

PSYCHIATRY DRUG ALERTS

2016 Issue Collection

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Adjunctive Ziprasidone for Depression

In a randomized trial, adjunctive ziprasidone showed both antidepressant and anxiolytic efficacy in patients with persistent symptoms of unipolar major depression despite escitalopram treatment.¹

Background: Antipsychotics are common adjunctive treatments for residual symptoms in major depressive disorder. Ziprasidone has pharmacological features that differ from other antipsychotics approved for antidepressant augmentation (i.e., aripiprazole, olanzapine, quetiapine) and was shown in an open-label study to be an effective adjunct in treatment-resistant depression.² The present study appears to be the first controlled trial to attempt to replicate those results.

Methods: This 2-phase study enrolled 458 patients, aged 18–65 years, with a primary diagnosis of unipolar major depressive disorder. In the lead-in phase, study patients received 8 weeks of open-label, flexible-dose escitalopram. Following this phase, the 139 patients (mean age, 44 years; 71% women) who continued to meet diagnostic criteria for major depression underwent 8 additional weeks of double-blind adjunctive treatment with either ziprasidone, flexibly dosed between 20 and 80 mg b.i.d., or placebo. The primary outcome measure was clinical response, defined as a $\geq 50\%$ reduction in Hamilton Rating Scale for Depression (HAM-D) score. Two key secondary endpoints were selected to measure effects based on the pharmacological profile of ziprasidone: the Hamilton Anxiety Rating Scale (HAM-A) and the Visual Analog Scale for Pain.

Results: Adjunctive ziprasidone produced significantly higher rates of both clinician- and self-rated antidepressant response. Response rates for the clinician-rated HAM-D were 35% and 21% in the ziprasidone and placebo groups, respectively ($p=0.04$). Response rates for the self-rated Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) were 31% and 13%, respectively ($p=0.03$). HAM-D remission (i.e., final score of ≤ 7) was achieved by 38% of the ziprasidone group, compared with 31% of the placebo group, a nonsignificant difference. However, the remission rate on the self-rated QIDS-SR (i.e., final score of ≤ 5) was significantly higher in the ziprasidone group: 24% versus 10% ($p=0.02$).

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Overall, patients had mild anxiety symptoms (mean HAM-A score, 14) in addition to depression. Anxiety response (i.e., $\geq 50\%$ reduction in HAM-A score) and remission (i.e., final score of ≤ 7) rates were also significantly higher with ziprasidone than with placebo: 35% versus 10% ($p < 0.001$) and 45% versus 21% ($p < 0.01$), respectively. The number needed to treat (NNT)* for a HAM-D response was 7, similar to other atypical antipsychotics approved for adjunctive treatment of depression, and the NNT for a HAM-A response was 4. Ziprasidone was not superior to placebo at reducing pain.

Ziprasidone was associated with significantly more somnolence/fatigue (34%), irritability (10%), anxiety/agitation (6%), and muscle twitching (11%) than placebo. Ten patients withdrew from the ziprasidone treatment arm (and none from the placebo group) because of adverse effects that included anxiety/agitation and akathisia, sedation, insomnia, and QTc prolongation. Ziprasidone was associated with an average QTc prolongation of 8.8 msec and a significantly greater mean weight gain of 8 lbs. compared with about 2 lbs. for placebo.

Discussion: Based on these results, ziprasidone appears to be a suitable option for adjunctive treatment of resistant depression. It may be particularly useful for patients with comorbid anxiety symptoms. The high rate of somnolence/fatigue in this study, 34%, was a surprising finding given the pharmacologic profile of ziprasidone but is similar to some other atypicals approved for this indication.

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

¹Papakostas G, Fava M, Baer L, Swee M, et al: Ziprasidone augmentation of escitalopram for major depressive disorder: efficacy results from a randomized, double-blind, placebo-controlled study. *American Journal of Psychiatry* 2015;172 (December):1251–1258. From Massachusetts General Hospital, Boston; and other institutions. **Funded by the NIMH. Four study authors disclosed financial relationships with commercial sources; the remaining 3 authors reported no financial relationships with commercial sources.**

²Papakostas G, et al: Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. *Journal of Clinical Psychiatry* 2004;65:217–221.

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

*See Reference Guide.

Antidepressants for Seasonal Depression

According to the results of a Cochrane Review, owing to a lack of randomized controlled trials of other agents, bupropion is the only evidence-based second-generation antidepressant suitable for prevention of seasonal affective disorder (SAD).

Methods: The investigators searched registries, databases, and other sources for published and unpublished comparative clinical trials of second-generation antidepressants for prevention of SAD in adults with a history of the disorder who were free of symptoms at study entry. Included studies were required to use random assignment and to compare an antidepressant with placebo or another antidepressant, light therapy, psychological therapy, melatonin, agomelatine, or lifestyle changes.

Results: The search identified only 3 randomized placebo-controlled trials of bupropion XL. No studies of alternate antidepressants or studies comparing an antidepressant with the other treatments of interest met inclusion criteria. Two additional studies (both evaluating citalopram) narrowly missed meeting these criteria because patients were already symptomatic at baseline. The 3 included studies, funded by the manufacturer of bupropion XL, included a total of 1100 patients with a history of SAD. The studies were judged to be at low risk for most sources of bias.

Patients were enrolled between September and November and provided treatment with 300 mg/day bupropion until the first week of spring. The primary outcome was time to onset of major depressive disorder, defined as meeting DSM-IV criteria or a threshold score on the

Structured Interview for the Hamilton Rating Scale for Depression-Seasonal Affective Disorder (SIGH-SAD) version. Bupropion was associated with a reduced risk of depression (15% vs. 27%; risk ratio,* 0.56). Numbers needed to treat* to prevent 1 episode of SAD depended on patients' baseline risk and ranged from 5 in populations with a yearly recurrence rate of 50% to 8 in populations with a 30% recurrence rate.

Bupropion was associated with an overall similar adverse event rate to placebo but with significantly elevated rates of headache, insomnia, and nausea (risk ratios: 1.26, 1.46, and 1.63, respectively).

Discussion: The predictable pattern of SAD makes it particularly amenable to preventive treatment. Given the lack of comparative evidence, decisions regarding preventive treatment should be based on patient preferences and should consider the possibility that non-pharmacological treatments—such as light therapy, psychological therapies, and lifestyle interventions—may be effective and carry a lower side-effect burden.

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

Gartlehner G, Nussbaumer B, Gaynes B, Forneris C, et al: Second-generation antidepressants for preventing seasonal affective disorder in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 11, Art. No. CD011268. From Cochrane Austria, Danube University Krems, Austria; and other institutions. **This review was conducted without external funding. One study author disclosed financial relationships with commercial sources; the remaining 12 authors declared no competing interests.**

Common Drug Trade Names: agomelatine (not available in U.S.)—*Valdoxan*; bupropion—*Wellbutrin*; citalopram—*Celexa*

*See Reference Guide.

Dasotraline Pharmacokinetics

In a manufacturer-sponsored, multicenter clinical trial of adults with a primary diagnosis of ADHD of moderate-or-greater severity, the investigational medication dasotraline was associated with significant improvement in ADHD symptoms.¹ Scores on both the hyperactivity/impulsivity and the inattention subscales of the ADHD Rating Scale-IV (ADHD-RS-IV) were significantly improved, and 52% of patients who received 8 mg/day dasotraline met response criteria ($\geq 30\%$ reduction in ADHD-RS-IV total score). Pharmacokinetic data collected from this study, along with data from several other early-phase clinical studies of dasotraline, suggest that maintaining constant steady-state dopamine and norepinephrine reuptake inhibition with once-daily dosing is potentially effective in managing ADHD symptoms.²

Dopamine and norepinephrine are associated with the pathophysiology of ADHD, and drugs that maintain synaptic concentrations of the 2 neurotransmitters, such as methylphenidate (*Ritalin*), are useful in management of the disorder. Dasotraline is a potent inhibitor of dopamine and norepinephrine transporters and a weaker inhibitor of serotonin transporters. Once-daily administration is associated with stable plasma concentrations over 24 hours, a unique property among current ADHD medications.

According to data collected from multiple studies comprising 395 patients who received single or multiple oral administrations of 0.2–36 mg dasotraline, the drug reached peak plasma concentrations 10–12 hours post-dose and had dose-proportional peak concentrations. Elimination of the drug was slow, with a mean half-life of 47–77 hours. Steady-state plasma concentrations were reached after 10 days of dosing. Pharmacokinetics were influenced by body weight but not by age, gender, ethnicity, total bilirubin, or alanine aminotransferase. Dasotraline plasma concentrations were associated with decreases in the norepinephrine metabolite 3,4-dihydroxyphenylglycol plasma concentrations, indicating that norepinephrine

transporter inhibition was dose-dependent. Time to study dropout was similar for 4 mg dasotraline (the minimum effective dose) and placebo and significantly higher for the 8-mg dosage. Based on simulations, the average effect size* on ADHD symptoms was 0.25 standard deviations for 4 mg dasotraline after 4 weeks. The simulations predicted stronger effect sizes for trials lasting 8 weeks but only small additional increases in trials lasting 12 weeks, indicating an optimal trial duration of 8 weeks.

¹Koblan K, et al: Dasotraline for the treatment of attention-deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled, proof-of-concept trial in adults. *Neuropsychopharmacology* 2015; doi 10.1038/npp.2015.124. See *Psychiatry Drug Alerts* 2015;29 (June):41–42.

²Hopkins S, Sunkaraneni S, Skende E, Hing J: Pharmacokinetics and exposure-response relationships of dasotraline in the treatment of attention-deficit/hyperactivity disorder in adults. *Clinical Drug Investigation* 2015; doi 10.1007/s40261-015-0358-7. From Sunovion Pharmaceuticals, Inc., Marlborough, MA, and Fort Lee, NJ; and Cognigen Corporation, Buffalo, NY. **Funded by Sunovion. All 7 study authors disclosed financial relationships with commercial sources including Sunovion.**

*See Reference Guide.

Combined Treatment for Depression and Cognitive Impairment

In an open-label pilot study, the combination of memantine and escitalopram in patients with depression and cognitive impairment improved cognition and may have delayed conversion to dementia.

Methods: Study participants, aged 50–90 years, were recruited from clinics for late-life depression or memory disorders. All patients had a DSM-IV diagnosis of unipolar major depression or dysthymia of at least moderate severity. They were also required to have cognitive impairment, based on subjective complaints, Clinical Global Impression–Severity (CGI-S) scores of "mild" or greater for cognition, mini-mental state exam (MMSE) scores of ≥ 24 , and either errors on the MMSE 5-minute recall task or abnormal performance on a neuropsychological test. Following a taper of previous antidepressants, escitalopram was started at 10 mg/day and increased to 20 mg/day if tolerated. After 2 weeks, memantine was added and also titrated to a maximum of 20 mg/day. Antidepressant response was measured using the 24-item Hamilton Rating Scale for Depression (HAM-D), with remission defined as a final score of < 8 . The Selective Reminding Test with Immediate Recall (SRT-IR) was the primary outcome measure for cognitive performance.

Results: Of 35 patients who began treatment, 28 completed 12 weeks and 26 completed 48 weeks. Mean age at study entry was 65 years, and 63% of patients were women; 29 patients had major depressive disorder, and 6 had dysthymia. Average age at depression onset was 45 years, and the average duration of the current episode was 32 months. Either because of adverse effects or lack of efficacy, 4 patients received bupropion augmentation during the study period and 14 were switched from escitalopram to another antidepressant (i.e., desvenlafaxine, duloxetine, or venlafaxine).

