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Efficacy, Safety of Newer Antidepressants in Depression

The newer second-generation antidepressants levomilnacipran, vilazodone, and vortioxetine do not offer any advantage in efficacy or safety compared with other second-generation agents, according to a systematic review and network meta-analysis.

Methods: A comprehensive literature search identified antidepressant studies published since 2010, or unpublished, conducted in adult outpatients with major depressive disorder. The efficacy analysis included head-to-head randomized controlled comparisons between all available second-generation drugs representing all current drug classes, used in the recommended dosage range. Placebo-controlled trials were included in the network meta-analysis, and the analysis of harms also was planned to include non-randomized trials with a sample size of ≥100. The preferred efficacy outcome was response, defined as a ≥50% improvement from baseline in Hamilton Rating Scale for Depression (HAM-D) score.

Results: The analysis included 7 head-to-head trials involving 1 of the 3 newer antidepressants and 17 placebo- and active-controlled trials for the network meta-analysis. No additional non-randomized trials were identified for inclusion in the safety analysis.

Although there were no head-to-head comparisons involving levomilnacipran, it did not show superior efficacy to other second-generation antidepressants as a class. Vilazodone was directly compared with citalopram, showing no efficacy difference; vilazodone also had similar efficacy to the class of second-generation agents. In head-to-head comparisons, vortioxetine showed generally similar effects to duloxetine, paroxetine, and venlafaxine. The network meta-analysis showed that vortioxetine was associated with about one-third higher response rates than bupropion and fluoxetine, but this comparison was strongly determined by a single study with a high response rate for vortioxetine relative to placebo, and did not survive removal of that study from the analysis.

The safety analysis was based on limited evidence. Five trials compared safety and tolerability between 1 of the 3 newer antidepressants and an existing second-generation agent. The newer

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drugs had similar rates of overall adverse events and related discontinuation relative to other second-generation agents. There were some differences in rates of individual adverse events, but the quality of evidence for these differences was low.

Discussion: The present results suggest that levomilnacipran, vilazodone, and vortioxetine do not differ significantly in efficacy from each other or from older second-generation antidepressants. The choice of the initial antidepressant treatment for major depression should be based on patient preference after a thorough discussion of the advantages and disadvantages and the feasibility (e.g., costs, likely adherence) of different agents.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Wagner G, Schultes M-T, Titscher V, Teufer B, et al: Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: a systematic review and network meta-analysis. *Journal of Affective Disorders* 2017; doi 10.1016/j.jad.2017.11.056. From Danube University Krems, Austria; and other institutions. **Funded by the Drug Effectiveness Review Project of the Pacific Northwest Evidence-Based Practice Center. The authors did not include disclosure of potential conflicts of interest.**

Common Drug Trade Names*: bupropion—*Wellbutrin*; citalopram—*Celexa*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; levomilnacipran—*Fetzima*; paroxetine—*Paxil*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Trintellix

***See Reference Guide.**

Ketamine for Suicidal Ideation

In a randomized trial, ketamine infusion resulted in a rapid reduction in suicidal ideation in patients with major depressive disorder. The effects were moderate relative to IV midazolam, the control treatment.

Methods: Study participants were clinically- or self-referred individuals with a DSM-IV diagnosis of major depressive disorder, a score of ≥16 on the 17-item Hamilton Rating Scale for Depression (HAM-D), and clinically significant suicide risk as indicated by a score of ≥4 on the Scale for Suicidal Ideation (SSI). Study participants were voluntarily admitted to the inpatient research unit for the study and discharged when they were no longer deemed at risk. In the unit, participants were randomly assigned to receive a single 40-minute infusion of 0.5 mg/kg ketamine or 0.02 mg/kg midazolam, a short-acting benzodiazepine anesthetic chosen as the control treatment because it has a similar half-life to ketamine and no established antidepressant or antisuicidal effects. Following the 24-hour assessment, patients received optimized standard clinical pharmacotherapy for 6 months and underwent weekly research ratings for the first 6 weeks. The primary efficacy outcome measure was change in SSI score 24 hours post infusion. Patients who did not experience response to midazolam were offered an open-label infusion of ketamine, usually on the second study day.

Results: A total of 80 patients (mean age, 40 years; 60% women) received randomized treatment. At baseline, patients had been experiencing depression for a median of about 1 year and had a mean SSI score of 15; 39 had made a prior suicide attempt. About half of the patients were currently taking an antidepressant, and use of other psychotropic medications was high.

At 24 hours post infusion, SSI scores decreased on average by 5 more points with ketamine than with midazolam (effect size,* 0.75; $p<0.001$). At the 24-hour assessment, response (i.e., ≥50% decrease in SSI score) was achieved by 55% of the ketamine group and 30% of the midazolam group (odds ratio,* 2.85; $p=0.024$; number needed to treat,* 4). The decrease in suicidal ideation was greater with ketamine than midazolam beginning with the first evaluation, 230 minutes (nearly 4 hours) post-infusion.

Patients who received open-label ketamine had a nearly 8-point average reduction in the SSI, comparable to those who had received double-blind ketamine. Mean HAM-D scores decreased

somewhat in both groups. Improvements in depression and suicidal ideation persisted during 6 weeks of follow-up.

Adverse effects of ketamine, mainly blood pressure increase and dissociative symptoms, were similar to those reported in other ketamine studies. There was no evidence of ketamine abuse at the 6-month follow-up. There were 3 suicide attempts after the study procedures were carried out, 2 completed suicides occurred after the end of the study, and 3 patients were hospitalized for increased suicidal ideation during follow-up.

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

Grunebaum M, Galfalvy H, Choo T-H, Keilp J, et al: Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17060647. From Columbia University Medical Center; and New York State Psychiatric Institute, New York. **Funded by the NIMH. Five of 12 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: ketamine—*Ketalar*; midazolam—*Versed

***See Reference Guide.**

Intranasal Esketamine for Depression

In a phase-II clinical trial, intranasal esketamine, an enantiomer with a higher NMDA affinity than racemic ketamine, produced rapid, dose-related reductions in depression when added to antidepressant medication.[1] Efficacy persisted after reduction in the dosing frequency and eventual discontinuation.

Methods: Study participants were adults with treatment-resistant depression, defined as an inadequate response to ≥2 agents, with ≥1 inadequate response in the current episode. Participants were required to have moderate-to-severe depression, as measured using the clinician-rated Inventory of Depressive Symptomatology. All patients continued the antidepressants they were taking at study entry. After screening, patients were randomly assigned to double-blind treatment with intranasal esketamine or placebo for 1 week (study phase 1). At the end of this phase, those in the placebo group who continued to have moderate-to-severe symptoms were re-randomized to placebo or esketamine treatment for another week (study phase 2). Subsequently, patients could enter an optional 60-day phase of open-label treatment with flexible-dose esketamine, followed by 8 weeks of post-treatment follow-up. Active treatment consisted of 2 weekly administrations of esketamine, mixed in a uniform solution and inhaled in 1, 2, or 3 sprays, resulting in doses of 28 mg, 56 mg, or 84 mg. Esketamine was given in decreasing dosing intervals during the open-label phase: twice weekly for the first 2 weeks, and then weekly for 3 weeks and every other week thereafter. The primary study endpoint was change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) score.

Results: A total of 67 patients (mean age, 45 years; 38 women) were randomized in study phase 1. Of the 33 patients initially assigned to placebo, 28 continued to experience moderate to severe depressive symptoms at the end of the first phase and were re-randomized at the start of phase 2. Of the 60 patients who completed the second phase, 57 entered open-label treatment, 51 entered the follow-up phase, and 41 completed this phase.

Efficacy was significantly greater with esketamine than placebo after 1 week, and the 2 higher doses were significantly more effective than placebo after 2 weeks. (See table, next page.) Efficacy was dose related and seemed to be better sustained between treatments with the 2 higher doses. MADRS scores continued to improve during the open-label phase, with an average decrease of 7.2 additional points from the open-label baseline. Improvement was maintained over the 8-week follow-up phase without additional esketamine. Adverse effects of esketamine were similar to those reported for ketamine and included transient dissociative symptoms and blood-pressure elevations.

Mean change in MADRS scores from baseline to end of phase 1 and phase 2				
	Placebo	Esketamine, twice-weekly dose		
		28 mg	56 mg	84 mg
Phase 1 baseline MADRS score	35	31.3	33.2	35
MADRS score after week 1	30.1	21.5	20.8	19.7
Significance vs placebo	—	p=0.05	p=0.006	p<0.001
Phase 2 baseline MADRS score±	29.3	31.3	34.9	30.4
MADRS score after week 2	24.8	23.7	26	19
Significance vs placebo	—	p=ns	p=0.08	p=0.03
±Includes re-randomized placebo-treated patients, making scores higher than period 1 endpoint				

Discussion: The unusual design of this study allowed for a smaller sample size than the traditional parallel-group design and also minimized interference from a placebo response. A phase-III trial is underway. According to an editorial,[2] the results are notable not only because of the rapid, lasting effects of esketamine, but also the intranasal route of administration. This route allows patient self-administration, leading to wider general use. Bioavailability is increased, and it is possible that there is a direct nose-to-brain neural link, bypassing the blood-brain barrier. However, variations in nasal cavity physiology and poor self-administration practices may present a challenge.

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

[1]Daly E, Singh J, Fedgchin M, Cooper K, et al: Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy: a randomized clinical trial. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3739. From Janssen Research and Development, LLC, Titusville, NJ; and other institutions. **Funded by Janssen. Eight of 11 study authors disclosed financial relationships with commercial sources, including Janssen; the remaining authors declared no competing interests.**

[2]Quintana D, Steen N, Andreassen O: The promise of intranasal esketamine as a novel and effective antidepressant [editorial]. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3738. From the University of Oslo, Norway. **All 3 authors declared financial relationships with commercial sources.**

Common Drug Trade Names*: esketamine (not available in the U.S.)—*Ketanest*; ketamine—*Ketalar

***See Reference Guide.**

Samidorphan for Olanzapine-Induced Weight Gain

In a proof-of-concept study in healthy volunteers with no psychiatric disorder, adding the opioid antagonist samidorphan to olanzapine treatment had a modest effect in reducing weight gain associated with olanzapine (*Zyprexa*).

Methods: This multicenter U.S. study enrolled healthy, non-overweight men, aged 18–40 years. Study subjects were required to have stable weight for ≥3 months prior to enrollment. Participants were randomized into 4 treatment groups: 10 mg/day olanzapine plus placebo, 5 mg/day samidorphan plus placebo, both drugs, or double placebos. The primary study outcome was change in body weight after 3 weeks of study medication.

Results: A total of 106 men were randomized, and 91 (86%) completed the study. Men in both olanzapine groups gained weight, but the increase was significantly less in those who also received samidorphan: 6.8 lbs versus 4.8 lbs (p=0.02). Participants receiving samidorphan alone or placebo gained <0.25 lbs and 1.8 lbs, respectively. Following drug discontinuation, average weight of the 2 olanzapine groups began to return to previous levels. The olanzapine-only group was the only treatment group to show a statistically significant (relative to placebo) decrease from baseline in the fasting glucose-to-insulin ratio and increase in triglycerides and total cholesterol. LDL and HDL cholesterol did not differ among the 4 groups. Adverse effects observed in the trial were generally those associated with olanzapine. Samidorphan treatment

was associated with transient nausea, which is consistent with opioid antagonist treatment. However, the incidence was lower in those who received samidorphan plus olanzapine, possibly due to the antiemetic effects of olanzapine.

Discussion: While olanzapine is considered one of the most effective treatments of schizophrenia, weight gain and adverse metabolic effects limit its clinical use. Concomitant samidorphan appears to improve olanzapine tolerability, but the study is limited by the small sample of only men with no psychiatric disease. A combined formulation of samidorphan–olanzapine (ALKS-3831) is now being evaluated in phase-III clinical trials in patients with schizophrenia.

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

Silverman B, Martin W, Memisoglu A, DiPetrillo L, et al: A randomized, double-blind, placebo-controlled proof-of-concept study to evaluate samidorphan in the prevention of olanzapine-induced weight gain in healthy volunteers. *Schizophrenia Research* 2017; doi 10.1016/j.schres.2017.10.014. From Alkermes, Inc., Waltham, MA; and other institutions. **Funded by Alkermes. All study authors disclosed financial relationships with commercial sources including Alkermes.**

***See Reference Guide.**

Prenatal Safety of Methylphenidate

According to the results of a study conducted by the International Pregnancy Safety Study Consortium, methylphenidate exposure during pregnancy is associated with a small increase in risk of congenital cardiac malformations, while amphetamine exposure is not.[1]

Methods: The study was conducted in 2 populations in tandem. The primary analysis included pregnant women enrolled in Medicaid during 2000–2013. Results of this analysis were validated in a cohort of all women enrolled in the national health registries of 5 Scandinavian countries during a similar time span. A pregnancy was considered exposed if a woman filled a prescription for a stimulant—methylphenidate or amphetamine/dextroamphetamine—during the first 90 days of pregnancy, the period of embryogenesis. Pregnancy was considered unexposed if no ADHD medication prescription was filled in the 3 months before conception to the end of the first trimester. Pregnancies were excluded from the analysis if there was a fetal chromosomal abnormality or exposure to a known teratogen. Outcomes were analyzed separately for all malformations and for cardiovascular malformations. The analyses were adjusted for a broad range of known or possible risk factors, and sensitivity analyses were carried out using a propensity score* based on 200 potential confounding factors. The primary U.S. methylphenidate analysis was repeated in the Nordic cohort, but the amphetamine analysis was not because there were too few exposed pregnancies.

Results: Of >1.8 million U.S. pregnancies ending in a live birth, only about 2000 (0.11%) were exposed to methylphenidate and about 5500 (0.31%) to amphetamine. In the U.S. cohort, the fully adjusted model found no association for either category of malformation with amphetamine exposure. In contrast, for methylphenidate-exposed pregnancies, the fully adjusted relative risks* were 1.11 for any malformation and 1.28 for cardiac malformations. Propensity score adjustment had a negligible effect on these results. When specific cardiac malformations were examined, methylphenidate was associated with increased occurrence of conotruncal defects (relative risk, 3.44), but this finding was based on a small number of cases. The observations were generally confirmed in the Nordic cohort. In pooled data from the 2 cohorts, the relative risks for any malformation and a cardiac malformation with methylphenidate were 1.07 and 1.28, respectively.

Discussion: Methylphenidate was associated with a 28% increased risk of cardiac malformations; this increase corresponds to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy. ADHD

medication use is increasing in women of childbearing age, in whom a substantial portion of pregnancies are unplanned, as well as in pregnant women.[2] Although the absolute risk with methylphenidate is small, it should be considered for women who are or could become pregnant.

[1]Huybrechts K, Broms G, Christensen L, Einarsdottir K, et al: Association between methylphenidate and amphetamine use in pregnancy and risk of congenital malformations: a cohort study from the International Pregnancy Safety Study Consortium. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3644. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

[2]Cooper W: Shedding light on the risks of methylphenidate and amphetamine in pregnancy [editorial]. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3882. From Vanderbilt University School of Medicine, Nashville, TN. **The author declared no competing interests.**

Common Drug Trade Names*: amphetamine/dextroamphetamine—*Adderall, Dexedrine*; methylphenidate—*Concerta, Ritalin

***See Reference Guide.**

Cardiovascular Safety of Valbenazine

According to a pooled analysis of the manufacturer's registration trials, valbenazine (*Ingrezza*), introduced in mid-2017 for treatment of tardive dyskinesia in adults, confers minimal cardiac risk. The drug's labeling contains a single cardiovascular warning, of possible QT prolongation; although there are no explicit contraindications, it is recommended to avoid valbenazine in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. The present examination of the clinical-trial data has revealed no additional cardiovascular concerns.

Methods: The analysis was based on pooled data from 6-week phase II/III clinical trials (n=3) and a single extension study lasting up to 42 additional weeks. Study participants were patients, aged 18–85 years, with clinically stable schizophrenia, schizoaffective disorder, or mood disorder, and tardive dyskinesia of at least moderate severity. Among the studies' exclusion criteria were a history of long QT syndrome or cardiac tachyarrhythmia; QTcF (Fridericia correction) of >450 ms for men and >470 ms for women; or any clinically significant cardiac abnormality. Patients requiring concomitant medications known to prolong the QT interval were enrolled based on a medical review.

Results: The pooled safety population of the 3 trials comprised 400 patients: 178 who received placebo, 110 who received 40 or 50 mg/day valbenazine (referred to as the 40-mg/day group), and 112 who took 75 or 80 mg/day (referred to as the 80-mg/day group). At study entry, 53% of participants had a diagnosis of hypertension, and nearly 12% had a specific cardiac disorder, most commonly coronary artery disease or a prior myocardial infarction. Nearly 75% of patients were taking a concomitant medication with known potential to increase the QT interval.

The incidence of treatment-emergent cardiovascular adverse events was low and similar with valbenazine and placebo. During the 6-week double-blind trials, 5 cardiac events occurred in 1 patient each: chest pain and bradycardia with 40 mg/day valbenazine, blood pressure increase and a sudden death that may have been cardiac in nature with 80 mg/day valbenazine, and a fatal myocardial infarction in the placebo group. In the acute and extension studies, orthostatic hypotension and dizziness/falls, potentially related to hypotension, occurred in 24 valbenazine-treated patients and in 4 placebo-treated patients. None resulted in treatment discontinuation. There were no statistically significant differences in changes in vital signs between valbenazine and placebo except for a small mean increase in orthostatic diastolic blood pressure with 40 mg valbenazine.

Mean changes from baseline in ECG parameters were small and not considered clinically significant. During the double-blind trials, QTcF intervals >450 were recorded in 11 members of the placebo group, 11 receiving low-dose valbenazine, and 5 receiving the higher dose. During

the extension study, 5 patients taking valbenazine had a QTcF >480 ms, 1 had a QTcF >500 ms, and 6 had an increase of ≥60 ms.

Discussion: Although patients with significant cardiac abnormalities were excluded from the studies, the population was otherwise generally representative of a real-world population. More information on the cardiovascular effects of the drug should become available with post-marketing surveillance data and ongoing studies.

Thai-Cuarto D, O'Brien C, Jimenez R, Liang G, et al: Cardiovascular profile of valbenazine: analysis of pooled data from three randomized, double-blind, placebo-controlled trials. *Drug Safety* 2017; doi 10.1007/s40264-017-0623-1. From Neurocrine Biosciences, Inc., San Diego, CA. **Funded by Neurocrine Biosciences. All 5 study authors disclosed financial relationships with commercial sources including Neurocrine Biosciences.** See related stories in *Psychiatry Drug Alerts* 2017;31 (April):25–26 and 2017;31 (December):89–90.

Estrogen for Perimenopausal Depression

In a randomized trial, transdermal estradiol plus progesterone reduced depressive symptoms during the early stage of the menopause transition.[1]

Background: Research suggests that estrogen, with or without progesterone, could minimize estradiol fluctuation and/or withdrawal and may be effective treatment for perimenopausal depression. The present study was undertaken to determine whether estrogen treatment could prevent depressive symptoms in euthymic women during the perimenopausal or early postmenopausal periods.

Methods: Study participants were self-referred women, aged 45–60 years, who were early premenopausal or postmenopausal according to the Stages of Reproductive Aging Workshop Criteria. All women were euthymic at study entry, but one-third had a history of major depression. Active treatment consisted of 0.1 mg 17β-estradiol patches for 12 months, with 200 mg/day oral micronized progesterone taken for 12 consecutive days every 2–3 months. Women were evaluated at the end of months 1 and 2, and then at 2-month intervals until the 12th month. The primary study outcome was the development of depressive symptoms, defined as a score of ≥16 on the Center for Epidemiologic Studies–Depression scale (CES-D).

Results: A total of 172 women (mean age, 51 years) entered the trial, of whom the majority (57.5%) were in late perimenopause at study entry. During randomized treatment, 43 women (25%) had a CES-D score of ≥16 on at least 1 occasion. Women who received placebo were more likely than those who received hormone therapy to experience a score above the threshold (odds ratio,* 2.5; p=0.03). Placebo-treated women also had more follow-up evaluations with CES-D scores above the threshold than women receiving active treatment (p=0.002) and had higher mean CES-D scores (p=0.03) across the 12 months of the study.

Subgroup analysis showed that the benefits of hormone therapy were confined to women in the early perimenopause stage (p<0.001) but did not extend to those in late perimenopause or early postmenopause. Benefits were also more apparent in women who had a recent history of multiple stressful life events. Effects of hormone therapy were not modified by a history of depression or physical or sexual abuse, baseline estradiol levels, or annoyance from vasomotor symptoms at baseline. The only evident adverse effect of treatment was vaginal bleeding, as expected from the progesterone regimen.

Editorial.[2] While the present study results suggest a potential role for gonadal steroids in the regulation of mood, they must be considered preliminary in light of important limitations and do not support a change in recommendations for women in the menopausal transition. Based on the study's measure of depression, it is not possible to determine whether hormone therapy can prevent syndromal depression because the CES-D has limited sensitivity and specificity in identifying a depressive episode. In addition, the estradiol dosage used in the

study is substantially higher than recommended and the progestin dosage is lower than recommended to prevent adverse endometrial effects of exogenous estrogen. Hormone therapy is currently approved for the treatment of hot flashes and vaginal dryness. The median duration of the menopausal transition is 4 years, and risks of long-term hormone therapy—e.g., venous thromboembolic disease, cardiovascular disease, and breast cancer—should be considered before prolonged off-label use for preventing depressive symptoms or other chronic disease.

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

[1]Gordon J, Rubinow D, Eisenlohr-Moul T, Xia K, et al: Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: a randomized clinical trial. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2017;3998. From the University of Regina, Canada; and other institutions. **Funded by the NIH; and the Fonds de la Recherche du Quebec-Sante. The authors declared no competing interests.**

[2]Joffe H, Hickey M: Should hormone therapy be used to prevent depressive symptoms during the menopause transition? [editorial]. *JAMA Psychiatry* 2018; doi 10.1001/jamapsy.1007.3945. From Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and the University of Melbourne, Australia. **Funded by the National Institute on Aging and the Australian National Medical Health and Medical Research Council. One author disclosed relationships with commercial sources.**

***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.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias, making it possible to obtain average treatment effects.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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.

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PSYCHIATRY DRUG ALERTS

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APA Guideline for Alcohol Use Disorder

Fewer than 1 in 10 Americans with a diagnosis of alcohol use disorder receives any treatment, and receipt of evidence-based care is even less common. According to a guideline on the pharmacological treatment of the disorder from the American Psychiatric Association (APA), naltrexone and acamprosate are first-line drug treatments for moderate-to-severe alcohol use disorder. This recommendation reflects a moderate degree of confidence that the benefits of these drugs outweigh the harms. Disulfiram, topiramate, and gabapentin may also have greater benefits than harms and may be appropriate in patients who have not experienced response with first-line medications. The guideline recommends against treating alcohol use disorder with antidepressants or prescribing benzodiazepines except for acute alcohol withdrawal.

The guideline, which is based on evidence from clinical trials, expert opinion, and patient values and preferences, ranks the level of confidence that the benefit of a treatment outweighs its harms. Harms included not only adverse effects, but direct and indirect costs of the intervention. In addition to treatment, assessment of patients' alcohol use disorder is discussed.

Assessment: The APA recommends that patients with suspected alcohol use disorder be assessed for use of tobacco and misuse of other substances, including prescription medications. Alcohol use should be assessed with a quantitative behavioral measure, and patients should be assessed for co-occurring conditions that may influence the choice of pharmacotherapy. Patients should have a documented, comprehensive, person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments. Additional suggestions, based on lower quality evidence, include use of physiological biomarkers to identify ongoing high levels of alcohol use, as well as documented discussions of risks of continued alcohol use and treatment goals (e.g., abstinence, reduction of alcohol use).

Treatment: Naltrexone or acamprosate are recommended in patients with moderate or severe alcohol use disorder who prefer pharmacotherapy or have not experienced response with nonpharmacological treatments alone. Both drugs have shown positive effects overall,

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although they have not shown a statistically significant benefit in all studies or for all outcomes. Benefits are generally small, but the harms of treatment with these drugs are considered minimal in patients without contraindications. Acamprosate should not be used in patients with renal impairment, and naltrexone should not be used in those with acute hepatitis or hepatic failure. Both drugs should be avoided in pregnant women. Lower quality evidence also suggests that disulfiram may be used in patients who have a goal of achieving abstinence, can understand the risks of alcohol consumption while taking the drug, and either prefer it or have not had response with naltrexone or acamprosate. Disulfiram efficacy is mainly supported by open-label trials, but effect sizes have been medium to large. Topiramate has had moderate effect sizes in alcohol use disorder, but harms include cognitive dysfunction, dizziness, and weight loss. Gabapentin has a small beneficial effect and minimal harms, but the strength of evidence is low.

The APA notes that "Practice Guidelines are assessments of current scientific and clinical information provided as an educational service and should not be considered as a statement of the standard of care or inclusive of all proper treatments or methods of care and are not continually updated and may not reflect the most recent evidence. They are not intended to substitute for the independent professional judgment of the treating provider."

Reus V, Fochtmann L, Bukstein O, Eyler A, et al: The American Psychiatric Association practice guideline for the pharmacological treatment of patients with alcohol use disorder. *American Journal of Psychiatry* 2018;175 (January):86–90. From the APA Practice Guideline Working Group.

Common Drug Trade Names*: acamprosate—*Campral*; disulfiram—*Antabuse*; gabapentin—*Neurontin*; naltrexone—*ReVia*; topiramate—*Topamax

Asenapine Maintenance in Bipolar I Disorder

In a manufacturer-sponsored randomized withdrawal study, asenapine (*Saphris*) prevented recurrence of a mood episode in patients with bipolar I disorder who initially experienced response to the drug. No new safety concerns became apparent during the trial.

Methods: Study participants were adults with bipolar I disorder, currently experiencing a manic or mixed episode. Following taper and discontinuation of previous psychotropic medications, all patients received open-label monotherapy with 5 or 10 mg asenapine b.i.d. for 12–16 weeks. Response criteria were Young Mania Rating Scale (YMRS) and Montgomery-Asberg Depression Rating Scale (MADRS) scores of ≤12 for 5 consecutive visits. Patients who met these criteria for 8 weeks went on to the second phase of the study, in which they received randomly assigned, double-blind asenapine or placebo for 26 weeks. The primary study outcome was time to recurrence of a mood episode, defined as either initiation of a non-study medication to treat mood symptoms, YMRS or MADRS score of ≥16, need for psychiatric hospitalization, or study discontinuation because of a mood event. There were no prespecified key secondary endpoints, but time to recurrence of specific types of mood episode was analyzed post hoc.

Results: A total of 549 patients began the open-label phase. Of these, 296 discontinued treatment during this phase because of adverse events (n=91), lack of efficacy (n=45), or other reasons. Thus 253 patients who met response criteria entered the randomized withdrawal phase. Mean patient ages were 41 years in the placebo group and 43 years in the asenapine group, and 45% of participants were men. The majority of patients (78%) entered the randomized phase in a manic episode as opposed to a mixed episode (22%). Medication compliance was nearly 100% during the second phase.

Asenapine was associated with a longer time to mood episode recurrence than placebo, both overall and for mania and depression individually. Among the asenapine-treated patients, 11 experienced any mood episode recurrence, compared with 42 in the placebo group (hazard ratio [HR],* 0.22; p<0.0001; number needed to treat [NNT],* 5). Manic episodes affected 5 and 24

patients in the asenapine and placebo groups, respectively (HR, 016; p<0.0001; NNT, 7). Depressive episode recurrence was also significantly less likely with asenapine than with placebo, although the effect was smaller than for manic episodes: 5 patients versus 13 patients (HR, 0.35; p=0.045; NNT, 16). Occurrence of mixed episodes did not differ significantly between the groups (HR, 0.10; NNT, 32), but the number of patients experiencing these episodes was small: 1 in the asenapine group and 5 in the placebo group.

Of the prespecified adverse events of interest, during open-label treatment, 18% of patients experienced somnolence/sedation/hypersomnia, 10% had clinically significant weight gain, 10% extrapyramidal symptoms, 10% oral hypoesthesia/dysgeusia, and 8% akathisia. Few patients had lab abnormalities. There were no significant differences between asenapine and placebo in adverse events of interest during the second study phase.

Discussion: Asenapine is currently FDA approved for acute treatment of bipolar mania and acute and maintenance treatment of schizophrenia. This trial confirms the known safety and tolerability profile of asenapine. The observation that it may prevent depressive episodes is noteworthy because few atypical antipsychotics are effective in bipolar depression.

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

Szegedi A, Durgam S, Mackle M, Yu S, et al: Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with an acute manic or mixed episode associated with bipolar I disorder. *American Journal of Psychiatry* 2018;175 (January):71–79. From Allergan, Jersey City, NJ; Merck, Whitehouse Station, NJ; and Forest Research Institute, Jersey City, NJ. **Funded by Forest Laboratories. All 7 study authors disclosed financial relationships with commercial sources, including Allergan, Merck, or Forest Laboratories.**

***See reference guide.**

Ghrelin Agonist for Anorexia Nervosa

In a preliminary placebo-controlled study, the investigational ghrelin receptor agonist relamorelin was associated with accelerated gastric emptying and modest weight gain in women with anorexia nervosa.

Background: There are currently no approved agents to stimulate gastric motility in anorexia nervosa, although pro-kinetic agents such as erythromycin or metoclopramide (*Reglan*) are used off-label. These agents' adverse effects may preclude long-term use. Ghrelin is a hormone produced in the stomach that stimulates appetite and gastric motility. Relamorelin is an agonist of the ghrelin receptor, or growth hormone secretagogue receptor 1a (GHS-R1a).

Methods: Study participants were 22 adult women who met DSM-5 criteria for anorexia nervosa and who had gastrointestinal symptoms, such as fullness, bloating, and constipation, thought to be caused by delayed gastric emptying. All were outpatients during the study, and none were receiving hyperalimentation therapy, tube feedings, or agents to reduce gastric motility. At the baseline study visit, participants were randomized and taught to self-administer subcutaneous injections. Patients then self-administered 100 µg relamorelin or placebo subcutaneously every morning for 4 weeks and returned to the clinic for weekly evaluations.

Results: The study participants had a mean age of 29 years and were at about 80% of their ideal body weight on average. Nine of 12 patients in the placebo group and all 10 in the relamorelin group were receiving long-term outpatient therapy, which continued during the study. Mean baseline gastric emptying time was about 87 minutes.

A total of 20 patients were included in the intent-to-treat analysis; the other 2 patients, both in the active treatment group, withdrew from the study because of increased hunger and had no available outcome data. Patients in the relamorelin group gained more weight than the placebo group (1.9 lbs vs 0.08 lbs; p<0.07). At 4 weeks, 7 of 8 patients in the relamorelin group and 6 of

12 patients in the placebo group gained weight (88% vs 50%). Mean gastric emptying time after 4 weeks was 58 minutes with relamorelin and 85 minutes with placebo (p=0.03). Patients in both groups reported similar effects on hunger, measured with a visual analog scale. Changes in self-reported gastric symptoms did not differ between the groups.

