

# PSYCHIATRY DRUG ALERTS

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## Betahistine for Antipsychotic Weight Gain

In a preliminary, placebo-controlled trial, betahistine prevented weight gain in patients taking clozapine or olanzapine, but not other antipsychotic agents.

**Background:** Histaminergic effects are a proposed mechanism for the weight gain many patients experience while taking antipsychotics. Betahistine is a histaminergic agonist used in some countries to treat Meniere's disease but currently unavailable in the U.S.

**Methods:** The study was conducted at 1 center in the U.S. and 1 in China, with slightly different protocols in each. Data for the present report are based on 51 patients, including 12 adolescents. Study participants were currently taking first- or second-generation antipsychotics for schizophrenia, schizoaffective disorder, bipolar disorder, autism, psychosis NOS, or other indication and had gained substantial weight. Definitions of substantial weight gain differed among the protocols and were based on  $\geq 1$  of the following: percentage weight gain of  $\geq 7\%$ , body mass index (BMI) of  $\geq 30$  plus weight gain of  $\geq 10$  lbs in previous 8 months or  $\geq 85\%$  percentile. Patients were randomly assigned to double-blind treatment with betahistine or placebo. Betahistine was prepared by compounding pharmacies in both countries. In the U.S., which furnished most of the study participants, betahistine dosage was started at 8 mg/day, increased to 48 mg/day over 2 weeks, and then maintained at that level for the remaining 10 weeks of the study. Dosage was slightly lower in the study arm conducted in China. Background antipsychotics could not be changed, but dosages could be adjusted if clinically indicated.

**Results:** A total of 54 patients were randomized (40 at the U.S. sites, 14 in China), 26 of whom were taking clozapine or olanzapine. The mean baseline BMI was 33, and most patients had long-term illness and treatment. Patients who were taking clozapine or olanzapine had similar baseline BMI but higher glucose and triglyceride levels than those receiving other antipsychotics.

During the study, patients taking clozapine or olanzapine plus betahistine lost an average of 2.3 lbs (and 0.33 BMI points), while those on placebo gained 4.6 lbs on average, a nearly 7-lb difference ( $p=0.0027$ ). Results were similar when the U.S. sample was analyzed separately. Beneficial effects of betahistine were limited to the patients taking olanzapine or clozapine.

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Waist circumference increased in all subjects, but to a significantly lesser degree in those who received betahistine compared with placebo (0.10 in vs 1.64 in;  $p=0.035$ ). Betahistine had no apparent effect on appetite or food consumption as ascertained with test meals. The drug had no effects on glucose or lipid measures. There were no apparent effects of betahistine on psychopathology and few if any adverse events.

**Discussion:** Although olanzapine has been shown to be among the most effective antipsychotics, many clinicians avoid its use for fear of inducing weight gain, diabetes, and cardiovascular risks. The present observations provide a rationale for a more systematic study of betahistine as an add-on to clozapine and olanzapine.

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

Smith R, Maayan L, Wu R, Youssef M, et al: Betahistine effects on weight-related measures in patients treated with antipsychotic medications: a double-blind placebo-controlled study. *Psychopharmacology* 2018;235 (December): 3545–3558. doi 10.1007/s00213-018-5079-1. From the Nathan Kline Institute for Psychiatric Research, Orangeburg, NY; and other institutions. **Funded by the Stanley Foundation. The authors declared no competing interests.**

**Common Drug Trade Names:** clozapine—*Clozaril*; olanzapine—*Zyprexa*

\*See Reference Guide.

## Tachyphylaxis with Antidepressant Drugs

Patients with major depressive disorder often experience a re-emergence or worsening of symptoms in spite of previously effective treatment. This loss of antidepressant response during maintenance therapy, termed tachyphylaxis, can have a negative impact on treatment outcomes and patient quality of life. Because antidepressant tachyphylaxis is believed to affect a substantial percentage of patients with major depression, a comprehensive review was undertaken to assess its prevalence and the evidence for interventions to manage it.

**Definition.** Antidepressant tachyphylaxis is best defined as the loss of efficacy of an antidepressant that had a prior established response. It can occur within the continuation phase of treatment or during maintenance therapy. It should be distinguished from the loss of a placebo response, which can occur even with an active antidepressant but is limited to the acute phase of treatment, usually the first 4 weeks. A patient can only experience tachyphylaxis if they have had continuous pharmacotherapy, which is not true of a relapse or recurrence. Tachyphylaxis also differs from a failed antidepressant trial, in that a patient must have experienced initial effectiveness, with a  $\geq 50\%$  decrease in symptoms, before the effect is lost.