At study end, HAM-D scores were significantly improved from a baseline mean of 20 to a final score of 5 ($p < 0.001$). Depression remitted in 56% of patients. CGI–Improvement scores were significant for both depression and cognition ($p < 0.001$ for both). A single patient had conversion to an Alzheimer's disease diagnosis during the study. Patients showed improvement in SRT-IR scores during the study from a mean of 39 at baseline to 47 at endpoint ($p = 0.01$). The mean MMSE score was 28 at baseline and did not change. Patients showed improvement on tests of category fluency for letters and the Boston Naming test, but not on other neuropsychiatric tests. The drug combination was well tolerated, with no major adverse effects.

Discussion: In other pilot studies, treatment of depression and mild cognitive impairment with antidepressants and acetylcholinesterase inhibitors was associated with cognitive

improvement of a similar magnitude to that observed in the present study. The conversion rate to Alzheimer's disease was at the lower end of the range reported in naturalistic studies of patients with depression and cognitive impairment. Because memantine and escitalopram act on different neurotransmitter systems, they may have additive or synergistic effects on cognition, an attractive possibility that merits further investigation.

Pelton G, Harper O, Roose S, Marder K, et al: Combined treatment with memantine/escitalopram for older depressed patients with cognitive impairment: a pilot study. *International Journal of Geriatric Psychiatry* 2015; doi 10.1002/gps.4375. From the New York State Psychiatric Institute, New York; and other institutions. **Funded by Forest Laboratories, Inc.** **Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

Common Drug Trade Names: bupropion—*Wellbutrin*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; memantine—*Namenda*; venlafaxine—*Effexor*

Adjunctive Fluvoxamine with Clozapine

Preliminary evidence suggests fluvoxamine may be a useful adjunct to clozapine, particularly for patients with negative or depressive symptoms and those who cannot achieve sufficient plasma clozapine levels.

About half of patients with refractory schizophrenia experience response with clozapine. Adjunctive fluvoxamine may increase clozapine efficacy by increasing plasma drug levels, prolonging the half-life, and altering the ratio of the parent compound to its primary metabolite. Clozapine is mainly metabolized by the cytochrome P450 enzyme CYP1A2. The half-life is short enough to cause breakthrough symptoms in some patients with once-daily dosing. *N*-desmethylclozapine (NDMC) is the major active metabolite, and the ratio of clozapine to NDMC may be more predictive of response than clozapine levels. Fluvoxamine potentially inhibits CYP1A2, resulting in higher clozapine plasma levels, a marked prolongation of the half-life by as much as 370%, and correspondingly lower levels of NDMC. A potent serotonin 5-HT_{2c} antagonist, NDMC contributes to the clozapine side effects of weight gain, seizures, and possibly bone-marrow suppression.

A systematic literature review identified 21 case reports and 3 case series (a total of 29 patients) of adjunctive fluvoxamine with clozapine published through October 2015. Initial average dosages were 500 mg/day for clozapine and 130 mg/day for adjunctive fluvoxamine. The most frequent indication (in 33% of patients) for adjunctive fluvoxamine was obsessive-compulsive symptoms. In these patients, the mean clozapine-to-NDMC ratio nearly doubled, from 1.63 to 3.08. The studies reported significant clinical improvement with augmentation in 18 patients (75%), adverse effects in 14 (58%), and dose adjustments in 21 (88%).

In addition, 7 prospective cohort studies and 2 open-label randomized trials (a total of 212 patients, a majority with schizophrenia) were also identified. Clozapine was most often given as a flexible dosage of >100 mg/day, and fluvoxamine as a fixed dosage of ≤100 mg/day. Clozapine steady state was achieved after 2 weeks of adjunctive fluvoxamine in most studies. The indication for augmentation was negative symptoms in 4 cohort studies; the other 3 were pharmacokinetic studies. The 2 controlled trials assessed the metabolic side effects of clozapine as affected by fluvoxamine. These clinical studies found significant improvement in various measures of overall symptoms and functioning. Adjunctive fluvoxamine appeared to have little effect on positive symptoms, mixed effects on negative symptoms, and possible effects on depression and obsessive-compulsive symptoms. However, the clinical effects of augmentation were difficult to quantify because the studies did not report outcomes in a consistent manner and did not attempt to correlate symptoms with clozapine blood levels.

In 1 study, adjunctive fluvoxamine prevented weight gain, and increases in body mass index and glucose, compared with clozapine monotherapy. The other controlled study showed no

metabolic benefit of added fluvoxamine, but mean granulocyte counts were higher with clozapine monotherapy than with adjunctive fluvoxamine, despite a lack of association of fluvoxamine with lower NDMC plasma levels. No studies investigated seizure risk with augmentation or reported seizures as an adverse event. The pharmacokinetic studies showed that adjunctive fluvoxamine increased clozapine and NDMC in a dose-dependent manner.

Although the evidence is too preliminary to warrant recommending adjunctive fluvoxamine for general clinical use, it might be considered in certain situations. Additional research is warranted. The authors caution that if adjunctive fluvoxamine is used, it should be titrated slowly and regular therapeutic monitoring should be conducted. Special precaution should be taken with patients who have experienced dose-related adverse effects with clozapine monotherapy.

Polcwiartek C, Nielsen J: The clinical potentials of adjunctive fluvoxamine to clozapine treatment: a systematic review. *Psychopharmacology* 2015; doi 10.1007/s00213-015-4161-1. From Aalborg University Hospital and Aalborg University, Denmark. **This review was conducted without funding. One study author disclosed financial relationships with commercial sources; the second author declared no competing interests.**

Common Drug Trade Names: clozapine—*Clozaril*; fluvoxamine—*Luvox*

Levomilnacipran and Depression-Related Fatigue

According to an exploratory post-hoc analysis of pooled clinical trial data, levomilnacipran (*Fetzima*) reduces depression-related symptoms of fatigue.¹

Background: In the large-scale STAR*D study, nearly 61% of patients with depression continued to have residual fatigue after 14 weeks of treatment.² These patients experienced significantly worse functional outcomes and had a reduced likelihood of depression remission. However, little research has addressed residual fatigue. The SNRI levomilnacipran was considered a candidate treatment for depression-related fatigue because of its stronger noradrenergic activity. Reduced noradrenergic activity may underlie reduced motivation and energy, loss of interest, and decreased pleasure.

Methods: A secondary analysis of pooled data from 5 manufacturer-sponsored, placebo-controlled studies was undertaken to evaluate the effects of levomilnacipran treatment on fatigue. Patients, aged 18–80 years, received treatment for 8–10 weeks with 40–120 mg/day extended-release levomilnacipran in fixed-dose or flexible-dose designs. The primary depression endpoint in each study was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. The present analysis assessed the effect of levomilnacipran on 4 different measures of fatigue: the MADRS item 7 (lassitude: difficulty or slowness in initiating and/or performing daily activities; scored from 0 to 6) and 3 items on the 17-item Hamilton Rating Scale for Depression (HAM-D) measuring work and activities, retardation (slowing of thought and speech or decreased motor activity), and general somatic symptoms.

Results: Of the studies' pooled population of 2598 patients, 74% had high levels of fatigue at study entry, as defined by a MADRS item-7 score of ≥ 4 (with 4 defined as difficulties in starting simple routine activities that are then carried out with effort). Compared with placebo, levomilnacipran was associated with a small but statistically significant average decrease in the item 7 score (0.3 points; effect size,* 0.18). Effects were also statistically significant for the 3 HAM-D items, with effect sizes ranging from 0.09 for retardation to 0.21 for work/activities. For all fatigue symptoms, patients who received levomilnacipran were more likely than those in the placebo groups to achieve remission of fatigue symptoms (odds ratio,* 1.3 for MADRS item 7; $p < 0.001$ vs. placebo; and similar results from the HAM-D items).

Patients with high and low initial fatigue experienced similar improvement in MADRS total score. Levomilnacipran had similar effect sizes on most fatigue measures in men and women,

in patients older or younger than 60 years, and in pre- and postmenopausal women. Patients with obesity (BMI of ≥ 30) showed little-or-no treatment-related effects on fatigue symptoms.

Discussion: These results suggest that treatment with levomilnacipran may be effective in reducing fatigue in patients with depression, regardless of patient age or gender. However, because of the study design, no conclusions can be drawn about the relative efficacy of levomilnacipran and other antidepressants.

¹Freeman M, Fava M, Gommoll C, Chen C, et al: Effects of levomilnacipran ER on fatigue symptoms associated with major depressive disorder. *International Clinical Psychopharmacology* 2015; doi 10.1097/YIC.000000000000104. From Harvard Medical School, Boston, MA; Forest Research Institute, Jersey City, NJ; and other institutions. **Funded by Forest Laboratories. All 6 study authors disclosed financial relationships with commercial sources.**

²Ferguson M, et al: Impact of fatigue on outcome of selective serotonin reuptake inhibitor treatment: secondary analysis of STAR*D. *Current Medical Research and Opinion* 2014;30:2109–2118.

*See Reference Guide.

Cholinesterase Inhibitor Adverse Events

According to a large, international pharmacovigilance study, neuropsychiatric problems are the most frequent type of cholinesterase inhibitor-related adverse drug reaction (ADR). The global pattern of reported adverse events differs from the package labeling, which lists gastrointestinal (GI) problems as the most frequent ADR.

Methods: The World Health Organization's ADR database, VigiBase, contains >8 million case reports from >100 countries. Suspected ADRs are spontaneously reported by health professionals, patients, and drug manufacturers. Data for the present analysis were extracted from all reports to VigiBase in 1998–2013 that involved the 3 cholinesterase inhibitors available for treatment of dementia: donepezil, rivastigmine, and galantamine.

Results: Nearly 44,000 cholinesterase inhibitor-related ADRs were the subject of about 19,000 reports (each consisting of a single patient with, possibly, multiple events). Nearly 90% of reports were from Europe, the U.S., and Canada. The mean patient age was 77 years, and 40% of the events occurred in men. Donepezil and rivastigmine each accounted for about 41% of reports, and galantamine for 17%.

Contrary to the adverse event data from clinical trials that showed GI effects to be most common, nearly one-third of all reported ADRs in this study were neuropsychiatric events. Among the more frequent were disturbances in consciousness; syncope and related symptoms; neurological signs and symptoms; confusion and disorientation; hallucinations; anxiety symptoms; and behavioral and social disturbance. GI events accounted for 15% of all reports, general events (e.g., fever and administration site reactions) accounted for 12%, and cardiovascular disorders for 12%.

Information on severity of ADRs was available in VigiBase only after 2005. About 70% of the reported ADRs between 2006 and 2013 were serious, resulting in death, hospitalization, disability, or other important negative outcomes; 2% of the ADRs were fatal. Neuropsychiatric disturbances accounted for 34% of serious ADRs, general disorders 14%, and cardiovascular disorders 12%. Expected cholinergic adverse effects were frequently reported as serious, including nausea and vomiting, confusion, and diarrhea. More than 900 reports (5.5% of the total) described serious events related to excitatory reactions of the central nervous system, such as seizures, anxiety, aggression, and insomnia. About 2% of the serious incidents were linked with medication error or maladministration.

Discussion: The global occurrence of cholinesterase inhibitor-related adverse events is consistent with the global market for these agents, which are mainly used in affluent countries. The high proportion of reports related to donepezil and rivastigmine is consistent with these agents'

position as market leaders. Cholinesterase inhibitors may not be the cause of some proportion of reported neuropsychiatric and cardiovascular adverse events, given the high background incidence in this patient population. However, there is a pharmacological rationale for some types of neuropsychiatric events: increased acetylcholine levels in the brain, possibly leading to an increase in neuronal excitation. In clinical practice, the possibility that a neuropsychiatric disturbance is cholinesterase inhibitor-related should be considered before treating the disturbance with specific drugs.