Discussion: Based on these results, relamorelin may have a role in the nutritional rehabilitation of patients with anorexia nervosa and additional study appears to be warranted. It should be noted that in the present study, 3 patients discontinued relamorelin because of increased hunger (although 1 remained in the study), suggesting that not all patients with anorexia nervosa may tolerate the ghrelin agonist.

Fazeli P, Lawson E, Faje A, Eddy K, et al: Treatment with a ghrelin agonist in outpatient women with anorexia nervosa: a randomized clinical trial. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11585. From Massachusetts General Hospital, Boston; and other institutions including Motus Therapeutics, Boston. **Funded by Motus Therapeutics. One study author disclosed a financial relationship with Motus Therapeutics; the remaining 9 authors declared no competing interests.**

Metabolic Effects of Newer SGAs

Despite recent evidence, ziprasidone does not appear to have a more benign metabolic profile than the second-generation antipsychotics aripiprazole or quetiapine in patients with first-episode psychosis.[1]

Background: Among SGAs, aripiprazole and ziprasidone have been proposed to have relatively neutral metabolic effects, and a previous study by these investigators showed more benign effects of ziprasidone after 12 weeks of treatment.[2] The present study was conducted to compare the effects of the 3 drugs during patients' first year of antipsychotic treatment.

Methods: Patients were participants in a larger study of first-episode non-affective psychosis, conducted at a regional hospital in Spain. To be eligible for the study, patients (n=198; mean age, 32 years) were required to be aged 15–60 years, to have at least moderately severe psychotic symptoms, and to be antipsychotic-medication-naive. Participants were randomly assigned to receive open-label treatment with 5–30 mg/day aripiprazole, 100–600 mg/day quetiapine, or 40–160 mg/day ziprasidone. Medication doses were adjusted as clinically indicated to target the lowest effective dose. Patients were followed clinically for 1 year. Those who did not experience response to their initial antipsychotic after 6 weeks and those who had significant adverse effects were switched to another agent. The study's main outcomes were changes in weight and metabolic parameters after 1 year.

Results: About 5% of the study subjects were obese (body mass index [BMI] ≥30) at study entry. Nine individuals with baseline outlier values for ≥1 of the laboratory parameters were excluded from the analysis, and 33 patients (17 in the quetiapine group, 6 in the ziprasidone group, 10 in the aripiprazole group) were lost to follow-up or refused evaluation at 1 year; thus 165 were included in the analysis. Of these patients, about 40% were still receiving their initial medication (18% for quetiapine, 43% for ziprasidone, 62% for aripiprazole). Reasons for the switch were inefficacy (22%), adverse effects (15%), and nonadherence (10%). Patients in the ziprasidone group were significantly more likely to receive a prescription for an antidepressant during the year than others (31% vs 18% for quetiapine and 11% for aripiprazole; p=0.03).

After 1 year of follow-up, there were no differences among the 3 medication groups in any metabolic outcome. There was no change from baseline in mean fasting glucose and insulin levels or in the HOMA index of insulin resistance. Overall, patients had statistically significant increases in fasting total and LDL cholesterol and triglycerides, averaging 16 mg/dL, 13 mg/dL, and 20 mg/dL, respectively (p<0.001 for all). The triglyceride/HDL index increased by 0.4 points, and patients gained an average of about 15 lbs and 2.4 points in BMI (p<0.001 for all).

The proportion of patients with hypercholesterolemia and hypertriglyceridemia increased, to 40% and 14%, respectively. A secondary analysis according to gender showed that the weight gain in patients taking aripiprazole was significantly greater in women than men.

Discussion: These results suggest that none of the SGAs can be considered metabolically neutral. Results of short-term studies have suggested that ziprasidone has the most benign metabolic profile. The present results indicate that this assumption should be re-evaluated as the differences among agents that appear after 3 months of treatment may disappear after 1 year.

[1]Vazquez-Bourgon J, Perez-Iglesias R, Ortiz-Garcia de la Foz V, Pinilla P, et al: Long-term metabolic effects of aripiprazole, ziprasidone, and quetiapine: a pragmatic clinical trial in drug-naïve patients with a first-episode of non-affective psychosis. *Psychopharmacology* 2018;235 (January):245–255. From the University Hospital Marques de Valdecilla-IDIVAL, Santander, Spain; and other institutions. **Funded by the Instituto de Salud Carlos III; and other sources. The authors declared no competing interests.**

[2]Perez-Iglesias R, et al: Comparison of metabolic effects of aripiprazole, quetiapine and ziprasidone after 12 weeks of treatment in first treated episode of psychosis. *Schizophrenia Research* 2014;159:90–94.

Common Drug Trade Names*: aripiprazole—*Abilify*; quetiapine—*Seroquel*; ziprasidone—*Geodon

Low-Grade Infection and Antidepressant Resistance

In a nationwide retrospective cohort study from Taiwan, a history of frequent low-grade upper respiratory infections was associated with increased incidence of depression and also contributed to patients' refractoriness to antidepressant drugs.

Methods: Two independent cohorts of patients were identified from the Taiwan National Health Insurance Research Database: Cohort 2002 (followed between 2002 and 2011) and Cohort 2004 (followed between 2004 and 2011). Cohort members were medically healthy adults who had any recorded history of low-grade infections, defined as common upper airway infections. Patients were stratified based on the frequency of repeated low-grade infections (RLGI), and depression diagnoses were compared between the RLGI positive (top tertile of frequency) and negative groups (lowest tertile of frequency). The treatment responsiveness analysis was based on the period from 1 year before to 1 year after the depression diagnosis. Patients' depression was defined as easy-to-treat (requiring no antidepressants or a single antidepressant), intermediately difficult-to-treat (requiring 2 drugs), and difficult-to-treat (not responsive to ≥2 antidepressants in adequate doses for ≥60 days each).

Results: The analysis included >78,000 patients in Cohort 2002 and >49,000 in Cohort 2004. The RLGI groups within the 2 cohorts had an average of 5–7 low-grade infections per year at baseline. Depression onset was more frequent in persons with RLGI in both the 2002 and 2004 cohorts, with hazard ratios* of 1.37 and 1.91, respectively ($p<0.001$ for both hazard ratios after adjustment for gender, age, and income). Responsiveness to antidepressant medications differed significantly according to RLGI status (see table), with significantly higher rates of difficult-to-treat depression among those with recurrent infections.

Depression Symptom Responsiveness by RLGI Status

	2002 Cohort		2004 Cohort	
	RLGI	**No RLGI**	**RLGI**	**No RLGI**
Number in cohort	489	328	238	115
Easy to treat	67.5%	75.9%	67.2%	83.5%
Intermediate	21.1%	16.5%	21.0%	12.2%
Difficult to treat	11.5%	7.6%	11.8%	4.3%

Discussion: Many types of pathogen, both viral and bacterial, can trigger short-term depression for a period following infection. Conceivably, repeated infections could activate the immune system and elevate proinflammatory cytokines, leading to depression via multiple mechanisms, among them an activation of stress pathways by cytokines.

Jeng J-S, Li C-T, Chen M-H, Lin W-C, et al: Repeated low-grade infections predict antidepressant-resistant depression: a nationwide population-based cohort study. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11540. From Taipei Veterans General Hospital, Taiwan; and other institutions. **Funded by the Taipei Veterans General Hospital; and the Ministry of Science and Technology. The authors declared no competing interests.**

***See Reference Guide.**

Prazosin in Military PTSD

In a multicenter randomized trial in U.S. military veterans, prazosin was not significantly more effective than placebo at reducing posttraumatic stress disorder-related nightmares. These results contrast those of previous studies with shorter durations and smaller populations that suggested the drug was beneficial for reducing trauma-related nightmares and improving sleep quality and PTSD symptoms.

Methods: The trial, conducted at 12 VA medical centers, enrolled 304 patients (mean age, 52 years; 98% men) with DSM-IV PTSD who had a score of ≥50 on the Clinician-Administered PTSD Scale (CAPS) and recurrent combat-related nightmares following life-threatening events in a war zone. Previous medications and/or psychotherapy were required to be stable for ≥4 weeks before randomization. Among the exclusion criteria were active suicidal ideation and psychosocial instability. Patients were randomized to receive flexible-dose prazosin or placebo for 10 weeks. Prazosin dosage was adjusted to a maximum of 5 mg at mid-morning and 15 mg at bedtime for men and to 2 and 10 mg, respectively, in women. The 3 primary study outcome measures were the CAPS recurrent distressing dreams item, the Pittsburgh Sleep Quality Index, and the Clinical Global Impression (CGI)–Change score. After the 10-week evaluation, double-blind treatment was continued for an additional 16 weeks, with the modification that other treatments could be added or changed as needed. Outcomes were re-assessed at 26 weeks.

Results: A total of 90% of the randomized study patients completed the 10-week evaluation, with no differences in completion rates between the groups. Change from baseline to 10 weeks did not differ between the prazosin and placebo groups for any of the 3 primary study outcomes. Based on CGI-Change scores, patients in both groups showed minimal improvement. Outcomes did not appear to be affected by concurrent antidepressant use. There were no significant between-treatment differences on any of the secondary outcomes including CAPS total scores, Patient Health Questionnaire depression scores, health-related quality of life, or alcohol use. Findings at 26 weeks showed a similar pattern, with no significant differences between the groups and no substantial improvement compared with week 10. Adverse events related to blood pressure-lowering effects were more common with prazosin than placebo. New or worsening suicidal ideation was less common with prazosin than placebo (8% vs 15%; p=0.048).

Discussion: Results of this study contrast with previous randomized trials involving smaller samples of both military and civilian participants. Unlike previous trials, concern about suicidal or violent behavior led the present investigators to exclude patients with psychosocial instability, possibly biasing the sample. The study also had a high threshold for frequency and severity of nightmares, possibly biasing selection toward patients less likely to experience response to prazosin. Despite high levels of symptoms, recruitment criteria ensured that study participants had clinically stable PTSD, potentially making them less likely to experience response. It is also possible that clinicians may have not referred their more vulnerable

patients to the study, preferring to treat them with open-label prazosin. The authors note that the current trial is not the first multicenter, randomized trial involving male military veterans with psychiatric disorders to fail to show efficacy for a treatment that was effective in initial studies and that has been made available within the VA health care system. Similar results have been found with sertraline and trauma-focused psychotherapy, which are considered the first-line pharmacological and psychotherapeutic options for PTSD within the VA system.

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

Raskind M, Peskind E, Chow C, Harris C, et al: Trial of prazosin for post-traumatic stress disorder in military veterans. *NEJM* 2018;378 (February 8):507–517. From the VA Northwest Network Mental Illness Research, Education, and Clinical Center, Seattle, WA; and other institutions. **Funded by the VA. Four of 18 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names: **prazosin—*Minipress*; sertraline—*Zoloft***

***See Reference Guide.**

Lavender Oil for Subthreshold Anxiety

According to a manufacturer-sponsored meta-analysis, silexan, a standardized extract of lavender oil, reduces subthreshold anxiety symptoms.

Background: Silexan, the active ingredient of a medicinal product manufactured in Germany and licensed in 14 countries, contains an essential oil extracted from lavender flowers. Active substances in silexan cause inhibition of voltage-dependent calcium channels in synaptosomes thought to be important in anxiety and depression. Inhibition of these channels could dampen the excessive stress response associated with anxiety and mood disorders.

Methods: Data were obtained from 3 phase-III clinical trials. A literature and clinical trial registry search for other studies of silexan for anxiety was also conducted, but none were found. The trials were similar in design but targeted different disorders: subthreshold anxiety; restlessness, agitation, and disturbed sleep; and mixed anxiety and depressive disorder. Participants in all studies were required to have a baseline total score of ≥18 on the Hamilton Rating Scale for Anxiety (HAM-A). In all 3 trials, patients received randomly assigned 80 mg/day silexan or placebo for 10 weeks. The primary efficacy outcome was change from baseline to end of treatment in the HAM-A total score. The analysis also assessed treatment response (HAM-A total score decrease of ≥50% or Clinical Global Impression–Improvement [CGI-I] rating of much or very much improved) and remission (HAM-A <10 points at study end).

Results: A total of 697 patients received treatment and were assessed in the 3 trials. Premature withdrawal rates in the pooled studies were 12.6% for silexan and 10.5% for placebo. Silexan was significantly superior to placebo in reducing the mean HAM-A total score from baseline (standardized mean difference* between groups, 0.45; p=0.003). The overall effect of silexan was comparable for the psychic and somatic anxiety subscales of the HAM-A. Differences between silexan and placebo in patient-rated anxiety also favored silexan.

The overall rate of HAM-A response was significantly higher with silexan than with placebo (risk ratio,* 1.47; p=0.002; number needed to treat,* 6). Response based on CGI criteria was also significantly more likely with silexan (risk ratio, 1.69; p<0.001; number needed to treat, 5). Remission was also more likely to occur with silexan (p=0.008; number needed to treat, 8). Silexan also had positive effects on sleep disturbance and health-related quality of life.

Silexan was well tolerated. According to this and other reports, the predominant adverse effects are belching, dyspeptic symptoms, and allergic skin reactions.

Discussion: Although data on the use of silexan in anxiety are sparse, the results of this meta-analysis suggest it may be useful in the treatment of subthreshold anxiety. The authors note, however, that the study results apply only to silexan, not to the many other lavender oil products available.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Moller H-J, Volz H-P, Dienel A, Schlafke S, et al: Efficacy of Silexan in subthreshold anxiety: meta-analysis of randomised, placebo-controlled trials. *European Archives of Psychiatry and Clinical Neuroscience* 2017; doi 10.1007/s00406-017-0852-4. From Ludwig Maximilian University, Munich, Germany; and other institutions. **Funded by Dr. Willmar Schwabe GmbH & Co KG, manufacturer of Silexan. All study authors disclosed financial relationships with commercial sources, including 2 with Dr. Willmar Schwabe GmbH & Co KG.**

***See Reference Guide.**

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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.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Risk Ratio: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Standardized Mean Difference: The difference between 2 normalized means—i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

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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Safety of Serotonergic Coprescription

The incidence of serotonin syndrome was low in patients who received concomitantly prescribed serotonergic antidepressants and triptan antimigraine drugs, according to an analysis of 14 years of electronic medical records from a large data registry.

Background: In 2006, the FDA issued a warning regarding the risk of serotonin syndrome with concomitant use of triptans and SSRIs or SNRIs. However, the warning was based on a small number of cases, and population-based studies were not conducted to confirm the association. In addition, based on their receptor affinity, the biological plausibility of triptans as a cause of serotonin syndrome is questionable.

Methods: The present analysis was based on the Partners Research Patient Data Registry, which includes information on >6.5 million patients receiving care in the Boston area. Patients were identified who received prescriptions for a triptan and an SSRI or SNRI in 2001–2014. Within this population, investigators searched for all cases of potential serotonin syndrome and examined the records of these patients.

Results: The number of patients who received prescriptions for triptans increased steadily during the study period. In spite of the warning, the proportion of patients who concomitantly received an SSRI or SNRI remained stable between 21% and 29%.

More than 19,000 patients received prescriptions for both a triptan and an SSRI or SNRI during the study period; 229 (0.01%) experienced extrapyramidal symptoms. Serotonin syndrome was clinically suspected in 17 of these patients. Of these, 7 cases met criteria for serotonin syndrome based on ≥1 set of standardized criteria. Detailed record review indicated that triptans had been used in close temporal association with serotonin syndrome-like symptoms in only 2 cases, but in both cases, symptoms had onset before triptans were started. Using a strict, conservative case definition, the incidence of serotonin syndrome in this population was 0.6 per 10,000 person-years. Assuming, less conservatively, that serotonin syndrome

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occurred in all 17 suspected cases, the estimated incidence was 2.3 per 10,000 person-years. No cases of serotonin syndrome, either suspected or confirmed, were life-threatening.

Discussion: These observations suggest there is reason to be skeptical that triptans increase the risk of serotonin syndrome beyond that associated with SSRIs and SNRIs alone. They also provide evidence that patients with affective disorders and migraine do not necessarily need to forgo treatment of 1 disorder to manage the other.

Orlova Y, Rizzoli P, Loder E: Association of coprescription of triptan antimigraine drugs and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants with serotonin syndrome. *JAMA Neurology* 2018; doi 10.1001/jamaneurol.2017.5144. From Brigham and Women's Hospital, Boston, MA; and other institutions. **Funded by Harvard Catalyst; and other sources. The authors declared no competing interests.**

Adjunctive Mifepristone in Psychotic Depression

Mifepristone, a glucocorticoid receptor antagonist that blocks the activity of cortisol, can reduce positive symptoms in patients with psychotic depression, according to a combined analysis of 5 clinical trials. Efficacy in the trials was limited to patients who had relatively high drug plasma levels.

Background: There are no agents specifically FDA approved to treat psychotic depression. In several studies, mifepristone produced response rates numerically superior to placebo; however, statistical significance was not consistently observed.

Methods: The present analysis included 5 similarly designed manufacturer-sponsored phase II or III trials. The trials enrolled patients with psychotic depression, and all but 1 trial required a score of ≥8 on the Brief Psychiatric Rating Scale (BPRS) positive symptom subscale. Following a ≥7-day washout of antidepressant and/or antipsychotic medications, 1460 participants (mean age, 45 years; 59% women) were started on an FDA-approved antidepressant and randomly assigned to 7 days of treatment with either placebo or 300, 600, or 1200 mg/day mifepristone. The primary efficacy outcome of the trials was the proportion of patients in each group who had a ≥50% decrease from baseline on the BPRS positive symptom scale at both day 7 (rapid response) and the final study visit (sustained response; days 28 or 56, depending on the study). Trough plasma levels were measured on day 7, before the final administration of the drug.

Results: A total of 833 patients received mifepristone, and 627 received placebo. Dropout rates were about 19% in each group. Rates of rapid, sustained response were 37% with mifepristone and 29% with placebo (p=0.004). Outcomes of mifepristone and placebo diverged statistically beginning in week 2 of follow-up and continued through week 8.

A mifepristone plasma level of 1637 ng/mL was identified as a cutoff between responders and nonresponders. Patients with mifepristone plasma levels below the cutoff did not have a higher response rate than the placebo group. Higher plasma levels were superior to placebo, with a psychotic symptom response rate of 43%, a number needed to treat* of 7, and an effect size* of 0.30. Although some patients in all dosage groups achieved high plasma drug levels, the likelihood was higher as the dosage increased: 25% with 300 mg/day, 44% with 600 mg/day, and 65% with 1200 mg/day. Change from baseline in adrenocorticotropic hormone (ACTH) and cortisol levels were significantly correlated with the day-7 mifepristone level (for cortisol, p<0.0001; for ACTH, p<0.0001).

Mifepristone was also significantly superior to placebo at improving scores on the Hamilton Rating Scale for Depression (HAM-D), but only in patients who achieved plasma mifepristone levels above the cutoff. In these patients, HAM-D reductions ranged from 46% to 53% at the final study visit, compared with 42–48% in the placebo groups (p≤0.05). Mifepristone was well tolerated, with a comparable safety profile to placebo.

Discussion: Patients with psychotic depression have elevated cortisol levels, perhaps leading to overstimulation of the glucocorticoid receptor and increasing responsiveness to dopamine and glutamate. The finding of greater increases in cortisol and ACTH in the highest dosage group likely reflects increased glucocorticoid receptor antagonism. Although 4 of the 5 included studies had higher-than-expected placebo response rates, mifepristone showed clinically meaningful effects, as demonstrated by the number needed to treat, in patients who achieved therapeutic plasma levels

Block T, Kushner H, Kalin N, Nelson C, et al: Combined analysis of mifepristone for psychotic depression: plasma levels associated with clinical response. *Biological Psychiatry* 2018; doi 10.1016/j.biopsych.2018.01.008. From Corcept Therapeutics Inc., Menlo Park, CA; and other institutions. **Funded by Corcept Therapeutics Inc. All study authors disclosed financial relationships with commercial sources including Corcept Therapeutics.**

Common Drug Trade Names*:** **mifepristone—*Korlym, Mifeprex

***See Reference Guide.**

Stimulants in Schizophrenia

In a population-based, naturalistic study, treatment with CNS stimulants was associated with improved functional outcomes in patients with schizophrenia. However, the effect was largely confined to women.

Methods: Study data were collected from the Danish national registries of population, psychiatric treatment, and prescriptions. All patients with a diagnosis of schizophrenia and all exposure of these patients to CNS stimulants were identified. In a mirror-image model, the number of psychiatric hospitalizations, days of psychiatric hospitalization, and antipsychotic use were compared within individual patients for the 2-year periods before and after the initial stimulant prescription. In a whole-population analysis, psychiatric hospitalizations were compared between stimulant-exposed and unexposed patients. In this analysis, patients who stopped filling stimulant prescriptions were considered unexposed 3 months after the last prescription. In addition, patients were censored during admission to a psychiatric facility and reentered the study at discharge.

Results: More than 50,000 patients with schizophrenia were identified, including 1438 (nearly 3%) who received a prescription for a stimulant. The mirror-image analysis included 605 patients whose stimulant prescription was initiated after the onset of schizophrenia. Most of these patients (93%) received methylphenidate (*Ritalin*), and only about 30% had a comorbid ADHD diagnosis.

Stimulant use was not significantly associated with reduced psychiatric hospitalization overall. In women, the mean number of admissions was somewhat lower during stimulant use compared with before (1.33 vs 1.02 hospitalizations), but the difference was not statistically significant. However, subgroup analysis of 214 patients with a history of hospitalization in the pre-mirror-image period found stimulant effects to be significant for the whole population (3.43 vs 2.62 admissions; $p=0.009$), with a larger effect in women and a nonsignificant effect in men. Antipsychotic exposure, measured as the defined daily dose, was also lower during stimulant use, both overall ($p=0.001$) and in women ($p=0.002$). Rates of SSRIs and benzodiazepines use were also significantly lower in the post-stimulant mirror-image period than in the pre-stimulant period.

Average days of hospitalization could not be compared in the full mirror-image sample, as many had no history of admission in the pre-mirror-image period. However, among patients with a previous hospitalization, the number of bed-days was significantly lower in the post-stimulant period than before, both overall (78.3 vs 38.3 days; $p<0.001$) and in separate analyses of men and women ($p<0.001$ for both). In the whole-population analysis, rates of hospitalization

were lower in women during stimulant use, compared with periods of non-use (adjusted hazard ratio,* 0.72).

Serious adverse effects were rare during stimulant use. Seizures or epilepsy developed in 3 patients after starting stimulant treatment, acute myocardial infarction occurred in 1 patient, and renal disease developed in 4 patients. Despite concerns that stimulants could worsen positive symptoms by increasing the availability of synaptic dopamine in the limbic system, the reductions in hospitalization suggest they did not.

Discussion: Results of previous studies suggest stimulant use may improve cognition in schizophrenia, resulting in fewer negative symptoms; but these effects have been small. The present study aimed to examine the effect of stimulants on naturalistic outcomes that reflect patient function. The stronger response to stimulants in women, which has been previously observed, may reflect mediation of the neural response by ovarian hormones. While these results are encouraging, further study is needed before stimulants can be recommended for patients with schizophrenia.

Rohde C, Polcwiartek C, Asztalos M, Nielsen J: Effectiveness of prescription-based CNS stimulants on hospitalization in patients with schizophrenia: a nation-wide register study. *Schizophrenia Bulletin* 2018;44 (January):93–100. From Aalborg University, Denmark; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

***See Reference Guide.**

Minocycline plus Aspirin for Bipolar Depression

In a preliminary randomized trial, the combination of minocycline (*Minocin*) plus aspirin was effective as adjunctive treatment of bipolar depression. Neither of the 2 antiinflammatory agents was effective without the other.

Background: Given the few safe and effective options for treating bipolar depression, interest in drugs with antiinflammatory activity is increasing. Aspirin and minocycline were investigated because they are well tolerated, penetrate the brain, and act by different antiinflammatory mechanisms.

Methods: Study subjects were adults with bipolar disorder type I, II, or NOS, with a current major depressive episode lasting ≥4 weeks and of at least moderate severity, who were receiving stable ongoing medication. Participants received randomized, double-blind treatment for 6 weeks with 100 mg minocycline b.i.d. plus aspirin placebo; 81 mg aspirin b.i.d. plus minocycline placebo; both active agents; or double placebo. Midway through the study design, an interim analysis revealed that the double-treatment and double-placebo groups were separating statistically, but that the 2 single-agent groups were not, and no new patients were enrolled in the 2 single-agent groups. The primary study outcome was durable response, defined as a >50% decrease in Montgomery-Asberg Depression Rating Scale score for the final 2 study visits. Levels of interleukin-6 (IL-6) were measured to assess inflammation, and the Young Mania Rating Scale (YMRS) was used to evaluate whether minocycline and/or aspirin would precipitate hypomania or mania.

Results: A total of 99 patients with an average age of about 41 years (75% women) were randomized: 37 with bipolar I disorder, 57 with bipolar II disorder, and 5 with bipolar disorder NOS. A total of 31 patients received minocycline plus aspirin, 30 received double placebo, and 19 patients each received minocycline plus placebo or aspirin plus placebo. Mean baseline MADRS scores ranged from 26 to 29 and did not differ between groups. Patients receiving both active agents had a higher response rate than the placebo group: 44% versus 21% (odds ratio,* 2.93; p=0.034; number needed to treat,* 4.7). When groups receiving active agents were combined, the 2 groups that received aspirin had a significantly higher response rate than those who received

placebo (odds ratio, 3.67; p=0.019), but no such effect occurred for the minocycline groups. Response to minocycline was associated with higher initial interleukin-6 (IL-6) levels and with greater IL-6 decreases during treatment. One patient in the minocycline–aspirin group experienced hypomania during the study. There was no difference between groups in YMRS scores.

Discussion: These results provide preliminary evidence that aspirin and minocycline may be effective adjunctive therapies for the treatment of bipolar depression. Additional study appears to be warranted.

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

Savitz J, Teague T, Misaki M, Macaluso M, et al: Treatment of bipolar depression with minocycline and/or aspirin: an adaptive, 2x2 double-blind, randomized, placebo-controlled, phase IIA clinical trial. *Translational Psychiatry* 2018; doi 10.1038/s41398-017-0073-7. From the Laureate Institute for Brain Research, Tulsa, OK; and other institutions. **Funded by the Stanley Medical Research Institute; and the Laureate Institute for Brain Research. Five of 11 study authors disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

***See Reference Guide.**

Fluvoxamine Augmentation in Schizophrenia

Augmentation of risperidone with fluvoxamine improved cognitive function and negative symptoms in a small randomized trial in patients with schizophrenia.

Background: Fluvoxamine is a candidate drug for improving cognitive function because of its affinity for the sigma-1 receptor, which is believed to be involved with cognitive impairment in schizophrenia. Previous studies have evaluated both cognitive- and negative-symptom effects of adjunctive fluvoxamine in schizophrenia with mixed results.

Methods: The study enrolled 68 inpatients (46 men) with chronic schizophrenia (DSM-5) who were receiving risperidone as maintenance treatment. Patients were aged 19–61 years (mean age, 42 years) and free of dementia, depression, and extrapyramidal symptoms. Participants were randomly assigned to receive fluvoxamine (50 mg/day for 2 weeks and then increased to 100 mg/day) or placebo. Fluvoxamine was tapered between weeks 8 and 10. Patients were evaluated with the Scale for the Assessment of Negative Symptoms (SANS) and Positive Symptoms (SAPS), the Wechsler Memory Scale (WMS), and the World Health Organization Quality of Life scale.

Results: Neither treatment group showed a significant decline in positive symptoms, and scores on the SAPS did not differ between the groups at week 10. Negative symptoms scores improved significantly in both treatment groups, from baseline means of 48 and 49, respectively, to 38 and 44 ($p<0.001$). SANS score improvement was significantly greater with fluvoxamine than with placebo ($p=0.004$). Among the subdomains of the SANS, fluvoxamine was associated with improvement in poverty of speech, attention deficit, and curbing of interests, but not apathy or diminished emotional range. Patients in the fluvoxamine group had higher memory scores at baseline than the placebo group, and the difference widened over the course of the trial. At week 10, the between-group difference in WMS scores significantly favored fluvoxamine ($p=0.02$). Changes in quality of life scores were significantly improved with fluvoxamine compared with placebo ($p\leq0.001$).

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial, but the funding source was not declared.

Javadi A, Shafikhani A, Zamir S, Khanshir Z: Evaluation of the effect of fluvoxamine in patients with schizophrenia under risperidone treatment: a clinical trial. *Journal of Clinical Psychopharmacology* 2018;38 (April):119–124. From the Qazvin University of Medical Sciences, Iran. **Source of funding not stated. The study authors declared no competing interests.**

Common Drug Trade Names*: fluvoxamine—*Luvox*; risperidone—*Risperdal

***See Reference Guide.**

Comparative Efficacy of Antidepressants

According to the results of a systematic review and network meta-analysis including 21 different antidepressants, all antidepressants are more effective than placebo in patients with unipolar major depression, and several agents are significantly more effective than the others.[1] The analysis also identified differences among the antidepressants in patient acceptability.

Methods: This research is an update and extension of a major meta-analysis of antidepressant efficacy and tolerability, published in 2009.[2] The analysis includes all second-generation antidepressants approved in the U.S., Europe, and Japan, plus trazodone, nefazodone, and 2 widely prescribed tricyclics and was based on randomized controlled trials comparing the agents with placebo or other antidepressants as oral monotherapy in adults with major depressive disorder. The primary efficacy outcome was response, defined as a ≥50% improvement in a standardized, observer-rated depression scale score. Acceptability was measured using the rate of withdrawal for any reason.

Results: A total of 522 controlled trials performed between 1979 and 2016 in >116,000 patients were included. Trial durations were generally 6–8 weeks. Most of the included trials (n=421) were identified by literature search, an additional 86 were unpublished and found on clinical trial registries or pharmaceutical company websites, and 15 came from other sources. The majority of studies (78%) were funded by pharmaceutical companies. Nearly all drugs were evaluated in ≥1 placebo-controlled trial, and most were also evaluated in ≥1 head-to-head comparison.

All medications were more effective than placebo at producing a response. (See table.) Relative to placebo, amitriptyline had the highest odds ratio* for response at 2.13. Odds ratios for other antidepressants compared with placebo ranged from 1.37 to 1.89, with wide confidence intervals. In head-to-head studies, several antidepressants—agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine—were shown to be superior to others, with odds ratios ranging from 1.19 to 1.96. The least effective drugs in head-to-head comparisons were fluoxetine, fluvoxamine, reboxetine, and trazodone. Overall, antidepressants were also more effective than placebo at inducing remission (effect size,* 0.30; p<0.0001).

Two drugs—agomelatine and fluoxetine—were associated with a lower rate of all-cause discontinuation than placebo; however, all active drugs were associated with higher withdrawal rates for adverse events than placebo. In comparative studies, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were significantly better tolerated than other drugs, with odds ratios for dropout ranging from 0.43 to 0.77. Amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine were associated with the highest dropout rates.