**Influencing factors.** Onset of depression later in life, a history of  $\geq 3$  previous depressive episodes, and presence of residual symptoms all appear to be independent risk factors for antidepressant tachyphylaxis. In addition, risk may be affected by depressive subtype, with tachyphylaxis more likely to occur in patients with melancholic depression.

**Presentation and diagnosis.** Patients with tachyphylaxis typically present with alterations in energy level, motivation/interest, cognitive function, sleep disturbance, and sexual function, as opposed to depressed mood. Standardized rating scales may be helpful in evaluating tachyphylaxis. The Rothschild Scale for Antidepressant Tachyphylaxis includes self-ratings in these 5 domains along with measurement of weight gain and clinician affect rating. It is also important to rule out bipolar disorder, since an initial, transient improvement in mood may be incorrectly attributed to medication response.

**Incidence.** According to recent data, the incidence of antidepressant tachyphylaxis has been estimated as between 25% and 50%. Tachyphylaxis may play a role in the development of treatment-resistant depression, possibly as a result of neuroreceptor tolerance or downregulation.

**Treatment.** There has been little research to illuminate the most effective long-term strategies for antidepressant tachyphylaxis. Many clinical trials have failed to distinguish between lack of

response and loss of response. However, strategies are generally similar to those for treatment-resistant depression: dose increases/decreases; medication switching or switching to cognitive behavioral or other therapy; and combination or augmentation strategies. Common augmentation drugs include lithium and atypical antipsychotics. Rapid depression-relief strategies—e.g., repetitive transcranial magnetic stimulation and other neuromodulation techniques, ketamine, and low-dose naltrexone (*ReVia*)—may be an important focus for future research.

Kinrys G, Gold A, Pisano V, Freeman M, et al: Tachyphylaxis in major depressive disorder: a review of the current state of research. *Journal of Affective Disorders* 2019;245 (February 15):488–497. doi 10.1016/j.jad.2018.10.357. From Massachusetts General Hospital, Boston; and other institutions. **This review was conducted without funding. Six of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

## Psychotropic/Antiretroviral Interactions: Stimulants

According to a comprehensive review, interactions between psychostimulants and antiretroviral therapies (ART) for HIV have not been widely described. However, research has suggested that certain genotypes associated with development of ADHD may also increase risk of future HIV acquisition. In addition, stimulants have been shown to effectively treat depression, fatigue, and cognitive dysfunction in patients with HIV, and >25% of children with HIV are also affected by ADHD. As a result, psychostimulants and antiretrovirals are likely to be coprescribed.

Many antiretrovirals are metabolized by the hepatic cytochrome P450 (CYP450) system (see the printable ART cytochrome P450 properties table at [www.alertpubs.com/sdaonlinecontent for details](http://www.alertpubs.com/sdaonlinecontentfor details)), but interactions between stimulants and ART based on the cytochrome CYP450 system are not well defined. Amphetamine metabolism appears to involve CYP2D6, and methylphenidate metabolism may involve CYP2D6 and 2B6. Concomitant use of amphetamines or methylphenidate with ART drugs that inhibit CYP2D6, such as the protease inhibitor ritonavir and the integrase strand transfer inhibitor (INSTI) cobicistat may increase stimulant levels. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine have CYP2B6 activity and may interact with methylphenidate. Patients receiving amphetamines or methylphenidate with ART should be carefully monitored for stimulant adverse effects. In contrast, dexamethylphenidate and lisdexamfetamine do not undergo CYP450 metabolism and may be more appropriate options for patients also receiving ART.

Stimulant/Antiretroviral Interactions		
Stimulant	CYP450 Interaction Potential	Recommendations
Amphetamines	Theoretical	Patients should receive the lowest possible stimulant dose and be carefully monitored for stimulant adverse effects when receiving an ART agent that inhibits CYP isoenzymes.
Methylphenidate	Theoretical	
Lisdexamfetamine	None	These agents may be preferable stimulant options for patients with HIV.
Dexamethylphenidate	None	

One of the most common stimulant adverse effects is insomnia, which is also associated with ART regimens that include INSTIs or NNRTIs; it is unclear if concomitant use produces an additive effect on insomnia. Patients with central nervous system involvement of HIV who receive high-dose stimulants may be at increased risk for seizure and should be carefully monitored. In these patients, stimulants should be titrated carefully to the lowest effective dose. Stimulant treatment also carries a risk for cardiovascular effects including increased blood pressure and heart rate. This may be particularly concerning in patients with HIV who are already at increased risk of cardiovascular diseases, including myocardial infarction, atherosclerosis, and

coronary heart disease. Additionally, among ART therapies, protease inhibitors are known to have adverse metabolic effects, which could compound the cardiovascular effects of stimulants.