Kroger E, Moulds M, Wilchesky M, Berkers, M, et al: Adverse drug reactions reported with cholinesterase inhibitors: an analysis of 16 years of individual case safety reports from Vigibase. *Annals of Pharmacotherapy* 2015;49 (November): 1197–1206. From the Centre Hospitalier Universitaire de Quebec, Canada; and other institutions. **Funded by the Canadian Institutes for Health Research; and other sources. The authors declared no competing interests.**

Common Drug Trade Names: donepezil—Aricept; galantamine—Razadyne; rivastigmine—Exelon

Reference Guide

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.

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.

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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Low-Dose Buprenorphine for Suicidal Ideation

In a placebo-controlled trial, very-low-dose, time-limited, sublingual buprenorphine was associated with decreased suicidal ideation in severely suicidal patients.

Background: For many years during the last 2 centuries, opioids were widely used to treat depression; however, because of their addictive potential and lethality in overdose, they were replaced by current antidepressants. Several lines of evidence point to a connection between separation distress, mental pain, depression, suicidal ideation, and endogenous opioids, leading to the hypothesis that opioids at very low doses might alleviate suicidal ideation. Buprenorphine is a partial mu-opioid agonist chosen for this study because of its low lethality. The very low doses used in the study were crucial for enabling independent home-based use for a short period.

Methods: Participants, aged 18–65 years (n=88; 63 women), were recruited from 4 centers in Israel over a 3.5-year period. All had clinically significant suicidal ideation, defined as a score of ≥ 11 on the Beck Scale for Suicide Ideation (BSSI) for ≥ 1 week. Those with a lifetime history of opioid abuse or a history of any substance or alcohol abuse within 2 years were excluded. Concurrent medication use was not an exclusion criteria, but antidepressant use had to have been stable for ≥ 28 days and no changes were allowed during the study period. Clinicians could modify other background pharmacotherapy as needed. Patients were randomly assigned in a 2:1 ratio to receive double-blind buprenorphine or placebo for 4 weeks. Buprenorphine was started at 0.1–0.2 mg/day and could be increased to a maximum of 0.8 mg/day. A week's supply of medication was dispensed at a time; this amount was not considered to present an overdose risk. The primary study outcome was change from baseline on the BSSI.

Results: A total of 62 patients (71%) who received ≥ 1 dose of study medication and completed ≥ 1 post-baseline assessment were included in the analysis. Most patients were considered clinically unstable, and many were unable to cooperate with study staff, which resulted in a high dropout rate of 30% during the first week. Patients were severely suicidal; two-thirds had made ≥ 1 suicide attempt, nearly 30% of which were within the prior month. More than half met

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criteria for borderline personality disorder, and about 40% had major depressive disorder. The majority of patients were receiving additional therapy with an antidepressant (70%), a benzodiazepine or other hypnotic (49%), an antipsychotic (20%), and/or a mood stabilizer (18%). About one-fourth were currently hospitalized.

Patients in the buprenorphine group had a reduction of about 50% in mean BSSI score that was statistically significant, relative to placebo, by the end of week 2 ($p=0.04$) and remained so at 4 weeks ($p=0.004$). Concurrent treatment with antidepressants did not affect the relative likelihood of response, nor did the presence of borderline personality disorder. Patients who received buprenorphine also had better secondary outcomes, including reductions on the Suicide Probability Scale ($p=0.03$), Beck Depression Inventory ($p=0.09$), and an item of the Suicide Probability Scale thought to reflect mental pain ($p=0.03$).

The predominant adverse effects of buprenorphine were fatigue (49%), dizziness (40%), nausea (37%), and headache (32%). One patient in each treatment group attempted suicide during the study. No patient experienced withdrawal during the week after drug discontinuation.

Discussion: Despite the efficacy and favorable safety profile in this study, buprenorphine is potentially addictive and possibly lethal. The study authors caution that even at very low doses, the drug should be tested only in individuals who have been screened for the possibility of substance abuse.

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

Yovell Y, Bar G, Mashiah M, Baruch Y, et al: Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: a randomized controlled trial. *American Journal of Psychiatry* 2015; doi 10.1176/appi.ajp.2015.15040535. From the University of Haifa, Israel; and other institutions. **Funded by the Hope for Depression Research Foundation; and other sources. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Zinc Augmentation in Schizophrenia

In a small, short-term, controlled trial, adding zinc sulfate to risperidone (*Risperdal*) resulted in significantly greater improvement in schizophrenia symptoms.

Background: Among its crucial roles in many essential brain functions, zinc is a neuromodulator of NMDA, GABAergic, and cholinergic neurotransmission, all of which are important in schizophrenia. Zinc deficiencies have been documented in patients with the disorder, but supplementation has not previously been investigated as a potential treatment.

Methods: Study subjects were inpatients, aged 18–65 years ($n=30$; 28 men), at a psychiatric hospital in Iran who were experiencing an acute episode of schizophrenia. Patients met DSM-IV-TR criteria for the disorder and had a score of ≥ 80 on the Positive and Negative Syndrome Scale (PANSS). Prior to study entry, patients received no oral antipsychotics for 1 week and no depot antipsychotics for ≥ 2 months. All patients received 6 mg/day risperidone. In addition, they were randomized to receive double-blind treatment with either 220 mg zinc sulfate t.i.d. (for a total daily dose of 150 mg elemental zinc) or placebo. Outcomes were assessed biweekly for 6 weeks using the PANSS, including the PANSS supplemental aggression risk subscale.

Results: Zinc supplementation was associated with significantly larger improvement than placebo in positive and negative symptoms, the PANSS total score, and aggression, but not general psychopathology. (See table, next page.) Change from baseline differed significantly between the 2 groups beginning at week 4 for most symptoms and at week 2 for positive symptoms. Adverse effects were not systematically investigated, but metallic taste appears to be the only effect that occurred more frequently with active treatment.

PANSS Scores After 6 Weeks					
	Zinc Sulfate		Placebo		Significance
	Baseline	6 Weeks	Baseline	6 Weeks	
Total Score	148	50	150	61	p=0.003
Positive Symptoms	31	10	32	13	p=0.04
Negative Symptoms	33	10	34	13	p=0.02
General Psychopathology	70	25	69	28	p=ns
Aggression	13	5	15	7	p=0.001

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

Mortazavi M, Farzin D, Zarhghami M, Hosseini S, et al: Efficacy of zinc sulfate as an add-on therapy to risperidone versus risperidone alone in patients with schizophrenia: a double-blind randomized placebo-controlled trial. *Iranian Journal of Psychiatry and Behavioral Sciences* 2015; doi 10.17795/ijpbs-853. From Mazandaran University of Medical Sciences, Sari, Iran. **Funded by the university. The authors declared no competing interests.**

*See Reference Guide.

Adjunctive Raloxifene in Schizophrenia

Raloxifene (*Evista*), a selective estrogen receptor modulator (SERM), was an effective adjunctive treatment in postmenopausal women with schizophrenia in a placebo-controlled trial.¹ Its primary benefit was in reducing negative symptoms.

Background: Research indicates that estrogen levels are significantly lower in women with schizophrenia than in healthy women and that illness onset and relapses often coincide with the phases of the menstrual cycle when estrogen levels are low. A few studies have evaluated short-term therapeutic use of estrogen in women, but long-term use has the potential for negative effects on breast and uterine tissue. Raloxifene acts as an agonist of AMPA, NMDA, and serotonin receptors in some brain areas, has antiinflammatory activity, and can act as an agonist of dopamine D2 and D3 receptors. It was shown in a previous, small, 12-week trial to be an effective adjunct to antipsychotics in postmenopausal women.² The present study, conducted by the same researchers, was undertaken to replicate earlier results in a larger sample.

Methods: Subjects in this 24-week trial were 70 postmenopausal women (56 inpatients) with schizophrenia who were receiving stable antipsychotic medication and had prominent negative symptoms. Postmenopausal status was defined as age >50 years and ≥1 year of amenorrhea, or age 45–50 years with ≥1 year of amenorrhea and postmenopausal levels of follicular stimulating hormone (FSH). Women receiving hormone replacement therapy or with sex hormone abnormalities were not included. In addition to their current antipsychotic therapy, which remained unchanged for the duration of the study, patients were randomly assigned to receive double-blind adjunctive 60 mg/day raloxifene or placebo. Efficacy was assessed with the Positive and Negative Syndrome Scale (PANSS).

Results: Patients had a mean age of about 62 years and had schizophrenia onset in their mid-to-late 20s on average. The majority were taking second-generation antipsychotics or drug combinations. By chance, baseline PANSS symptom severity was greater in the women who received raloxifene—significantly so for the general psychopathology subscale (p=0.02).

In a last observation carried forward analysis,* compared with placebo, adjunctive raloxifene was associated with significant improvement in the PANSS total score and the negative and general psychopathology subscales (see table, next page), but not in positive symptoms. The

rate of negative symptom response ($\geq 20\%$ reduction in PANSS negative symptom score) was also significantly higher with raloxifene. A secondary analysis using the Scale for the Assessment of Negative Symptoms (SANS) found raloxifene was associated with significant improvement relative to placebo on the alogia subscale ($p=0.048$), but on none of the other 4 subscales or the total SANS score.

Mean change from baseline to week 24 in PANSS symptoms and negative symptom response rates					
	Raloxifene		Placebo		Significance
Mean scores	Baseline (n=38)	Endpoint (n=30)	Baseline (n=32)	Endpoint (n=27)	Raloxifene vs. placebo
Total score	80	70	75	75	$p=0.005$
Negative symptoms	24	20	23	22	$p=0.027$
General psychopathology	39	34	35	36	$p=0.003$
Positive symptoms	17	15	17	17	$p=ns$
Negative symptom response	37%		13%		$p=0.02$

Raloxifene was not associated with extrapyramidal or other adverse effects, including those related to menopausal symptoms. There were no apparent adverse effects on breast or uterine tissue, vaginal bleeding, or thrombophlebitis.

Discussion: Results of this study suggest that adjunctive raloxifene may reduce general psychopathology and negative symptom burden in postmenopausal women with schizophrenia. Although positive symptoms were not affected, the authors speculate that the sample size may have been too small to detect small differences in these symptoms. Additional research appears to be warranted.

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

¹Usall J, Huerta-Ramos E, Labad J, Cobo J, et al: Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a 24-week double-blind, randomized, parallel, placebo-controlled trial. *Schizophrenia Bulletin* 2015; doi 10.1093/schbul/sbv149. From the Parc Sanitari Sant Joan de Deu, Sant Boi de Llobregat, Spain; and other institutions. **Funded by the Stanley Medical Research Institute. The authors declared no competing interests.**

²Usall J, et al. Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. *Journal of Clinical Psychiatry*. 2011;72:1552–1557.

*See Reference Guide.

Asenapine/Ciprofloxacin Interaction

A 44-year-old woman with bipolar I disorder was admitted for worsening depression. She had been receiving 5 mg/day asenapine for 1.5 months prior to admission. Additional medications, all of which were continued on admission, included 20 mg/day baclofen, 60 mg/day dextlansoprazole, 20 mg/day fluoxetine, 1 mg/day lorazepam, and 2250 mg/day divalproex. A urinary tract infection detected on admission precipitated additional treatment with 500 mg ciprofloxacin b.i.d. Within 33 hours of starting ciprofloxacin, the patient was unable to close her jaw, which was consistent with an acute dystonic reaction. Treatment with 50 mg intramuscular diphenhydramine resolved the dystonia, and the antibiotic was switched to 100 mg nitrofurantoin b.i.d. with no further complications. The patient had previously experienced a severe dystonic reaction to haloperidol.