Antidepressant Efficacy Relative to Placebo

Agent	Odds Ratio for Response
Amitriptyline	2.13
Mirtazapine	1.89
Duloxetine	1.85
Venlafaxine	1.78
Paroxetine	1.75
Milnacipran	1.74
Fluvoxamine	1.69
Escitalopram	1.68
Nefazodone	1.67
Sertraline	1.67
Vortioxetine	1.66
Agomelatine±	1.65
Vilazodone	1.60
Levomilnacipran	1.59
Bupropion	1.58
Fluoxetine	1.52
Citalopram	1.52
Trazodone	1.51
Clomipramine	1.49
Desvenlafaxine	1.49
Reboxetine±	1.37

± Not available in the U.S.

Smaller and older studies generally produced larger positive effects for the active medication versus placebo. This was particularly the case for amitriptyline, bupropion, fluoxetine, and reboxetine. A "novelty" effect was observed, in which newer or experimental drugs performed better than older ones or controls. Adjusting for this effect diminished the differences among drugs. The strength of evidence supporting efficacy was moderate at best and low for a number of drugs.

Discussion: The summary effect sizes for most antidepressants were relatively modest. However, several agents emerged as combining a relatively high response rate and a low dropout rate: escitalopram, mirtazapine, paroxetine, agomelatine, and sertraline.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

[1]Cipriani A, Furukawa T, Salanti G, Chaimani A, et al: Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018; doi 10.1016/S0140-6736(17)32802-7. From the University of Oxford, U.K.; and other institutions. **Funded by the National Institute for Health Research Oxford Health Biomedical Research Centre; and the Japan Society for the Promotion of Science. Six of 18 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Cipriani A, et al: Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatment meta-analysis. *Lancet* 2009;373:746–758.

Drug Trade Names*: agomelatine (not available in the U.S.)—*Valdoxan*; amitriptyline—*Elavil*; bupropion—*Wellbutrin*; citalopram—*Celexa*; clomipramine—*Anafranil*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; levomilnacipran—*Fetzima*; milnacipran—*Savella*; mirtazapine—*Remeron*; nefazodone—*Serzone*; paroxetine—*Paxil*; reboxetine (not available in the U.S.)—*Edronax*; sertraline—*Zoloft*; trazodone—*Oleptro*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Brintellix

***See Reference Guide.**

Injection Reactions with Paliperidone

The recently introduced 3-month formulation of injectable paliperidone was associated with low rates of injection-site pain and reactions, according to a retrospective analysis of a phase III clinical trial.[1] Despite a larger injection volume, the 3-month formulation had similar rates of local pain and reactions to 1-month long-acting injectable (LAI) paliperidone.

Methods: Safety data were analyzed from a previously published multinational noninferiority study comparing 3-month with 1-month LAI paliperidone.[2] Patients were adults with moderately severe and worsening schizophrenia who were discontinuing other antipsychotics or who preferred injectable medications. All patients received open-label, flexible-dose, once-monthly paliperidone injections. After 17 weeks, patients who were clinically stable (i.e., a Positive and Negative Syndrome Scale score <70) were randomly assigned to continue fixed doses of 1-month paliperidone or 3-month paliperidone with placebo injections in other months. Randomized treatment continued for 48 weeks. After the first few injections (all in the deltoid), the site of injection (deltoid or gluteal) was generally at the clinician's discretion and remained the same in each patient throughout the study, with the site switched between left and right each month. Injection site pain was assessed within 30 minutes after the injection, using a 100-point visual-analog scale. Trained observers rated injection-site reactions for induration, redness, and swelling.

Results: More than 1400 patients entered the open-label phase, and 1015 received double-blind treatment. During the double-blind period, 59% of patients were receiving injections in the deltoid, 30% in the gluteal muscle, and 11% in both sites.

Mean pain scores decreased from about 22 points with the first injection to 19 at the end of open-label treatment. Average scores decreased further during randomized treatment, to 18.4 with 1-month paliperidone and to 15.5 with the 3-month formulation. Pain ratings did not

differ between deltoid and gluteal injections. Treatment-emergent redness, induration, or swelling was observed in ≤6% of patients in the open-label phase and ≤5% in the double-blind phase, with no difference between the 2 formulations. Swelling and redness were generally mild. During the double-blind phase, 6% of patients in the 1-month group and 8% in the 3-month group spontaneously reported injection-site reactions. One patient had mild panniculitis at the injection site with 3-month paliperidone, and 1 had moderately severe swelling; both of these events resolved. Two patients were withdrawn from the study for injection-site pain in the open-label phase, and none in the double-blind phase.

Discussion: A dose of 3-month paliperidone has 1.75 times the volume of an equivalent dose of 1-month paliperidone. Despite little research evidence on injection volumes, most guidelines specify that deltoid injections should not exceed 2 mL, a volume that is exceeded with higher doses of 3-month paliperidone. In this study, >200 patients in both treatment groups received injections that exceeded 2 mL. These results suggest that, with proper injection technique, deltoid injections of 3-month paliperidone are well tolerated.

[1]Sliwa J, Savitz A, Nuamah I, Mathews M, et al: An assessment of injection site reaction and injection site pain of 1-month and 3-month long-acting injectable formulations of paliperidone palmitate. *Perspectives in Psychiatric Care* 2018; doi 10.1111/ppc.12267. From Janssen Scientific Affairs, Titusville NJ. **Funded by Janssen. All study authors disclosed financial relationships with commercial sources including Janssen.**

[2]Savitz A, et al: Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study. *International Journal of Neuropsychopharmacology* 2016; doi 10.1093/ijnp/pyw018. See *Psychiatry Drug Alerts* 2016;30 (May):38–39.

Common Drug Trade Names*: paliperidone, monthly—*Invega Sustenna*; paliperidone, 3-month—*Invega Trinza

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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.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison 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.

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Lithium in Chronic Kidney Disease

In a population-based cohort study, continued use of lithium after a diagnosis of mild chronic kidney disease (CKD) did not increase the rate of progression to end-stage renal disease. In addition, switching patients to an anticonvulsant did not confer any protection against kidney failure.

Methods: Data were collected from linked Danish nationwide medical and vital records databases. The study cohort consisted of all patients who received a diagnosis of CKD between 1995 and 2012 who also had a history of lithium or anticonvulsant use during this period. CKD was defined broadly as either definite or possible disease, not requiring dialysis or transplantation. Study outcomes were progression to end-stage renal disease or death. Outcomes were compared in separate cohorts of patients with a history of lithium use or anticonvulsant use. The indication for prescription of these agents was not available, but separate analyses were carried out in subcohorts of patients with a diagnosis of bipolar disorder.

Results: A total of 754 patients received a diagnosis of CKD and were exposed to lithium, including 238 with a bipolar-disorder diagnosis. The anticonvulsant cohort consisted of 5004 patients, of whom 199 had bipolar disorder. The median age of each cohort was 66 years.

Among patients with a history of lithium treatment, about one third continued to use lithium after the diagnosis of CKD, including 32% of those treated for bipolar disorder. In the cohort who continued anticonvulsants after the diagnosis of CKD, 70% of those with bipolar disorder continued anticonvulsants and 21% added on or were switched to lithium.

The absolute risk of progression to end-stage renal disease was 20% over the 10 years post diagnosis, with little difference between patients with lithium or anticonvulsant exposure. Rates of progression to renal failure were decreased by about half in patients who continued taking lithium or anticonvulsants compared with those who discontinued (see table, next page), although the decreased risk was not statistically significant in patients with bipolar disorder receiving anticonvulsants. Risk of the combined outcome of renal failure and death was

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lowered by a similar proportion. For both lithium and anticonvulsants, relative risk of renal failure decreased as the number of prescriptions increased.

Adjusted hazard ratios* for end-stage CKD (ESKD) and death		
Outcome	**All with CKD**	**Bipolar disorder and CKD**
Patients with continued lithium exposure		
ESKD	0.58	0.40
ESKD or death	0.57	0.50
Patients with continued anticonvulsant exposure		
ESKD	0.53	0.70
ESKD or death	0.55	0.50

Discussion: Concerns have been raised that long-term lithium treatment can impair renal function, but modern treatment within recommended serum levels may have eliminated the risk of end-stage renal disease. The present results, while encouraging, require confirmation because it is likely that at least part of the association between medication and reduced end-stage renal disease was the result of bias toward switching medications in patients with more severe kidney disease.

Kessing L, Feldt-Rasmussen B, Andersen P, Gerds T, et al: Continuation of lithium after a diagnosis of chronic kidney disease. *Acta Psychiatrica Scandinavica* 2017;136 (December):615–622. From the University of Copenhagen, Denmark; and other institutions. **Funded by Aalborg University Hospital, Denmark. Three of 5 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Discontinuing Antipsychotics After First Episode

In patients with first-episode psychosis who experienced a full response to medication, early discontinuation of maintenance therapy was associated with poor clinical outcomes at 10 years.[1]

Methods: This follow-up study was conducted in patients who had received treatment for first-episode schizophrenia in a randomized maintenance trial.[2] Patients were aged ≥18 years at initial study entry, had received antipsychotic medication for ≥1 year before enrollment, were free of positive symptoms, and had no history of relapse. Among the exclusion criteria were treatment with clozapine, poor medication adherence, and risk of suicide. At the outset of the trial, patients were randomly assigned to early discontinuation with placebo or maintenance with 400 mg/day quetiapine. The present report describes outcomes in this patient cohort after 10 years of follow-up. Patients had received an average of about 2 years of maintenance treatment before enrollment in the trial and 1 year of treatment during the trial. After the acute trial, patients received naturalistic treatment from non-study physicians and were recontacted after 10 years. The primary outcome of the follow-up study was a composite of positive symptoms or treatment with clozapine at the 10-year evaluation, and suicide. Poor long-term outcome was defined as persistent positive symptoms, requirement for clozapine treatment, or death by suicide.

Results: Charts were reviewed for all 178 patients who participated in the randomized trial, and 142 patients were interviewed during follow-up. All 178 patients were included in the 10-year analysis. Patients received antipsychotics for a mean of nearly 9 of those years. Patients in the placebo group had a higher rate of relapse during the first year after randomization than those receiving maintenance therapy, as previously reported (79% vs 41%; $p<0.0001$). During the 10-year follow-up period, poor long-term outcomes occurred in 39% of patients in the discontinuation group, compared with 21% of the maintenance group (relative risk,* 1.84; $p=0.012$). A mediation analysis showed that relapse during the first year was a significant predictor of poor long-term outcome, accounting for 58% of the difference between the 2 groups.

Discussion: Absent reliable evidence, clinical guidelines recommend antipsychotic maintenance therapy for 12–24 months, with ambivalent recommendations for longer treatment. The present study suggests that for patients who have had a full response, continuing antipsychotic medication for at least the first 3 years after starting treatment may prevent relapse and reduce the risk of a poor outcome.

[1]Hui C, Honer W, Lee E, Chang W, et al: Long-term effects of discontinuation from antipsychotic maintenance following first-episode schizophrenia and related disorders: a 10 year follow-up of a randomised, double-blind trial. *Lancet Psychiatry* 2018; doi 10.1016/S2215-0366(18)30090-7. From the University of Hong Kong, China; and other institutions. **Funded by the Research Grants Council of Hong Kong; and other sources including AstraZeneca. Three of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Chen E, et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *British Medical Journal* 2010; doi 10.1136/bmj.c4024.

Common Drug Trade Names*: clozapine—*Clozaril*; quetiapine—*Seroquel

***See Reference Guide.**

Antipsychotics and Venous Thromboembolism

According to a review of observational studies, antipsychotics are likely associated with increased risk of venous thromboembolism (VTE). There are no well-documented differences between first- and second-generation agents or between individual drugs.

VTE encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE). Uncontrolled observational studies identified a high incidence of PE in patients with schizophrenia as early as the 1950s, but the association was not widely acknowledged. Following reports of PE and VTE in patients taking clozapine (*Clozaril*) in the 1990s, numerous case–control and cohort studies and meta-analyses were carried out to investigate whether risk was associated with aspects of underlying psychosis, lifestyle factors, or antipsychotic treatment.

A literature review identified 27 observational studies examining the risk of VTE in antipsychotic-treated patients. Although results of some studies were inconclusive, the general direction of this research has been to support an association. Risk estimates are based on heterogeneous studies with different methods, populations, and drug-use patterns. Overall, odds ratios* for VTE ranged from as low as 0.7 to >24. (See table.) It should be noted that most of the evidence comes from case-control studies (n=15), which may overestimate risks. Additional cohort studies are needed to confirm these observations.

Range of odds ratios for VTE in antipsychotic-treated patients	
All antipsychotics	1.1–13.3
First-generation agents	0.89–7.1
Low-potency first-generation agents	0.7–24.1
High-potency first-generation agents	1.5–3.3
Second-generation agents	0.9–3.4
New antipsychotic use	2.0–3.3
Current vs past antipsychotic use	2.0–3.5

The highest risk of antipsychotic-associated VTE occurs during the first 3 months of drug use. Studies comparing risk in users of first- and second-generation agents have not had conclusive results. Although some larger studies of individual agents have been carried out, no agents have been identified with higher or lower risk of VTE than others.

The etiology of antipsychotic-associated VTE is not known and is likely to be multifactorial. Drug-related factors include adverse effects such as sedation, weight gain, and hyperprolactinemia. Obesity and sedentary lifestyle are relatively common in patients with schizophrenia and aggravate risk. Physical restraints can also increase the risk of VTE. Risk for VTE can be estimated using a score that incorporates established nonpsychiatric risk factors such as age, obesity, hormone therapy, dehydration, immobilization, acute infection, and history of DVT

or PE. Risk should be re-evaluated when the clinical situation changes—e.g., infections, surgery, or reduced mobility. Preventive measures include reducing modifiable risk factors and starting prophylactic antithrombotic treatment in hospitalized patients with reduced mobility.

Jonsson A, Schill J, Olsson H, Spigset O, et al: Venous thromboembolism during treatment with antipsychotics: a review of current evidence. *CNS Drugs* 2018;32 (January):47–64. From Linkoping University, Sweden. **This review was conducted without funding. The authors declared no competing interests.**

***See Reference Guide.**

Adjunctive Cannabidiol in Schizophrenia

In a preliminary placebo-controlled trial, adjunctive cannabidiol improved psychotic symptoms and clinical status in patients with schizophrenia.

Background: Cannabidiol (CBD) is 1 of the 2 major components of *Cannabis sativa*. Preliminary research has suggested that it may have antipsychotic properties, and because it acts via a different mechanism than antipsychotics, it may be a promising adjunctive treatment for schizophrenia.

Methods: The present study used a standardized, oral liquid formulation of CBD. The study, conducted at 3 centers in Europe, enrolled adult patients with schizophrenia or a related disorder who had at least a partial response to antipsychotic medication but continued to have a Positive and Negative Syndrome Scale (PANSS) score of ≥60 despite a stable antipsychotic dose for ≥4 weeks. Substance use was not an exclusion criterion. However, patients in whom psychosis may have been induced by substance use were excluded. Participants were randomly assigned to double-blind adjunctive treatment with 1000 mg/day CBD, taken in 2 divided doses, or placebo for 6 weeks. Baseline antipsychotic therapy was continued without change through the study period. Because this was an exploratory study, a number of key endpoints—symptom severity, cognitive performance, and level of functioning—were defined, rather than a single primary outcome.

Results: Of 88 participants (mean age, 41 years; 58% male) enrolled in the trial, 2 discontinued because of adverse events and 3 left the study for other reasons. In the remaining 83 participants, PANSS positive symptom scores (baseline mean, 18 in both groups) were decreased to a significantly greater degree with CBD (mean difference, 1.4 points; p=0.019). The groups did not differ significantly in changes on the PANSS total, negative, or general symptom subscales, or on the Scale for the Assessment of Negative Symptoms, although numeric differences generally favored CBD. Clinical Global Impression–Improvement (CGI-I) ratings showed greater gains in the CBD group, with 78.6% rated by their clinicians as "improved" or better, compared with 54.6% of the placebo group (p=0.018). The proportion of patients rated with mild, borderline, or no illness according to the CGI–Severity scale increased from 16.7% to 45.2% in the CBD group and from 20.5% to 36.4% in the placebo group (p=0.044). Cognitive testing (using the Brief Assessment of Cognition in Schizophrenia (BACS) showed a significantly greater improvement in motor speed in the CBD group than the placebo group (p<0.05). BACS scores for overall cognitive function and executive function favored CBD but the differences were not statistically significant. The difference in scores on the Global Assessment of Functioning scale, while favoring CBD, also did not reach statistical significance.

There were no significant changes in weight, prolactin levels, abnormal movements, or sleep quantity or quality in either group. Adverse events, mostly gastrointestinal, were mild and resolved without treatment.

Discussion: Although the effects of CBD seemed modest, they were achieved with good tolerability and on top of ongoing antipsychotic treatment. The changes in CGI ratings indicate that

CBD-related improvement was apparent to clinicians and therefore probably clinically meaningful. The trend for cognitive improvement raises the possibility that CBD may have positive effects on cognition. The mechanism by which CBD improves psychotic symptoms is unclear, but it does not act via dopamine receptor antagonism like currently available antipsychotic drugs.

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

McGuire P, Robson P, Cubala W, Vasile D, et al: Cannabidiol (CBD) as adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. *American Journal of Psychiatry* 2018;175 (March):225–231. From Kings College London, U.K.; and other institutions. **Funded by GW Research Ltd.; and other sources. Six of 8 study authors disclosed financial relationships with commercial sources including GW Research Ltd; the remaining authors declared no competing interests.**

***See Reference Guide.**

Psilocybin in Resistant Depression

In a small, open-label study, administration of psilocybin with psychological support was well tolerated and had long-term beneficial effects in patients with treatment-resistant depression.

Background: Psilocybin is a naturally occurring plant alkaloid that is being increasingly evaluated as treatment for a range of psychiatric disorders including depression. Like other serotonergic psychedelics, psilocybin effects are driven by serotonin 2A receptor activity.

Methods: Study participants (n=20) had unipolar depression of at least moderate severity, with scores of ≥16 on the 21-item Hamilton Rating Scale for Depression (HAM-D), despite receiving ≥2 courses of pharmacologically distinct antidepressants for ≥6 weeks each during the current episode. Following a washout of previous antidepressant therapy, all patients received 2 treatments with psilocybin, first 10 mg and then 25 mg, separated by 1 week. Psychological support began with an introductory preparation visit, in which the therapist built a relationship with the patient and provided information on what to expect. Patients also received emotional support before, during, and after the psilocybin sessions and a follow-up debriefing visit that could include interpretation and advice about maintaining positive changes in outlook and lifestyle. The primary efficacy outcome measure was change from baseline on the self-reported Quick Inventory of Depressive Symptomatology (QIDS-SR), collected 1–3 weeks, 5 weeks, and 3 and 6 months after the high-dose psilocybin session. The psilocybin experience was evaluated using an 11-dimension altered states of consciousness questionnaire.

Results: Of the 20 participants (age range, 27–64 years; 6 women), depression was severe in 18 and moderate in 2. The mean lifetime number of previous treatment trials was 4.6, and 7 patients had previously tried psilocybin. None of these factors was predictive of treatment response.

Outcomes were analyzed for the 19 patients who completed both treatments and all assessments. The average QIDS-SR score was near 20 at study entry and was significantly reduced at all post-treatment time points, with the maximum effect at 5 weeks (9.2-point mean reduction; $p<0.001$; effect size,* 2.3). All 19 patients had reduced QIDS-SR scores beginning 1 week after treatment, and most had sustained improvement at 3–5 weeks. These results were supported by significant reductions in HAM-D and Beck Depression Inventory scores (effect sizes at 1 week, 2.3 and 2.5, respectively; $p<0.0001$ for both). At 6 months, the mean QIDS-SR score was still significantly lower than baseline ($p=0.0035$). Of the 19 patients who completed the study, 5 obtained additional psilocybin on their own between 3 and 6 months after the study treatments. Removing these patients from the analysis did not alter the long-term results.

A total of 14 patients reported experiencing autobiographical visions, usually regarded as insightful and informative. The altered states of consciousness evaluation identified several items that differed between the low and high doses: experience of unity, spiritual experience,

blissful state, insightfulness, and complex imagery. When these interrelated items were combined into a single factor, the factor was significantly associated with improvement on the QIDS-SR.

Psilocybin was generally well tolerated. One patient had an "overwhelming," although "blissful" experience during high-dose psilocybin and refused some follow-up measures. Adverse effects of psilocybin included transient anxiety, headache, nausea, and paranoia. There were no flashbacks or persisting perceptual changes.

Carhart-Harris R, Bolstridge M, Day C, Rucker J, et al: Psilocybin with psychological support for treatment-resistant depression: six month follow-up. *Psychopharmacology* 2008;235 (February):399–408. From Imperial College London, U.K.; and other institutions. **Funded by the UK Medical Research Council; and the Alex Mosley Charitable Trust. The authors declared no competing interests.**

***See Reference Guide.**

Psychotic Symptoms in Parkinson's Disease

Although they consist of hallucinations and delusions, psychotic symptoms in Parkinson's disease differ greatly from positive symptoms of schizophrenia. Hallucinations are generally emotionally neutral, often consisting of people silently conducting activities in the margins of the patient's visual field. When acknowledged by the patient, the figures typically disappear. They return regularly, and can become a problem when the patient feels threatened by their appearance. In many cases, patients and their families are willing to tolerate benign hallucinations as medication-induced. Delusions in Parkinson's disease are generally paranoid and may precipitate agitation. Treatment may be required if the symptoms are bothersome and should be considered in anticipation of an increase in antiparkinsonian medications.

Before initiating treatment for psychosis in patients with Parkinson's disease, medical illnesses should be ruled out; infections can exacerbate Parkinson's disease and cause delirium with psychotic features. Next, possible medication associations should be evaluated as a contributing factor. Psychoactive drugs such as anxiolytics and antidepressants, anticholinergic medications for urinary incontinence, and pain medications may all contribute to psychotic symptoms. These drugs should be reduced to their lowest tolerated doses, and then medications for Parkinson's disease motor function should be assessed. The sequence for reducing these dosages should be individualized. It has been suggested that the dosage of anticholinergics, amantadine, dopamine agonists, and MAO-B inhibitors be reduced, in that order, before considering a reduction of L-dopa and COMT inhibitors. Worsening of parkinsonism should be anticipated when these drugs are reduced.

If the symptoms continue to require treatment, there are 2 medications with convincing evidence of efficacy in Parkinson's disease psychosis: pimavanserin (the only FDA-approved drug for the indication) and clozapine. Although not supported by clinical trial evidence, many clinicians have also reported good results with quetiapine. Pimavanserin is well tolerated and moderately effective. Clozapine appears to be highly effective in Parkinson's disease psychosis in the dosage range of 6.25–50 mg/day and does not compromise motor function. However, sedation, which can worsen delirium, along with neutropenia and agranulocytosis, are potential concerns.

Onset of pimavanserin efficacy may take 4–6 weeks, while clozapine may reduce symptoms within 1 week, suggesting that for patients who can tolerate symptoms temporarily, pimavanserin may be the best option while clozapine may be more beneficial when a rapid symptom reduction is required.

Friedman J: Pharmacological interventions for psychosis in Parkinson's disease patients. *Expert Opinion on Pharmacotherapy* 2018; doi 10.1080/14656566.2018.1445721. From Butler Hospital and Brown University, Providence, RI. **Funded by the NIH; and other sources. The author disclosed potentially relevant financial relationships.**

Common Drug Trade Names*: amantadine—*Symmetrel*; clozapine—*Clozaril*; pimavanserin—*Nuplazid*; quetiapine—*Seroquel

Timing of Antidepressant Response

According to results of a meta-analysis of long-term acute treatment trials, patients whose depressive symptoms do not initially respond to antidepressant monotherapy may continue to experience improvements over 3 months without a change in their treatment. However, the likelihood of improvement after the first 12 weeks of nonresponse is relatively small.

Background: Current recommendations on how long to persist with acute antidepressant treatment vary widely, largely because of a scarcity of data on response and remission after 4–6 weeks. The present study was undertaken to estimate the time point at which the likelihood of response and/or remission ceases to increase.

Methods: The meta-analysis synthesized data from trials of clinically common treatment durations. The included studies compared antidepressant monotherapy with placebo in adults with unipolar major depressive disorder. Trials in patients with treatment-resistant disease and those in patients with concurrent disorders were included, but continuation trials were excluded because patients in these trials had already experienced response to acute medication. The eligible trials had continuous outcome reporting every 4 weeks for ≥12 weeks (and up to 24 weeks), during which time patients continued to receive their randomly assigned antidepressant or placebo. The primary outcome of the meta-analysis was the additional number of previously nonresponsive patients who met response criteria at each time point, with response defined as a ≥50% decrease in score on a standardized depression rating scale.

Results: A total of 9 studies, with 3466 patients, met the inclusion criteria. About two-thirds of the study patients received active medication (citalopram, desvenlafaxine, duloxetine, fluoxetine, levomilnacipran, mianserin, paroxetine, sertraline, or venlafaxine), and one-third received placebo.

Five studies had complete data through weeks 5–8 and 9–12. Previously nonresponsive patients continued to have response to medication during these periods, with about twice the likelihood as response to placebo. (See table.) Rates of remission also increased in previously unremitted patients receiving active medication, by 17% in weeks 5–8 and 13.5% in weeks 9–12. The corresponding remission rates in placebo-treated patients were 16% and 8%. Two studies had complete data on patients treated for 24 weeks. In these studies, response rates with both medication and placebo plateaued after week 12.

Rates of new response in patients previously nonresponsive to antidepressant or placebo

Weeks	Percentage of New Responders		Odds Ratio*	Number Needed to Treat*
	Drug	Placebo		
5–8	21.6%	13%	1.97	11
9–12	9.9%	2.4%	2.25	17

Discussion: These results suggest the additional likelihood of a response after 4 weeks may be substantial enough to weigh against the possible adverse effects of second-stage treatment strategies, at least until week 12. Previous evidence has suggested that if response is not achieved by week 12, switching to another antidepressant monotherapy may not be any more effective than continuing with the same drug. However, efficacy may be improved by

augmentation with lithium or a second-generation antipsychotic, adding a second antidepressant, increasing the dose of the initial antidepressant, or ECT.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Henssler J, Kurschus M, Franklin J, Bschor T, et al: Trajectories of acute antidepressant efficacy: how long to wait for response? A systematic review and meta-analysis of long-term, placebo-controlled acute treatment trials. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17r11470. From the University of Cologne Medical School. Germany. **Funded by the University of Cologne; and other sources. The authors declared no competing interests.**

Common Drug Trade Names*: citalopram—*Celexa*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; levomilnacipran—*Fetzima*; mianserin (not available in the U.S.)—*Tolvon*; paroxetine—*Paxil*; sertraline—*Zoloft*; 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.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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.

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Quetiapine/Venlafaxine Interaction

Co-administration of quetiapine was associated with increased levels of the active metabolite of venlafaxine in an observational study. The increase in the venlafaxine metabolite and active moiety is moderate but clinically significant, possibly influencing antidepressant action and adverse effects.

Methods: The study was based on serum drug measurements from inpatients with various psychiatric disorders who received treatment at a single facility in 2013–2016. Trough blood samples were drawn before the morning dose during steady state drug administration. The database included 153 patients who received an oral formulation of venlafaxine alone and 71 who were co-medicated with quetiapine. The analysis excluded patients taking other drugs that influenced the relevant cytochrome P450 pathways. Samples were analyzed for levels of venlafaxine, the active metabolite *O*-desmethylvenlafaxine, and the active moiety (venlafaxine plus *O*-desmethylvenlafaxine).

Results: The 2 groups were similar in age and gender distribution and received a similar mean dosage of venlafaxine: 171 mg/day in the monotherapy group and 183 mg/day in the comedicated group. The mean dosage of quetiapine was 241 mg/day. Most patients (n=65) received extended-release quetiapine.

The group receiving quetiapine had significantly higher levels of *O*-desmethylvenlafaxine (265 ng/mL vs 205 ng/mL; p=0.003) and the active moiety (354 ng/mL vs 305 ng/mL; p=0.002) than the monotherapy group. Levels of venlafaxine were numerically but not statistically higher in comedicated patients (81 ng/mL vs 66 ng/mL). The ratio of the active metabolite to parent compound did not differ significantly between the 2 groups. Dose-adjusted levels of *O*-desmethylvenlafaxine and the active moiety were also elevated significantly in the comedicated group (p=0.015 and p=0.038, respectively).

Discussion: Venlafaxine and quetiapine partially share the same metabolic pathway, which influences metabolism of *O*-desmethylvenlafaxine but not the major inactive venlafaxine

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metabolite, *N*-desmethylvenlafaxine. In the present analysis, comedication was associated with a 29.3% increase in levels of *O*-desmethylvenlafaxine and a 15.8% increase in the active moiety, indicating reduced venlafaxine clearance. The authors note that CYP2D6 genotype, which could affect venlafaxine metabolism, was not evaluated in the study patients, possibly limiting the generalizability of the findings.

Paulzen M, Schoretsanitis G, Hiemke C, Grunder G, et al: Reduced clearance of venlafaxine in a combined treatment with quetiapine. *Progress in Neuropsychopharmacology & Biological Psychiatry* 2018;85 (July):116–121. From Aachen University, Germany; and other institutions. **This research was conducted without funding. Three authors disclosed relevant relationships with commercial sources; the remaining 3 authors declared no competing interests.**

Common Drug Trade Names*: quetiapine—*Seroquel*; venlafaxine—*Effexor

Lamotrigine Immune System Reaction

The FDA has issued a warning that the anticonvulsant lamotrigine (*Lamictal*) can cause hemophagocytic lymphohistiocytosis (HLH), a rare but serious immune system reaction that can result in severe inflammation throughout the body. HLH triggers an uncontrolled immune response that can lead to serious liver, kidney, lung, and blood cell issues. Patients with HLH typically present with persistent fever, rash, or other nonspecific symptoms. The diagnosis of HLH is based upon the patient exhibiting ≥5 of the following 8 symptoms: fever and rash; enlarged spleen; cytopenia; elevated triglyceride levels or low fibrinogen levels; high serum ferritin levels; hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy; decreased or absent natural killer cell activity; or elevated blood levels of CD25 indicating prolonged immune cell activation. Lamotrigine should be discontinued if HLH is suspected.

Lamictal (lamotrigine): Drug Safety Communication - Serious Immune System Reaction. Available at https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm605628.htm.

Safety of Clozapine Rechallenge

According to a review of published case reports, rechallenge with clozapine (*Clozaril*) may be an option for patients who have stabilized following drug-induced neutropenia or neuroleptic malignant syndrome. Rechallenge after agranulocytosis or myocarditis is not advised.