Another important consideration with concomitant stimulant and ART use involves the temporal proximity of dosing to food consumption. Onset of stimulant effects occurs during the absorption phase, and high-fat meals may delay the time to peak concentration for some stimulant formulations (e.g., immediate-release methylphenidate, dexamethylphenidate, lisdexamfetamine). Several antiretrovirals, including the NNRTI rilpivirine and the INSTI elvitegravir, require administration with food to facilitate absorption. If rapid onset of stimulant action is needed, the stimulant should be taken  $\geq 1$  hour before ART and meals, or an extended-release stimulant formulation that is less affected by food should be considered.

**Editor's Note.** This is the second report in a 5-part series on psychotropic/antiretroviral interactions. We covered interactions with antidepressants in last month's issue. (See Psychotropic/Antiretroviral Interactions: Antidepressants in the November 2018 issue.) Interactions involving antipsychotics, mood stabilizers, and medications for opioid and alcohol use disorders will be addressed over the next 3 issues.

Goodlet K, Zmarlicka M, Peckham A: Drug-drug interactions and clinical considerations with co-administration of antiretrovirals and psychotropic drugs. *CNS Spectrums* 2018; doi 10.1017/S109285291800113X. From Midwestern University College of Pharmacy, Glendale, AZ; and other institutions. **Source of funding not stated. Two of 3 study authors disclosed potentially relevant relationships; the remaining author declared no competing interests.**

**Common Drug Trade Names:** amphetamine salts, mixed—*Adderall*; cobicistat—*Tybost*; dexamethylphenidate—*Focalin*; efavirenz—*Sustiva*; elvitegravir—*Vitekta*; lisdexamfetamine—*Vyvanse*; methylphenidate—*Concerta*, *Ritalin*; nevirapine—*Viramune*; rilpivirine—*Edurant*; ritonavir—*Norvir*

## Baclofen for Alcohol Use Disorder

According to the international Cagliari Statement,<sup>1</sup> the GABA<sub>B</sub> receptor agonist baclofen (*Lioresal*) may be a promising second-line treatment for patients with alcohol use disorder that has not responded to other pharmacotherapies. The consensus statement is not intended to promote off-label baclofen use. Rather, the panel acknowledges that off-label use of baclofen does occur in alcohol-dependent patients and attempts to provide objective information on its efficacy and safety that may help physicians who are already prescribing it.<sup>2</sup>

Clinical trials of baclofen in alcohol use disorder have yielded inconsistent results. However, use of the drug became popular following a case report by a French physician who treated his own alcohol craving and drinking successfully with very high doses of baclofen. Three meta-analyses conducted to date have not led to definitive conclusions on the efficacy of baclofen in alcohol use disorders. One analysis found no superiority over placebo, while 2 showed positive results for some outcomes or in some patient subgroups. All 3 meta-analyses found only small overall effects and high heterogeneity among studies.

The statement contains several safety recommendations, including close supervision in patients with renal impairment and careful use in patients with epilepsy, mood disorders, and suicidal ideation in order to reduce risk of inducing seizures, manic or hypomanic episodes, and intentional overdose, respectively. The primary adverse effect of baclofen is sedation; thus it should not be combined with sedatives, including alcohol. Abrupt discontinuation can induce withdrawal symptoms.

The Cagliari Statement endorses consideration of baclofen as a second-line treatment in most patients and a first-line treatment in those with contraindications to approved medications. In most clinical trials, baclofen was introduced after detoxification and abstinence. However, in clinical practice, it is sometimes prescribed while patients are still drinking. Nonabstinent patients should be warned about the possibility of sedation. The effective daily dose in individual patients can vary over a 10-fold range. Dosing should start at 5 mg t.i.d and be titrated

upward—e.g., by 5 or 10 mg/day every 3 days—to avoid adverse effects. A maximum daily dose was not included in the statement.