A potential interaction between asenapine and ciprofloxacin has not been previously reported. However, ciprofloxacin is a potent inhibitor of CYP1A2, the pathway via which asenapine is primarily metabolized, and interactions between it and other second-generation antipsychotics that are metabolized through this pathway have been reported. Other possible contributing

factors to the reaction include the effects of inflammation/infection on CYP1A2, as well as potential inhibition of asenapine glucuronidation by divalproex. These may have exacerbated the patient's symptoms, but the dystonia was more likely related to ciprofloxacin as it was not noted until after the drug was initiated. According to the Drug Interaction Probability Scale,* the likelihood of a drug/drug interaction in this case is considered probable.

Ridout K, Ridout S, Pirnie L, Puttichanda S: Sudden-onset dystonia in a patient taking asenapine: interaction between ciprofloxacin and asenapine metabolism. *American Journal of Psychiatry* 2015;172 (November):1162–1163. From Brown University, Providence, RI. **The authors declared no competing interests.**

Common Drug Trade Names: asenapine—*Saphris*; ciprofloxacin—*Cipro*; dextlansoprazole—*Dexilant*; divalproex—*Depakene, Depakote*; haloperidol—*Haldol*; fluoxetine—*Prozac*; lorazepam—*Ativan*; nitrofurantoin—*Macrobid, Macrochantin*

*See Reference Guide.

Flibanserin for Hypoactive Sexual Desire in Women

The only FDA-approved treatment for hypoactive sexual desire disorder (HSDD), flibanserin can be considered for use in selected premenopausal women, according to a review. However, use should be limited to patients who are premenopausal; not pregnant; in stable, healthy relationships; willing to abstain from alcohol; and who do not take medications that may cause interactions.

Flibanserin was approved by the FDA in August 2015 for treatment of HSDD. The disorder is recognized by the American College of Obstetrics and Gynecology but has been dropped from the DSM-5, where its symptoms were instead included in the criterion for female sexual interest/arousal disorder. Other treatments for diminished sexual desire in women include off-label bupropion, transdermal testosterone (in postmenopausal patients), and various psychological treatments. Other medications and supplements, including sildenafil, have been shown to be ineffective.

Flibanserin addresses the proposed pathophysiology of HSDD, a relative deficiency in noradrenergic and dopaminergic activity and a relative excess in serotonergic activity in the prefrontal cortex. Flibanserin has a terminal half-life of about 11 hours and requires administration for 3 days to achieve steady-state levels. Because it may cause CNS depression leading to hypotension and dizziness, bedtime administration is required. Its availability is limited to a REMS (Risk Evaluation and Mitigation Strategy) program because of the risk of hypotension/syncope, which is increased with concomitant alcohol use. Patients should discontinue flibanserin after 8 weeks if they do not experience any benefit.

A total of 4 industry-sponsored phase III clinical trials of flibanserin have been conducted, along with an extension study, and a phase II pharmacokinetic trial. Three of the placebo-controlled trials were 24 weeks in duration, 1 was 48 weeks, and the extension trial lasted 1 year. Study participants experienced a strong placebo response but a marginal, statistically significant increase in the average number of satisfying sexual events per month with flibanserin. A variety of secondary outcome measures also showed improvement, although inconsistently across trials. Flibanserin was generally well tolerated, with dizziness, somnolence, nausea, fatigue, and insomnia the most common adverse events. Some women became pregnant while participating in the trials, and several spontaneous abortions or other pregnancy complications occurred, but investigators did not attribute them to study medication.

Additional concerns regarding flibanserin include the use of industry-supported questionnaires in the trials, the possibility of unpublished negative trials, and the perception of external

pressure on the FDA to approve the drug. There is also concern about possible off-label use, particularly in postmenopausal women, who may be more likely to take interacting medications and to experience dangerous falls as a result of dizziness.

Robinson K, Cutler J, Carris N: First pharmacological therapy for hypoactive sexual desire disorder in premenopausal women: flibanserin. *Annals of Pharmacotherapy* 2016;50 (February):125–132. From the University of South Florida, Tampa. **This review was not funded. The authors declared no competing interests.** See related story in *Psychiatry Drug Alerts* 2015;29 (September):69.

Common Drug Trade Names: bupropion—*Wellbutrin*; flibanserin—*Addyi*; sildenafil—*Viagra*

Quetiapine plus Lamotrigine for Bipolar Depression

In a randomized trial, augmenting quetiapine with lamotrigine resulted in greater improvement in bipolar depression than treatment with quetiapine alone.¹ This approach takes advantage of the differing time scales and mechanisms of action of the 2 drugs, with quetiapine providing relief of acute symptoms while allowing slower-acting lamotrigine to gain traction.²

Background: A number of agents are FDA approved as monotherapy for bipolar depression, including both quetiapine and lamotrigine. However, most guidelines recommend avoiding monotherapy when possible, especially in bipolar I disorder.

Methods: Study participants, recruited from multiple sites in the U.K., were 266 patients aged ≥16 years with type I or II bipolar disorder who, in their clinician's judgement, required new treatment for a depressive episode. All patients were started on quetiapine monotherapy for 1 or 2 weeks, with an eventual minimum dosage of 150 mg/day and a target dosage of 300 mg/day. Patients who tolerated and adhered to the quetiapine run-in (n=202) received double-blind, randomly assigned add-on treatment with either lamotrigine, increased gradually to 200 mg/day, or placebo. In addition, patients not already taking folic acid were randomized to either 500 µg/day folic acid or placebo. Treatment was continued for 52 weeks. The primary outcome was depressive symptoms, rated with the 16-item Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR16) at 12, 22, and 52 weeks.

Results: In the full sample including patients receiving both active and placebo folic acid, adjunctive lamotrigine was associated with numerically lower QIDS-SR16 scores than placebo beginning at week 12 and lasting throughout the study. (See table.) The between-group difference was statistically significant only at 52 weeks (p=0.017). Rates of depression remission, defined as a QIDS-SR16 score of ≤5, were significantly higher with lamotrigine than placebo at week 12 (31% vs. 16%; p=0.026) and week 52 (36% vs. 13%; p=0.012). Lamotrigine was associated with a modest increase in manic symptoms during the first 12 weeks, but not afterward.

Improvement in Bipolar Depression—Adjunctive Lamotrigine vs. Placebo				
QIDS-SR 16 Score	Baseline	12 Weeks	22 Weeks	52 Weeks
Lamotrigine	15.3	10.9	9.6	9.2
	(n=101)	(n=83)	(n=61)	(n=56)
Placebo	15.0	12.5	11.6	12.0
	(n=101)	(n=81)	(n=63)	(n=47)

Patients randomly assigned to folic acid did not have an antidepressant response that differed from placebo. Among patients who received lamotrigine, those who also received folic acid had no change from baseline to week 12 in the QIDS-SR16; instead, the response was confined to those who received lamotrigine with a folic-acid placebo, for whom scores were an average of 4 points lower (p=0.004).

Discussion: In previous short-term clinical trials, lamotrigine has shown only weak antidepressant effects probably because it requires a 6-week titration period. The present study suggests that the rapid onset of action of quetiapine might make this slow titration less of a problem.

¹Geddes J, Gardiner A, Rendell J, Voysey M, et al: Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): a 2 x 2 factorial randomised trial. *Lancet Psychiatry* 2016;3 (January):31–39. From the University of Oxford, Warneford Hospital, U.K.; and other institutions. **Funded by the Medical Research Council. Three study authors declared financial relationships with commercial sources; the remaining 9 authors declared no competing interests.**

²Malhi G: CEQUEL the sequel: bipolar disorder combination therapy [editorial]. *Lancet Psychiatry* 2016;3 (January):2–3. From the University of Sydney and Royal North Shore Hospital, Australia. **The author declared financial relationships with commercial sources.**

Common Drug Trade Names: lamotrigine—*Lamictal*; quetiapine—*Seroquel*

Experimental Neurogenic Antidepressant

In an early-phase clinical study, NSI-189, an experimental compound that promotes hippocampal neurogenesis, was safe and efficacious in a small group of patients with depression.¹

Background: Currently available antidepressants generally share monoaminergic activity as their mechanism of action. NSI-189, a benzylpiperazine-aminiopyridine, stimulates neurogenesis of human hippocampus-derived neural stem cells and has shown behavioral efficacy in animal models of depression. The present study was undertaken to identify the maximum safe dose of NSI-189 that could be administered for ≥ 28 days in patients with major depression and to explore its effects on depressive symptoms, electroencephalogram (EEG) measures, and hippocampal volumetric changes.

Methods: Study participants were 24 patients, aged 18–60 years (12 women), who were experiencing a current episode of recurrent major depressive disorder. At study entry, patients were either medication free with a history of antidepressant therapy or underwent a washout of current antidepressant therapy. Eligible patients with a Montgomery-Asberg Depression Rating Scale (MADRS) score of 15–30 were randomly assigned to double-blind treatment with 1 of 3 NSI-189 dosage groups—40 mg/day, 40 mg b.i.d., or 40 mg t.i.d.—or placebo. Each group consisted of 6 patients receiving active treatment and 2 receiving placebo, and all patients received study medication as inpatients for the 28 study days. Treatment was discontinued at discharge (day 28). Depression was evaluated on days 14 and 28 and at regular intervals through an additional 8 weeks of follow-up.

Results: NSI-189 was well tolerated throughout the dosage range. Adverse events were generally similar to placebo, and none were serious. NSI-189 had a half-life of about 19 hours, and steady state levels were reached after 4 days. Drug exposure was nearly dose-proportional.

In a pooled analysis, the 3 NSI-189 dosages were associated with greater improvement in depression than placebo as measured using the clinician-rated MADRS (effect size, * 0.95) and Clinical Global Impression–Improvement scale (effect size, 0.57), and the patient-rated Symptoms of Depression Questionnaire (effect size, 0.9) and Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (effect size, 0.94). Improvements were maintained throughout the 12-week follow-up, for the most part. Of the 18 patients who received active treatment, 12 were considered responders on day 28, with a $\geq 50\%$ decrease in MADRS score; 4 were considered partial responders, with post-treatment MADRS scores indicating mild depression; and 2 were nonresponders, with MADRS scores remaining within the original moderate depression range.

Structural MRI scans, used to measure volumes of the hippocampus where NSI-189 is believed to induce neurogenesis, showed a modest, nonsignificant increase in left hippocampal volume in treated patients, but no change on the right side. EEG data did not raise any safety concerns.

Discussion: Results of this study suggest a potentially new target or mechanism for antidepressant drug development. Although results are preliminary and require replication, NSI-189 appears to be a promising treatment for major depression with effects that may be more durable than existing antidepressant agents.

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

Fava M, Johe K, Ereshefsky L, Gertsik L, et al: A phase 1B, randomized, double blind, placebo controlled, multiple-dose escalation study of NSI-189 phosphate, a neurogenic compound, in depressed patients. *Molecular Psychiatry* 2015; doi 10.1038/mp.2015.178. From Massachusetts General Hospital, Boston; and other institutions including Neuralstem Inc., Germantown, MD. **Funded by Neuralstem. All study authors disclosed financial relationships with commercial sources including Neuralstem.**

*See Reference Guide.