Methods: A literature search was undertaken to identify all reports of rechallenge after adverse reactions to clozapine reported in 1971–2017. The rechallenge was considered successful if the patient did not experience the previous complication or any other serious adverse event during the reported follow-up interval. The outcome of rechallenge after each complication was considered favorable if there were ≥5 reported cases and more than half were successful.

Results: The search identified 259 clozapine rechallenge reports, all of which were single case reports. Rechallenge was successful in 157 patients (61%). Outcome was favorable in 3 of 17 cases of agranulocytosis (18%), 128 of 203 cases of neutropenia (63%), 11 of 17 cases of myocarditis (65%), and all 7 cases of neuroleptic malignant syndrome (100%). There were also isolated reports of successful rechallenge following eosinophilia, cardiac complications other than myocarditis, and gastrointestinal hypermotility. Rechallenge was unsuccessful in 3 cases of pancreatitis, 2 of renal insufficiency, and 1 of clozapine-induced lupus. No fatal outcomes were reported in any of the cases.

Discussion: Based on the reviewed case reports, the authors conclude that clozapine-associated agranulocytosis, pancreatitis, renal failure, and lupus should be considered "nonrechallengeable." Seemingly positive results after myocarditis should be interpreted cautiously because of the small number of cases reported.

Manu P, Lapitskaya Y, Shaikh A, Nielsen J: Clozapine rechallenge after major adverse effects: clinical guidelines based on 259 cases. *American Journal of Therapeutics* 2018; doi 10.1097/MJT.0000000000000715. From Hofstra Northwell School of Medicine, Hempstead, NY; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

Clozapine and All-Cause Mortality

Continuous use of clozapine (*Clozaril*) was associated with reduced mortality compared with other antipsychotics in a meta-analysis of studies lasting >1 year. This observation calls into question existing concern that clozapine-associated cardiovascular effects may increase mortality risk.

Methods: A comprehensive literature search identified studies published through March 2018 conducted in patients with schizophrenia spectrum disorders who received treatment with clozapine and were followed for >1 year. Included studies were required to have mortality as an outcome, and rates were compared between patients treated continuously or ever with clozapine or other antipsychotics.

Results: The analysis included 24 studies (1 randomized trial and 23 observational studies) with a median follow-up of 5.4 years and a maximum of 12.5 years. Crude mortality rates in patients who used clozapine varied widely across the studies, from 0 to 41 per 1000 patient-years. Mortality did not differ substantially in studies that reported continuous versus ever use of clozapine, or as a function of demographic or study characteristics. A comparison of patients who took clozapine throughout a mean observation period of >7 years found that compared with continuous use of other antipsychotics, clozapine was associated with a significant reduction in mortality (crude mortality rate ratio, 0.56; p=0.007). Mortality rates were numerically but not significantly lower in studies of patients ever exposed to clozapine compared with those exposed to other antipsychotics (mortality rate ratio, 0.74). In the few studies that compared any use of clozapine with no antipsychotic use, clozapine had a mortality rate ratio of 0.34 (p≤0.001).

Data were inconsistent or insufficient to analyze clozapine effects on specific causes of death. However, 13 studies reported data on suicide mortality. Rates ranged widely in individual studies, and patients exposed to clozapine compared with other antipsychotics were found to have a numerically lower suicide rate that did not reach statistical significance.

Discussion: These findings suggest that benefits of continuous clozapine use in prolonging life expectancy may be diminished or lost when the drug is discontinued. Possible explanations for the reduced mortality with clozapine include superior efficacy, leading to improved function and self-care, and closer clinical monitoring and surveillance.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis; however, the source of funding was not disclosed.

Vermeulen J, van Rooijen G, van de Kerkhof M, Sutterland A, et al: Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1.1–12.5 years. *Schizophrenia Bulletin* 2018; doi 10.1093/schbul/sby052. From the University of Amsterdam, the Netherlands; and other institutions. **Source of funding not stated. One of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Aripiprazole–Sertraline in Resistant Depression

In a manufacturer-sponsored trial, a combined formulation of aripiprazole and sertraline was superior to sertraline plus placebo in patients with resistant depression.[1] Aripiprazole is FDA approved as adjunctive treatment for antidepressant-resistant depression, and research in other medical specialties has shown that adherence may be improved with fixed-dose combination preparations as opposed to separate pills.[2]

Methods: The trial recruited patients in Asia and Australia who met DSM-5 criteria for major depressive disorder, with the current episode lasting ≥8 weeks and nonresponsive to 1–3 courses

of adequate antidepressant medication. After their baseline medication was tapered to a level considered safe for switching, patients were required to meet a minimum symptom score of ≥18 on the 17-item Hamilton Rating Scale for Depression (HAM-D). Qualifying patients received sertraline monotherapy for 8 weeks. Inadequate response was defined as a <50% reduction in HAM-D score, a HAM-D score of ≥14, and a Clinical Global Impression (CGI) Improvement* score of ≥3. Patients who experienced an inadequate response to sertraline at week 8 were randomly assigned to receive aripiprazole–sertraline, formulated as a single tablet, or a placebo–sertraline combination. The active study medication contained 3, 6, 9, or 12 mg aripiprazole and 100 mg sertraline. Aripiprazole was titrated to the minimum effective/maximum tolerated dose by week 4, and treatment was continued through 6 weeks. The primary efficacy measure was mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) score.

Results: Of 735 patients who completed the sertraline monotherapy phase, 412 (average age, nearly 40 years; 63% men) had an inadequate response and entered the randomized study phase. More than 90% of these patients completed the full trial. At study endpoint, 27% of patients were receiving aripiprazole at 3 mg/day, 23% at 6 mg/day, 12% at 9 mg/day, and 38% at 12 mg/day.

The mean MADRS score, about 25 at baseline, decreased by 9.2 points in the aripiprazole–sertraline group and by 7.2 points in the placebo–sertraline group (p=0.007). Differences were statistically significant beginning by week 1 of double-blind treatment. The MADRS response rate (≥50% decrease) was 37.5% with the active combination and 25.6% with the placebo combination (p<0.05; odds ratio,* 1.73). Remission rates (MADRS ≤10) were 29.3% and 20.2%, respectively (p<0.05; odds ratio, 1.65). Secondary outcome measures, including CGI Improvement and Severity scores, the HAM-D, and measures of apathy and social adaptation, all showed significantly greater improvement with aripiprazole–sertraline.

Akathisia occurred in 12.9% of the aripiprazole–sertraline group and 3.4% of the placebo–sertraline group. Other adverse effects occurred in similar proportions of the 2 treatment groups. Weight gain of ≥7% occurred in nearly 10% of patients who received aripiprazole and <2% of the comparison group (p=0.0003).

Discussion: These observations are similar to those observed in previous trials of aripiprazole augmentation using separate pills. The low incidence of akathisia, relative to other trials, may be due to the relatively low aripiprazole dose.

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

[1]Kamijima K, Kimura M, Kuwahara K, Kitayama Y, et al: A randomized, double-blind comparison of aripiprazole/sertraline combination and placebo/sertraline combination in patients with major depressive disorder. *Psychiatry and Clinical Neurosciences* 2018; doi 10.1111/pcn.12663. From Showa University; and other institutions including Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan. **Funded by Otsuka. All 5 study authors declared financial relationships with commercial sources, including Otsuka.**

[2]van Galen K, Nellen J, Nieuwkerk P. The effect on treatment adherence of administering drugs as fixed-dose combinations versus as separate pills: systematic review and meta-analysis. *AIDS Research and Treatment* 2014; 2014: 967073.

Common Drug Trade Names*:** **aripiprazole—*Abilify*; sertraline—*Zoloft

***See Reference Guide.**

Mazindol for Adult ADHD

In a phase-II placebo-controlled trial, controlled-release mazindol was effective in adults with ADHD, with an effect size comparable to stimulants. Mazindol is a serotonin, noradrenaline, and dopamine reuptake inhibitor (SNDRI) previously introduced for treatment of obesity but withdrawn from the market because of low sales. This is the first clinical trial

of a controlled-release formulation, following promising results of an open-label study of immediate-release mazindol in children with ADHD.

Methods: Study participants were adults, aged 18–65 years, with a diagnosis of ADHD meeting minimum severity criteria when unmedicated. Those with concurrent DSM-5 disorders requiring treatment were excluded. Patients received mazindol or placebo for 6 weeks, with mazindol dosed flexibly within a range of 1–3 mg/day. The primary efficacy measure was change from baseline in the ADHD Rating Scale for DSM-5 (ADHD-RS-DSM5). Efficacy was also assessed with the Clinical Global Impression–Improvement* (CGI-I) scale and with the Target Impairment Scale, which measures changes in 3 functional goals selected by the patient.

Results: A total of 84 patients (42% men) were randomized and had ≥1 post-baseline assessment. Average patient age was 33–35 years; 42% were moderately ill, 51% were markedly ill, and 7% were severely ill according to the CGI–Severity scale. Nearly 30% were ADHD medication-naive. A total of 5 patients did not complete the study—2 in the mazindol group and 3 in the placebo group—all because of noncompliance or protocol violations. By week 4, after which dosage changes were not allowed, 10 patients were receiving 2 mg/day mazindol and 31 were receiving 3 mg/day.

The mean ADHD-RS-DSM5 score at baseline was 39. Mazindol was associated with a significantly larger improvement after 6 weeks of treatment (19 vs 6 points; $p<0.001$; effect size,* 1.09). Effects of mazindol differed statistically from placebo after the first week of treatment, and differences grew larger over the subsequent weeks. Significantly more patients were classified as "excellent responders" (≥50% improvement on the ADHD-RS-DSM5) in the mazindol group beginning at 2 weeks. By 6 weeks, 55% of the mazindol group and 16% of the placebo group were classified as excellent responders ($p=0.002$). CGI-I ratings of much or very much improved were observed in 62.5% of the mazindol group and 21% of the placebo group ($p<0.001$). Improvement in target areas was also significantly greater with mazindol.

The most common adverse effects of mazindol, relative to placebo, were dry mouth, nausea, fatigue, increased heart rate, decreased appetite, and constipation. Patients receiving mazindol lost an average of nearly 4 lbs during the 6-week study. However, previous experience indicates the effects of mazindol on weight are short-lived.

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

Wigal T, Newcorn J, Handal N, Wigal S, et al: A double-blind, placebo-controlled, phase II study to determine the efficacy, safety, tolerability and pharmacokinetics of a controlled release (CR) formulation of mazindol in adults with DSM-5 attention-deficit/hyperactivity disorder (ADHD). *CNS Drugs* 2018;32 (March):289–301. From AVIDA Inc., Newport Beach, CA; and other institutions. **Funded by NLS-1 Pharma AG. All study authors disclosed relevant financial relationships with NLS-1 Pharma AG and other sources.**

Common Drug Trade Names*: mazindol (not available in the U.S.)—*Mazanor, Sanorex

***See Reference Guide.**

Lofexidine for Opioid Withdrawal Symptoms

Physical dependence is an expected physiological response to opioid use. In patients using the medications appropriately, opioid withdrawal is typically accomplished using a slow taper. In patients with opioid use disorder, the abused medication is typically replaced with an alternate opioid medicine, which is then gradually reduced and followed by transition to maintenance therapy with an agent such as methadone, buprenorphine, or naltrexone.

The FDA recently approved lofexidine hydrochloride, the first nonopioid medication for the alleviation of opioid withdrawal symptoms in adults in order to expedite abrupt discontinuation. Lofexidine is a selective alpha 2-adrenergic receptor agonist that reduces the release of norepinephrine, the effects of which are thought to have a role in many of the symptoms of

opioid withdrawal. The newly approved drug is not a treatment for opioid use disorder; however, it can lessen the severity of withdrawal symptoms including anxiety, agitation, sleep difficulty, muscle ache, runny nose, sweating, nausea, vomiting, diarrhea, and drug craving. In clinical trials, the most common adverse effects associated with lofexidine were hypotension, bradycardia, somnolence, sedation, and dizziness. Because lofexidine can affect cardiac conduction, patients may experience a marked blood pressure increase when the agent is stopped. Safety and efficacy have not been established in children or adolescents, and the approval covers only a 14-day course of treatment in adult patients.

FDA News Release: FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults. Available at https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607884.htm.

Common Drug Trade Names*: buprenorphine—*Buprenex*; lofexidine—*Lucemyra*; methadone—*Methadose*; naltrexone—*ReVia

Cardiovascular Safety of Antismoking Agents

In a large trial in a general population of smokers with or without established psychiatric disorders, smoking cessation medications were not associated with cardiovascular risk.

Background: Early clinical trials of bupropion and varenicline did not show excess risk of cardiovascular events in treated patients. However, in 2011, the FDA mandated that smoking-cessation medications carry warnings of possible cardiovascular events in smokers with established cardiovascular disease. Findings of subsequent studies were mixed, and the FDA mandated the extension of a large clinical trial to monitor cardiovascular safety.

Methods: Participants in the original multinational study were adults, aged 18–75 years, who smoked ≥10 cigarettes per day and wanted to quit. Those with recent clinically significant cardiovascular or cerebrovascular disease were excluded. Randomized treatment, provided for 24 weeks in a triple-dummy fashion, consisted of 1 mg varenicline b.i.d., 150 mg bupropion b.i.d., a nicotine-replacement patch as an active control, or placebo. Patients were invited to participate in the extension study regardless of whether they stopped study medication prematurely, as long as they remained in follow-up throughout the 24-week trial. During the nontreatment extension, patients were evaluated in the clinic every 4 weeks up to week 52. The primary outcome was time to a major adverse cardiovascular event (i.e., cardiovascular death, nonfatal myocardial infarction [MI], or nonfatal stroke). The incidence of these events was compared during treatment, during the 30 days after completion, and at 1 year.

Results: More than 8000 patients received randomized medication or placebo in the original 24-week study. Their average age was 46 years, 44% were men, and about half had a neuropsychiatric disorder. Between 77% and 79% of each treatment group completed the 24-week trial, and 56% of the original cohort enrolled in the extension trial. Of this group, 90% completed the additional half year of follow-up. Patients were exposed to medication (or placebo) an average of about 74 days.

Major adverse cardiovascular events were infrequent, occurring in <0.5% of all groups. Overall there were 14 nonfatal MIs, 8 nonfatal strokes, and 5 cardiovascular deaths. The groups also did not differ in time to major adverse cardiovascular event or a composite outcome consisting of a major adverse cardiovascular event plus new-onset or worsening peripheral vascular disease requiring treatment, coronary revascularization, or hospitalization for unstable angina. Results of the analysis did not differ for each of the 3 observation periods or in patients in low, medium, or high baseline cardiovascular risk categories.

Discussion: Participants in the present study were in generally good health and representative of the population of smokers in general medical practice. No evidence was found in these patients that smoking-cessation agents increase the risk of serious cardiovascular events during

or after treatment. In addition, the number of adverse cardiac events that did occur was small and the incidence of serious events was low, suggesting that any absolute increase in risk is low and not clinically meaningful.

Benowitz N, et al: Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. *JAMA Internal Medicine* 2018; doi 10.1001/jamainternmed.2018.0397. From the University of California, San Francisco; and other institutions. **Funded by Pfizer; and GlaxoSmithKline. All 9 study authors disclosed financial relationships with commercial sources including Pfizer and/or GlaxoSmithKline.**

Common Drug Trade Names*: bupropion—*Zyban*; nicotine patch—*Nicoderm*; varenicline—*Chantix

Brexpiprazole Versus Lurasidone

In a network meta-analysis that compared placebo-controlled acute treatment trials in patients with schizophrenia, brexpiprazole and lurasidone were found to have similar efficacy. However, lurasidone was associated with somewhat less weight gain and better metabolic outcomes.

Background: Metabolic effects and weight gain can be problematic with atypical antipsychotic treatment, and weight-neutral options may be an important consideration for patients with potential metabolic issues. Brexpiprazole and lurasidone are both believed to have neutral effects on weight, but there have been no head-to-head comparisons reported.

Methods: The analysis, conducted by the manufacturer of lurasidone, identified phase II, III, or IV trials of the drugs that were published or presented at major conferences through the third quarter of 2015. Trials were included if they had ≥1 arm treated with the FDA-approved doses of either drug and assessed the efficacy of the drug at reducing symptoms of schizophrenia during acute episodes. Using placebo as a common comparator, outcomes were compared over 6 weeks of treatment. The primary efficacy outcome was response, defined as a ≥20% decrease in the Positive and Negative Syndrome Scale (PANSS) score. Metabolic outcomes were the proportion of patients gaining ≥7% of their baseline weight as well as mean changes in weight, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Results: The analysis included 3 trials of brexpiprazole and 5 trials of lurasidone. Patient populations were generally comparable with regard to age, gender, disease severity, and baseline metabolic characteristics or weight. Response rates did not differ significantly between the 2 drugs, ranging from 39% to 53% for brexpiprazole and from 44.4% to 63.2% for lurasidone. Differences in the response rates and mean changes in the PANSS and the Clinical Global Impression–Severity scale scores favored lurasidone but were not statistically significant.

At 6 weeks, patients receiving lurasidone were less likely to gain ≥7% of their baseline weight, although the between-group difference was not statistically significant (odds ratio,* 0.50). Patients taking lurasidone gained significantly less weight than those receiving brexpiprazole (mean difference, 1.5 lbs) and had significant reductions in total and LDL cholesterol relative to brexpiprazole (about 7 mg/dL each).

Discussion: Long-term studies and head-to-head comparisons are required to determine if the differential effects of these drugs on weight and lipid metabolism are lasting and whether the reduced weight gain with lurasidone translates to improved cardiovascular outcomes.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis. However, individual study quality does not appear to have been systematically evaluated.

Ng-Mak D, Tongbram V, Ndirangu K, Rajagopalan K, et al: Efficacy and metabolic effects of lurasidone versus brexpiprazole in schizophrenia: a network meta-analysis. *Journal of Comparative Effectiveness Research* 2018; doi 10.2217/cer-2018–0016. From Sunovion Pharmaceuticals, Inc., Marlborough, MA; and ICON Health Economics, New York, NY. **Funded by Sunovion. All study authors disclosed relevant financial relationships with commercial sources including Sunovion or ICON Health Economics.**

Common Drug Trade Names*: brexpiprazole—*Rexulti*; lurasidone—*Latuda

***See Reference Guide.**

Reference Guide

Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

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.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison 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.

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PSYCHIATRY DRUG ALERTS

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Augmenting Clozapine in Resistant Schizophrenia

More than half of patients with resistant psychosis do not achieve response with clozapine treatment. According to the results of a comprehensive review, the agents with the best evidence for efficacy as clozapine augmentation are aripiprazole, fluoxetine, and valproate. Memantine may be effective for negative symptoms.

Methods: A comprehensive literature search identified all randomized controlled trials of clozapine augmentation published in any language with a target patient population of adults with ongoing psychotic symptoms unresponsive to an adequate trial of clozapine. The primary outcome was total psychotic symptoms. Secondary outcomes were positive symptoms, negative symptoms, and adverse drug reactions. The search identified 46 articles describing 25 different interventions. Studies ranged from 3 weeks to 12 months, and most were conducted in community settings. Augmentation agents were antipsychotics (19 studies), antidepressants (10 studies), mood stabilizers (5 studies), glutamatergic agents (7 studies), "other" pharmacotherapies (2 studies), and nonpharmacological strategies (3 studies).

Results: Ten different antipsychotic agents were evaluated in a total sample of 1131 patients: aripiprazole, risperidone, haloperidol, penfluridol, pimozide, sulpiride/amisulpride, sertindole, olanzapine, quetiapine, and ziprasidone. However, only 3 agents—aripiprazole, risperidone, sulpiride/amisulpride—were evaluated in >1 study. Among the antipsychotics, only aripiprazole was superior to placebo for total psychosis scores (standardized mean difference [SMD],* -0.57). It was not superior in terms of positive or negative symptoms. In addition, aripiprazole was the only agent with sufficient data to examine specific adverse drug reactions. It was associated with more restlessness and less sedation than placebo, but no differences in weight gain, abnormal electrocardiography, hyperprolactinemia, or other adverse effects. Risperidone and sulpiride/amisulpride were not superior to placebo, and single studies of other antipsychotics were negative or inconclusive.

Antidepressant analyses included fluoxetine, paroxetine, duloxetine, and mirtazapine in a total of 476 patients. Fluoxetine was found to be superior to placebo for total symptoms (SMD, -0.73),

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as well as for positive and negative symptoms; however, after removal of low-quality studies the effects on positive and negative symptoms were no longer significant. Studies of other antidepressants had negative results or were limited by small sample sizes or other quality issues.

The mood stabilizers valproate, lithium, topiramate, and lamotrigine were evaluated in 278 patients. Among these, valproate was effective for total symptoms (SMD, -2.36,) and positive symptoms (SMD, -1.54), but study quality was low. Topiramate appeared to be effective for positive and negative symptom clusters, and lithium appeared to have positive effects on total and positive symptom scores, but each agent was evaluated in only 1 study. Lamotrigine did not produce improvement in any symptom domain.

The glutamatergic agents memantine, glycine, and sarcosine were evaluated in 212 patients. Only memantine had positive effects and only in terms of negative symptoms (SMD, -0.56). Other agents with very limited supporting evidence include Gingko biloba for total and negative symptom scores and minocycline for negative symptoms. In single studies of nonpharmacologic interventions, ECT reduced total psychosis scores, but cognitive behavioral therapy and transcranial magnetic stimulation were not effective.

Siskind D, Lee M, Ravindran A, Zhang Q, et al: Augmentation strategies for clozapine refractory schizophrenia: a systematic review and meta-analysis. *Australian & New Zealand Journal of Psychiatry* 2018; doi 10.1177/0004867418772351. From Metro South Health, Brisbane, Australia; and other institutions. **This research was conducted without funding. The study authors declared no financial relationships with commercial sources.**

Common Drug Trade Names*: amisulpride (not available in the U.S.)—*Solian*; aripiprazole—*Abilify*; clozapine—*Clozaril*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; haloperidol—*Haldol*; lamotrigine—*Lamictal*; memantine—*Namenda*; mirtazapine—*Remeron*; olanzapine—*Zyprexa*; paroxetine—*Paxil*; penfluridol (not available in the U.S.)—*Semap*; pimozide—*Orap*; quetiapine—*Seroquel*; risperidone—*Risperdal*; sertindole (not available in the U.S.)—*Serdolect*; sulpiride (not available in the U.S.)—*Dogmatil*; topiramate—*Topamax*; valproate—*Depakene, Depakote*; ziprasidone—*Geodon

***See Reference Guide.**

Inhaled Loxapine for Acute Agitation

In a multicenter, randomized, controlled trial, inhaled loxapine had a more rapid onset of action than injected aripiprazole in patients with acute agitation associated with bipolar I disorder or schizophrenia.

Methods: This randomized head-to-head comparison, funded by the manufacturer of loxapine, was conducted at 23 centers in 4 European countries. Participants, aged 18–65 years, had a diagnosis of schizophrenia or bipolar I disorder and presented with agitation during hospitalization or at an emergency department, with a score of ≥4 on the Clinical Global Impression–Severity (CGI-S) scale.* Randomized treatment consisted of either 10 mg inhaled loxapine or 9.75 mg/1.3 mL intramuscular (IM) aripiprazole, with the option of a second dose ≥2 hours after the first if needed. Patients could receive rescue medication if needed to treat agitation beginning 20 mins after the second dose of study medication. Baseline and post-treatment clinical assessment was carried out by a blinded rater at prespecified intervals up to 24 hours after the first dose. The primary efficacy outcome was time to response, defined as the first time point at which a CGI-S score of 1 or 2 was registered.

Results: Of 359 patients randomized to treatment, 297 had schizophrenia and 60 had bipolar I disorder. The mean patient age was 40 years, and 51% were men. The median time to onset of action was 50 min for inhaled loxapine and 60 min for IM aripiprazole (treatment difference, 10 mins; p=0.0005). The time to onset was shorter for loxapine in both patients with schizophrenia and those with bipolar disorder, although in the latter group, the difference was not statistically significant, probably owing to the small sample size. The treatments differed as early as the first assessment, 10 mins after the first dose, when response rates were 14% in the loxapine group and 4% in the aripiprazole group (p=0.0009). There continued to be more responders in the

loxapine group at every assessment time point up to 1 hour (70% vs 56%; p=0.0075). At 2 hours, response rates were 83–84% in the 2 groups. A second dose of randomized medication was required in 7% of patients in the loxapine group and 10% of those in the aripiprazole group. A single patient, in the loxapine group, required rescue medication for agitation at 2.5 hours. Patient satisfaction was greater with loxapine—with 54% very satisfied or extremely satisfied with their treatment—compared with 36% of aripiprazole-treated patients. Common adverse effects of loxapine included occasional altered taste, cough, and throat irritation.

Discussion: Although oral medication administration is often preferred, it may not have a sufficiently rapid onset of action in acutely agitated patients. IM antipsychotics generally provide faster symptomatic control than oral formulations, but administration via this route may distress the patient. In addition to the more rapid action than IM injection, inhaled loxapine may have other advantages that are relevant to treating agitation, including a non-coercive, noninvasive mode of administration and a sustained therapeutic effect.

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

San L, Estrada G, Oudovenko N, Montanes F, et al: PLACID study: a randomized trial comparing the efficacy and safety of inhaled loxapine versus intramuscular aripiprazole in acutely agitated patients with schizophrenia or bipolar disorder. *European Neuropsychopharmacology* 2018; doi 10.1016/j.euroneuro.2018.03.010. From Parc Sanitari Sant Joan de Deu, Barcelona, Spain; and other institutions. **Funded by Ferrer Internacional. All 8 study authors disclosed potentially relevant financial relationships.**

Common Drug Trade Names*:** **aripiprazole, intramuscular—*Abilify Maintena*; loxapine, inhaled—*Adasuve

***See Reference Guide.**

Vortioxetine Pharmacology and Interactions

According to a review of phase-I study data compiled by the manufacturer, vortioxetine can be administered without adjustments to the recommended dosage in most patient populations and there are few clinically significant potential drug interactions.

Vortioxetine is a multimodal antidepressant with 2 actions: agonist activity at multiple serotonin receptors and inhibition of the 5-HT transporter. It may owe its antidepressant effects to modulation of neurotransmission in multiple systems including serotonin, norepinephrine, dopamine, acetylcholine, histamine, glutamate, and GABA. The therapeutic dose range is 5–20 mg, taken once daily. Oral bioavailability is about 75%, and the peak plasma concentration of vortioxetine is reached within 7–11 hours post-dose. Administration with food has no important effect on drug absorption.

Vortioxetine is metabolized almost entirely by the liver through oxidation by cytochrome P450 (CYP) enzymes, predominantly CYP2D6. Six metabolites have been identified, but the parent compound is responsible for pharmacologic activity. Renal clearance accounts for less than 1% of total clearance. The elimination half-life has ranged from 59 to 69 hours in various studies. Vortioxetine pharmacokinetics are dose-proportional and linear within the range that has been studied—2.5–75 mg for single-doses or 2.5–60 mg for multiple doses. Steady-state levels are reached after about 2 weeks of daily dosing.

Vortioxetine pharmacokinetics have been investigated in populations classified by gender, age, race/ethnicity, body size, and existence of hepatic or renal impairment. Dosage adjustments are not needed for any of these categories. Variations in the CYP2D6 genotype can affect drug exposure, but these variations were not found to be clinically significant, and routinely genotyping patients before starting treatment is not recommended. Depending on the individual response, patients known to have the poor metabolizer genotype may require a dose adjustment.

A range of potential drug interactions have been investigated. Bupropion, a strong CYP2D6 inhibitor, can double vortioxetine peak serum concentrations and area under the plasma drug

concentration-time curve. It is recommended that the vortioxetine dose be reduced by half when given with bupropion or other strong inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine. Ketoconazole has modest, clinically insignificant effects on vortioxetine kinetics, and no effects were found for aspirin, ethanol, or omeprazole. Vortioxetine was not found to have clinically important effects on levels of other drugs that are metabolized by CYP2D6.

In pharmacodynamic studies, vortioxetine was found not to affect cardiac repolarization or to impair driving, cognitive function, or psychomotor skills. For the most part, it did not increase impairment induced by alcohol or diazepam. Like other serotonergic agents, its use can lead to serotonin syndrome, especially when combined with other drugs that affect that system.

Chen G, Hojer A-M, Areberg J, Nomikos G: Vortioxetine: clinical pharmacokinetics and drug interactions. *Clinical Pharmacokinetics* 2018;57 (June):673-686. From Takeda Development Center Americas, Inc., Deerfield, IL; and H. Lundbeck A/S, Copenhagen-Valby, Denmark. **Funded by Takeda Development Center Americas, Inc.; and H. Lundbeck A/S. All 4 study authors disclosed potentially relevant financial relationships.**

Common Drug Trade Names*: bupropion—*Wellbutrin*; fluoxetine—*Prozac*; ketoconazole—*Nizoral*; omeprazole—*Prilosec*; paroxetine—*Paxil*; vortioxetine—*Trintellix

Antipsychotics and Gestational Diabetes

In a cohort of women who received antipsychotic treatment before pregnancy, those who continued taking some antipsychotics during pregnancy had an elevated risk of gestational diabetes, compared with those who stopped. Olanzapine use was associated with the highest risk, which was dose-related.

Methods: This analysis was based on nationwide Medicaid claims data on pregnancies occurring in 2000–2010. Women without preexisting diabetes were included in the cohort if they were taking 1 of the 5 most frequently used antipsychotics—aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone—during the 3 months before their last menstrual period. Those receiving antipsychotic polypharmacy and those whose antipsychotic was changed during pregnancy were excluded. Risk of gestational diabetes was compared between women who continued to receive the same antipsychotic during the first 20 weeks of pregnancy and those who stopped. Analyses were conducted separately for each individual drug and for 3 groups classified according to the potential to induce weight gain and diabetes in nonpregnant patients. Aripiprazole and ziprasidone were classified as low-risk, quetiapine and risperidone were medium-risk, and olanzapine was high-risk. The analysis was adjusted for propensity scores* incorporating a large number of covariates.

Results: The study cohort comprised >10,000 women who received aripiprazole (n=1924), ziprasidone (n=673), quetiapine (n=4533), risperidone (n=1824), or olanzapine (n=1425) before pregnancy. The proportion continuing on the same drug after becoming pregnant ranged from 19% (risperidone) to 34% (quetiapine). The absolute risk of gestational diabetes ranged from 4.2% to 12% among continuers and from 3.8% to 4.7% among discontinuers. After adjustment, risk for gestational diabetes was elevated for olanzapine (relative risk,* 1.61) and quetiapine (relative risk, 1.28), but not for the other agents. In a dose-response analysis, risk increased

Risk of gestational diabetes during pregnancy		
Risk Group‡	**Incidence**	**Adjusted Relative Risk**
Low-risk		
Continuers	4.6%	0.91
Discontinuers	4.3%	
Medium-risk		
Continuers	7.0%	1.37
Discontinuers	4.1%	
High-risk		
Continuers	12.0%	1.61
Discontinuers	4.7%	

‡Low-risk: aripiprazole, ziprasidone. Medium-risk: quetiapine and risperidone. High-risk: olanzapine.

with an increasing cumulative dose of olanzapine, reaching a plateau at 700 mg, but dose did not affect risk with the other agents. Stratification by diagnostic class (i.e., psychiatric vs nonpsychiatric indication for treatment) did not alter the results.