Based on the results of an evidence-based assessment in France that concluded the risks of baclofen for alcohol use disorder outweighed its benefits, an accompanying commentary challenges the recommendation for this off-label use.<sup>3</sup> (The use of baclofen in alcohol-dependent patients is approved in France.) The authors also cite a very large pharmacoepidemiological study that found patients who received baclofen had a dose-related increase in mortality compared with those using approved drugs for alcohol use disorder (hazard ratio,\* 1.31). Although the specific causes of excess mortality were unknown or ill-defined, in some cases, deaths were the result of intentional self-poisoning.

<sup>1</sup>Agabio R, Sinclair J, Addolorato G, Aubin H-J, et al: Baclofen for the treatment of alcohol use disorder: the Cagliari Statement. *Lancet Psychiatry* 2018; doi 10.1016/S2215-0366(18)30303-1. From the University of Cagliari, Italy; and other institutions. **Funded by the University of Cagliari; the European Foundation for Alcohol Research; and other sources. Six of 26 authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

<sup>2</sup>Agabio R, et al: Baclofen and alcohol in France [response]. *Lancet Psychiatry* 2018; doi 10.1016/S2215-0366(18)30433-4.

<sup>3</sup>Naudet F, Braillon A: Baclofen and alcohol in France [comment]. *Lancet Psychiatry* 2018; doi 10.1016/S2215-0366(18)30419-X. From the University of Rennes; and the University Hospital Amiens, France. **The authors declared no competing interests.**

\*See Reference Guide.

## Cardiovascular Mortality in Schizophrenia

According to the results of a large retrospective study, cardioprotective drugs for secondary prevention after a myocardial infarction (MI) are associated with reduced mortality in patients with schizophrenia, particularly if multiple medications are prescribed.<sup>1</sup>

**Background:** Excess cardiovascular mortality is known to exist in patients with schizophrenia who have also been shown to have worse outcomes after MI. Results of a recent population-based study showed that patients with serious mental illness were less likely to receive recommended long-term secondary preventive medications after percutaneous procedures.<sup>2</sup>

**Methods:** Study subjects were Danish adults, aged >30 years, hospitalized with a first MI in 1995–2015. Within this population, patients who had a diagnosis of schizophrenia that preceded the MI were identified and included in the schizophrenia cohort. Patients' post-MI exposure to 5 different classes of drugs that could be prescribed for secondary prevention—antiplatelet agents, vitamin K antagonists, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins—was extracted from the Danish National Patient registry. The primary study outcome was mortality from any cause.

**Results:** More than 105,000 patients with an MI were identified, of whom 684 had schizophrenia. Prescription rates for preventive drugs from each of the 5 categories were significantly lower among patients with schizophrenia than those without by margins of about 10–15% ( $p < 0.001$  for all). About 8% of patients with schizophrenia and 3% of those without schizophrenia received no cardioprotective medication.

Mortality rates were 45% in patients with schizophrenia and 27% in those without ( $p < 0.001$ ). About two-thirds of all deaths were from cardiovascular disease. Patients from the general population who received no treatment had similar mortality to patients with schizophrenia who received  $\geq 1$  drug; both groups had 2–3 times the mortality of treated patients from the general population, while mortality was nearly 9-fold higher in patients with schizophrenia receiving no treatment compared with patients without schizophrenia receiving any treatment.

Mortality generally decreased in proportion to the number of preventive drugs prescribed. (See table, next page.) Among patients who received triple therapy, there was no difference in

mortality between those with schizophrenia and the general population, but differences widened as fewer cardioprotective agents were prescribed.

**Editorial.**<sup>3</sup> The results of the present study indicate that medications can play a critical role in reducing mortality in patients with schizophrenia, as they do in the general population. The study also highlights a critical need to improve access to cardioprotective interventions in people with serious mental illness.

Hazard ratios* for mortality in patients with schizophrenia compared with the general population		
Therapy Strategy	General Population	Patients with Schizophrenia
Triple therapy	1 (reference)	1.05
Dual therapy	1.86	6.65
Monotherapy	3.90	6.89
No treatment	4.38	13.10

<sup>1</sup>Kugathasan P, Horsdal H, Aagaard J, Jensen S, et al: Association of secondary preventive cardiovascular treatment after myocardial infarction with mortality among patients with schizophrenia. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.2742. From Aalborg University Hospital, Denmark; and other institutions. **Source of funding not stated. One study author disclosed potentially relevant financial relationships; the remaining 5 authors declared no competing interests.**

<sup>2</sup>Jakobsen L, et al: Severe mental illness and clinical outcome after primary percutaneous coronary intervention. *American Journal of Cardiology* 2017;120:550–555.