Orally Disintegrating Mixed Amphetamine Salts

Adzenys XR (extended-release mixed amphetamine salts) has received FDA approval as the first orally disintegrating extended-release product for the treatment of ADHD in children aged ≥ 6 years and adults. The agent was determined to be bioequivalent to *Adderall XR*, and will be available in the same 6 dosage strengths. *Adzenys XR* contains amphetamine in a mixture of immediate-release and polymer-coated delayed-release resin particles; it is not a generic version of *Adderall XR*. Product launch is expected after March 2016.

Neos Therapeutics announces FDA approval of *Adzenys XR ODT*TM (amphetamine extended-release orally disintegrating tablet) for the treatment of ADHD in patients 6 years and older: first and only approved extended-release orally disintegrating tablet for the treatment of ADHD. [Press release]. Dallas and Fort Worth, TX: Neos Therapeutics Inc.; Jan. 27, 2016.

Reference Guide

Drug Interaction Probability Scale (DIPS): A tool similar to the Naranjo Probability Scale designed to evaluate the causation of an adverse event thought to be produced by the interaction between 2 drugs. Based on a score generated by answering 10 questions, the probability is assigned as doubtful, possible, probable, or highly probable. The DIPS is available online at <http://www.pmidcalc.org>.

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.

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.

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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Treating Impulsive Aggression

Pharmacotherapy for impulsive aggression depends on 2 critical factors: characterization of the aggressive behavior and identification of anti-impulsive aggressive agents (AIAs) with evidence-based efficacy. However, there are no AIAs that are FDA-approved for this indication, and clinicians are left with little guidance in drug selection.

Impulsive aggressive behavior can be defined as "behavior that is angry or rageful, eruptive, unplanned, and lacking in self-control." This is in contrast to premeditated aggression. Most clinical-trial research involving aggression has been based on DSM-IV diagnostic definitions. The DSM-5 expanded the criteria for intermittent explosive disorder to include aggressive outbursts of high frequency but low intensity. This revision will likely increase the number of patients eligible for drug treatment. However, it remains the case that most aggressive behavior can be controlled with nonpharmacological measures such as psychotherapy or placing the patient in a controlled or structured environment.

In patients who require pharmacological treatment, several factors inform treatment selection. In addition to characterizing the behavior and identifying effective AIAs, other factors to consider (although at a later decision point and in no specific order) are the risks, adverse effects, and contraindications of specific agents; the severity of a patient's aggressive outbursts; and identification of co-occurring conditions.

Many potential AIAs have been investigated in clinical trials. Those whose efficacy is supported by >1 high-quality study include phenytoin, carbamazepine or oxcarbazepine, valproate or divalproex, lithium, and fluoxetine. The choice among these agents is influenced by their risks and adverse-effect profiles and the severity of aggression. For milder forms of aggression (e.g., infrequent, verbal; or not resulting in property damage or physical harm), fluoxetine can be considered first-line treatment. Sertraline is a reasonable alternative, although supported by less evidence, if there is concern about high risk of drug interactions with fluoxetine involving the cytochrome P450 system. For severe aggression (i.e., ≥ 3 outbursts within 1 year that caused property damage or physical harm), the first treatment may be

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lithium or an anticonvulsant. Co-occurring disorders or symptoms can also help guide treatment selection. Signs of depression could favor selection of fluoxetine; increased affective drive or mood and affect lability could favor a mood stabilizing AIAA.

Felthous A, Stanford M: A proposed algorithm for the pharmacotherapy of impulsive aggression. *Journal of the American Academy of Psychiatry and the Law* 2015;43 (December):456–467. From St. Louis University School of Medicine, MO; and Baylor University, Waco, TX. **Source of funding not stated.**

Common Drug Trade Names: carbamazepine—*Epitol, Tegretol*; fluoxetine—*Prozac*; oxcarbazepine—*Trileptal*; sertraline—*Zoloft*; valproate—*Depakene, Depakote*

High-Dose Pramipexole in Refractory Depression

Adjunctive pramipexole (*Mirapex*), used at the maximum tolerated dose and taken at bedtime, was highly effective in a series of patients with treatment-resistant depression.

The study sample consisted of 42 consecutive outpatients, aged 25–84 years, with either major depressive disorder (n=24) or bipolar depression (n=18) who were treated over a 5.5-year period. No patient had psychotic depression. All patients had undergone ≥ 4 adequate but unsuccessful antidepressant medication trials (mean, 6 trials), and 8 had also undergone ≥ 1 unsuccessful course of ECT. Pramipexole was added to background medication starting at 0.25 mg/day in those under age 45 years and at 0.5 mg/day in older patients, based on evidence of reduced dopamine D3 receptors in older persons. The pramipexole dosage was increased every 3 days in 0.25- and 0.5-mg increments, respectively, to an initial goal of 2 mg/day. If necessary because of adverse effects, the dosage was reduced to the previous level for 1–2 weeks and then increased again if tolerated. Patients were typically seen every 2 weeks during pramipexole titration.

Remission (based on patients reporting no depressive symptoms to their clinicians) occurred in 20 patients (48%), and response (patient-reported significant improvement with some residual symptoms) in another 12 (29%). (See table.) The mean dosage for patients whose symptoms responded or remitted was about 2.5 mg/day. Of the 8 patients who had undergone unsuccessful ECT, 4 achieved remission and 4 others achieved response with pramipexole. Intolerance, usually due to nausea, occurred within the first weeks of treatment, typically at low doses. Other acute adverse effects included sleeplessness, sleepiness, increased anxiety, panic attacks (in 1 patient), and early insomnia. Two patients, both men with bipolar disorder, reported hypersexuality.

Outcomes of adjunctive pramipexole treatment in 42 patients with resistant depression				
Group	Remission	Response	Nonresponse	Intolerance
Bipolar Disorder (n=18)	9	5	1	3
Unipolar Depression (n=24)	11	7	1	5
Total (n=42)	20	12	2	8

The 32 patients who achieved response or remission were followed for an average of 16 months. Relapse occurred in 2 patients, after 12 and 18 months. A total of 7 patients discontinued pramipexole during follow-up; 2 remained depression-free; and in the other 5, depression recurred within 1–2 weeks but improved when pramipexole was restarted in 4.

Clinical Recommendations: The authors offer some practical guidance, based on their experience, for the use of pramipexole in resistant depression. The therapeutic dosage range appears to be 1–5 mg/day. They recommend low starting doses, slower titration in younger patients, and temporarily reducing the dosage if nausea occurs. Pramipexole should be taken once a day at bedtime unless the patient has trouble with sleep. Good candidates for pramipexole are patients with severe anhedonia, lack of motivation, inability to initiate behaviors, and unreactive mood. Benefit should occur after 4 weeks on the maximum tolerated dose. Pramipexole should be withdrawn gradually to avoid dopamine agonist withdrawal syndrome.

Fawcett J, Rush A, Vukelich J, Diaz S, et al: Clinical experience with high-dosage pramipexole in patients with treatment-resistant depressive episodes in unipolar and bipolar depression. *American Journal of Psychiatry* 2016;173 (February): 107–111. From the University of New Mexico, Albuquerque; and other institutions. **Source of funding not stated. Two study authors disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

Cariprazine for Hostility in Schizophrenia

According to results of a post-hoc analysis of clinical-trial data, cariprazine (*Vraylar*) reduces hostility in patients with schizophrenia.

Methods: Pooled data were analyzed from 3 short-term, randomized, placebo-controlled trials of cariprazine, conducted between 2008 and 2011. Two of the trials were fixed-dose (range 1.5–6 mg/day), and the third was a fixed/flexible-dose design, with randomization to 3–6 or 6–9 mg/day cariprazine. Patients met DSM-IV-TR criteria for schizophrenia with a current psychotic episode duration of <2 weeks and at least moderate symptom severity. Hostility was assessed at every weekly visit using the Positive and Negative Syndrome Scale (PANSS) hostility item. Scores on this item were used to classify severity of patients' hostility as minimal, mild, or at least moderate (scores of ≥ 2 , 3, or 4, respectively).

Results: In the 3 trials, >1000 patients, aged 18–60 years, received cariprazine and >400 received placebo. Baseline scores on the PANSS hostility item averaged 2.5 points, indicating mild severity. Most patients had at least a minimal level of severity, and about 19% had at least moderate hostility.

Compared with placebo, cariprazine was associated with significantly greater change from baseline in PANSS hostility scores, which decreased from 2.5 to 2.11 with placebo and to 1.83 with cariprazine (least squares mean* difference, -0.28; $p < 0.0001$). (See table.) Differences between cariprazine and placebo were statistically significant beginning in the first week. The difference remained significant after adjusting for change from baseline in PANSS positive symptoms and sedation. The effect of cariprazine was largest in the group with the most severe hostility at baseline. Differences in the PANSS-Excited Component subscale (a secondary endpoint), which measures acute agitation and aggression, also favored cariprazine.

Least squares mean change from baseline in average PANSS hostility scores			
Baseline score	Cariprazine (n=1024)	Placebo (n=442)	Significance
≥ 2	-0.96	-0.64	$p=0.0001$
≥ 3	-1.27	-0.91	$p=0.0007$
≥ 4	-1.84	-1.33	$p=0.0085$

Discussion: These results suggest cariprazine may be associated with a specific antihostility effect that is independent of general antipsychotic or sedating effects. The findings appear to be consistent with post-hoc analyses of other atypical antipsychotics compared with placebo in patients with schizophrenia.

Citrome L, Durgam S, Lu K, Ferguson P, et al: The effect of cariprazine on hostility associated with schizophrenia: post hoc analyses from 3 randomized controlled trials. *Journal of Clinical Psychiatry* 2016;77 (January):109–115. From New York Medical College, Valhalla, NY; and other institutions. **Funded by Forest Laboratories, LLC; and Gedeon Richter, Plc. All study authors declared financial relationships with commercial sources.**

*See Reference Guide.

Esketamine in Resistant Depression

In a proof-of-concept study, multi-dose IV esketamine (investigational) was highly efficacious and safe in patients with treatment-resistant major depressive disorder.

Background: Ketamine has been shown to have rapid antidepressant effects in patients with treatment-resistant depression, but the effects typically last ≤ 1 week and most studies have focused on a single IV infusion. The present study was undertaken to identify a strategy that would maintain the antidepressant effects using multiple infusions of esketamine, the S-enantiomer of ketamine, which has a 3- to 4-fold higher binding to NMDA receptors than the R-enantiomer.

Methods: Study participants were 30 non-elderly adults (mean age, 43 years; 60% women) with severe or very severe resistant depression, as measured with the Inventory of Depression Symptomatology–Clinician Rated. Patients who had been acutely suicidal in the previous 12 months were excluded. Treatment resistance was defined as inadequate response to ≥ 1 antidepressant in the current episode and ≥ 1 other antidepressant in the current episode or an earlier one. Patients were randomly assigned to a single, double-blind infusion of 0.2 mg/kg or 0.4 mg/kg esketamine or placebo. Response was defined as a $>50\%$ reduction in Montgomery-Asberg Depression Rating Scale (MADRS) score. On day 4, patients who met response criteria with the first infusion received a second. Patients who did not achieve response with the initial esketamine infusion received a second infusion at 0.40 mg/kg, and nonresponders to placebo were re-randomized to receive 1 of the 2 esketamine doses. After the 7-day double-blind phase of the study, patients could continue to receive up to 4 additional open-label treatments with 0.4 mg/kg esketamine on days 7, 10, 14, and 17. The primary study endpoint was change from baseline in MADRS score.