Discussion: Women who received olanzapine before pregnancy had a lower prevalence of diabetes risk factors than other groups, which suggests that despite selective prescribing, women who received olanzapine continued to have the highest risk of gestational diabetes, relative to discontinuers. Continued weight gain is the most plausible explanation for the increased risk with olanzapine. Reasons for discontinuation of treatment, which could be associated with illness severity or indication for treatment, were not available in the study data. However, the authors note that illness severity is not likely to explain the observed associations, as increased risk for gestational diabetes with found only with select antipsychotics.

Park Y, Hernandez-Diaz S, Bateman B, Cohen J, et al: Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.17040393. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by the NIMH. Seven of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*; ziprasidone—*Geodon

***See Reference Guide.**

Aripiprazole and Worsening Psychosis

According to a meta-analysis of randomized trials, switching to aripiprazole was not associated with increased risk of psychotic worsening compared with other antipsychotics. However, a switch to aripiprazole was associated with study discontinuation due to lack of efficacy.

Background: Numerous case reports have described worsening of psychotic symptoms following initiation of aripiprazole, often after simply adding aripiprazole to an existing regimen. Psychotic worsening is presumed to be caused by the drug's partial agonist activity at dopamine D_2 receptors, particularly after receptor up-regulation as a consequence of long-term exposure to other antipsychotics.

Methods: The meta-analysis was based on published randomized, parallel-group clinical trials conducted in patients with schizophrenia-spectrum disorders. The studies compared switching to aripiprazole versus switching to another antipsychotic (excluding those that share the partial D_2 agonist profile of aripiprazole) or that compared adding aripiprazole versus placebo as augmentation of another antipsychotic. Studies were excluded if ≥70% of patients were antipsychotic-naive or antipsychotic-free. Psychotic worsening, the primary outcome of the meta-analysis, could be reported as either lack of efficacy or an adverse event; all studies identified for the analysis reported this as an adverse event. Separate analyses were conducted for switching and augmentation studies.

Results: A total of 22 studies were identified—13 of switching and 9 of augmentation—with a total of nearly 5800 participants. All studies used an oral formulation of aripiprazole, with the mean daily dose ≥10 mg. The studies investigating a switch to aripiprazole found no significant difference between the groups in the number of patients experiencing worsening of psychotic symptoms as an adverse event, a serious adverse event, or an adverse event leading to study discontinuation. (See table, next page.) There were also no between-group differences in emergence of anxiety or agitation. For the studies of aripiprazole augmentation, no difference was found in the incidence of psychotic worsening reported as an adverse event or as a serious adverse event.

Neither aripiprazole switching nor augmentation was associated with an increased rate of all-cause study discontinuation. However, switching to aripiprazole was associated with a significantly increased likelihood of discontinuation for lack of efficacy. This difference was particularly robust in the 3 studies that compared switching to aripiprazole with continuing or switching to olanzapine (risk ratio,* 20.12; p=0.003).

Outcome of switching to or adding aripiprazole			
Outcome	**Studies**	**Patients**	**Risk Ratio***
Psychotic worsening			
Switching	7	3458	1.17
Adding	3	383	0.61
Discontinuation for lack of efficacy			
Switching	13	4858	1.46
Adding	8	881	2.08

Discussion: While the present results do not support an association between aripiprazole and worsening psychosis, the authors caution that industry sponsorship can have an effect on adverse-event reporting and two-thirds of the included studies had pharmaceutical industry funding. In practice, these observations suggest clinicians should closely monitor for worsening psychotic symptoms in patients switched to aripiprazole from another antipsychotic. The evidence on augmentation is insufficient to draw conclusions.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Takeuchi H, Fathi A, Thiyanavadivel S, Agid O, et al: Can aripiprazole worsen psychosis in schizophrenia? A meta-analysis of double-blind, randomized, controlled trials. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17r11489. From the Centre for Addiction and Mental Health, Toronto, Canada; and other institutions. **Funded by the Canadian Institutes for Health Research; and other sources. Three of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: **aripiprazole—*Abilify*; olanzapine—*Zyprexa***

***See Reference Guide.**

Preventing Rehospitalization in Bipolar Disorder

In a nationwide cohort study, lithium was associated with the lowest rate of rehospitalization due to mental or physical illness of all drug treatments for bipolar disorder.[1] The study also showed that long-acting injectable (LAI) medications resulted in better outcomes than their oral counterparts.

Methods: The cohort study included >18,000 patients (mean age, 47 years; 47% men) hospitalized for bipolar disorder in Finland between 1987 and 2012. The analysis had 3 outcomes: rehospitalization for any mental disorder (a proxy for treatment failure), hospitalization for all causes including somatic reasons (a proxy for overall drug effectiveness versus tolerability), and hospitalization for cardiovascular diseases (a proxy for cardiovascular tolerability). The incidence of each of these outcomes was compared within each patient during periods of exposure and nonexposure to specific medications and medication categories. Risk estimates were adjusted for demographic factors and concomitant psychotropic use.

Results: During an average follow-up of >7 years, 54% of patients were rehospitalized for psychiatric reasons. As a therapeutic group, mood stabilizers were associated with the lowest risk of psychiatric hospitalization, although the benefit was modest. Among individual drugs, lithium was associated with a largest reduction in risk of psychiatric rehospitalization (hazard ratio,* 0.67; p<0.001). Several other drugs were associated with large risk reductions, but these associations did not survive statistical correction for multiple comparisons or sensitivity analyses, in part due to small sample sizes. These agents included risperidone LAI, followed by gabapentin and perphenazine LAI. As a group, LAI formulations were associated with fewer hospitalizations than their oral counterparts (hazard ratio, 0.70; p=0.005), although few LAI

formulations were prescribed. The most commonly prescribed antipsychotic, quetiapine, was only modestly effective at reducing psychiatric hospitalization (hazard ratio, 0.92; p=0.02).

Only lithium was associated with a significantly lowered rate of all-cause hospitalization (hazard ratio, 0.71; p<0.001) after sensitivity analysis. Again, LAI antipsychotics were superior to oral formulations for all-cause hospitalization, and quetiapine was only modestly effective. Mood stabilizers, and particularly valproic acid and carbamazepine, were associated with increased risk of cardiovascular hospitalization. Benzodiazepines were associated with the highest rates of all 3 hospitalization outcomes.

Discussion: According to the authors, these results suggest lithium should remain the first-line treatment for bipolar disorder. LAI antipsychotics might provide a safe and effective alternative for patients who cannot take lithium. The results for quetiapine contrast those of a recent meta-analysis suggesting the agent is among the most effective at preventing mood episodes.[2] Although hospitalization is a clinically relevant outcome in bipolar disorder, not all patients who relapse experience full episodes or suicidality thus requiring hospitalization. The present findings do not necessarily apply to alleviating other symptoms, such as subthreshold depressive symptoms, that do not require hospitalization. In addition, because mania is a more common reason for hospitalization than depression in patients with bipolar disorder, the present results may favor drugs with more antimanic than antidepressant efficacy, as well as those with antisuicidal efficacy, as suicidal patients are hospitalized more often.

[1]Lahteenvuo M, Tanskanen A, Taipale H, Hoti F, et al: Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. *JAMA Psychiatry* 2018;75 (April):347–355. From the University of Eastern Finland; and other institutions. **Funded by the Finnish Ministry of Social Affairs and Health. All study authors disclosed potentially relevant financial relationships.**

[2]Leucht S, Davis J: Enthusiasm and skepticism about using national registers to analyze psychotropic drug outcomes [editorial]. *JAMA Psychiatry* 2018;75 (April):314–315. From the Technische Universitat Munchen, Munich, Germany; and other institutions. **One study author disclosed potentially relevant financial relationships; the other author declared no competing interests.**

Common Drug Trade Names*: carbamazepine—*Tegretol*; gabapentin—*Neurontin*; perphenazine—*Trilafon*; quetiapine—*Seroquel*; risperidone LAI—*Risperdal Consta*; valproate—*Depakene, Depakote

***See Reference Guide.**

Sustained-Release Amantadine for Dyskinesia

In a pooled analysis of 2 randomized controlled trials of patients taking levodopa for Parkinson's disease, sustained-release amantadine (*Gocovri*) was associated with significant reductions in both dyskinesia and total daily "off" time.

Methods: The 196 study participants were receiving a stable levodopa regimen to which placebo or sustained-release amantadine was added and increased to 274 mg/day (equivalent to 340 mg immediate-release amantadine). The primary efficacy measure was the Unified Dyskinesia Rating Scale (UDysRS), which includes patient ratings of "on" dyskinesia, "off" dystonia, and their effects on daily living, as well as more detailed clinician ratings of dyskinesia.

Results: At baseline, patients reported a mean of 2.8 hours of "off" time per day, 4.9 hours per day of "on" time with troublesome dyskinesia, and about 8.5 hours of "on" time without dyskinesia. Compared with placebo, sustained-release amantadine was associated with significantly greater improvement in dyskinesia (p<0.0001) at all study time points. By week 12, scores on the UDysRS decreased by 41% in the active treatment group, compared with 14% in the placebo group (p<0.0001). The magnitude of improvement was similar on the patient- and clinician-rated sections of the UDysRS. Patients receiving sustained-release amantadine reported increases in "on" time without troublesome dyskinesia. According to clinician global illness ratings, 57 patients in the active treatment group and 15 in the placebo group showed moderate-to-marked improvement. The benefits of amantadine were not significantly affected by baseline dyskinesia

severity. Hallucinations were the most troubling adverse effect of amantadine. One patient experienced suicidal ideation thought to be related to the study drug. Dizziness, dry mouth, peripheral edema, constipation, falls, and orthostatic hypotension were also common with sustained-release amantadine, affecting 13–16% of treated patients. Amantadine did not worsen the underlying Parkinson's disease or impair the motor activities of daily living.

Elmer L, Juncos J, Singer C, Truong D, et al: Pooled analyses of Phase III studies of ADS-5102 (amantadine) extended-release capsules for dyskinesia in Parkinson's disease. *CNS Drugs* 2018;32 (April):387–398. From the University of Toledo College of Medicine, OH; and other institutions. **Funded by Adamas Pharmaceuticals, Inc. Seven of 9 study authors disclosed potentially relevant financial relationships; the remaining 2 authors declared no competing interests.**

Reference Guide

Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Risk Ratio: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Standardized Mean Difference: The difference between two normalized means - i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

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.

"Change is the law of life and those who look only to the past or present are certain to miss the future."—John F. Kennedy

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PSYCHIATRY DRUG ALERTS

Volume XXXII / July 2018 / Number 7 www.alertpubs.com

Change Coming . . . See back page for details.

New Aripiprazole Formulation

The FDA has approved a new injectable aripiprazole formulation (*Aristada Initio*) to be used in combination with a single 30-mg dose of oral aripiprazole (*Abilify*) to initiate treatment for schizophrenia, along with any available dose of long-acting injectable aripiprazole lauroxil (*Aristada*) on day one. Previously, the standard initiation regimen for *Aristada* included 21 consecutive days of oral aripiprazole treatment starting concurrently with the first *Aristada* dose. The new *Aristada Initio* regimen produces relevant aripiprazole levels within 4 days of initiation. The first dose of *Aristada* can be administered on the same day as *Aristada Initio* or within the subsequent 10 days.

Although both *Aristada* and *Aristada Initio* contain aripiprazole lauroxil, they are not interchangeable because of differing pharmacokinetic profiles. *Aristada Initio* uses a proprietary NanoCrystal® technology designed to provide an extended-release formulation using a smaller particle size that enables faster dissolution and leads to more rapid achievement of relevant levels of aripiprazole.

FDA approves Aristada Initio™ for the initiation of Aristada® for schizophrenia [press release]. Dublin, Ireland; Alkermes: July 2, 2018. Available at http://phx.corporate-ir.net/phoenix.zhtml?c=92211&p=irol-corporateNewsArticle&ID=2356744.

Psychotropic Drugs and Breastfeeding

Use of psychotropic drugs, primarily antidepressants and benzodiazepines, during breastfeeding was not associated with long-term adverse effects in infants followed for up to 33 months. Exposed children had normal growth and met normal developmental milestones.

Methods: Study subjects were mothers who called in to a hospital's drug-consultation center for advice about the safety of psychotropic medications during breastfeeding. A comparison group consisted of women who called the consultation center to inquire about receiving short-term antibiotic monotherapy during breastfeeding, which is generally considered safe. Women taking psychotropic drugs were given information about their particular medication but were

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not discouraged or encouraged to use any specific medication or given advice on less-risky alternatives. Women were administered a structured questionnaire during their initial call. In a follow-up telephone call several months to 5 years after the first call, women were asked about the specifics of drug exposure during pregnancy and lactation, adverse reactions in the infant, growth as recorded on well-baby forms, and developmental milestones.

Results: After excluding those who decided not to breastfeed, took no medication, or took multiple medications, the study enrolled 280 women taking psychotropic medication. These women were contacted for follow-up a median of 32 months after the initial call, when their infants were a median of 20 months old (range, 11–33 months). The 152 women in the antibiotic group were followed a median of 35 months after the initial call, when their babies were a median of 36 months old (range, 20–48 months).

Most of the women in the exposed group were receiving treatment for depression (60%) or anxiety (34%). The most common medications were SSRIs (69%), followed by benzodiazepines (13%) and other types of antidepressants; 13 women were taking antipsychotics. All were receiving doses within the recommended range.

Rates of maternal pregnancy complications did not differ between groups, overall. However, there were 15 cases of fetal distress in the exposed group, compared with none in the comparison group (p=0.002), but no other differences in neonatal complications.

At follow-up, children in the 2 groups did not differ in height, weight, head circumference, or weight/length ratio percentile. Adverse reactions were reported in 14 exposed infants: transient sleepiness in 8, poor weight gain in 4, and shivering in 2. Diarrhea was reported in 7 unexposed children and no psychotropic-exposed children. Some developmental milestones—e.g., smiling and lifting the head—occurred a few days to weeks later on average in exposed children than controls (p≤0.001), but all were within the normal developmental range.

Women taking psychotropic drugs stopped breastfeeding earlier than controls (24 vs 36 weeks; p<0.001) and were less likely to breastfeed exclusively (35% vs 61%; p<0.001). To eliminate these effects, a further analysis was conducted in 120 pairs of propensity score-matched* women. The results were similar to the larger cohort.

Discussion: Existing information on the effects of psychotropic drugs during breastfeeding is limited to case reports, drug-specific studies, or observation of small samples. The present study suggests the drugs do not result in growth retardation or important developmental delays. Sleepiness, which usually had onset soon after birth and resolved quickly, may reflect the previously reported phenomenon of poor neonatal adaptation.

Kronenfeld N, ziv Baran T, Berlin M, Karra N, et al: Chronic use of psychotropic medications in breastfeeding women: is it safe? *PLOS One* 2018; doi 10.1371/journal.pone.0197196. From the Hebrew University of Jerusalem, Israel; and other institutions. **This study was conducted without specific funding. The authors declared no competing interests.**

***See Reference Guide.**

Antipsychotics and Kidney Disease

According to the results of a population-based case-control study, second-generation antipsychotics may be associated with increased risk of chronic kidney disease (CKD).

Methods: A cohort of >13,600 patients hospitalized for psychiatric disorders in 2000–2013 and discharged with a diagnosis of schizophrenia were identified in a Taiwanese nationwide claims database. Within the cohort, case patients (n=3411) were those who subsequently received a diagnosis of CKD. Each case patient was matched for gender and the age and year of schizophrenia diagnosis with 3 controls free of CKD. The analysis compared CKD incidence in 4

separate groups of patients receiving: first-generation antipsychotics as a class, second-generation antipsychotics as a class and individually, combined first-and second-generation drug combinations, and no antipsychotic therapy.

Results: Patients had a mean age of 41 years and supplied an average of nearly 8 years of follow-up data after discharge. Rates of several relevant comorbidities, such as diabetes, cardiovascular disease, lipid abnormalities, and obesity, were significantly higher in the patients with CKD, but analyses were adjusted for these factors. A large majority of patients (87%) were receiving combined treatment with both first- and second-generation antipsychotics; 12% received only a first-generation agent; and <1% each received only a second-generation agent or no medication.

Using patients who received first-generation agents alone as the reference group, adjusted odds ratios* (OR) for CKD were 0.53 for those receiving no antipsychotic medication, 1.06 for those receiving only a second-generation agent, and 1.28 for those receiving both first- and second-generation agents. The only difference that reached statistical significance was for those receiving both types of antipsychotic (p= 0.0009). When analyzed by cumulative exposure, CKD risk was significantly increased in patients taking second-generation antipsychotics (alone or in combination) for durations of 90–180 days and >1000 days. Risks were also significantly elevated for several individual second-generation antipsychotics, although associations did not follow a consistent pattern of relationship to days of exposure and were not corrected for multiple comparisons. The analysis did not reveal a dose-dependent relationship of second-generation antipsychotics to CKD.

Discussion: Because the study data were drawn from a claims database, variables such as lifestyle factors, family history, and other factors that could affect outcomes and medication choice could not be examined. However, the results do support further investigation of the association between second-generation agents and kidney disease.

Wang H-Y, Huang C, Feng I, Tsuang H-C: Second-generation antipsychotic medications and risk of chronic kidney disease in schizophrenia: population-based nested case-control study. *BMJ Open* 2018; doi 10.1136/bmjopen-2017–019868. From Chi Mei Medical Center, Yung Kang, Taiwan; and other institutions. **Funded by Chi Mei Medical Center. The authors declared no competing interests.**

***See Reference Guide.**

Adjunctive Thyroid Hormones in Rapid Cycling

In a randomized 3-group trial, adjunctive levothyroxine favorably altered mood cycles in patients with rapid cycling bipolar disorder refractory to lithium.

Methods: Study participants, aged 18–65 years, were receiving treatment at a single university-based bipolar disorders clinic and met criteria for rapid cycling, with ≥4 mood episodes in the 12 months before study entry. All were taking lithium and continued to do so throughout the study, with dosages adjusted to maintain therapeutic serum levels. All patients were clinically euthyroid at study entry. Following pre-treatment evaluation lasting through at least 1 full mood cycle or ≥1 month for patients with the most rapid cycling, patients were randomly assigned to receive: levothyroxine, at doses that maintained the free thyroxine (T_4) index in a target range or achieved thyroid stimulating hormone suppression; triiodothyronine (T_3) at doses that maintained T_3 resin uptake in a target range; or placebo. All groups received placebo tablets as well. Thyroid status was measured approximately every week starting 1 month after the achievement of desired thyroid hormone levels (or a plausible interval for placebo) and continuing for ≥3 months. Outcomes were measured weekly by raters unaware of treatment assignment, using the Hamilton Rating Scale for Depression and Young Mania Rating Scale. Patients' mood switches were tracked, and the amount of time patients spent in each of 4 mood

states (euthymic, manic/hypomanic, depressed, mixed) was estimated using each individual's personal symptom threshold, which was established during pretreatment evaluation. Patients were followed for a minimum of 3 months (range, 4–11 months).

Results: A total of 32 patients (22 women) were included in the analysis. Of these, 7 had a history of hypothyroidism and were receiving thyroid hormone therapy at study entry: 4 in the levothyroxine group, 1 in the T_3 group, and 2 receiving placebo. Patients reached stabilization on thyroid hormones within a mean of 7 months (T_3) or 11 months (levothyroxine and placebo). Adverse effects were minimal, except for 1 patient who withdrew prematurely because of tachycardia.

Compared with pre-treatment, patients who received levothyroxine spent significantly less time in a depressed state (-18%; p=0.022) or in a mixed state (-13%; p=0.031) and more time euthymic (33%; p=0.022). Changes in the T_3 group followed a similar pattern but were smaller and not statistically significant. There was no change in the percentage of time spent in any mood state in placebo-treated patients. Between-group comparisons showed that favorable mood changes in patients who received levothyroxine were significantly superior to placebo for time spent euthymic and time spent in a mixed state (p=0.033 and p=0.045, respectively). Patterns for the T_3 group were similar but did not reach significance compared with placebo.

Discussion: Previous studies of levothyroxine in bipolar disorder have focused mainly on treating depression rather than on mitigating the course of rapid cycling. Therefore the finding in the present study of a reduction in time spent in mixed states is an important one. Results of the present study suggest that T3 may also be beneficial, although a larger sample size may be required to confirm this suggestion. The study was limited by its smaller-than-expected sample size, which did not allow investigators to analyze the results by gender or thyroid disease history. Gender differences in thyroid axis function are a well-known influence on response to pharmacologic treatments, and previous controlled studies suggest high-dose levothyroxine particularly benefits women with bipolar depression.

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

Walshaw P, Gyulai L, Bauer M, Bauer M, et al: Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder: a double-blind placebo-controlled trial of levothyroxine (L-T4) and triiodothyronine (T3). *Bipolar Disorders* 2018; doi 10.1111/bdi.12657. From the University of California Los Angeles; and other institutions. **Funded by the NIMH. Two of 7 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Anticholinergics and Dementia Risk

Exposure to anticholinergic antidepressant, antiparkinsonian, and urological drugs was associated with an increase in the incidence of dementia in a population-based study. Increased risk for several other anticholinergic categories could not be ruled out.

Methods: The study was based on data from the U.K.'s Clinical Practice Research Datalink, which contains primary-care records for >11 million patients. Case patients were aged ≥65 years and had received a diagnosis of dementia between 2006 and 2015. Each was matched with up to 7 control patients based on gender, age, and other factors. An anticholinergic drug exposure period was defined as a prescription lasting ≥1 year and ending ≥4 years before the date of dementia diagnosis. Anticholinergic drugs were classified according to the 3-point Anticholinergic Cognitive Burden (ACB) scale, based on serum anticholinergic activity, blood-brain penetration, and known associations with delirium. Drugs with serum anticholinergic activity or affinity for muscarinic receptors, but without known clinically

relevant negative cognitive effects are assigned an ACB score of 1 (possibly anticholinergic). Drugs with established and clinically relevant anticholinergic effects are assigned a score of 2, and drugs that meet those criteria and also have reported associations with delirium are assigned a score of 3. Drugs were further classified according to indication, and exposures were quantified by the defined daily dose, based on average maintenance doses. The analysis was adjusted for covariates suspected to be linked to dementia incidence and many other factors.

Results: The study population consisted of nearly 41,000 patients with dementia and >280,000 controls. Patients had a median age of 83 years at the index date (diagnosis of dementia). The median drug exposure period was >7 years.

During the anticholinergic drug exposure period, 35% of cases and 30% of controls were given a prescription for a drug with an ACB score of 3. The most frequently prescribed ACB-3 drugs were amitriptyline (29%), dosulepin or dothiepin (16%), paroxetine (8%), oxybutynin (7%), and tolterodine (7%). Use of drugs with an ACB score of 2 was rare, and use of drugs with an ACB score of 1 was near-universal. After adjustment, each ACB category was associated with a significant increase in risk for dementia. (See table.) A dose-response relationship was evident for drugs with an ACB score of 2 or 3. When drugs were analyzed by indication, significant risk of dementia was associated with ACB-3 anticholinergics prescribed as antidepressants, antiparkinsonian agents, and urologic treatments. Associations were also positive for ACB-2 antiparkinsonian drugs and for ACB-1 antidepressants. Anticholinergic antidepressants were consistently associated with dementia across the board, and these associations persisted after controlling for the presence and severity of depression. Gastrointestinal drugs had a negative association with dementia.

Odds ratios* for dementia by ACB score

ACB score	Incidence of dementia		Adjusted odds ratio†
	% of cases	% of controls	
0	10.5%	12.8%	1.00 (reference)
1	89.4%	87.1%	1.11
2	3.5%	2.8%	1.10
3	35.5%	30.4%	1.16
ACB-3 drug class			
Antidepressant	21.6%	17.9%	1.13
Antiparkinsonian	0.7%	0.3%	1.45
Urologic	8.0%	5.9%	1.23

†Odds ratios are adjusted for covariates present at start of the drug exposure period

Exposure times were also classified in 3 different periods: 4–10, 10–15, and 15–20 years before the index date. Associations for drug classes with an ACB score of 3 were consistent across all of these timespans, with no decrease when used 15–20 years in the past. In contrast, associations of dementia with drugs with an ACB-1 or 2 rating were more apparent closer to the index date.

Discussion: The study included a 4-year diagnostic lag designed to reduce the chances that the anticholinergic drugs were prescribed for early or prodromal symptoms of dementia. The present findings suggest that the relationship of anticholinergic drugs to dementia is specific to the drugs, not the underlying conditions that they treat; however, a link to underlying disorders other than dementia cannot be ruled out. The observed class-specific effects may be related to differential ability of drugs to cross the blood-brain barrier.

Richardson K, Fox C, Maidment I, Steel N, et al: Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018; doi 10.1136/bmj.k1315. From the University of East Anglia, Norwich, U.K.; and other institutions. **Funded by the Alzheimer's Society. Four of 16 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: amitriptyline (not available in the U.S.)—*Elavil*; dosulepin/dothiepin (not available in the U.S.)—*Prothiaden*; oxybutynin—*Ditropan*; paroxetine—*Paxil*; tolterodine—*Detrol

***See Reference Guide.**

Roluperidone: Secondary Benefits in Schizophrenia

Results of a manufacturer-sponsored clinical trial of roluperidone (MIN-101), an investigational drug for negative symptoms of schizophrenia, suggest possible secondary benefits on cognitive performance.[1] The drug also appears to have the potential to improve negative symptoms and cognitive deficits, addressing 2 important unmet needs in schizophrenia treatment.

Background: Roluperidone has specific affinities for the sigma-2, 5-HT_{2a} and α_1-adrenergic receptors and weak activity at other receptors. It lacks the anticholinergic and antihistaminergic activity associated with other medications that can worsen cognitive function in patients with schizophrenia.

Methods: This report describes a post-hoc analysis from a trial whose primary aim was to evaluate roluperidone for negative symptoms of schizophrenia.[2] (See *Psychiatry Drug Alerts* August 2017 for study details.) Participants had clinically evident negative symptoms over the 3 months before enrollment and scores of ≥20 for negative symptoms on the Positive and Negative Syndrome Scale (PANSS). All psychotropic drugs were discontinued before the trial; concomitant antipsychotics were not permitted. Patients, aged 18–60 years, were randomly assigned to 2 different daily doses of roluperidone (32 mg or 64 mg) or placebo and received treatment for 12 weeks. Cognitive performance was assessed at weeks 4 and 12 with the Brief Assessment of Cognition in Schizophrenia (BACS), which measures 6 domains of cognitive function.

Results: A total of 244 patients participated in the study, which met its primary endpoint of improving negative symptoms with both roluperidone doses; 234 of those patients completed the cognitive assessment at baseline and were included in the present analysis. Overall, about 40% of patients showed a potentially clinically meaningful improvement in BACS composite score. At week 12, patients who received 32 mg/day roluperidone (n=78) showed significant improvement relative to placebo on the BACS composite score and the token motor and verbal fluency subscales ($p \leq 0.05$ for all). In patients who received the 64-mg dose (n=83), improvement was significant only for motor speed (p=0.05) and approached significance for verbal fluency (p=0.06). No group showed significant gains in executive function. Although the higher dose generally produced smaller, nonsignificant cognitive improvements than the lower dose, among patients who received the 64-mg dose, improvement in PANSS negative symptoms was significantly correlated with improvement in the BACS cognitive composite at 12 weeks (correlation coefficient [r],* -0.408; p=0.002). No significant correlations were seen in the 32-mg dose group.

Discussion: The positive effects of roluperidone shown on the token motor and verbal fluency tests suggest that it may improve the ability to process information, complete simple tasks, and express knowledge. It is not clear whether the drug would have the same results when used as add-on therapy.

[1]Keefe R, Harvey P, Khan A, Saoud J, et al: Cognitive effects of MIN-101 in patients with schizophrenia and negative symptoms: results from a randomized controlled trial. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11753. From Duke University Medical Center, Durham, NC; and other institutions. **Funded by Minerva Neurosciences, Inc., Waltham, MA. All 7 study authors disclosed potentially relevant financial relationships.**

[2]Davidson M, et al: Efficacy and safety of MIN-101: a 12-week randomized, double-blind, placebo-controlled trial of a new drug in development for the treatment of negative symptoms in schizophrenia. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17010122. See *Psychiatry Drug Alerts* 2017;314 (August):60–61.

***See Reference Guide.**

VMAT-2 Inhibitors for Tardive Dyskinesia

Robust evidence supports the efficacy of deutetrabenazine and valbenazine for treating tardive dyskinesia, according to a systematic review and meta-analysis. Both of these drugs received FDA approval for this indication in 2017. A third member of the vesicular monoamine

transporter-2 (VMAT-2) inhibitor drug class, tetrabenazine (approved for treatment of Huntington's disease), has no high-quality evidence of safety or efficacy in tardive dyskinesia and should therefore be considered a third-line, off-label treatment.

Background: VMAT-2 inhibitors work by reducing transport of dopamine from the cytoplasm into presynaptic vesicles, leading to less dopamine release into the synaptic cleft and less stimulation of neurons in the nigrostriatal pathway, thought to be involved in involuntary movements.

Methods: Literature databases, clinical-trials registries, and conference proceedings were systematically reviewed for studies of VMAT-2 inhibitors. All types of studies were eligible for inclusion in the review, but the meta-analysis was limited to double-blind, randomized, placebo-controlled trials that reported results using the Abnormal Involuntary Movement Scale (AIMS).

Results: The systematic review included information from 8 double-blind controlled trials, 2 single-blind controlled studies, 7 open-label studies, and 3 retrospective studies or case series. Tetrabenazine, the first VMAT-2 inhibitor to be introduced, was investigated in 12 studies, including 2 randomized trials conducted in the 1970s. The studies had small sample sizes, flawed measurement of outcomes, and other design issues, and could not be included in the meta-analysis.

Deutetrabenazine and valbenazine were evaluated in 6 randomized trials. Meta-analysis of these trials found the 2 drugs as a class reduced AIMS scores significantly more than placebo (standardized mean difference,* -0.46; $p<0.001$). The 2 drugs' effect sizes were similar. The 2 VMAT-2 inhibitors were associated with a higher likelihood than placebo of a ≥50% reduction in the AIMS score (risk ratio,* 2.66; $p<0.001$), with a number needed to treat* of 5. Similar results were seen for response according to Clinical Global Impression criteria, although when the agents were analyzed individually, superiority to placebo was statistically significant for valbenazine but not deutetrabenazine.

A second meta-analytic comparison was also performed for adverse effects of the 2 newer drugs. Neither the VMAT-2 inhibitors as a class nor either of the drugs individually was associated with an increased risk of adverse events relative to placebo. The drugs did not increase risk of depression, suicidal ideation, sedation, or somnolence.

