5 (February):119–133. From University College London, U.K.; and other institutions. **Funded by the Department for Children, Schools and Families and the Department of Health. No study author disclosed financial relationships with commercial sources.**

***See Reference Guide.**

Medication Algorithm for Youth At-Risk of Bipolar Disorder

As part of a randomized trial of psychosocial interventions, researchers developed a pharmacological treatment algorithm for children and adolescents at high risk for bipolar disorder.[1] The algorithm guided background medication in study participants with mood symptoms and a first-degree relative with bipolar disorder, a group for whom treatment guidelines are lacking.

Methods: The randomized trial, whose main results were previously reported,[2] compared a 4-month family-focused therapy with an educational control therapy in 40 young people at high familial risk of bipolar disorder. Study participants were aged 9–17 years; had a diagnosis of bipolar disorder NOS, major depressive disorder, or cyclothymia; had active mood symptoms; and had a first-degree relative with bipolar I or II disorder. The study's pharmacotherapists developed the algorithm based on the few available treatment studies, existing guidelines for treating syndromal bipolar disorder and depression in young people, and, in areas where these sources were not available, expert opinion and consensus among the study psychiatrists. During the study, medication selection was based on collaborative decision-making by clinicians, patients, and family members using the algorithm and was monitored by a pharmacotherapy oversight committee. Physician adherence to the algorithm was rated by the study's supervising psychiatrists.

Results: The initial step in the algorithm is a determination of whether medication is necessary, followed if appropriate by starting pharmacotherapy or optimizing existing medication, with the goal of stabilizing symptoms to the point that the patient can participate in therapy.

Although conversion to bipolar disorder was not evaluated in the study, no patient experienced antidepressant- or stimulant-induced mania. Physician adherence to the treatment algorithm was high, with only 2% of study visits involving nonadherent prescribing and 14% of visits involving partially adherent prescribing.

Medication Recommendations for Patients at High Risk for Bipolar Disorder	
Unipolar Depression	Bipolar Disorder NOS
No history of antidepressant-induced mania **First-line treatments:** citalopram, bupropion, sertraline, or escitalopram **Second-line treatment:** venlafaxine, duloxetine, lamotrigine **History of antidepressant-induced mania** **First-line treatment:** lamotrigine **Second-line treatment:** lithium or quetiapine **Comorbid ADHD, not receiving antidepressant therapy** **First-line treatment:** bupropion **Comorbid ADHD, receiving antidepressant therapy** **First-line treatment:** methylphenidate or mixed amphetamine salts **Second-line treatment:** atomoxetine	**Experiencing manic/mixed symptoms** **First-line treatment:** aripiprazole,[±] quetiapine,[±±] risperidone, lithium[±±±] **Second-line treatment:** lithium, divalproex, lamotrigine **Third-line treatment:** olanzapine, ziprasidone, carbamazepine, oxcarbazepine, asenapine, paliperidone **Experiencing depressive symptoms** **First-line treatment:** lamotrigine, lithium,[±] quetiapine **Second-line treatment:** asenapine **Comorbid ADHD** **First-line treatment:** methylphenidate, mixed amphetamine salts **Second-line treatment:** guanfacine **Third-line treatment:** atomoxetine
Comorbid Anxiety in Unipolar Depression or Bipolar Disorder	
No history of antidepressant-induced mania **First-line treatment:** citalopram, sertraline, escitalopram, fluvoxamine **Second-line treatment:** clonazepam, gabapentin **History of antidepressant-induced mania** **First-line treatment:** clonazepam, gabapentin	

[±]Especially if comorbid ADHD is present
[±±]Check EKG if dose is >600 mg
[±±±]Especially if there is a family history of lithium response

[1]Schneck C, Chang K, Singh M, DelBello M, et al: A pharmacologic algorithm for youth who are at high risk for bipolar disorder. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (November):796–805. From the University of Colorado School of Medicine, Aurora; and other institutions. **Funded by the NIMH; and the National Association for Research on Schizophrenia and Depression. Four of 5 study authors declared financial relationships with commercial sources.**

[2]Miklowitz D, et al: Early intervention for symptomatic youth at risk for bipolar disorder: a randomized trial of family-focused therapy. *Journal of the American Academy of Child and Adolescent Psychiatry* 2013;52:121–131.

Common Drug Trade Names*: aripiprazole—*Abilify*; asenapine–*Saphris*; atomoxetine—*Strattera*; bupropion—*Wellbutrin*; carbamazepine—*Tegretol*; citalopram—*Celexa*; clonazepam—*Klonopin*; divalproex—*Depakene, Depakote*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; gabapentin—*Neurontin*; guanfacine—*Intuniv, Tenex*; lamotrigine—*Lamictal*; lurasidone—*Latuda*; methylphenidate—*Ritalin*; mixed amphetamine salts—*Adderall*; olanzapine—*Zyprexa*; oxcarbazepine—*Trileptal*; paliperidone—*Invega*; quetiapine—*Seroquel*; risperidone—*Risperdal*; sertraline—*Zoloft*; venlafaxine—*Effexor*; ziprasidone—*Geodon

Reference Guide

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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