Results: The 30 study participants had severe (80%) or very severe (20%) depression. The most common previously ineffective antidepressants were duloxetine and venlafaxine. Both esketamine dosages were associated with a large improvement in MADRS scores after 24 hours. Mean MADRS scores decreased from 34 at baseline to 17 with both esketamine doses, compared with a decrease to 30 with placebo ($p=0.001$). Effect sizes* for esketamine were 1.5 with the lower dose and 1.7 with the higher dose. No placebo-treated patient achieved response, compared with 64–67% of the esketamine groups. Esketamine response was evident within 2 hours of administration. Nonresponders to placebo and the lower esketamine dose improved after receiving the second treatment. Of the 30 patients enrolled, 26 opted to receive additional open-label esketamine and 4 opted out due to travel issues. Improvement was maintained throughout the treatment period and out to 35 days of follow-up.

One patient withdrew from the study after experiencing intolerable dissociative and psychotic symptoms during infusion of 0.4 mg/kg esketamine. Another patient had moderate dissociation during treatment, which became severe afterward. Dissociation

resolved within 4 hours in both cases. The second patient remained in the study, eventually receiving 6 doses of esketamine and experiencing antidepressant response throughout follow-up. There were no emergent suicidal effects.

Discussion: Response rates observed with esketamine were similar to those previously reported with racemic ketamine. The outcome was expected because the dose was adjusted to reflect the differences in NMDA receptor binding between the 2 drugs. No difference in safety or efficacy was observed between the 2 esketamine doses. Therefore the minimum effective dose remains unknown.

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

Singh J, Fedgchin M, Daly E, Xi L, et al: Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. *Biological Psychiatry* 2015; doi 10.1016/j.biopsych.2015.10.018. From Janssen Research and Development. **Funded by Janssen. All study authors disclosed financial relationships with commercial sources, including Janssen.**

Common Drug Trade Names: duloxetine—*Cymbalta*; esketamine—*Ketanest S*; ketamine—*Ketalar*; venlafaxine—*Effexor*

*See Reference Guide.

Antidepressants and Glycemic Control in Diabetes

In an epidemiologic study, treating depression with pharmacotherapy in patients with type 2 diabetes was associated with improved glycemic control.

Background: Major depression and diabetes often co-occur, and the relationship between the disorders is bidirectional—i.e., diabetes increases depression risk, and depression increases diabetes risk. Patients with both disorders have particularly poor glycemic control and functioning.

Methods: Data for the study were extracted from electronic medical records from a primary care registry consisting of family medicine and general internal medicine practices affiliated with a U.S. academic health system. Study subjects were patients, aged 18–90 years, who had ≥ 1 clinical contact between July 2008 and July 2013. Medical records of patients with type 2 diabetes were examined for a diagnosis of depression recorded on ≥ 2 visits within a 12-month span and for treatment with any available antidepressant drug, regardless of dose, duration, or adherence. The analysis was adjusted for covariates including demographic characteristics, anxiety disorders, health behaviors, and any other identifiable factors that could confound the relationship among depression, its treatment, and glycemic control. The effects of antidepressant therapy on glycemic control were the primary outcome.

Results: The sample consisted of 1399 patients with type 2 diabetes (mean age, 62 years; 74% with obesity). Of these, 265 patients (19%) also had a diagnosis of major depression, 225 of whom (85%) received treatment with antidepressants and 40 who did not. Cardiovascular comorbidities were common. Anxiety disorders were present in 15% of patients with untreated depression, 21% of patients who received treatment, and in 1% of those with no depression. Comorbid medical conditions were not significantly associated with depression.

The proportion of patients who met the American Diabetes Association definition of glycemic control (i.e., glycated hemoglobin A1c level of $< 7\%$) was higher, and the average A1c was lower in patients with treated depression than in those with untreated depression. (See table, next page.) After adjusting for all confounders considered to be associated with the disorder, depression treatment, or glycemic control (e.g., obesity, hyperlipidemia, hypertension, use of insulin or other diabetic medication, volume of health care utilization),

patients with treated depression were significantly more likely to achieve A1c control than those with untreated depression (odds ratio,* 1.95). Anxiety was associated with lower A1c values and the prescription of insulin or oral hypoglycemics with higher values.

Percent A1c Control and Mean A1c Values			
	No Depression (n=1134)	Untreated Depression (n=40)	Treated Depression (n=225)
Percent with A1c control	43%	35%	51%
Mean A1c value	7.76%	8.13%	7.41%

Discussion: There have been few randomized controlled trials of the effect of depression treatment on glycemic control. The present study shows an association but does not shed additional light on the directionality of the association. It is possible that some antidepressants directly affect glucose metabolism. Depression symptom severity was not measured in the study so it could not be determined whether glycemic control and depression relief were associated. In addition, the relatively small number of patients with both diabetes and depression who did not receive antidepressants may be cause for concern regarding the extent to which the results can be generalized.

Brieler J, Lustman P, Scherrer J, Salas J, et al: Antidepressant medication use and glycaemic control in co-morbid type 2 diabetes and depression. *Family Practice* 2016;33 (February):30–36. From St. Louis University School of Medicine, MO; and other institutions. **This study was conducted without funding. The authors declared no competing interests.**

*See Reference Guide.

Benzodiazepines and Dementia Risk

Results of a population-based cohort study do not support a causal association between benzodiazepines and dementia.

Background: Studies have shown that benzodiazepines may impair memory and attention; however, it remains uncertain whether long-term use is associated with global cognitive decline. Evaluating the relationship is challenging because dementia can be preceded by insomnia, anxiety, and depression, all of which can be treated with benzodiazepines. Research on the cognitive risks of long-term use has had conflicting results.

Methods: The study was conducted within an integrated healthcare delivery system in the northwestern U.S. Participants were a random sample of plan members, aged ≥65 years, living in the Seattle area, who did not have dementia at baseline. The analysis was limited to persons who had ≥10 years of plan membership and had a valid cognitive score at baseline. Participants were followed until the onset of dementia, disenrollment from the health plan, or last study visit before October 2012. Cognition was measured every 2 years using the Cognitive Abilities Screening Instrument (CASI) to screen for dementia and to calculate a cognitive trajectory. Patients whose scores fell below a threshold underwent a standardized diagnostic evaluation, and diagnoses of dementia and Alzheimer's disease were made using standard research criteria. Benzodiazepine use was ascertained from prescriptions filled during the 10 years before dementia onset or end of study, excluding the most recent year, which could have been for treatment of prodromal symptoms of dementia. Use was categorized as low, medium, or high based on the distribution of exposure and clinically meaningful cutpoints. The highest

level of exposure was equivalent to a total of >4 months of use, which could have been continuous or intermittent.

Results: The 3434 study participants had a median age of 74 years at study entry, and 60% were women. A total of 30% had filled ≥ 1 benzodiazepine prescription. The mean follow-up was 7.3 years, during which 23% of participants had onset of dementia.

No association was found between dementia and the highest level of benzodiazepine exposure, relative to non-exposed individuals (hazard ratio,* 1.07). There was a slight, but not statistically significant, increase in risk of dementia in patients with ≤ 1 month of exposure (hazard ratio, 1.25) and those with 1–4 months of exposure (hazard ratio, 1.31). This slight increase could represent treatment of prodromal symptoms. Results were similar for Alzheimer's disease, which represented about 80% of all dementia diagnoses. Cognitive trajectories did not differ according to benzodiazepine use.

Discussion: Although these results do not support a causal relationship between benzodiazepine use and incident dementia or cognitive decline, given the known adverse effects of these agents in the elderly, the authors suggest that avoiding their use in this population might be prudent.

Gray S, Dublin S, Yu O, Walker R, et al: Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. *BMJ* 2016; doi 10.1136/bmj.i90. From the University of Washington School of Pharmacy, Seattle; and other institutions. **Funded by the NIH; and the Branta Foundation. Four study authors disclosed financial relationships with commercial sources; the remaining 4 authors disclosed no competing interests.**

*See Reference Guide.

Long-Term Tamoxifen and Dementia Risk

In a population-based cohort study, tamoxifen was associated with reduced risk of dementia in women with breast cancer.

Background: In experimental studies, estrogen has had neurotrophic and neuroprotective effects in the brain, providing a convincing rationale for estrogen replacement therapy in preventing and treating dementia. Tamoxifen is a partial agonist or antagonist of the estrogen receptor, depending on the target tissue.

Methods: The study was based on Taiwanese national health data covering nearly the entire population. The investigators identified >24,000 women, aged ≥ 20 years, with a new diagnosis of breast cancer in 2000–2004 and free of dementia at the time. The cohort included >16,500 women who had received treatment with tamoxifen and >7600 who had not. A control group consisted of nearly 97,000 women without any type of cancer or dementia. Among the potential confounders included in the analysis were diabetes, hypertension, stroke, head injury, and different cancer treatments.

Results: Women with breast cancer had a median age of nearly 50 years when diagnosed. The mean follow-up was >7 years in women with breast cancer and >8 years in controls. Between 2% and 3% of each group had onset of dementia during follow-up.

The incidence of dementia in women with breast cancer was somewhat lower than in controls, but not significantly. Among women with breast cancer, dementia incidence was significantly lower in those who received tamoxifen than in those who did not (adjusted hazard ratio,* 0.83; $p < 0.05$). Tamoxifen use was not associated with increased incidence of dementia in separate comparisons of age groups 20–54 years or ≥ 55 years. The apparent benefit of tamoxifen was limited to women receiving treatment for ≥ 5 years, in whom the adjusted hazard ratio for dementia was 0.47 ($p < 0.001$) compared with breast cancer patients who did not receive tamoxifen.

Discussion: These study results do not support previously raised concerns that tamoxifen could increase dementia risk due to estrogen deprivation. The present study accounted for many potential confounders of the relationship, including a longer life expectancy in patients treated with tamoxifen and the adverse effects of chemotherapy and benzodiazepines on cognitive function.

Sun L-M, Chen H-J, Liang J-A, Kao C-H: Long-term use of tamoxifen reduces the risk of dementia: a nationwide population-based cohort study. *QJM: An International Journal of Medicine* 2016;109 (February):103–109. From Kaohsiung Armed Forces General Hospital, Taiwan; and other institutions. **Funded by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence; and other sources.** The authors declared no competing interests.

Common Drug Trade Names: tamoxifen—*Nolvadex, Soltamox*

*See Reference Guide.

Reference Guide

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.

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.

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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Levomilnacipran: Spectrum of Antidepressant Activity

According to results of a post-hoc analysis of 5 randomized trials, levomilnacipran (*Fetzima*) is superior to placebo across a spectrum of depression subgroups based on chronicity and duration of symptoms. The most pronounced antidepressant effects appear to occur in patients with chronic depression.

Methods: Included in the analysis were data from 5 previously published, placebo-controlled clinical trials of extended-release levomilnacipran. The 3 patient groups of interest in this analysis were those with first-episode depression, those with highly recurrent depression (≥ 3 lifetime episodes), and those with chronic depression (current episode ≥ 2 years). The first 2 groups were mutually exclusive, but the chronic depression group was made up of patients from the other groups. Participants were required to have a Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≥ 30 , a Sheehan Disability Scale (SDS) score of ≥ 10 , and to meet other severity criteria. Those with treatment-resistant depression were excluded. Patients received treatment for 8 or 10 weeks, using fixed or flexible doses of levomilnacipran that ranged from 40 to 120 mg/day. The primary efficacy outcome in the pooled analysis was change from baseline in MADRS score, and the secondary outcome was change in SDS score.

Results: The 5 studies had an overall pooled population of 2598 patients, with mean ages in their early-to-mid 40s; nearly two-thirds of the patients were women. There were about 500 with first-episode depression, nearly 2000 with highly recurrent depression, and 218 with chronic depression. The mean durations of the current episode were 34 months, 11 months, and 74 months, respectively.