Discussion: At present, deutetrabenazine and valbenazine have not been directly compared in a head-to-head trial, and the choice between them is based on individual medication properties. Due to its short half-life of about 5 hours, tetrabenazine has large variations in drug levels that have off-target effects such as sedation, acute motor syndromes, and possibly depression and suicidality. The 2 newer VMAT-2 inhibitors appear to lack these effects. Deutetrabenazine has a half-life of 9–10 hours, requiring twice-daily dosing, while valbenazine's half-life of 20 hours allows once-daily dosing.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis. However, the source of funding was not disclosed.

Solmi M, Pigato G, Kane J, Correll C: Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. *Drug Design, Development and Therapy* 2018;12:1215-1238. From the University of Padua, Italy; and other institutions. **Source of funding not stated. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining 2 authors declared no competing interests.**

Common Drug Trade Names*: deutetrabenazine—*Austedo*; tetrabenazine—*Xenazine*; valbenazine—*Ingrezza

***See Reference Guide.**

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Correlation Coefficient (r): A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1. An r value near 1 indicates a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r-value indicates a negative relationship.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics.

Risk Ratio: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Standardized Mean Difference: The difference between 2 normalized means—i.e., the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

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Folic Acid Supplements for Schizophrenia

According to a meta-analysis, folic acid supplementation may produce modest negative-symptom improvement in patients with schizophrenia.

Background: It has been suggested that folic acid may improve schizophrenia symptoms by decreasing levels of homocysteine. Various biochemical, genetic, and epidemiologic studies have linked low folic acid levels to the development of schizophrenia.

Methods: Studies were identified in the literature that were double-blind, randomized, placebo-controlled trials of folic acid or its relatives (folate, methylfolate, and folinic acid) as a supplement to antipsychotic drugs for the treatment of schizophrenia. A total of 10 trials, comprising 925 patients, were identified; none were sponsored by pharmaceutical companies. The primary outcome of the meta-analysis was improvement in total symptoms, measured using the Positive and Negative Syndrome Scale (PANSS). Other outcomes were subscales of the PANSS and tolerability (discontinuation and individual adverse events).

Results: Studies had a mean treatment duration of 14 weeks; most were small and had inconsistent results. Three trials were excluded from the analysis because they did not report sufficient data. In 3 of the 7 included trials, patients also received concomitant vitamins B_6 and B_{12}.

The 7 included studies all evaluated folic acid supplementation, and mean baseline PANSS total scores ranged from 70 to 97. While most studies showed at least a small decrease in PANSS total score (range, <1–11 points), folic acid supplementation was not superior to placebo; nor was it superior for most secondary measures. However, PANSS negative symptoms showed a larger improvement with folic acid than with placebo (standardized mean difference,* 0.25; p=0.04). Subgroup analyses indicated that concomitant vitamin B supplementation did not account for the significant difference in negative symptoms. Incidence of adverse effects did not differ between folic acid supplementation and placebo.

Discussion: The authors note several important limitations that could affect the interpretation of the study results. Sample sizes were small in the individual studies, and treatment durations

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were short. In addition, the results were not corrected for multiple comparisons, and differing national practices of food fortification with folic acid may have been an unmeasured source of error. In spite of these limitations, the present results suggest that a larger study, specifically examining the effects of folic acid on negative symptoms, may be warranted.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Sakuma K, Matsunaga S, Nomura I, Okuya M, et al: Folic acid/methylfolate for the treatment of psychopathology in schizophrenia: a systematic review and meta-analysis. *Psychopharmacology* 2018;235 (August):2303–2314. From Fujita Health University School of Medicine, Japan. **This study was conducted without funding. The authors declared no direct competing interests.**

***See Reference Guide.**

Adjunctive Cariprazine in Depression

In a phase II clinical trial in patients with treatment-resistant major depressive disorder, adjunctive low-dose cariprazine (*Vraylar*) showed modest benefit.[1] The study results fell short of statistical significance, perhaps as a result of small sample size, low dosage, too-gradual titration, or a large placebo effect.

Methods: Participants were adults with major depressive disorder, without psychotic features, with the current episode duration of ≥8 weeks and nonresponsive to 1 or 2 adequate antidepressant trials. After 8 weeks of treatment with an open-label antidepressant plus placebo, patients still not meeting response criteria were randomly assigned to adjunctive double-blind treatment with cariprazine or placebo for an additional 8 weeks. Cariprazine dosage ranges of 0.1–0.3 mg/day and 1.0–2.0 mg/day were based on a previously established maximum tolerated dosage of 1 mg/day in healthy individuals. (In patients with schizophrenia, dosages up to 12.5 mg/day are tolerated.) The primary study outcome was change in Montgomery-Asberg Depression Rating Scale (MADRS) score.

Results: Of 502 patients enrolled in open-label treatment, 231 were nonresponders (average age, 45 years; 69% women) and entered the randomized phase; 205 completed treatment. The frequency and causes of discontinuation were generally comparable in all 3 treatment groups.

The mean MADRS total score at randomization was 26 across the groups. In a last observation carried forward analysis,* MADRS changes were not statistically significantly different from placebo in either cariprazine group, but the higher-dose group showed a larger average reduction than the placebo group. (See table.) The higher-dose cariprazine group also demonstrated numerically, but not statistically, greater positive change in the Clinical Global Impression–Improvement scale than the placebo group, as well as numerically higher rates of MADRS response (≥50% decrease in MADRS score) and remission (MADRS score ≤10).

Improvements from Baseline to Week 16			
Outcome Measure	**Placebo**	**0.1–0.3 mg/day Cariprazine**	**1–2 mg/day Cariprazine**
Change in MADRS Total Score	-8	-7.5	-9.8
MADRS Response	26%	30%	38%
MADRS Remission	20%	22%	27%

The higher cariprazine dosage was associated with generally mild-to-moderate adverse effects: headache, restlessness, fatigue, increased appetite, insomnia, dry mouth, and constipation. One patient in this dosage group discontinued because of adverse effects. Akathisia occurred in 4 patients in the higher-dosage group.

Discussion: Although the differences between placebo and adjunctive cariprazine were not statistically significant, the 1.8-point difference between the groups in MADRS change approaches the 2-point threshold generally considered clinically relevant, and a previous trial,[2] with cariprazine dosages of up to 4.5 mg/day, showed a mean MADRS score difference of 2.2 points. Consequently, further studies to establish the optimal therapeutic dosage of cariprazine in resistant depression appear to be warranted.

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

[1]Fava M, Durgam S, Earley W, Lu K, et al: Efficacy of adjunctive low-dose cariprazine in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *International Clinical Psychopharmacology* 2018; doi 10.1097/YIC.0000000000000235. From Massachusetts General Hospital, Boston; Allergan, Madison, NJ; and Gedeon Richter Plc, Hungary. **Funded by Allergan; and Gedeon Richter Plc. All study authors disclosed potentially relevant financial relationships.**

[2]Durgam S, et al: Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. *Journal of Clinical Psychiatry* 2016;77:371–378.

***See Reference Guide.**

Adjunctive Brexpiprazole for Depression

In a randomized, multi-site trial, adjunctive brexpiprazole was effective in patients with depression that had not been adequately responsive to antidepressant drugs.

Methods: The trial enrolled patients with a current nonpsychotic major depressive episode of ≥8 weeks' duration and an inadequate response to 1–3 antidepressants during the current episode. During the first 8 study weeks, patients received open-label treatment with an investigator-selected antidepressant, plus a single-blind placebo. Inadequate response was defined using a combination of scores on the Hamilton Rating Scale for Depression (HAM-D), Clinical Global Impression–Improvement (CGI-I) scale,* and Montgomery-Asberg Depression Rating Scale (MADRS). Patients who did not meet response criteria (i.e., ≥50% reduction in HAM-D score to a final score of <14 plus a CGI-I score of 1 or 2) with antidepressant monotherapy were randomly assigned to an additional 6 weeks' treatment with either brexpiprazole (titrated to 2 mg/day over 3 weeks) or placebo, in addition to the same SRI or SNRI antidepressant. The primary efficacy endpoint was change from baseline in the MADRS total score.

Results: Of 837 patients who entered single-blind treatment, 14.5% withdrew from the study and 38.5% experienced response to the antidepressant. The remaining 394 (mean age, 43 years; 74% women) received adjunctive brexpiprazole or placebo. Background antidepressants in these patients included 10 or 20 mg/day escitalopram (n=74); 40 or 60 mg/day duloxetine (n=69); 20 or 40 mg/day fluoxetine (n=68); 75–225 mg/day extended-release venlafaxine (n=66); 100–200 mg/day sertraline (n=60); and 37.5 or 50 mg/day controlled-release paroxetine (n=57). More than 90% of this group completed the double-blind treatment phase.

Mean MADRS total scores at baseline were 26 and 27 in the placebo and brexpiprazole groups, respectively. Brexpiprazole was associated with a significantly larger change from baseline in MADRS score than placebo (-10.4 vs -8.1 points; p=0.0074). Significant differences were evident beginning in the third week of treatment, when the drug was titrated to the therapeutic dose. A key secondary efficacy endpoint, change from baseline in the Sheehan Disability Scale score, favored brexpiprazole numerically but did not reach statistical significance. Among the other secondary endpoints, brexpiprazole was superior to placebo in patients with DSM-5 anxious distress (p=0.0099) and in those with <25% improvement during antidepressant monotherapy (p=0.026).

Adverse effects were similar to those observed in other brexpiprazole studies. The most common were akathisia and restlessness (8% each). Patients gained an average of 3.3 lbs with

brexpiprazole and 1.1 lb with placebo ($p<0.0001$). There were no clinically significant adverse effects on prolactin levels, sexual function, or suicidality.

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

Hobart M, Skuban A, Zhang P, Augustine C, et al: A randomized, placebo-controlled study of the efficacy and safety of fixed-dose brexpiprazole 2 mg/d as adjunctive treatment of adults with major depressive disorder. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m12058. From Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ; and H. Lundbeck A/S, Copenhagen, Denmark. **Funded by Otsuka and Lundbeck. All study authors disclosed financial relationships with Otsuka or H. Lundbeck.**

Common Drug Trade Names*: brexpiprazole—*Rexulti*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; paroxetine, controlled release—*Paxil CR*; sertraline—*Zoloft*; venlafaxine, extended release—*Effexor XR

***See Reference Guide.**

Prenatal Antidepressants and Child Motor Development

Maternal antidepressant use during pregnancy was associated with a small negative effect on motor development in children, according to a systematic review and meta-analysis.

Background: Many studies have evaluated the risk of structural abnormalities and immediate physiologic effects of antidepressant exposure in newborns, but there have been few studies of long-term neurodevelopmental outcomes. A causal association is biologically plausible because SSRI medications cross the placenta and the blood-brain barrier and may possibly alter serotonin signaling and the development of serotonin circuitry.

Methods: The analysis was based on English-language cohort or case-control studies using an accepted measure of motor performance in children or infants exposed to antidepressants in utero. Studies were excluded if they focused solely on the neonatal period. Few studies compared exposed children with those whose mothers had depression but did not receive antidepressants; therefore the meta-analysis was limited to 18 studies with a healthy control group of unexposed women. In the included studies, the Bayley Scales of Infant Development was the most commonly used assessment tool; several other rating scales were used, and a handful of studies were based on clinician or parent observation.

Results: The overall effect size* for impaired motor function in children exposed to antidepressants in utero was 0.22. Researchers in 7 of the 18 studies reported outcome with categorical data. The pooled effect size from these studies (0.40) was statistically significant, while the pooled effect size from researchers reporting numerical scores (0.08) was not. The study results were significantly heterogeneous, with most heterogeneity attributable to the type of data. There was no evidence of publication bias.

Discussion: The present analysis suggests that any effects antidepressants have on offspring motor development are small. In addition, the effects could be accounted for in a number of ways (e.g., effects of maternal depression itself) that do not directly implicate antidepressants. In addition, developmental scores in the exposed children generally fell within the normal developmental range, and abnormalities were not discernible on clinical examination. Thus the clinical significance of these findings remains unclear and they do not warrant changing antidepressant prescribing guidelines during pregnancy. However, monitoring of exposed children may be prudent.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Grove K, Lewis A, Galbally M: Prenatal antidepressant exposure and child motor development: a meta-analysis. *Pediatrics* 2018; doi 10.1542/peds.2018–0356. From Graylands Hospital, Mount Claremont, Australia; and other institutions. **This research was conducted without external funding. The authors declared no competing interests.**

***See Reference Guide.**

Antidepressant Increase for Resistant Disease

According to a meta-analysis of randomized controlled trials, increasing the dose of an SSRI is not effective in patients with unipolar major depression and initial treatment failure.

Background: Rates of antidepressant nonresponse have been shown to be as high as 30–40%. Current guidelines recommend switching antidepressants, augmenting with a second-generation antipsychotic or lithium, or increasing the initial antidepressant dose. Surveys show that nearly half of clinicians prefer to increase the dose in cases of nonresponse. Studies of this strategy have had mixed results or have been inconclusive.

Methods: A comprehensive literature search was undertaken to identify all randomized trials comparing a dose increase with unchanged medication continuation in patients with study-defined antidepressant treatment failure following ≥3 weeks of initial treatment. The primary outcome of the meta-analysis was efficacy of a dose increase compared with unchanged continuation, with efficacy described as a standardized mean difference* in rating scale scores.

Results: The search identified 9 studies with a total of 1273 patients. All of the studies reported on an SSRI, and 1 study also reported on maprotiline (*Ludiomil*). Initial treatment phases ranged from 3 to 9 weeks, and the double-blind phase ranged from 3 to 10 weeks.

The difference in outcome between dosage increase and unchanged continuation was not statistically significant (standardized mean difference, 0.053) but favored dose increase. Several of the studies had sample sizes too small to detect a medium-sized effect. Removing individual studies did not affect the outcome, indicating that no study strongly influenced the analysis. Secondary outcomes—response, remission, and dropout rates—did not favor either strategy.

Discussion: The study authors suggest that a possible explanation for their observations is that a dosage increase may not lead to increased serotonin transporter occupancy. Although the present conclusions apply only to SSRIs, some studies of antidepressant switches have also had negative results and the authors recommend other, empirically supported second-line treatments such as augmentation with lithium or a second-generation antipsychotic.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Rink L, Braun C, Bschor T, Henssler J, et al: Dose increase versus unchanged continuation of antidepressants after initial antidepressant treatment failure in patients with major depressive disorder: a systematic review and meta-analysis of randomized, double-blind trials. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17r11693. From the University of Cologne Medical School, Germany; and other institutions. **This analysis was conducted without funding. The authors declared no competing interests.**

***See Reference Guide.**

Vortioxetine for Physical Symptoms of Depression

According to a meta-analysis of short-term, manufacturer-sponsored, placebo-controlled trials, vortioxetine (*Trintellix*) is associated with improvement in the somatic symptoms of depression.

Methods: Of 17 short-term (6–8 week) trials that were conducted as part of the vortioxetine clinical development program, 5 were selected for the meta-analysis based on the use of both the Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) to measure physical symptoms. The meta-analysis combined data from the 5 studies, and then conducted separate analyses for each of the physical symptoms rated with the HAM-D or the HAM-A and for the 2 therapeutic doses of vortioxetine, 5 and 10 mg/day. Study participants were adults, aged 18–75 years, with a major depressive episode of ≥3 months' duration. Patients with significant anxiety (i.e., a baseline HAM-A score of ≥20) were analyzed as a subgroup.

Results: Nearly 2100 patients were randomized and received vortioxetine or placebo. The outcome analysis was based on 1729 patients who completed the individual study's treatment protocol. Baseline symptom ratings indicated that patients had, on average, moderate-to-severe depression and a significant level of anxiety. Vortioxetine was associated with statistically significant improvement in most HAM-D somatic items, although in some cases, improvement was limited to the higher dose. (See table.) Several HAM-A somatic items also improved with vortioxetine. In the subset of patients with a high level of anxiety, who made up nearly half of the study population, significant effects were seen for both vortioxetine doses on HAM-D early and middle insomnia, general somatic symptoms, somatic anxiety symptoms, and genital symptoms.

Significant Differences from Placebo in Somatic Symptom Categories		
Vortioxetine Dosage	**HAM-D Symptoms**	**HAM-A Symptoms**
5 mg/day	Middle insomnia (p=0.006) Late insomnia (p=0.002) General somatic (p=0.013)	Somatic muscular (p=0.021) Genitourinary (p=0.02)
10 mg/day	Early insomnia (p<0.001) Middle insomnia (p<0.001) Late insomnia (p=0.038) Somatic anxiety (p<0.001) General somatic (p<0.001) Genital (p<0.001)	Genitourinary (p<0.001) Autonomic (p=0.025)

HAM-D gastrointestinal symptoms and weight loss were unaffected by vortioxetine treatment. Nonsignificant differences were observed for HAM-A somatic sensory, cardiovascular, respiratory, and gastrointestinal items.

Discussion: The presence of physical symptoms in depression predicts a more chronic course of disease, and residual physical symptoms may increase the risk of recurrence. Vortioxetine has multimodal interacting mechanisms of action that may affect somatic symptoms. Both serotonin and norepinephrine are probably involved in physical symptoms of depression and in pain. In addition, nonclinical studies indicate vortioxetine modulates multiple neurotransmitter symptoms involved in centrally mediated pain.

Study Rating*—16 (89%): This study met most criteria for a meta-analysis; however, while the authors disclosed that data was collected from studies funded by H. Lundbeck A/S, Valby, and Takeda Pharmaceuticals Inc., the funding source for the present analysis was not declared.

Christensen M, Florea I, Lindsten A, Baldwin D: Efficacy of vortioxetine on the physical symptoms of major depressive disorder. *Journal of Psychopharmacology* 2018; doi 10.1177/0269881118788826. From H. Lundbeck A/S, Denmark; and other institutions. **Source of funding not stated. All study authors declared potentially relevant financial relationships.**

***See Reference Guide.**

Depression as Medication Adverse Effect

Use of medications that have depression as a potential adverse effect is common and increasing, according to a longitudinal series of surveys of American adults. Use of ≥3 of these medications was associated with simultaneous depression.

Methods: The authors analyzed 5 waves of data from the U.S. National Health and Nutrition Examination Survey, an in-person audit of a representative sample of community-dwelling adults, which is conducted in 2-year cycles. The final sample included >26,000 persons interviewed between 2005 and 2014. Participants showed interviewers containers for all prescription medications taken in the past 30 days. Information about the relationship of drugs to depression and suicidal thoughts or behavior was obtained from Micromedex, an online database

that lists FDA-labeled adverse events. Depression was assessed using the Patient Health Questionnaire 9 (PHQ-9).

Results: Use of any medication with depression as a side effect increased from an estimated 35% of the population in 2005–2006 to 38% in 2013–2014. Concurrent use of ≥3 of these medications increased from 7% to 9.5%, and use of medications with suicidal symptoms as a potential adverse effect increased from 17% to 23.5%. Overall, antidepressants with depression as a labeled adverse effect were the most widely used medication class, and use increased significantly between the study waves, from 11% to 15% of surveyed patients (p=0.001). Use of gastrointestinal agents (in particular, proton pump inhibitors and histamine H_2 antagonists), anxiolytics and sedative/hypnotics, and anticonvulsants also increased significantly (p≤0.01 for all). Use of depression-related antihypertensives, analgesics and muscle relaxants, hormonal contraceptives, and hormone replacement therapy was frequent but did not increase over the 10 study years.

The estimated prevalence of depression increased from 4.7% in patients taking no medications with depression as a labeled adverse effect to 6.9% in those taking 1 medication (p=0.002), 9.5% for those taking 2 (p<0.001), and 15.3% for those taking ≥3 medications (p<0.001). A similar trend was seen for patients taking increasing numbers of medications with suicidal symptoms as potential adverse effects. Most of the combinations associated with depression involved the beta-blockers atenolol or metoprolol, the narcotic hydrocodone, or the anticonvulsant gabapentin. Use of multiple medications without depression as an adverse effect was not associated with depression risk, compared with no medication use. The associations persisted in analyses that excluded users of psychotropic drugs, suggesting the association was not dependent upon the underlying psychiatric diagnosis.

Discussion: The study population reported using >200 different drugs with depression or suicidal symptoms as a labeled adverse effect. Some of these drugs, including proton pump inhibitors and emergency contraceptives, are also available over the counter, and product labeling does not always include full information about adverse effects. Furthermore, commonly used screening instruments for depression do not include evaluation of prescribed medications that have depression as a potential adverse effect.

Qato D, Ozenberger K, Olfson M: Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. *JAMA* 2018:319 (June 12):2289–2298. From the University of Illinois College of Pharmacy, Chicago; and other institutions. **Funded by the Robert Wood Johnson Foundation; and other sources. Two of 3 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

Common Drug Trade Names*: atenolol—*Tenormin*; gabapentin—*Neurontin*; hydrocodone—*Hysingla, Zohydro*; metoprolol—*Lopressor

Escitalopram and Cardiac Outcomes

In a placebo-controlled trial, patients who received treatment with escitalopram (*Lexapro*) for depression following acute coronary syndrome (ACS) had a reduced incidence of cardiovascular events in the subsequent 8 years.

Methods: This study was a planned secondary analysis of an escitalopram efficacy trial in patients with ACS. Potential patients were hospitalized for ACS at a central hospital in South Korea, treated by study cardiologists, and screened for depression within 2 weeks of admission. After further diagnostic evaluation by a study psychiatrist, patients who met criteria for minor or major depressive disorder were offered random assignment to escitalopram or placebo for 24 weeks of double-blind treatment. Previously published primary study results indicated that escitalopram was significantly superior to placebo for the principal outcome of depression remission. The focus of the present analysis is major adverse cardiac events (MACE), a composite of cardiovascular death, all-cause mortality, myocardial infarction (MI), and percutaneous coronary intervention.

Results: More than 4800 patients with ACS were screened for depression, 1152 underwent depression screening, 446 received a diagnosis of depression, and 300 were included in the randomized trial. Participants were followed for a mean of 8 years (range, 5–11 years). During follow-up, MACE occurred in 41% of the escitalopram group, compared with 54% of the placebo group (hazard ratio [HR],* 0.69; p=0.03). This difference was entirely accounted for by MIs (HR, 0.54; p=0.04). The treatment groups did not differ in rates of all-cause mortality, cardiac death, or percutaneous procedures. After adjustment for age, gender, and cardiac factors (e.g., hypertension, smoking, history of ACS, left ventricular ejection fraction), regardless of treatment group, patients in whom depression remitted had significantly lower hazards of MACE (HR, 0.52; p=0.001), all-cause mortality (HR, 0.46; p=0.01), and percutaneous procedures (HR, 0.48; p=0.05) compared with those without remission.

Discussion: These observations conflict with 2 previous, large trials of antidepressant treatment in patients with ACS, which found antidepressant treatment did not improve depression or long-term cardiac outcomes.[3,4] Escitalopram may modify the course of ACS through reduction of depressive symptoms or via positive effects on levels of brain-derived neurotrophic factor and proinflammatory cytokines and normalization of autonomic and platelet dysfunction.

[1]Kim J-M, Stewart R, Lee Y-S, Lee H-J, et al: Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: a randomized clinical trial. *JAMA* 2018:320 (July 24–31):350–357. From Chonnam National University Medical School, Republic of Korea; and other institutions. **Funded by the National Research Foundation of Korea; and other sources. One of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Kim J, et al: Escitalopram treatment for depressive disorder following acute coronary syndrome: a 24-week double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry* 2015;76:62–68.

[3]vanMelle J, et al: MIND-IT Investigators: effects of antidepressant treatment following myocardial infarction. *British Journal of Psychiatry* 2007;190:460–466.

[4]Glassman H, et al: Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: seven-year follow-up of SADHART participants. *Archives of General Psychiatry* 2009;66:1022–1029.

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Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

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.

Last Observation Carried Forward (LOCF): A method of data analysis in which missing data for individual patients is replaced by the last observed value of that variable.

Standardized Mean Difference: The difference between 2 normalized means—i.e., the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales, a value of 0 to 0.2 is considered a negligible effect, 0.2 to 0.5 a small effect, 0.5 to 0.8 a medium effect, and >0.8 a large effect.

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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Cannabis for Negative Affect

Individuals who used cannabis to relieve negative affect reported substantial but temporary reductions in depression, anxiety, and stress, according to results of a study based on anonymous data from a medical-cannabis user app. Patients did not become habituated to the effects of repeated cannabis use, but repeated use did not lead to long-term reductions in these symptoms.

Methods: The investigators analyzed data from a free app, Strainprint, that records users' demographic data, medical conditions and symptoms, use of specific cannabis products, and symptoms immediately before and after consuming cannabis. The study was conducted in Canada, where all licensed cannabis products are analyzed for content of the 2 cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD). The sample was limited to persons who used medical cannabis to treat symptoms of depression, anxiety, or stress and to users of inhalation but not oral administration methods.

Results: The analysis was based on nearly 12,000 tracked inhalation sessions in 561 medical cannabis users who used the app to track changes in depression symptoms, 770 who tracked anxiety, and 726 who tracked changes in stress.

Participants reported that cannabis reduced depressive symptoms in 89% of tracked sessions, anxiety in 93.5% of sessions, and stress in 93% of sessions ($p<0.001$ vs baseline for all 3 symptoms). Symptoms were increased in 2–3% of sessions. Women reported greater reductions in anxiety symptoms than men ($p<0.001$), but there were no differences between genders in reduction of depression or stress. Effects of treatment were somewhat dependent on the cannabinoid content of products and on dosage. Products with high CBD and low THC content were associated with the largest perceived improvement in depression, and those with high content of both cannabinoids were associated with the greatest improvement in stress. Ten or more puffs of cannabis were reportedly more effective in relieving stress than a smaller number; 2 or more puffs were most effective for anxiety; and changes in depression were apparently not dose-related. Participants reported no changes in the perceived efficacy of cannabis as they continued its use. Baseline symptom ratings immediately before each inhalation session showed a significant increase in depression symptoms with time, but no change in anxiety or stress.

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Discussion: The results of this uncontrolled naturalistic study are consistent with the reported anxiolytic and stress-relieving effects of cannabis. However, some research suggests that long-term use of cannabis to relieve depression may increase susceptibility to the disorder by altering CBD receptor type 1 availability; yet other research indicates these changes can be reversed by abstaining from cannabis for about 2 days.

Cuttler C, Spradlin A, McLaughlin R: A naturalistic examination of the perceived effects of cannabis on negative affect. *Journal of Affective Disorders* 2018;235:198–205. From Washington State University, Pullman. **Funded by Washington State University. The authors declared no competing interests.**

Quetiapine and Risk of Congenital Malformations

Exposure to quetiapine (*Seroquel*) during pregnancy is associated with little, if any, excess risk of fetal malformations, according to a preliminary analysis of data from a registry of second-generation antipsychotic exposures in pregnancy.

Methods: The National Pregnancy Registry for Atypical Antipsychotics (NPRAA) was established at Massachusetts General Hospital in 2008 to collect data on the reproductive safety of all second-generation agents. Any pregnant woman with a history of psychiatric illness may enroll. Women are prospectively interviewed during pregnancy and 12 weeks after delivery. Obstetric records and first 6 months of pediatric medical records are also evaluated for women who give consent. To avoid biasing the results, pregnancies with a birth defect identified by prenatal testing at the time of enrollment are excluded from the analysis. The present analysis compared pregnancies with exposure to quetiapine during the first trimester with pregnancies without first-trimester exposure to a second-generation antipsychotic.

Results: Of 888 women enrolled in the registry, 357 with evaluable data were exposed to a second-generation antipsychotic during the first trimester, including 152 who received quetiapine. A total of 205 comparison women with evaluable data were not exposed to any second-generation antipsychotic. Exposed women had a higher prevalence of bipolar disorder than controls (68% vs 28%), the latter being more likely to suffer from depression or an anxiety disorder. Most of the women who used quetiapine during the first trimester continued to take it throughout pregnancy.

In the exposed pregnancies, there were 2 infants (1.3%) with major malformations: 1 with transposition of the great arteries and 1 with pulmonary stenosis due to dysplastic pulmonary valve. There were 3 major malformations (1.4%) in the control group. The unadjusted odds ratio* for major malformations in exposed infants was 0.90. Adjustment for potential confounding variables (e.g., demographic characteristics, psychiatric diagnoses, and use of concomitant medications and illicit substances) did not change the results of the analysis.

Discussion: Available reproductive safety data do not suggest second-generation antipsychotics as a class are major teratogens. However, risk estimates based on existing studies are imprecise due to small sample sizes. Quetiapine is among the most commonly prescribed atypical antipsychotics in publicly insured pregnant women and is used primarily for the management of bipolar disorder. The risk of malformations in the present study is consistent with a pooled risk estimate derived from controlled trials, indicating no increased risk. The sample size in the registry is relatively large in comparison to these studies, and the risk estimates will become more precise as NPRAA data accumulate.

Cohen L, Góez-Mogollón L, Sosinsky A, Savella G, et al: Risk of major malformations in infants following first-trimester exposure to quetiapine. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.18010098. From Massachusetts General Hospital, Boston; and other institutions. **Funded by Alkermes, Forest/Actavis, Otsuka, Sunovion, and Teva. Four of 8 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Brexanolone for Postpartum Depression

Intravenous brexanolone had rapid antidepressant effects in women with postpartum depression, according to a combined analysis of 2 phase III clinical trials. Brexanolone is a proprietary formulation of allopregnanolone, an endogenous progesterone metabolite that modulates $GABA_A$ receptors. Perinatal fluctuations in this hormone have been implicated in the pathophysiology of postpartum depression.

Methods: The 2 studies enrolled women, aged 18–45 years, who were ≤6 months postpartum and experiencing depression with onset in the peripartum period. A baseline score on the 17-item Hamilton Rating Scale for Depression (HAM-D) of ≥26 was required for 1 study, and scores of 20–25 were required for the second. Participating women had stopped lactating or temporarily suspended breastfeeding while receiving study medication. Concomitant psychotropic medication was permitted. Women were randomly assigned to receive a single, 60-hour infusion of 90 µg/kg brexanolone per hour, 60 µg/kg brexanolone per hour (in 1 study only), or placebo. Patients received treatment in a medically supervised setting for the 60 hours of infusion and remained for an additional 12 hours for assessments. The primary efficacy outcome of both studies was change from baseline to 60 hours (end of infusion) in HAM-D score, which was administered throughout treatment and again at days 7 and 30 of follow-up.

Results: A total of 138 women participated in the first study, and 108 in the second. Across the studies, 13% of women did not complete the protocol, most because they did not begin the infusion or were lost to follow-up.