<sup>3</sup>Druss, B: Can better cardiovascular care close the mortality gap for people with schizophrenia [editorial]? *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.2726. From Emory University, Atlanta, GA. **The author declared no competing interests.**

\*See Reference Guide.

## Aspirin and N-Acetylcysteine in Bipolar Depression

In a small controlled trial, adjunctive aspirin plus N-Acetylcysteine (NAC) reduced depression in patients with bipolar disorder.

**Background:** Neuroinflammation has been suggested to have a role in the pathophysiology of bipolar disorder, and limited evidence supports the antidepressant effects of adjunctive antiinflammatory and antioxidant agents in bipolar disorder. However, head-to-head comparisons of aspirin and NAC have not been conducted and it is unclear whether the agents would have synergistic effects.

**Methods:** Study subjects were outpatients at the University of Texas Health Science Center at Houston. They had a DSM-IV-TR diagnosis of bipolar I or II disorder and were experiencing a depressive or mixed episode. To be eligible for the study, patients were required to be aged 18–65 years, have a Montgomery-Asberg Depression Rating Scale (MADRS) score of  $\geq 20$ , and be receiving therapeutic doses of a mood-stabilizing regimen for  $\geq 1$  month. To ensure safety, patients regularly receiving an NSAID or anticoagulant were excluded. Following baseline measurement of inflammatory markers (i.e., interleukin-6 [IL-6] and C-reactive protein [CRP]), participants (n=24; 15 women) were randomized to receive 16 weeks of double-blind adjunctive treatment with 500 mg aspirin b.i.d., 500 mg NAC b.i.d., both aspirin and NAC, or placebo. The primary outcome measure was the MADRS, with response defined as a  $\geq 50\%$  reduction in score. Antiinflammatory markers were reassessed at weeks 8 and 16.

**Results:** Background mood-stabilizing medications, administered as monotherapy or in combinations, included lithium (n=5), anticonvulsants (n=16), antidepressants (n=16), antipsychotics (n=10), and benzodiazepines (n=5). These were required to remain unchanged throughout the study period. Although participants were not stratified by potential confounders, baseline age, gender, symptom severity, background medications, comorbidities, and inflammatory marker levels were comparable across the groups.

Depression severity decreased in all groups. At the 8-week assessment, 67% of patients met MADRS response criteria. The probability of achieving response was similar across the treatment

groups: 70% with placebo, 67% with combined aspirin and NAC, 60% with NAC alone, and 50% with aspirin alone. At the 16-week assessment, the overall response rate declined to 55%. The probability of response remained the same in the combined aspirin and NAC group (67%) but decreased in all other groups (placebo, 55%; NAC, 57%; aspirin, 33%). There were no differential effects of treatment on IL-6 or CRP levels, and baseline inflammatory marker levels did not affect depression response. Three adverse events were reported (2 hospitalizations, 1 each for mania and suicidal behavior, and rash), but none occurred in patients who received NAC either alone or in combination with aspirin.

**Discussion:** Although preliminary due to small sample size, these results suggest that adding combined aspirin and NAC to mood-stabilizing therapy may improve depression in patients with bipolar disorder. Future study of the combination appears to be warranted and should evaluate differential effects of background medications as well as safety and tolerability.

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

Bauer I, Green C, Colpo G, Teixeira A, et al: A double-blind, randomized, placebo-controlled study of aspirin and N-acetylcysteine as adjunctive treatments for bipolar depression. *Journal of Clinical Psychiatry* doi 10.4088/JCP.18m12200. From The University of Texas Health Science Center Houston; and McGovern Medical School, Houston TX. **Funded by the Stanley Brain Foundation. One of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

\*See Reference Guide.

## Adult ADHD Treatment: European Consensus

The European Network Adult ADHD organization, which includes expert mental healthcare clinicians and researchers from 28 countries, has updated its consensus statement on adult ADHD, recognizing that the disorder often persists throughout the lifespan into old age, with significant impairment, high comorbidity, and personal distress.<sup>1</sup> The disorder is undertreated in adults, despite the availability of effective evidence-based treatments.