Mean baseline total MADRS scores were 34 in the first-episode and recurrent groups and 36 in the chronic group. Improvements were significantly greater with levomilnacipran than placebo in all 3 groups, with the largest difference observed in patients with chronic depression for whom the least squares mean difference* in score was nearly double that of the placebo group (-2.5 vs. -4.9 points; $p < 0.001$). Improvement occurred most rapidly in patients in the highly recurrent subgroup, with significant differences from placebo evident after 1 week.

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Response rates ranged from 22 to 35% in the placebo groups and were significantly superior in all actively-treated groups: 45% in first-episode patients, 44% in the highly recurrent patients, and 37% in those with chronic illness ($p \leq 0.02$ for all). Compared with placebo, odds ratios* for response were 1.56, 1.63, and 2.15 in the first-episode, highly recurrent, and chronic groups, respectively. Rates of remission were also numerically larger with levomilnacipran, but the difference was only statistically significant in the group with highly recurrent depression (28% vs. 21% for placebo; $p < 0.001$). Results for all other study outcome measures (i.e., SDS, Hamilton Rating Scale for Depression, and Clinical Global Impression–Improvement scale) also favored levomilnacipran in all 3 clinical groups.

Discussion: Highly recurrent and first-episode patients had similar responses by the end of treatment, underscoring the importance of treating first-episode depression for an adequate time.

Kornstein S, Gommoll C, Chen C, Kramer K: The effects of levomilnacipran ER in adult patients with first-episode, highly recurrent, or chronic MDD. *Journal of Affective Disorders* 2016;193 (March):137–143. From Virginia Commonwealth University School of Medicine, Richmond, VA; and Forest Research Institute, Jersey City, NJ. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Adjunctive Opioid Modulation for Depression

In a randomized trial, augmentation of antidepressant therapy with the combination of buprenorphine and the investigational opioid receptor antagonist samidorphan was superior to placebo in reducing depressive symptoms.

Background: Despite the known involvement of opioid-system dysregulation in mood disorders and the historical use of opioids to treat depression, drug development has not focused on opioid agonists. This study used a combination of the partial mu-opioid receptor agonist buprenorphine with samidorphan, which is known to block the addicting effects of buprenorphine and reduce abuse potential. Preliminary studies suggested promise for a single-tablet 8-mg/8-mg formulation. The present study additionally explored the potential efficacy of a lower dose, 2 mg/2 mg.

Methods: Study participants were adults, aged 18–65 years, with major depression who continued to have a Hamilton Rating Scale for Depression (HAM-D) score of ≥ 16 and also demonstrated $< 50\%$ improvement on the Antidepressant Treatment Response Questionnaire after ≥ 8 weeks of adequately-dosed SSRI or SNRI therapy. The study used a sequential parallel comparison design, which reduces interference from the placebo response. Patients were randomly assigned to 4 weeks of adjunctive daily treatment with placebo or buprenorphine–samidorphan at either 8 mg/8 mg or 2 mg/2 mg, followed by a 1-week washout. Placebo nonresponders were then re-randomized among the 3 treatments for an additional 4 weeks, while all other patients received placebo. The primary efficacy outcome was change in the HAM-D from baseline to the end of 4 weeks of treatment. Background antidepressant medications, which were unchanged during randomized treatment, included sertraline ($n=46$); citalopram ($n=34$); fluoxetine ($n=21$); duloxetine ($n=12$); escitalopram ($n=8$); desvenlafaxine ($n=7$); venlafaxine ($n=7$); paroxetine ($n=6$); and bupropion ($n=1$).

Results: A total of 142 patients (mean age, 46 years; 68% women) were randomized for the first phase of treatment: 43 to each buprenorphine–samidorphan dosage group, and 99 to placebo. In the placebo group, the 65 nonresponders in phase 1 were re-randomized to a phase 2 treatment. This design resulted in similar numbers of patients randomized to each treatment.

The lower dose of buprenorphine–samidorphan (2 mg/2 mg) had superior antidepressant efficacy to placebo in terms of HAM-D change (effect size,* 0.5), as well as secondary outcomes measured. (See table, next page.) The higher buprenorphine–samidorphan dose was more

effective than placebo, but did not reach significance. Neither dose differed from placebo on measures of function or health-related quality of life at any time point.

Efficacy analysis of adjunctive buprenorphine–samidorphan vs. placebo						
	Stage 1			Stage 2		
	Placebo (n=98)	2 mg/2 mg (n=24)	8 mg/8 mg (n=19)	Placebo (n=20)	2 mg/2 mg (n=23)	8 mg/8 mg (n=22)
HAM-D Baseline score	23	23	22	17	16	19
Week 4 score	16	13	15	16	11	15
Response [†]	26%	47%	36%	15%	33%	28%
MADRS Baseline score	31	31	28	24	22	26
Week 4 score	21	17	18	22	13	20
Response [†]	26	41	43	5	50	28

[†]For Both HAM-D and MADRS, response was defined as a ≥50% decrease in score.

The most common adverse events with buprenorphine–samidorphan were nausea, vomiting, dizziness, and headache. Nearly 20% of patients discontinued active treatment because of adverse events, primarily vomiting. No evidence of opioid withdrawal was observed during the study or follow-up.

Discussion: Results of this study suggest buprenorphine–samidorphan may be a promising adjunctive treatment for resistant depression. Preliminary reports from phase III clinical trials show mixed results for doses <2 mg/2 mg.

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

Fava M, Memisoglu A, Thase M, Bodkin J, et al: Opioid modulation with buprenorphine/samidorphan as adjunctive treatment for inadequate response to antidepressants: a randomized double-blind placebo-controlled trial. *American Journal of Psychiatry* 2016; doi 10.1176/appi.ajp.2015.15070921. From Massachusetts General Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by Alkermes, Inc., Waltham, MA. All study authors declared financial relationships with commercial sources related to the development of the study drug.**

Common Drug Trade Names: bupropion—*Wellbutrin*; buprenorphine—*Suboxone, Subutex*; citalopram—*Celexa*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor*

*See Reference Guide.

Cariprazine for Bipolar Depression

In a phase II clinical trial, cariprazine was superior to placebo at reducing depression in patients with bipolar I disorder.¹

Methods: The study, conducted at 88 international sites, enrolled patients with bipolar I disorder and a current depressive episode lasting between 4 weeks and 12 months. Participants were required to have scores of ≥20 on the 17-item Hamilton Rating Scale for Depression (HAM-D) and ≥4 on the Clinical Global Impression–Severity (CGI-S) scale. Following screening and a 1-week drug washout, patients were randomly assigned to 8 weeks of treatment with placebo or cariprazine at 0.75, 1.5, or 3.0 mg/day. The primary efficacy endpoint was the Montgomery-Asberg Depression Rating Scale (MADRS) score, obtained at week 6. Patients received treatment for an additional 2 weeks to assess the persistence of improvement.

Results: A total of 584 patients were enrolled, and nearly 73% completed the study. The intent-to-treat population comprised 571 patients. All 3 cariprazine doses appeared to be superior to

placebo with regard to change from baseline in the MADRS, but the difference was statistically significant only for the 1.5-mg dose (p=0.003; see table).

Cariprazine at 1.5 mg/day was also associated with significantly greater improvement in CGI-S and HAM-D scores. Analysis of patients who completed 8 weeks of treatment showed persistent significant change from baseline in the average MADRS for the 1.5-mg dose and further improvement with the 3.0-mg dose.

Clinical Outcomes at Week 6				
	Placebo	0.75 mg/day Cariprazine	1.5 mg/day Cariprazine	3.0 mg/day Cariprazine
MADRS Score–Baseline	30.4	31.1	30.3	30.6
MADRS Score–Week 6	19.3	18.1	15.2	16.9
CGI-S score–Baseline	4.4	4.4	4.4	4.4
CGI-S Score–Week 6	3.4	3.3	3.0	3.1
HAM-D Score–Baseline	24.1	24.6	23.9	24.0
HAM-D Score–Week 6	15.0	14.3	12.1	12.7
Response and Remission Week 6—% of Patients/Odds Ratio* vs. Placebo				
	Placebo	0.75 mg/day Cariprazine	1.5 mg/day Cariprazine	3.0 mg/day Cariprazine
MADRS Response [†]	32%	39% / 1.35	50% / 2.1	45% / 1.74
MADRS Remission [†]	20%	24% / 1.32	37% / 2.38	28% / 1.59

[†]MADRS Response is a ≥50% decrease in score. Remission is a final score of ≤10.

The most common adverse events associated with cariprazine were akathisia (3–14%) and insomnia (7–12%). The incidence of clinically significant weight gain was somewhat higher with cariprazine than placebo (4.7% vs. 4%).

Discussion: Cariprazine produces high and balanced occupancy of dopamine D₃ and D₂ receptors and has a high affinity for the serotonin 5-HT_{1A} receptors, making it a potentially suitable treatment for depression. The 4-point difference from placebo in MADRS score observed in this study is similar to the margin seen with the atypical antipsychotics approved for treatment of bipolar depression. According to an editorial, of the 3 drugs currently approved for bipolar depression, only quetiapine has also been tested in bipolar mania.² Given the extremely limited options for treating bipolar depression, cariprazine appears to warrant further study in more generalizable patient samples and for longer durations.

Although the study's implications are limited, cariprazine may present an important new option for these patients, especially since it already has approval to treat bipolar mania.

¹Durgam S, Earley W, Lipschitz A, Guo H, et al: An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. *American Journal of Psychiatry* 2016;173 (March):271–281. From Forest Research Institute, Jersey City, NJ; Gedeon Richter, Budapest, Hungary; and other institutions. **Funded by Forest Laboratories; and Gedeon Richter. All study authors disclosed financial relationships with commercial sources including Forest Laboratories and/or Gedeon Richter.**

²Swartz H, Tasosa J: A new option for treating bipolar I depression [editorial]. *American Journal of Psychiatry* 2016;173 (March):211–212. From the University of Pittsburgh School of Medicine, PA. **The authors declared no competing interests.**

Common Drug Trade Names: cariprazine—*Vraylar*; quetiapine—*Seroquel*

***See Reference Guide.**

New Targets for Rapid Antidepressant Action

Conventional antidepressants have few targets other than the hypothalamic-pituitary-adrenal (HPA) stress axis and monoamines. In recent years, the pharmaceutical industry has been investing less in psychiatry and mood disorders as a therapeutic area. Nevertheless, some promising targets have been identified, and new drugs with potentially rapid onset of action are in various stages of development.