In the first study, HAM-D total scores were significantly reduced with brexanolone relative to placebo at 24 hours and all subsequent time points, including the primary 60-hour time point. (See table.) In the second study, HAM-D scores were significantly lower with brexanolone than placebo from 48 hours until day 7. HAM-D remission (score ≤7) occurred at 60 hours in 51% of the 60-µg brexanolone group and 16% of the placebo group (odds ratio,* 6.0; p=0.0011); the remission rate for 90-µg brexanolone was not reported. In the second study, 61% of patients in the brexanolone group had remission at 60 hours, compared with 38% of the placebo group (odds ratio, 3.4; p=0.0033). Across both studies, dosages, and other efficacy endpoints, brexanolone was generally statistically superior to placebo at multiple time points, extending to 30 days. A total of 22% of women were receiving concomitant psychotropic medication; results were comparable in women who were and were not receiving other drugs.

Change from baseline to 60 hours in mean HAM-D scores

	Mean Baseline Score	Mean change from baseline	Least squares mean* difference from placebo	Significance
Study 1				
placebo	28.6	-14	—	—
brexanolone 60 µg/hr	29.1	-19.5	-5.5	p=0.0013
brexanolone 90 µg/hr	28.4	-17.7	-3.7	p=0.0252
Study 2				
placebo	22.7	-12.1	—	—
brexanolone 60 µg/hr	22.6	-14.6	-2.5	p=0.016

Brexanolone infusion was generally well tolerated, with dizziness and somnolence the most common adverse events. Five patients experienced excessive sedation due to brexanolone, which stopped shortly after the infusion was halted.

Meltzer-Brody S, Colquhoun H, Riesenberg R, Epperson C, et al: Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet* 2018; doi 10.1016/S0140-6736(18)31551-4. From the University of North Carolina School of Medicine, Chapel Hill; and other institutions including Sage Therapeutics, Cambridge, MA. **Funded by Sage Therapeutics. Of 12 study authors, 11 declared relevant financial relationships; the remaining author declared no competing interests.** See related stories in *Psychiatry Drug Alerts* 2017;31 (May):36–37 and 2017;31 (July):51–52.

***See Reference Guide.**

Prazosin for Alcohol Use Disorder

In a placebo-controlled trial of patients with alcohol dependence, prazosin (*Minipress*) was associated with reductions in drinking, but not with abstinence. This finding suggests prazosin may be most useful in reducing heavy drinking as part of a harm-reduction approach.

Methods: The study enrolled individuals with a DSM-IV diagnosis of alcohol dependence and a goal of abstaining from alcohol. Minimum required baseline alcohol consumption was ≥14 drinks per week for women and ≥21 drinks per week for men. The trial excluded subjects with PTSD to isolate the effects of prazosin, which has been shown to reduce PTSD symptoms, on alcohol use. Patients were randomly assigned to receive 12 weeks of double-blind treatment with either prazosin or placebo. Prazosin was titrated over 2 weeks to a target dosage of 4 mg in the morning, 4 mg in the afternoon, and 8 mg at bedtime. In addition to study medication, all patients received weekly brief medication-management counseling and were encouraged to attend self-help meetings. Primary study outcomes were the number of drinks per week, number of drinking days per week, and number of heavy drinking days per week. Patients reported their alcohol consumption, cravings, and medication adherence in a daily telephone call with automated prompts.

Results: Of 92 patients (19 women) enrolled, 8 in the prazosin group and 4 in the placebo group dropped out during the 2 weeks of titration and were not included in the efficacy analysis. Of 80 patients who completed titration, 35 in each group received the target drug dose; 26 prazosin-treated patients and 30 receiving placebo completed all 12 weeks of treatment.

Over the 90 days before randomization, participants consumed an average of 9 drinks per day. In the final week of treatment, average drinks per day were about 2 in both the prazosin and placebo groups. The number of drinks per week, drinking days per week, and heavy drinking days per week were reduced in both treatment groups. However, the effects of prazosin were significantly greater in terms of number of drinks per week and heavy drinking days. (See table.) The groups did not differ in changes in alcohol craving over time. The primary adverse effects of prazosin were drowsiness and edema.

Effects of Treatment on Drinking Outcomes

	Prazosin		Placebo		Significance of between-group difference in improvement
	Week 3	Week 12	Week 3	Week 12	
Drinks per week	21.3	13.3	14.6	13.1	p=0.03
Drinking days per week	3.2	2.8	2.8	2.3	p=ns
Heavy drinking days per week	1.8	1	1.5	1.2	p=0.01

Discussion: The present results indicate prazosin may be useful in reducing heavy drinking associated with negative consequences, rather than by promoting full abstinence. Similar moderate effects have been observed with other drugs for alcohol use disorder, including FDA-approved medications; the authors suggest that combining drugs with different mechanisms may be a useful approach.

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

Simpson T, Saxon A, Stappenbeck C, Malte C, et al: Double-blind randomized clinical trial of prazosin for alcohol use disorder. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.17080913. From the VA Puget Sound Health Care System, Seattle, WA; and other institutions. **Funded by the National Institute on Alcohol Abuse and Alcoholism. Two of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Bleeding Risk with Antidepressants

Serotonergic antidepressants are associated with increased risk of bleeding, especially early in the course of treatment, according to a nonsystematic literature review. Clinicians should be aware of options when prescribing for high-risk patients, including antidepressants with low potential to induce bleeding and strategies for preventing gastrointestinal (GI) bleeding.

SRI-related bleeding is believed to be the result of inhibition of the serotonin transporter on platelets, leading to reduced platelet aggregation. SRIs also increase gastric acidity, which can predispose to GI bleeding. SRIs with high serotonin transporter binding affinity may place patients at higher bleeding risk than agents with intermediate or low affinity. (See table.) Cytochrome P450-mediated drug interactions further contribute to bleeding risk with SSRIs, particularly duloxetine, fluoxetine, fluvoxamine, and paroxetine.

A literature search identified 9 meta-analyses of SRI-related bleeding and 1 meta-analysis of bleeding risk with bupropion and mirtazapine. SRIs have been associated with GI bleeding, intracranial hemorrhage, postpartum hemorrhage, and perioperative bleeding. Most of the studies have focused on GI bleeding, which makes it difficult to assess the risk at other sites. In 1 meta-analysis encompassing nearly 1.5 million patients, SSRIs increased bleeding risk by 41% (odds ratio,* 1.41; p<0.001). Risk was especially high for GI bleeding (odds ratio, 1.55) and lower for intracranial hemorrhage (odds ratio, 1.16). However, in another analysis, SSRIs were associated with elevated risk of brain hemorrhage (odds ratio, 1.61). Women who take antidepressants during pregnancy have an increased risk of postpartum hemorrhage (odds ratio, 1.32; p<0.001). It has been difficult to estimate risk of perioperative bleeding because of the use of other medications that affect coagulation. Concomitant medications can add to the risk of bleeding in patients taking SRIs. Increased risk has been documented in patients taking NSAIDs, antiplatelet therapy, and anticoagulants.

Serotonin transporter binding affinity		
High	**Intermediate**	**Low**
Clomipramine	Amitriptyline	Bupropion
Duloxetine	Citalopram	Doxepin
Fluoxetine	Escitalopram	Mirtazapine
Paroxetine	Imipramine	Nortriptyline
Sertraline	Venlafaxine	Phenelzine
Vilazodone		Tranylcypromine
Vortioxetine		Trazodone

Some evidence suggests that acid-suppressing agents decrease risk of GI bleeding in patients taking SRIs with NSAIDs. Proton pump inhibitors have not been investigated directly, but subgroup analyses in some studies suggest they may reduce bleeding risk. However, depression is a potential adverse effect of proton pump inhibitor use in the elderly.

Clinicians should consider preventive strategies for GI bleeding in high-risk patients and the elderly. Agents with low serotonin transporter binding affinity or bupropion, which has a mechanism independent of serotonin, may be prudent choices in patients with bleeding risk.

Bixby A, VandenBerg A, Bostwick J: Clinical Management of bleeding risk with antidepressants. *Annals of Pharmacotherapy* 2018; doi 10.1177/1060028018794005. From Michigan Medicine and the University of Michigan College of Pharmacy, Ann Arbor. **This review was not funded. The authors declared no competing interests.**

Common Drug Trade Names*: amitriptyline—*Elavil*; bupropion—*Wellbutrin*; citalopram—*Celexa*; clomipramine—*Anafranil*; doxepin—*Silenor*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; imipramine—*Tofranil*; mirtazapine—*Remeron*; nortriptyline—*Pamelor*; paroxetine—*Paxil*; phenelzine—*Nardil*; sertraline—*Zoloft*; tranylcypromine—*Parnate*; trazodone—*Oleptro*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Trintellix

***See Reference Guide.**

Lurasidone and Sexual Function in Mixed Depression

A secondary analysis of data from a clinical trial suggests lurasidone (*Latuda*) is not associated with sexual dysfunction in patients with major depressive disorder and subthreshold hypomanic features.[1]

Background: Impaired sexual function is common in patients with major depressive disorder and treatment initiation, particularly with SSRIs and/or atypical antipsychotics, which can exacerbate dysfunction. Lurasidone has a receptor binding profile that suggests low risk for sexual side effects and shares some similarities (e.g., 5-HT_{2A} antagonism and partial agonist effects on 5-HT_{1A}) with medications used to treat sexual dysfunction.

Methods: The analysis was based on a multicenter, placebo-controlled, 6-week clinical trial of flexibly dosed 20–60 mg/day lurasidone.[2] Participants met DSM-IV criteria for major depressive disorder and had 2 or 3 manic or hypomanic symptoms. (The maximum was set at 3 to reduce the likelihood of including patients with undiagnosed bipolar disorder.) Sexual function, a safety outcome of the study, was measured with the 14-item Changes in Sexual Functioning Questionnaire (CSFQ-14), which has separate versions for men and women. The CSFQ-14 has 5 subscales that assess pleasure, desire/frequency, desire/interest, arousal/excitement, and orgasm/completion. The questionnaire is scored from 14 to 70, with higher scores indicating better function and thresholds for sexual dysfunction of ≤47 in men and ≤41 in women. An improvement of 3 points is considered to be clinically meaningful.

Results: The study met its primary efficacy outcome, demonstrating superior antidepressant efficacy to placebo. The safety analysis included a total of 206 patients who had a CSFQ-14 assessment at baseline and received ≥1 dose of study medication. A high proportion of patients—84.5% of women and 81% of men—initially met CSFQ-14 criteria for sexual dysfunction. Baseline severity of sexual dysfunction was not correlated with depression severity.

At 6 weeks, the mean CSFQ-14 score improved by 5.1 points in patients receiving lurasidone, compared with 3.1 points in the placebo group (p=0.046). Men and women had similar improvements in sexual function relative to placebo (effect sizes,* 0.22 in women and 0.33 in men). Lurasidone was associated with numerically greater improvement than placebo on all 5 CSFQ-14 subscales in men and on 4 in women (with no treatment effect seen in desire/frequency in women). Effects on sexual function were not dose-related and did not vary by patient age or the presence or absence of sexual dysfunction at baseline. Mediation analysis showed that improvements in sexual function were largely due to improvement in depression. There were no adverse events related to sexual function in the lurasidone group. Relative to placebo, lurasidone was associated with a mean 2.5 ng/mL increase in prolactin in women and a negligible decrease in men.

Discussion: In addition to having a low risk for inducing sexual dysfunction, these study results suggest that treatment with lurasidone may improve existing dysfunction in patients with mixed depression, but the change is likely due to reductions in depressive symptoms.

[1]Clayton A, Tsai J, Mao Y, Pikalov A, et al: Effect of lurasidone on sexual function in major depressive disorder patients with subthreshold hypomanic symptoms (mixed features): results from a placebo-controlled trial. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.18m12132. From the University of Virginia, Charlottesville; and Sunovion Pharmaceuticals, Inc., Marlborough, MA, and Fort Lee, NJ. **Funded by Sunovion. All 5 study authors disclosed potentially relevant financial relationships; 4 of the 5 were employed by Sunovian.**

[2]Suppes T, et al: Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo-controlled study. *American Journal of Psychiatry* 2016;173(4):400–407.

***See Reference Guide.**

Tianeptine for Geriatric Depression

Tianeptine, an antidepressant with a unique mechanism of action, was effective in a controlled trial in elderly patients with recurrent depression.[1] Unlike most other antidepressants, tianeptine, which is not marketed in the U.S., is not metabolized by the hepatic cytochrome P450 system and has little liability for drug interactions.

Background: There have been few controlled trials of antidepressants in the elderly; instead, treatment guidelines are largely based on expert opinion. The efficacy of second-generation antidepressants in older individuals is modest. In addition, tolerability is often problematic in older patients. Tianeptine has a distinctive mechanism of antidepressant action: It modulates monoaminergic neurotransmission; counteracts the effects of stress on glutamatergic neurotransmission and limbic neuroplasticity; decreases stress-related hypothalamic-pituitary-adrenal axis overactivity; and has antiinflammatory properties.

Methods: Study participants were aged ≥65 years and experiencing a moderate-to-severe episode of recurrent unipolar major depression. Patients whose depression had not responded to ≥2 prior antidepressants (from different classes) were excluded from the trial. Participants were randomly assigned to 8 weeks of double-blind treatment with 25–50 mg/day tianeptine, 10 mg/day escitalopram as an active control, or placebo. The primary study outcome was change from baseline on the 17-item Hamilton Rating Scale for Depression (HAM-D).

Results: A total of 311 patients were enrolled in the study, and 309 were included in the efficacy and safety analyses. Patients had a mean age of 70 years, and more than one-third had severe depression. About 11% withdrew from study treatment, including 4% of patients in the tianeptine group and 6% of those in the escitalopram and placebo groups who withdrew because of adverse events.

Both tianeptine and escitalopram were associated with a larger mean decrease in depressive symptoms than placebo. (See table). The response rates were also larger with both active treatments than with placebo, although the difference for tianeptine was not statistically significant (p=0.06 for tianeptine; p=0.002 for escitalopram). Clinical Global Impression Severity and Improvement ratings also showed a statistically significant treatment effect for both active agents (p<0.001 for both). With both active medications, patients reported significantly greater improvement in social and family life (measured with the Sheehan Disability Scale), but work and total scores did not differ statistically from placebo.

Select Outcomes of Tianeptine, Escitalopram, and Placebo at 8 Weeks

HAM-D Total Score	Tianeptine (n=105)	Escitalopram (n=106)	Placebo (n=98)
Baseline	26.7	26.7	26.6
Endpoint	13.3	13.1	17.1
Significance vs Placebo	p<0.001	p<0.001	—
HAM-D Response (≥50% decrease)	47%	55%	34%

Rates of medication-related adverse events, mostly mild, were 23% for tianeptine, 41% for escitalopram, and 21% for placebo. The most common adverse events were similar in all 3 groups: headache, nausea, flatulence, fatigue, and dizziness. Adverse events led to treatment discontinuation in 4 patients in the tianeptine group, 6 in the escitalopram group, and 6 in the placebo group.

Editor's Note: Tianeptine is marketed in some European, Asian, and Latin American countries for treatment of depression and anxiety.[2] Although it is not approved in the U.S., it can be obtained online as a dietary supplement or research chemical. The drug acts upon opioid receptors in the brain, and there are indications that people are using it as an alternative to narcotics. At a standard dose, tianeptine does not produce a "high", but excessively high doses (e.g., up to a gram/day) can lead to euphoria and a high, and repeated use can lead to addiction and opiate withdrawal.[3]

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

[1]Emsley R, Ahokas A, Suarez A, Marinescu D, et al: Efficacy of tianeptine 25–50 mg in elderly patients with recurrent major depressive disorder: an 8-week placebo- and escitalopram-controlled study. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11741. From the University of Stellenbosch, South Africa; and other institutions. **Funded by Servier, Suresnes, France. Five of 15 study authors disclosed financial relationships with commercial sources, including Servier; the remaining authors declared no competing interests.**

[2]Opioid addicts turning to unapproved antidepressant. WebMD: available at https://www.webmd.com/mental-health/addiction/news/20180802/opioid-addicts-turning-to-unapproved-antidepressant#1.

[3]Ehrenfeld T: The Controversy Over the Antidepressant Tianeptine. Healthline: available at https://www.healthline.com/health-news/controversy-over-antidepressant-tianeptine#1.

Common Drug Trade Names*: escitalopram—*Lexapro*; tianeptine (not available in the U.S.)—*Coaxil, Stablon

***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.

Least Squares Mean: An average estimated from a linear model. In contrast to an arithmetic mean, which is a simple average of the values, least squares means are adjusted for other terms in the model and are less sensitive to missing data.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison 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.

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PSYCHIATRY DRUG ALERTS

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Transdermal Nicotine in Late-Life Depression

In a preliminary study, open-label nicotine patches resulted in a robust and rapid antidepressant response in nonsmokers with late-life depression. Transdermal nicotine also produced some cognitive benefits.

Background: Smoking rates are increased in individuals with depression, which may reflect self-medication. In a few small trials, transdermal nicotine was effective in midlife depression and it has been shown to have cognitive benefits. There is currently no approved medication that alleviates both mood and cognitive symptoms of late-life depression.

Methods: Study participants (n=15; 10 women) were aged ≥60 years and met DSM-IV-TR criteria for major depressive disorder, recurrent or single episode, with a baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥15. Participants were also required to have some degree of cognitive decline, with Montreal Cognitive Assessment scores of ≥24 and subjective decline, defined as endorsing ≥20% of items on the Cognitive Complaint Index. Participants were required to be nonsmokers for at least the past year and could be either antidepressant free or currently on stable antidepressant monotherapy.

All participants received treatment with open-label transdermal nicotine, escalated as tolerated to a target dosage of 21 mg/day. The primary efficacy outcome for mood was change from baseline to 12 weeks in MADRS score, and the primary cognitive outcome was change on the Conners Continuous Performance Test (CPT), a test of attention. Patients were also evaluated using standardized measures for: secondary symptoms of anhedonia, anxiety, apathy, fatigue, and rumination; self-referential negativity bias; subjective cognitive performance; as well as attention, executive function, episodic memory, working memory, and processing speed.

Results: Of the 15 patients who started the study, 14 completed all 12 weeks of patch use. The mean final daily dose was 15 mg. Most patients had early-onset depression, with an average onset age of 26 years, 5 were past smokers, and 6 were antidepressant free.

The mean MADRS score decreased by 18 points from a baseline of 28 (p=0.004). Statistically significant change from baseline was evident beginning at week 3. A total of 13 patients (87%)

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met response criteria (≥50% decrease in MADRS score), and 8 patients (53%) achieved remission (MADRS score ≤8). Changes in depression were not associated with nicotine dose, smoking history, or antidepressant use. Study participants also showed significant decreases in apathy and rumination.

Although there were no statistically significant changes in cognitive performance on the CPT, patients reported some improvement in subjective cognitive performance. Improvements in objectively measured working memory and immediate recall were significant (p=0.049). Measures of self-referential negativity bias were also significantly improved (p=0.046). Cognitive improvement was correlated with change in the MADRS, suggesting that cognitive effects may be dependent on the antidepressant effects of nicotine.

Discussion: Observations in the present study are consistent with results in younger patients. However, the results require replication, and future studies would benefit from measures of plasma nicotine levels to assess bioavailability.

Gandelman J, Kang H, Antal A, Albert K, et al: Transdermal nicotine for the treatment of mood and cognitive symptoms in nonsmokers with late-life depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.18m12137. From Vanderbilt University School of Medicine, Nashville, TN; and other institutions. **Funded by the NIH; and the National Center for Advancing Translational Sciences. The authors declared no competing interests.**

Psychiatric Adverse Effects of Oseltamivir

Prophylactic use of oseltamivir (*Tamiflu*) is associated with a small but statistically significant increase in psychiatric adverse events, according to an analysis of adverse-event data from clinical study reports.[1]

Background: Following the reports of 2 suicides in adolescents who received treatment with oseltamivir, as well as >100 reports of neuropsychiatric adverse effects with the drug, the FDA issued an alert in 2006 warning that patients should be carefully monitored for abnormal behavior during treatment.[2] Analyses of neuropsychiatric adverse effects conducted since then, including several Cochrane Reviews based on published trials, have been inconclusive. Clinical study reports—produced by manufacturers seeking regulatory approval of drugs and containing individual patient-level data on adverse events with a high level of detail, including duration and severity—have recently been made available to researchers by the European Medicines Agency and by some manufacturers. To further clarify the risk of neuropsychiatric effects with prophylactic oseltamivir use, the present study evaluated adverse events in clinical study reports.

Methods: The present analysis was based on clinical study reports from 4 placebo-controlled trials of oseltamivir. The analysis was limited to prophylactic trials to avoid counting any psychiatric symptoms related to existing influenza. Data on clinical adverse events classified under the psychiatric system organ class, representing a change from baseline that occurred after study treatment began, were collected from the reports irrespective of whether study investigators believed it was related to oseltamivir treatment. The primary outcome of the analysis was the proportion of days patients suffered from psychiatric adverse events. This method allowed grouping of multiple adverse events, regardless of their nature—e.g., days suffering from depression and from anxiety by a single patient could be combined. In a secondary analysis, adverse events were weighted based on severity.

Results: The main analysis was based on combined data from 1 trial conducted in adults (n=1559) and 2 trials in elderly nursing-home residents (n=920), all of whom received oseltamivir or placebo for 6 weeks. An additional short-term trial was conducted in adults and adolescents (n=955) who received treatment for 7 days. Psychiatric adverse events were not reported in the journal publications from any of the trials.

A total of 35 psychiatric adverse events (10 of depression) occurred with oseltamivir and 15 with placebo. Excluding the 7-day trial, which reported very few events, the proportion of days patients suffered from a psychiatric adverse event was significantly greater with oseltamivir than placebo (odds ratio,* 4.12). There was little difference between oseltamivir and placebo for less severe adverse events, but severe events occurred on more days with oseltamivir (odds ratio, 34.5). However, the absolute difference between oseltamivir and placebo was small: For every 290 days of treatment, there was 1 additional day of suffering from a psychiatric adverse event of any level of severity.

Discussion: The increasing chance of more severe adverse events with oseltamivir suggests a causal relationship. Although the relative effect of oseltamivir is very high for severe events, the absolute increase is small in the context of all patients included in the trials.

[1]Jones M, Tett S, Del Mar C: Psychiatric adverse events in oseltamivir prophylaxis trials: novel comparative analysis using data obtained from clinical study reports. *Pharmacoepidemiology and Drug Safety* 2018; doi 10.1002/pds.4651. From the University of Queensland, Brisbane; and Bond University, Gold Coast, Australia. **This research was conducted without specific funding. All 3 authors disclosed potentially relevant financial relationships.**

[2]Maxwell S: Tamiflu and neuropsychiatric disturbance in adolescents: the case is not proved but caution is advisable. *British Medical Journal* 2007;334 (June 16):1232–1233.

***See Reference Guide.**

Minocycline in Schizophrenia

The antibiotic minocycline (*Minocin*) has antiinflammatory and neuroprotective actions that have attracted attention as potential treatments for several psychiatric disorders, including schizophrenia. Several case reports, open-label studies, and small controlled trials have suggested the agent is beneficial, particularly for negative symptoms. However, in the largest randomized controlled trial to date, adjunctive minocycline, given for 1 year, did not produce added improvement in symptoms, functional status, or inflammatory markers in patients with recent-onset psychosis.

Methods: The BeneMin study enrolled >200 patients from centers in the U.K. Participants were experiencing a first episode of schizophrenia, schizophreniform disorder, or schizoaffective psychosis; were within 5 years of symptom onset; and were receiving stable antipsychotic medication. Study treatment consisted of 300 mg/day minocycline or placebo added to background antipsychotic medication. The primary study outcome was overall severity of negative symptoms, measured using the Positive and Negative Syndrome Scale (PANSS) at months 2, 6, 9, and 12. Imaging and inflammatory markers were also evaluated to explore the potential neuroprotective and antiinflammatory mechanisms of treatment.

Results: A total of 207 patients were randomly assigned to active treatment or placebo. Before completing 1 year of treatment, 38% of patients had withdrawn from the study. Dropout rates were similar in the minocycline and placebo groups.

Mean scores for positive, negative, and depression symptoms improved in both the minocycline and placebo groups. At no point was there a statistically significant difference between the minocycline and placebo groups in PANSS negative symptoms. Treatment did not influence measures of function or cognitive performance and had no effect on the biomarker outcomes of medial prefrontal gray matter volume, circulating IL-6, and functional MRI tests of the dorsolateral prefrontal cortex. Adverse events were similar in the minocycline and placebo groups. There were 15 hospital admissions in the minocycline group and 10 in the placebo group, all for worsening of psychosis, primarily due to discontinuing antipsychotic medication.

Discussion: These results differ from several earlier studies with smaller sample sizes. The present study is the largest to date, and the lack of symptomatic or functional improvement,

taken with the lack of evidence supporting persistent neurodegeneration or systemic inflammation that minocycline could target, suggest that additional studies may not be warranted.

Deakin B, Suckling J, Barnes T, Byrne K, et al: The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomised, double-blind, placebo-controlled trial. *Lancet Psychiatry* 2018; doi 10.1016/S2215-0366(18)30345-6. From the University of Manchester, U.K; and other institutions. **Funded by the Medical Research Council; and other sources. Eight of 23 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Single-Dose IV Ketamine: Optimal Dosage

Most placebo-controlled clinical trials of IV ketamine for depression have used a uniform single dose of 0.5 mg/kg infused over 40 minutes. According to a dose-ranging trial, the antidepressant efficacy of ketamine is dose related, with significantly greater efficacy of 0.5 mg/kg and 1.0 mg/kg relative to lower doses and to placebo.

Methods: The trial enrolled 99 adults (aged 18–70 years; 49 women) with treatment-resistant depression, defined as an inadequate response to ≥2 medications in the current episode. Patients with a primary Axis I disorder other than MDD, substance use disorder (abuse or dependence), with the exception of nicotine, and those with a history of bipolar disorder, schizophrenia, schizoaffective disorder, or psychotic symptoms were excluded. Patients were randomly assigned to double-blind ketamine doses of 0.1, 0.2, 0.5, and 1.0 mg/kg or to an active placebo (0.045 mg/kg midazolam [*Versed*]). The purpose of the active placebo was to reduce the risk of unblinding due to absence of adverse events. Patients also received optimized, stable doses of their current antidepressant. The primary efficacy outcome was change from baseline on the 6-item Hamilton Rating Scale for Depression (HAM-D-6), which was administered at baseline and on days 1, 3, and 5, and at weeks 1, 2, and 4.

Results: The study retention rate was high, with 95% of participants completing the day 3 evaluation and 87% evaluated 4 weeks post treatment. Patients had experienced inadequate response to an average of 2–3 prior antidepressants and had mean baseline scores of 12–13 on the HAM-D-6.

In a combined analysis of all ketamine doses versus placebo, active treatment was associated with a significantly greater 3.25-point reduction than placebo in HAM-D-6 score on day 1 (p=0.01; effect size,* 0.86). At day 3, active treatment remained marginally superior but was no longer significant (p=0.11; effect size, 0.44). When individual ketamine doses were compared with placebo, only the 0.5 and 1.0 mg/kg doses were statistically superior, and only on day 1. (See table.)

Antidepressant effects of ketamine versus placebo: change from baseline in HAM-D-6

	Difference from placebo	Adjusted significance†	Effect size
0.5 mg/kg	-4.79	p<0.01	1.21
1.0 mg/kg	-3.76	p=0.04	0.95

†Adjusted for multiple comparisons

Secondary study outcomes included a number of alternative measures of depression. There were medium-to-large, but statistically nonsignificant, effects of ketamine on all secondary outcomes at all but the 0.1-mg/kg ketamine dose. Effects tended to be larger on day 1 than day 3. Rates of response (≥50% improvement in the HAM-D-6) to ketamine were highest on day 1 and statistically superior to placebo on that day only. On day 1, response rates were 31% for 0.1 mg/kg ketamine, 21% for 0.2 mg/kg, 59% for 0.5 mg/kg, 53% for 1.0 mg/kg, and 11% for

midazolam. HAM-D-6 scores tended to remain lower with ketamine than placebo throughout the 30-day observation period.

Adverse effects of ketamine consisted of dissociation and transient blood-pressure alterations. Dissociation was more common at the 2 higher doses of ketamine than at lower doses.

Discussion: These observations suggest ketamine may have antidepressant effects throughout its dose range, although with greater effect at higher doses. It remains to be determined whether increasing the dose in patients who respond poorly to the standard 0.5-mg/kg dose is helpful and tolerated, or whether the dose can be reduced in those who cannot tolerate 0.5 mg/kg.

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

Fava M, Freeman M, Flynn M, Judge H, et al: Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Molecular Psychiatry* 2018; doi 10.1038/s41380-018-0256-5. From Massachusetts General Hospital, Boston; and other institutions. **Funded by the NIMH. Of 18 study authors, 14 disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Repeated Oral Ketamine for Resistant Depression

In a preliminary, placebo-controlled trial, repeated oral administration of ketamine was effective in patients with resistant depression. Oral at-home administration has been well described in patients with chronic pain and may be a promising alternative to IV ketamine in depression.

Methods: Study participants were adults, aged ≤75 years, with a diagnosis of major depressive disorder, a score of ≥19 on the Montgomery-Asberg Depression Rating Scale (MADRS), and inadequate response to ≥2 antidepressants. Patients with a psychotic disorder or psychotic symptoms, bipolar disorder, alcohol or substance misuse, unstable medical illness ,or any contraindication to ketamine were excluded. In addition to stable background antidepressant therapy, patients received double-blind, randomized treatment with either 1 mg/kg oral ketamine in solution or a liquid placebo. Both were administered orally, by syringe, 3 times/week for 3 weeks. Study medication was first administered in the clinic under observation. Patients were given subsequent doses, no more than 2 at a time, to take at home. The primary study outcome was change from baseline to day 21 in MADRS score. A follow-up evaluation was completed on day 28.

Results: A total of 40 patients (mean age, 38 years; 15 women) participated in the study, and 33 completed treatment. Two patients stopped ketamine and 1 stopped placebo due to lack of an effect; 1 stopped ketamine because of drowsiness; and 2 in the placebo group were withdrawn due to onset of suicidal ideation.

Baseline MADRS scores were 33 and 30 in the ketamine and placebo groups, respectively. Ketamine was associated with a significant decrease in the MADRS at all post-baseline time points. At day 21, ketamine was associated with significantly greater improvement in mean MADRS score than placebo and with higher rates of response (i.e., MADRS decrease of >50%) and remission (MADRS score of ≤10). (See table). The numbers needed to treat* with ketamine

Effects of repeated oral ketamine or placebo in treatment-resistant depression

Outcome	Ketamine (n=22)	Placebo (n=18)	Significance
MADRS: Mean Score Reduction	12.75	2.49	p<0.001
Achieved Response	7 (32%)	1 (5.6%)	p<0.05
Achieved Remission	6 (27.3%)	0	p<0.05

for response and remission were 3.8 and 3.7, respectively. At the 28-day follow-up evaluation, treatment effects were maintained and no rebound effects were evident.

Oral ketamine was well tolerated. Six patients experienced transient increases in blood pressure during ketamine treatment. Other transient adverse effects of ketamine included euphoria (n=4), dizziness (n=4), and drowsiness (n=2).