**General Approaches.** ADHD in adults requires multimodal treatment, including not only medication, but also psychoeducation, cognitive behavioral therapy, and coaching/mentoring. All comorbidities should be diagnosed before beginning treatment, so that the best order of treatment can be planned. The most severe comorbid disorders (e.g., psychosis, bipolar disorder, substance abuse, severe depression, and severe anxiety) should be prioritized for treatment over ADHD. Milder mood and anxiety disorders and emotional instability may respond to treatment for ADHD and can be treated at the same time. Drug and alcohol abuse should be stabilized first but can be treated at the same time as ADHD.

**Stimulants.** The recommended first-line treatment for adult ADHD is a stimulant medication. Meta-analyses of randomized trials of stimulants and atomoxetine for ADHD symptom reduction show effect sizes\* ranging from 0.4 to 0.7, with stimulants at the higher end of the range. The longest controlled trial in adults showed continued efficacy after 1 year, and national registry studies have also shown long-term benefits. Observational studies have found reduced rates of transport accidents (including fatalities), criminal convictions, suicidal behavior, violent re-offending, depression, and substance misuse during periods of ADHD medication use. According to a recent large meta-analysis,<sup>2</sup> among the stimulants, amphetamines are the most effective in adults, as rated by clinicians and patient self-report. The primary adverse effects of stimulants are increased heart rate and blood pressure and reduced appetite and sleep. These should be assessed at baseline and monitored at least twice per year during treatment. Methylphenidate may trigger cardiac arrhythmias in patients with congenital heart diseases, but the risk is small and requires caution rather than avoidance.

**Other Agents.** Atomoxetine has moderate efficacy in adult ADHD, but it may take 1–2 weeks for onset of action and up to 6 months for full effect. It may be a preferable alternative in patients

with co-occurring anxiety that may be exacerbated by stimulants. Other ADHD drugs used in children—guanfacine and clonidine—have not been the subject of clinical trials in adults. Several small studies have evaluated bupropion in adult ADHD with conflicting results. Although positive effects were seen with high dosages (400–450 mg/day), the consensus statement recommends it be reserved for patients who cannot tolerate other ADHD medications. There is limited evidence for the use of SNRIs and TCAs, while SSRIs and modafinil have not shown efficacy.

**Long-term Safety.** Because ADHD often persists throughout adulthood, long-term safety of recommended treatments is an important concern. There is no evidence of significant long-term risk with stimulant treatment. However, computed tomography scans have found higher striatal dopamine transporter availability in patients with ADHD who receive stimulants, but the clinical implications of the increase are unclear. Methylphenidate and guanfacine have a theoretical potential to cause heart valve toxicity, but the risk has not been confirmed and routine echocardiography is recommended only in patients aged >50 years.

**Special Considerations.** The high rate of comorbidity in adults with ADHD leads to frequent combined pharmacotherapy and the risk for drug interactions. MAOIs are generally contraindicated in patients receiving ADHD medications. Cytochrome P450 interactions are uncommon with methylphenidate but can be problematic with amphetamines and atomoxetine. Agents with noradrenergic effects (e.g., duloxetine, venlafaxine) can increase the risk for adverse cardiovascular effects including hypertension. Because of their abuse potential, immediate-release stimulants should be avoided in patients with comorbid substance use disorders; extended-release preparations are preferred for these patients. In patients with comorbid bipolar disorder, methylphenidate monotherapy can induce mania and stimulants should only be prescribed in combination with a mood stabilizer. There is limited evidence regarding the safety of ADHD medications in pregnancy.

<sup>1</sup>Kooij J, Bijlenga D, Salerno L, Jaeschke R, et al: Updated European consensus statement on diagnosis and treatment of adult ADHD. *European Psychiatry* 2019;56:14–34. doi 10.1016/j.eurpsy.2018.11.001. From the Expertise Center Adult ADHD, the Netherlands; and other institutions. **The consensus statement was created with no external funding. Of 64 study authors, 19 disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

<sup>2</sup>Cortese S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2018;5 (9):727–38.

**Common Drug Trade Names:** atomoxetine—*Strattera*; bupropion—*Wellbutrin*; clonidine—*Catapres, Kapvay*; duloxetine—*Cymbalta*; guanfacine—*Intuniv*; modafinil—*Provigil*; venlafaxine—*Effexor*

\*See Reference Guide.

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**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

**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](http://www.alertpubs.com).

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