Discussion: Oral administration of ketamine has rarely been reported for depression but is well recognized as an at-home treatment to manage chronic pain. The dosage used in this study was extrapolated from IV dosage, based on the known low oral bioavailability of ketamine. Among the questions still to be resolved are the optimal dosage and treatment duration, safety of long-term use, and the risk of misuse.

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

Domany Y, Bleich-Cohen M, Tarrasch R, Meidan R, et al: Repeated oral ketamine for out-patient treatment of resistant depression: randomised, double-blind, placebo-controlled, proof-of-concept study. *British Journal of Psychiatry* 2018; doi 10.1192/bjp. 2018.196. From Tel Aviv University, Israel; and other institutions. **Funded by the Tel Aviv Medical Center Brain Grant; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Residual Suicidal Ideation After CBT vs Medication

Individuals whose depression responds to antidepressant drugs or cognitive behavioral therapy have similar profiles of residual symptoms, according to a randomized comparison study. Those whose symptoms do not fully respond to medication still have significant reductions in suicidal thoughts.

Methods: The study was conducted to investigate the possibility that medications and CBT, which have different mechanisms of antidepressant action, may also have different trajectories of response for specific symptoms. Participants, treatment-naive adults with nonpsychotic major depressive disorder, were randomly assigned to 12 weeks of 30–60 mg/day duloxetine, 10–20 mg/day escitalopram, or CBT (16 1-hour individual sessions). Response was defined as a ≥50% reduction in the 17-item Hamilton Rating Scale for Depression (HAM-D) score, and remission as a final score of ≤7. Nonremitters were offered an additional 12 weeks of combined CBT and medication. For the present analysis, residual symptom profiles were assessed after the initial monotherapy phase using the Montgomery-Asberg Depression Rating Scale (MADRS), which rates 10 symptoms on a 6-point scale. Symptoms were considered persistent if they were scored as ≥2 at week 12.

Results: Of 315 patients who entered the study, 250 completed the first phase and were included in the analysis. A total of 166 patients were considered treatment responders: 123 (69%) of those who received medication and 43 (59%) of those who received CBT. Among responders, the 2 treatments did not differ in the mean number of residual symptoms at week 12: 2.02 for the CBT group and 2.22 for the combined medications group. Among patients who did not meet response criteria, the mean number of residual symptoms was 6.93 for CBT and 6.35 for medication.

In the group of patients who achieved response, the MADRS item with the most significant improvement was suicidal thoughts, which decreased by a mean of >95% in both treatment groups. However, among nonresponders, suicidal thoughts were less frequent in the medication group than the CBT group (0 of 54 patients vs 8 of 30 patients; p=0.001). CBT nonresponders showed a 15% decrease in suicidal thoughts, and medication nonresponders a 70% reduction. Patients in the CBT group were significantly more likely than those who received medication to experience a ≥2-point increase in scores for suicidal thoughts (p=0.007), with new onset in

3 CBT patients and worsening in 1. The frequencies of several other residual symptoms differed between treatment groups, but these differences did not survive statistical correction for multiple comparisons. A total of 69 nonresponders went on to receive combined treatment in the second study phase. After this phase, residual symptoms did not differ between patients who had medication added to CBT or vice versa.

Because suicidal ideation emerged as the most significant symptom in the overall analysis, the item was examined for its effect on outcomes. Suicidal ideation was present in significantly more patients who discontinued treatment (35% vs 23%; p=0.038), with a similar influence for both types of treatment. Equal proportions of patients with and without baseline suicidal ideation experienced response to their assigned treatment.

Discussion: These observations suggest that antidepressant medication may specifically reduce thoughts of suicide, even in the absence of overall improvement. In treatment responders, it appears that once the mechanisms of recovery from depression are engaged, the final symptom profile does not differ meaningfully between treatments. Even when treatments are ineffective overall, patients may experience limited benefits.

Dunlop B, Polychroniou P, Rakofsky J, Nemeroff C, et al: Suicidal ideation and other persisting symptoms after CBT or antidepressant medication treatment for major depressive disorder. *Psychological Medicine* 2018; doi 10.1017/S0033291718002568. **From Emory University School of Medicine, Atlanta, GA; and other institutions. Funded by the NIH. Four of 6 study authors disclosed potentially relevant financial relationships.**

Common Drug Trade Names*: duloxetine—*Cymbalta*; escitalopram—*Lexapro

Pimavanserin Safety

Patients with Parkinson's disease psychosis, for which pimavanserin (*Nuplazid*) is the only approved antipsychotic, are known to have a higher-than-normal mortality rate due to their older age, advanced Parkinson's disease, and other medical conditions. Following an extensive postmarketing review of deaths and serious adverse events, the FDA has concluded that the benefits of pimavanserin treatment for patients with hallucinations and delusions of Parkinson's disease psychosis continue to outweigh the risks. Although no new or unexpected safety risks were identified, some potentially concerning prescribing patterns emerged, such as the concomitant use of pimavanserin, which carries a boxed warning regarding QT prolongation and serious arrhythmia, and additional antipsychotics or other drugs that can also cause QT prolongation.

FDA News Release: FDA analysis finds no new or unexpected safety risks associated with Nuplazid (pimavanserin), a medication to treat the hallucinations and delusions of Parkinson's disease psychosis. Available at https://www.fda.gov/Drugs/DrugSafety/ucm621160.htm.

Fluvoxamine for Social Anxiety Disorder

According to the results of a meta-analysis, fluvoxamine (*Luvox*) is an effective, well-tolerated treatment for social anxiety disorder in adults.

Methods: The analysis was based on a literature search for randomized, placebo-controlled trials of fluvoxamine in patients, aged ≥18 years, with a diagnosis of social anxiety disorder according to DSM-III or later criteria. Trials were required to last ≥10 weeks. Primary efficacy outcome measures were the Liebowitz Social Anxiety Scale (LSAS) and the Clinical Global Impression (CGI)–Severity scale.* Secondary efficacy measures were response (i.e., CGI–Improvement ratings of much or very much improved) and change from baseline in the Sheehan Disability Scale (SDS). Tolerability was assessed using the rate of treatment discontinuation due to adverse effects.

Results: The search identified 5 studies with a combined sample size of 1001 subjects (range, 92–300). Fluvoxamine was flexibly-dosed, up to 300 mg/day, in all 5 studies. Change from

baseline in LSAS score in the 4 studies from which data could be pooled favored fluvoxamine over placebo with a 12-point between-group difference ($p<0.001$). CGI-Severity ratings, available from 3 studies, also favored fluvoxamine ($p<0.001$). The odds ratios* for response with fluvoxamine treatment versus placebo were 1.71 for the CGI-based measure and 2.11 for the SDS.

Discontinuation due to adverse events occurred significantly more often with fluvoxamine than placebo (90 vs 15 events; odds ratio, 5.99), but the number of serious adverse events did not differ between the treatment groups (4 and 3, respectively). The most frequent adverse effects of fluvoxamine were nausea, somnolence, insomnia, and abnormal ejaculation. Compared with placebo, fluvoxamine was not associated with an increased incidence of headache or with abnormal weight gain.

Discussion: SSRIs are often recommended as first-line pharmacotherapy for social anxiety disorder in adults; however, there has been little published analysis of the efficacy of fluvoxamine. The present results suggest it is effective and has acceptable tolerability in these patients.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Liu X, Li X, Zhang C, Sun M, et al: Efficacy and tolerability of fluvoxamine in adults with social anxiety disorder: a meta-analysis. *Systematic Review and Meta-Analysis* 2018; doi 10.1097/MD.0000000000011547. From Jilin University, Changchun, China. **The study was conducted with no external funding. The authors declared no competing interests.**

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Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison 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.

PSYCHIATRY DRUG ALERTS

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Benzodiazepines and Pneumonia Risk

Most commonly prescribed benzodiazepines are associated with a dose-related increased risk of pneumonia in patients with schizophrenia, according to a nationwide case-control study.

Methods: Data were collected from Taiwan's National Health Insurance Research Database for patients who were hospitalized with a first diagnosis of schizophrenia in 2000–2010. Case patients were those who were hospitalized with pneumonia after the baseline schizophrenia hospitalization. Each case patient was matched with up to 4 controls who had a hospitalization for schizophrenia but without any subsequent pneumonia hospitalization, based on gender, age, and the year of baseline psychiatric admission. Exposure to benzodiazepines was characterized as current (within 30 days of the pneumonia hospitalization) or past. Because patients with schizophrenia have been found to have higher rates of chronic lung disease and smoking, which could increase pneumonia risk, a separate sensitivity analysis including >63,000 patients with other psychiatric conditions was also conducted.

Results: The study group consisted of 2501 case patients and nearly 10,000 controls. Patients' average age at the baseline psychiatric hospital admission was 43 years. Current use of most benzodiazepines was associated with a higher incidence of pneumonia, compared with past or no use. After adjustment for potential confounders not included in the matching process (e.g., concomitant medications, psychiatric history, and physical illness comorbidity), relative risk (RR)* for pneumonia was significantly elevated with midazolam (RR, 6.6; $p<0.001$), diazepam (RR, 3.4; $p<0.001$), lorazepam (RR, 2.2; $p<0.001$), triazolam (RR, 1.8; $p=0.019$), clonazepam (RR, 1.7; $p<0.001$), and alprazolam (RR, 1.6; $p<0.001$).

For most of the benzodiazepines that were associated with increased risk of pneumonia, the risk increased with the duration of use and the cumulative defined daily dose. Pneumonia risk was highly correlated with GABA-A receptor binding affinity (correlation coefficients,* 0.92–0.96 for the 3 receptor subunits). Half-lives of the benzodiazepines were not associated with pneumonia risk, perhaps because the agents are dosed frequently for some indications, obscuring any potential relationship.

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Results of the sensitivity analysis confirmed the main findings, suggesting the association is not based on schizophrenia-specific factors. In this broader psychiatric population, RRs for pneumonia with the same agents ranged from 1.2 for alprazolam to 1.8 with diazepam ($p \leq 0.003$ for all).

Discussion: The mechanism by which benzodiazepines affect pneumonia risk are unclear. However, it may be related to benzodiazepine-receptor associated immunomodulation or to GABA-receptor associated sedation and muscle relaxation, which could lead to aspiration.

Cheng S-Y, Chen W-Y, Liu H-C, Yang T-W, et al: Benzodiazepines and risk of pneumonia in schizophrenia: a nationwide case-control study. *Psychopharmacology* 2018;235 (November):3329–3338. doi 10.1007/s00213-018-5039-9. From Taipei City Hospital, Taiwan; and other institutions. **Funded by the Taiwan Ministry of Science and Technology; and Taipei City Hospital. The authors declared no competing interests.**

Common Drug Trade Names*: alprazolam—*Xanax*; clonazepam—*Klonopin*; diazepam—*Valium*; lorazepam—*Ativan*; midazolam—*Versed*; triazolam—*Halcion

***See Reference Guide.**

Antidepressant Effects of Testosterone

According to the results of a meta-analysis, testosterone treatment may produce dose-related reductions in depressive symptoms in men.[1] However, the effect is small and the evidence shows a high risk of bias.

Background: Results of previous research on testosterone for mood symptoms have been mixed, and most studies were limited to hypogonadal or middle-aged men. The present analysis was undertaken to evaluate the treatment in eugonadal versus hypogonadal men and those aged older versus younger than 60 years.

Methods: The meta-analysis was based on 27 randomized, placebo-controlled trials conducted in 1890 men. Studies were included if they appeared in English-language peer-reviewed journals and reported on mood before and after the intervention, using a validated or original measurement scale for depressive symptoms. Of these, 4 of the trials reported the effects of testosterone monotherapy, and the remaining studies were conducted in patients who could be receiving other antidepressant treatments.

Results: One study was excluded from the analysis because it reported an extreme value for treatment effect. The remaining 26 studies had a combined effect size* (Hedges g) of 0.21 ($p<0.001$) for the standardized difference in depression scores between testosterone and placebo. This translates to a 2.2-point reduction in Beck Depression Inventory (BDI) score. This effect exceeds the efficacy threshold of 2.0 points proposed by the National Institute for Health and Care Excellence (NICE) for treatment-resistant depression, but not the 3.0-point threshold for treatment-responsive depression. Patients who received testosterone had about a 2-fold increased odds of a response, defined as a ≥50% symptom reduction from baseline (odds ratio,* 2.30; $p=0.004$).

Analysis of possible moderators found treatment success was associated with testosterone dose. Rates of response were higher with 1.0 g/week than with 0.3 or 0.1 g/week ($p=0.02$). Response rates were not affected by patient age, whether patients were hypo- or eugonadal, baseline depression symptom severity, HIV status, treatment duration, or mode of hormone administration. Attrition from treatment was comparable with testosterone and placebo.

Discussion: Few of the included trials had a low risk of bias. However, according to the authors, the risk of bias and "questionable research practices" were not likely to have materially affected the outcome of the meta-analysis. Even in the most conservative bias scenario, testosterone had a clinically significant effect at doses >0.5 g/week when the analysis was limited to studies with

low variability in baseline symptoms. There remains a need for sufficiently powered long-term studies of testosterone safety.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis. However, the source of funding was not disclosed.

Editorial.[2] Heterogeneity of the trials is an important flaw of this meta-analysis. In addition, few of the studies were conducted in men with a standardized diagnosis of depression, which prevents reaching a strong conclusion about the efficacy of testosterone for inducing remission. It is not known whether improvements of the magnitude shown in the meta-analysis are clinically meaningful; and the long-term safety of testosterone treatment for depression has not been demonstrated. However, a large U.S. multicenter, double-blind, placebo-controlled trial of topical testosterone in hypogonadal men at increased risk for cardiovascular disease is currently being conducted. A substudy of the trial will examine the effects of testosterone therapy on depression remission in middle-aged and older hypogonadal men with late-onset depressive disorders. Unless those results replicate the findings of the present analysis, the editorialists recommend that clinicians continue to follow the guidelines of the Endocrine Society, which do not support using testosterone, particularly in supraphysiologic doses, to treat depressive disorder in men.

[1]Walther A, Breidenstein J, Miller R: Association of testosterone treatment with alleviation of depressive symptoms in men: a systematic review and meta-analysis. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.2734. From the Technische Universität Dresden, Germany; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

[2]Bhasin S, Seidman S: Testosterone treatment of depressive disorders in men: too much smoke, not enough high-quality evidence [editorial]. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.2661. From Harvard Medical School, Brigham and Women's Hospital, Boston, MA; and other institutions. **One author disclosed potentially relevant financial relationships.**

***See Reference Guide.**

Psychotropic/Antiretroviral Interactions: Antidepressants

Most categories of psychotropic drug can interact with antiretroviral therapy (ART) agents prescribed to treat HIV. Because HIV is highly comorbid with mood, anxiety, and cognitive disorders, clinicians are likely to encounter patients on complex regimens that include both ART and psychotropics. The 2 drug types may also have compounding adverse effects, according to an extensive literature review.

Editor's Note. This is the first report in a 5-part series on psychotropic/antiretroviral interactions. We will cover interactions with antidepressants in this issue, and then stimulants, antipsychotics, mood stabilizers, and medications for opioid and alcohol use disorders over the next 4 issues.

A comprehensive search was undertaken to identify relevant materials published through December 2017, including research articles, drug package inserts, and, where clinical data were lacking, in-vitro data. Examined in the review were all ART interactions with antidepressants, stimulants, antipsychotics, mood stabilizers, and treatments for opioid or alcohol use disorders.

Many antiretrovirals are metabolized by the hepatic cytochrome P450 (CYP450) system, which can lead to pharmacokinetic interactions whose effects range from trivial to life threatening. Integrase strand transfer inhibitors (INSTIs) are a newer drug class, gaining prominence in part because of their favorable adverse-effect profile and, in some cases, a decreased potential for drug/drug interactions. All currently available protease inhibitors are metabolized by and inhibit CYP3A4, the most common enzyme pathway for hepatically metabolized drugs. Hepatic effects of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) vary widely. These agents can induce and/or inhibit CYP enzymes. The other major drug categories,

nucleoside reverse transcriptase inhibitors (NRTIs) and entry inhibitors, appear to have little potential for hepatic enzyme-related interactions. (See the printable ART cytochrome P450 properties table at www.alertpubs.com/sdaonlinecontent for details.)

The majority of newer antidepressants are also extensively metabolized by the CYP450 system and have the potential to interact with ART agents. (See table.) Antidepressant effectiveness and tolerability in the context of ART varies among individual patients, and no 1 drug or class can be broadly recommended. Individual patient risk factors and potential drug interactions should be considered when selecting an antidepressant.

Antidepressant/Antiretroviral Interactions

Antidepressant	Interaction Potential	Recommendations
Citalopram, Escitalopram	Minimal	May be a preferable antidepressant for patients with HIV, specifically those receiving protease inhibitors.
Fluoxetine	Limited	Serotonin toxicity has been reported with fluoxetine and concomitant ART. Titrating dose to clinical response and monitoring for loss of antidepressant efficacy are recommended.
Paroxetine	Limited	
Sertraline	Limited	
Fluvoxamine	Clinically significant	Increased adverse effects are possible; an alternate antidepressant should be considered.
Vortioxetine, Vilazodone	Unlikely	No empirical evidence to support or refute safety.
Venlafaxine, Desvenlafaxine	Unknown	Theoretical potential for reduced antiretroviral concentrations; an alternate antidepressant should be considered.
Duloxetine	Theoretical	Potential duloxetine concentration elevation with 2D6-inhibiting ART; an alternate antidepressant should be considered.
Milnacipran, Levomilnacipran	Unlikely	No empirical evidence to support or refute safety.
Trazodone	Clinically significant	Potential for clinically significant increase in trazodone adverse effects; an alternate antidepressant should be considered.
Mirtazapine	Not well described	Use lowest effective mirtazapine dose when coadministered with potent CYP1A2, 3A4, or 2D6 inhibitors or inducers.
Bupropion	Clinically significant	Bupropion dose increase may be necessary if administered with 2B6 inducers.
TCAs	Unknown	Caution and close monitoring recommended when coadministered with 3A4 or 2D6 inhibitors.
MAOIs	Unlikely	Despite a seemingly benign interaction potential with ART, MAOIs are not preferred due to limitations of the class (e.g., narrow therapeutic index, dietary precautions).
St John's wort	Clinically significant	Contraindicated in patients taking protease inhibitors, NNRTIs, or several INSTIs.

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*: bupropion—*Wellbutrin*; citalopram—*Celexa*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; levomilnacipran—*Fetzima*; milnacipran—*Savella*; mirtazapine—*Remeron*; paroxetine—*Paxil*; sertraline—*Zoloft*; trazodone—*Oleptro*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Trintellix

Injectable Olanzapine: Age Effects

A patient's age appears to have little effect on drug exposure with the long-acting injectable (LAI) formulation of olanzapine, in contrast to oral olanzapine, according to the results of an observational study.[1] According to the authors, these results suggest that modifying the dose of LAI olanzapine in older patients may not be necessary.

Background: It has been shown that dose-adjusted exposure with oral olanzapine increases with age,[2] suggesting that lowered doses may be required for older patients. However, the effects of increasing age on LAI administration have not been described.

Methods: Data for the analysis were collected retrospectively from therapeutic drug monitoring information routinely collected at a hospital in Norway over a 12-year period. The analysis included olanzapine trough serum samples drawn 10–30 hours after an oral dose or 10–30 days after LAI injection. Absolute olanzapine concentrations, as well as concentration/dose ratios were compared between patients aged 18–49 years and those aged ≥50 years. In addition, because elderly is often defined as age ≥65 years, the comparison was repeated with 65 years as the cutoff.

Results: After excluding serum measurements from patients with compliance issues and those taking concomitant oral and LAI olanzapine, CYP inducers (i.e., carbamazepine, phenytoin, phenobarbital), or CYP inhibitors (e.g., valproic acid, fluvoxamine), >21,000 measurements from 8288 patients were included. Average daily doses of oral olanzapine were higher in patients aged <50 years than in older patients (14.2 vs 11.7 mg/day; $p<0.001$). Younger patients also received higher doses of LAI olanzapine on average (20.8 vs 18 mg/day; $p<0.001$). For oral olanzapine, there was a clear age-related increase in the concentration/dose ratio of olanzapine in patients aged ≥50 years. Concentration/dose ratios did not differ between younger and older patients receiving LAI olanzapine. Results were similar when smokers and nonsmokers were analyzed separately and when the analysis was repeated using the standard geriatric cutoff of 65 years. The concentration/dose ratio was about 25% higher in women than in men for both oral and LAI formulations ($p<0.001$ for both).

Discussion: LAI antipsychotics are underused in many settings, and their use in the elderly has received little study. LAI formulations have higher bioavailability, requiring lower doses, and thus reducing the potential variability caused by oral dosing.

[1]Tveito M, Smith R, Molden E, Haslemo T, et al: Age impacts olanzapine exposure differently during use of oral versus long-acting injectable formulations: an observational study including 8,288 patients. *Journal of Clinical Psychopharmacology* 2018;38 (December):570–576. doi 10.1097/JCP.0000000000000961. From the University of Oslo, Norway; and other institutions. **Funded by the South-Eastern Norway Regional Health Authority. Two of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Castberg I, et al: Effects of age and gender on the serum levels of clozapine, olanzapine, risperidone, and quetiapine. *Acta Psychiatrica Scandinavica* 2017;136:455–464.

Common Drug Trade Names*: carbamazepine—*Epitol, Tegretol*; fluvoxamine—*Luvox*; olanzapine, LAI—*Zyprexa Relprevv*; olanzapine, oral—*Zyprexa*; phenytoin—*Dilantin*; valproic acid—*Depakene, Depakote

Perimenopausal Depression: Treatment Guidelines

Although perimenopause has been recognized as a window of vulnerability for the development of both depressive symptoms and major depressive episodes, clinical recommendations are lacking. The North American Menopause Society and the National Network of Depression Centers' Women and Mood Disorders Task Group convened an expert panel to review the literature on depressive symptoms and disorders in midlife women and to develop guidelines addressing epidemiology, clinical presentation, antidepressant treatment, hormone therapy, and other therapies for affected women.

According to the panel, midlife depression in women commonly presents with the classic depressive symptoms, combined with menopausal complaints such as vasomotor symptoms, sleep and sexual disturbances, weight and energy changes, and concentration problems. Often the situation is further complicated by bereavement and other losses and stressors such as career shifts or caring for an aging parent. Contrary to previous beliefs, grown children leaving the home (the "empty nest") is believed to have positive rather than negative effects on mood.

Antidepressants, cognitive behavioral therapy, and other proven psychotherapies should remain first-line treatments for depression during menopause. Women with a history of successful drug therapy for depression should receive the previously effective agent. Desvenlafaxine, the only agent that has been investigated specifically in perimenopausal women, has shown efficacy in short-term trials. Small open-label studies have shown SSRIs (e.g., citalopram, escitalopram, fluoxetine, sertraline, vortioxetine), SNRIs (e.g., desvenlafaxine, duloxetine, venlafaxine), and mirtazapine improved mood in perimenopausal women and also had positive effects on vasomotor symptoms, sleep, and other menopausal symptoms. Bupropion is often prescribed because it produces less weight gain, sexual dysfunction, and sleepiness than other agents.

Some evidence suggests concomitant estrogen can improve response to antidepressant drugs, but it is not FDA approved to treat depression. Hormonal contraceptives may improve mood in women approaching menopause. This and other evidence suggests there may a window of opportunity with estrogen that does not extend into the postmenopausal period. The available evidence is insufficient to recommend herbal or other alternative remedies for treatment of perimenopausal depression.

Maki P, Kornstein S, Joffe H, Bromberger J, et al: Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause: The Journal of the North American Menopause Society* 2018; doi 10.1097/GME.0000000000001174. From the University of Illinois at Chicago; and other institutions. **These guidelines were created without funding. Five of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: bupropion—*Wellbutrin*; citalopram—*Celexa*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; mirtazapine—*Remeron*; sertraline—*Zoloft*; venlafaxine—*Effexor*; vortioxetine—*Trintellix

Lacosamide in Bipolar Disorder

The third-generation anticonvulsant lacosamide (*Vimpat*), currently approved for treatment of partial-onset seizures, was at least as effective as other antiepileptic drugs at improving a spectrum of outcomes in patients with bipolar disorder. This nonrandomized study, which compared patients receiving lacosamide with control patients receiving other anticonvulsants, also found the agent to have better tolerability than other anticonvulsants.

Background: Lacosamide has little-to-no interaction with cytochrome P-450 enzymes and a low potential for drug interactions. It has shown incidental antidepressant and anxiolytic effects in patients with epilepsy.

Methods: The study retrospectively compared patients with bipolar disorder treated consecutively with lacosamide (n=102) or with other antiepileptic drugs (n=123). Eligible subjects had received lacosamide, had DSM-5 bipolar I or II disorder, and had been recently hospitalized with an acute mood episode. They had received treatment with 50–300 mg/day lacosamide for 30 days; they could also have received antipsychotics but not lithium. Outcome measures included the Brief Psychiatric Rating Scale (BPRS), the Young Mania Rating Scale (YMRS), the Hamilton Rating Scales for Depression (HAM-D) and Anxiety (HAM-A), the Clinical Global Impression–Severity (CGI-S) scale, and the Global Assessment of Functioning (GAF).

Results: Patients who received lacosamide were significantly younger than control patients and had significantly less substance use comorbidity. The groups did not differ with regard to the

number of prior mood episodes or duration of illness. Clinical measures showed no baseline differences between the groups on any symptom or functional rating scale.

Both patient groups showed striking improvements in all outcomes measured from baseline to nearly all time points beginning on day 7, with large effect sizes* at day 30. (See table.) Patients who received lacosamide showed significantly greater improvement in mania and overall illness severity than patients who received other anticonvulsants, who had significantly larger improvements in general psychopathology. Depression ratings did not differ between the groups. Drug dosages were not correlated, or only poorly correlated, with clinical effects. Improvement occurred regardless of the type of episode or the type of bipolar disorder.

Effect sizes for change from baseline to day 30		
	Lacosamide	Other Anticonvulsants
BPRS	1.59	2.30
YMRS	1.58	1.16
HAM-D	1.52	1.90
HAM-A	1.59	1.51
CGI-S	3.83	1.54
GAF	2.51	2.01

Previous observations have suggested that lacosamide may be associated with psychosis and sexual dysfunction, and there is a single known report of increased suicidal ideation. In the present study, no patient had onset of suicidal ideation, psychosis, or sexual dysfunction. Lacosamide adverse effects—headache, dizziness, nausea, confusion, and cognitive symptoms—were few, mild, and transient. Cognitive adverse effects occurred significantly less often with lacosamide than with the other drugs (1% vs 20%; $p<0.0001$).

Discussion: These preliminary results suggest that lacosamide may have some advantages over other antiepileptics in patients with bipolar disorder. Although the mechanism by which lacosamide exerts these effects is unclear, it appears to be achieved at dosages lower than those used to treat epilepsy. Additional study of lacosamide in bipolar disorder appears to be warranted.

Cuomo I, Piacentino D, Kotzalidis G, Lionetto L, et al: Lacosamide in bipolar disorder: a 30-day comparison to a retrospective control group treated with other antiepileptics. *Psychiatry and Clinical Neurosciences* 2018; doi 10.1111/pcn.12784. From the Clinica Von Siebenthal Neuropsychiatric Hospital, Rome, Italy; and other institutions.
Source of funding not stated. The authors declared no competing interests.

***See Reference Guide.**

Gabapentin Abuse

A 51-year-old man with a history of substance-induced mood disorder, as well as opioid, cocaine, and alcohol use disorders, presented to the emergency department following an intentional gabapentin overdose with suicidal intent. Following medical stabilization with supportive care, the patient was transferred to a psychiatric unit. His regular medication regimen included sertraline, divalproex, trazodone, and gabapentin. Review of his medication use suggested a pattern of gabapentin abuse characterized by overuse and requests for the medication from different physicians on varying pretexts. On questioning, the patient admitted that for ≥9 months he had been crushing and insufflating 3–4 600-mg gabapentin tablets at 2-hour intervals in bingeing episodes. He described the "high" he achieved as characterized by increased focus, energy, and productivity, followed by a calm/relaxation similar to opioid intoxication. Abrupt discontinuation resulted in withdrawal symptoms. The patient denied misuse of his other psychotropic medications, and a urine screen for illicit drugs was negative.

Gabapentin is widely used off-label as adjunct treatment for several psychiatric disorders including bipolar disorder, anxiety, PTSD, and depression. It has also shown potential for treatment of withdrawal and craving in alcohol, benzodiazepine, opioid, and cocaine dependence. The drug is well tolerated, has few interactions with other drugs, and is relatively inexpensive.

Because it is presumed to have no abuse potential, it is currently not scheduled as a controlled substance. However, there have been other reports of gabapentin abuse and misuse, mainly among patients with a history of substance abuse and psychiatric comorbidity. The pharmacologic properties that underlie gabapentin's abuse potential are unknown. Increasing rates of diversion, comparable to those with oxycontin, have also been documented. Although the present patient denied "cutting" heroine or buprenorphine with gabapentin, there have been reports of gabapentin being used illicitly in combination with opioids and to potentiate the effects of buprenorphine–naloxone. Gabapentin misuse by patients with opioid use disorder is especially concerning, given the recent increases in opioid-related mortality and evidence linking gabapentin use with increased risk of accidental opioid-related overdose deaths. Prescribers should be aware of the potential for gabapentin abuse in at-risk populations and should closely monitor these patients.

Khalid Z, Hennen M-A, Aldana-Bernier L: Gabapentin abuse by nasal insufflation: a case report [letter]. *Journal of Clinical Psychopharmacology* 2018 doi 10.1097/JCP.0000000000000983. From Rutgers New Jersey Medical School, Newark; and VA New Jersey Healthcare System, East Orange. **The authors declared no competing interests.**

Common Drug Trade Names*: buprenorphine–naloxone—*Suboxone*; divalproex—*Depakene, Depakote*; gabapentin—*Neurontin, Gralise*; sertraline—*Zoloft*; trazodone—*Desyrel, Oleptro

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Correlation Coefficient (r): A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1. An r value near 1 indicates a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r-value indicates a negative relationship.

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.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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.

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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 ≥1 of the following: percentage weight gain of ≥7%, body mass index (BMI) of ≥30 plus weight gain of ≥10 lbs in previous 8 months or ≥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 ≥50% decrease in symptoms, before the effect is lost.

Influencing factors. Onset of depression later in life, a history of ≥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), 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, dexmethylphenidate 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.
Dexmethylphenidate	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, dexmethylphenidate, 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 ≥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*; dexmethylphenidate—*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,[1] the $GABA_B$ 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.[2]

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.[3] (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.

[1]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.**

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

[3]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.[1]

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.[2]

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 ≥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.

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

Editorial.[3] 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.

[1]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.**

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

[3]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 ≥20, and be receiving therapeutic doses of a mood-stabilizing regimen for ≥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 ≥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.[1] 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,[2] 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.

[1]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.**

[2]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

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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.