Overview of Novel Antidepressants in Development		
Action	Examples	Status
Non-competitive NMDA receptor antagonists	esketamine	Phase II positive results
	memantine (<i>Namenda</i>)	Did not produce antidepressant response in a controlled study in major depressive disorder (MDD)
	dextromethorphan–quinidine (<i>Nuedexta</i>)	FDA approved to treat pseudobulbar affect
	lanicemine (AZD6765)	Phase II positive results in resistant MDD
GluN2B-specific NMDA receptor antagonists	traxoprodil (CP-101,606)	Despite promising preliminary findings, development was halted due to potential cardiovascular toxicity
	eliprodil	Undergoing phase II studies for MDD
	MK-0657	Concluded a phase II study for MDD
	rapastinel (GLYX-13)	Starting phase III for treatment-resistant MDD
Glycine receptor antagonist	AV-101	Starting phase IB trials
Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) agonists	Org 26576	Development halted after failed phase II in MDD
	basimglurant (RG-7090)	Undergoing phase II trials for treatment-resistant
mGluR5/NMDA antagonist	acamprosate (<i>Campral</i>)	Initial studies in MDD
Glucocorticoid receptor antagonist	mifepristone (<i>Korlym</i> , <i>Mifeprex</i>)	Disappointing clinical results
NK1 receptor antagonist	aprepitant (MK869)	Positive results from pilot studies were not replicated in follow-up phase II studies, and development was halted
Partial mu opioid and kappa opioid receptor antagonist	buprenorphine–samidorphan	Currently in phase III trials as an add-on therapy for treatment-resistant MDD
Selective MT1 and MT2 receptor agonist	ramelteon (<i>Rozerem</i>)	FDA approved to treat insomnia; reduced relapse rates when used as an adjunct to mood stabilizers in patients with bipolar disorder and sleep disturbances
MT1 and MT2 receptor agonist and 5-HT(2C) receptor antagonist	agomelatine	Results of randomized controlled trials suggest it may be an effective and safe antidepressant
Anticholinergic	scopolamine	Data from early trials showing rapid antidepressant effects have not been replicated by independent laboratories or in studies with inpatients using active placebo
Corticotropin releasing factor receptor antagonists	CP-316,311; NBI-30775/R121919	Initial positive result from a pilot study of NBI-30775/R121919 were not subsequently replicated in a phase II controlled trial of CP-316,311

Machado-Vieira R, Henter I, Zarate Jr C: New targets for rapid antidepressant action. *Progress in Neurobiology* 2016; doi 10.1016/j.pneurobio.2015.12.001. From the NIMH. **Funded by NIMH; and other sources. One study author disclosed a potential conflict of interest; the remaining 2 authors declared no conflicts of interest.**

Suicide Risk with Zolpidem

Zolpidem (*Ambien*) was associated with a 2-fold elevation in risk of suicidal behavior in patients with or without a psychiatric diagnosis, according to results of a population-based case-control study.

Background: Some evidence suggests zolpidem and other modern hypnotics may exacerbate existing depression. The FDA has warned that patients with depression who take zolpidem may develop suicidal tendencies and may be prone to intentional overdose. Patients with no known mood disorder have also committed suicide after taking zolpidem.

Methods: Claims data were analyzed from a sample of 1 million patients covered by national health insurance in Taiwan. Cases (n=2199; mean age, 43 years; 55% women) were patients who had completed suicides or who had been hospitalized because of a suicide attempt between 2002 and 2011. Each case was matched for age, gender, urbanization of residence, and general occupational category with 10 controls who had no history of a suicide attempt. Zolpidem exposure before the date of a suicide attempt was the major risk factor of interest. Psychiatric comorbidity was examined as a covariate and included the major categories of schizophrenia; major depressive disorder; bipolar disorder; anxiety; substance use disorders; and other mental disorders.

Results: Significantly more cases than controls had received treatment with zolpidem—45% versus 13%. The risk calculation was adjusted for mental-health disorders, benzodiazepine and antidepressant use, insomnia, substance use, and medical comorbidity. The adjusted odds ratio* for a suicide attempt in zolpidem users was 2.08. Cumulative exposure to zolpidem was associated with greater risk, with an odds ratio of 2.81 in patients with ≥ 180 cumulative defined daily doses ($p < 0.001$ for trend). Suicide risk was increased with zolpidem use in all age groups, but especially in those aged < 25 years (odds ratio, 13.01). Risk was increased by a similar magnitude regardless of use or nonuse of antidepressants or benzodiazepines. Psychiatric and medical comorbidities did not appear to affect risk.

There were a total of 208 completed suicides in the study. After adjusting for multiple factors, zolpidem was associated with an odds ratio of 1.45 for death from suicide. Nearly 60% of suicide attempts were by poisoning, some likely involving zolpidem overdose.

Discussion: While these results demonstrate a significant association between zolpidem use and suicide, the causality of the association is unclear. Zolpidem is likely to be abused and is associated with a high risk of dependency and withdrawal syndromes when used long term. In addition, zolpidem has been associated with unconscious complex behavior in some patients. These sleep-related behaviors include bizarre actions that can lead to potentially dangerous self-harm and fatality, and they should receive more attention and be considered a contributing factor to the high risk of suicide behavior and death associated with zolpidem use.

Sun Y, Lin C-C, Lu C-J, Hsu C-Y, et al: Association between zolpidem and suicide: a nationwide population-based case-control study. *Mayo Clinic Proceedings* 2016;91 (March):308–315. From En Chu Kong Hospital, New Taipei, Taiwan; and other institutions. **Funded by the Taiwan Ministry of Health and Welfare; and other sources. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Flibanserin: Benefits/Risks Reviewed

Despite its recent approval for treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women, flibanserin has minimal clinical benefits, potentially serious risks, and very low quality evidence supporting its efficacy and safety, according to a meta-analysis of published and unpublished clinical trials.¹

Methods: A comprehensive literature search identified all clinical trials of flibanserin, published or unpublished, and in any language, that were conducted in women of any age. Eight randomized, double-blind, placebo-controlled trials comprising nearly 6000 women were identified and included in the meta-analysis; 3 of the studies were unpublished. All participants met DSM-IV criteria for HSDD. Trials were conducted in the U.S., Canada, or Europe and included premenopausal women (6 studies) and postmenopausal women (2 studies). All studies used the number of satisfactory sexual events per month as a primary efficacy outcome.

Results: At baseline, participants had a mean of 2.5 satisfactory sexual events per month. Relative to placebo, flibanserin was associated with an average increase of 0.49 events per month. Average subjective ratings of improvement ranged from minimal to no change.

Several adverse effects had a higher incidence (1.6- to 4-fold) with flibanserin than placebo: dizziness, somnolence, nausea, and fatigue. Serious adverse events, including appendicitis, cholelithiasis, and concussion, were reported in 2 of the studies, in small percentages of patients. Concomitant use of flibanserin with alcohol or CYP3A4 inhibitors, such as fluconazole and oral contraceptives, can worsen adverse effects.

The quality of evidence for both efficacy and safety of flibanserin was rated as very low. Study publications were light on details; dropout rates were high; participants were not representative of all women who might be given the drug; efficacy endpoints changed during studies; and there was evidence of publication bias.

Editorial.² Flibanserin was presented for FDA review twice before receiving approval the third time. This occurred despite a lack of new efficacy data and a vote against approval by the FDA's regulatory clinical reviewers, which occurred in part because of evidence on flibanserin-related harms that was presented during the FDA hearings. In addition, substantial somnolence and dangerous hypotension due to interactions with alcohol and other drugs have been reported. A single study indicated little risk of impaired driving due to somnolence but identified additional risks of hypotension in poor metabolizers.

Discussion: Women with a wide range of concomitant diseases and medication use, as well as those not in a stable relationship, were excluded from participation in the flibanserin trials, potentially limiting the generalizability of the findings. In addition, it is unclear to what extent they represent typical women with HSDD, given that they reported an average of 2.5 satisfying sexual events per month. Because patient selection for the conducted trials may not have been representative of the population for whom the drug was approved, uncertainties remain about flibanserin, which provides minimal improvement and substantial adverse-effect risk, in a real world setting.

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

¹Jaspers L, Feys F, Bramer W, Franco O, et al: Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: a systematic review and meta-analysis. *JAMA Internal Medicine* 2016; doi 10.1001/jamainternmed.2015.8565. From Erasmus University Medical Center, Rotterdam, the Netherlands; and other institutions. **Source of funding not stated. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.** See related stories in *Psychiatry Drug Alerts* 2015;29 (September):69 and 2016;30 (February):13–14.

²Woloshin S, Schwartz L: US Food and Drug Administration approval of flibanserin: even the score does not add up [editorial]. *JAMA Internal Medicine* 2016; doi 10.1001/jamainternmed.2016.0073. From the Dartmouth Institute for Health Policy and Clinical Practice and Dartmouth-Hitchcock Medical Center, Lebanon NH. **Both study authors disclosed financial relationships with commercial sources.**

Common Drug Trade Names: flibanserin—*Addyi*; fluconazole—*Diflucan*

*See Reference Guide.

Reference Guide

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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Aripiprazole-Associated Impulse Control

Pathological gambling is a noted adverse effect in the current drug labeling for aripiprazole (*Abilify*). However, the FDA has identified additional compulsive behaviors—e.g., eating, shopping, and sexual activity—associated with the drug. While these impulse-control problems appear to be rare and resolve with dosage reduction or discontinuation, they can present risk of serious harm to the patient or others. As a result, the FDA has issued a warning regarding these compulsive or uncontrollable urges and recommends close monitoring particularly in patients with a personal or family history of obsessive-compulsive disorder; impulse-control disorder; bipolar disorder; impulsive personality; alcoholism; drug abuse; or other addictive behaviors, all of whom are at higher risk for impulse-control problems.

FDA MedWatch Alert: Aripiprazole (*Abilify*, *Abilify Maintena*, *Aristada*): Drug safety communication—FDA warns about new impulse-control problems. Available at <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm498823.htm>.

Riluzole Augmentation for OCD

In a randomized trial of patients with moderate-to-severe obsessive-compulsive disorder, the combination of riluzole and fluvoxamine was superior to fluvoxamine monotherapy.

Background: Serotonergic agents are first-line therapy for OCD, but other neurotransmitters may also be involved, particularly in patients with resistant or refractory symptoms. Disruption of glutamatergic transmission has been reported in patients with OCD. Riluzole may reduce release of glutamate in the brain via multiple presynaptic mechanisms and may also stimulate glutamate uptake by astrocytes. Previous clinical studies of riluzole suggest promise for the drug in OCD but have been limited to small samples of pediatric patients.

Methods: The 10-week trial was conducted in adults, aged 18–60 years, with a DSM-IV-TR diagnosis of moderate-to-severe OCD and a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥ 21 . All psychotropic medications were discontinued 6 weeks prior to the study. Patients received treatment with 100 mg/day fluvoxamine for the first 4 weeks and then 200 mg/day thereafter, plus randomly assigned 50 mg riluzole b.i.d. or placebo. The primary efficacy

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outcome was change from baseline in the Y-BOCS score. Secondary outcomes included partial response ($\geq 25\%$ reduction in Y-BOCS score), complete response ($\geq 35\%$ reduction), and remission (final score ≤ 16).

Results: A total of 54 patients were randomized to treatment, and 50 completed the trial. Patients were in their mid-30s on average and had been ill for a mean of 6–7 years; 70% were women.

Mean baseline Y-BOCS scores were 29 and 28 in the riluzole and placebo groups, respectively. Riluzole was associated with a larger reduction in the Y-BOCS total score than placebo by trial end. Final Y-BOCS scores were 17 in the riluzole group, compared with 20 in the placebo group (effect size;* 0.59; $p=0.04$). Riluzole had a greater effect than placebo on compulsion subscale scores, but not obsession subscale scores. Riluzole was associated with significantly higher rates of complete or partial response (56% vs. 24%; $p=0.042$) and remission (52% vs. 20%; $p=0.038$). However, patients in both groups continued to experience residual symptoms. Adverse events—drowsiness; constipation; dizziness; abdominal pain; appetite changes; nausea; headache; dry mouth; cough; and diarrhea—were similar in the 2 groups, affecting 12–24% of patients. No serious adverse events occurred.

Discussion: These study results appear to indicate that riluzole is an effective adjunct to fluvoxamine in OCD. However, additional research is needed to confirm the findings and to extend them to larger populations.

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

Emanzadehfard S, Kamaloo A, Paydary K, Ahmadipour A, et al: Riluzole in augmentation of fluvoxamine for moderate to severe obsessive compulsive disorder: randomized, double-blind, placebo-controlled study. *Psychiatry and Clinical Neurosciences* 2016; doi 10.1111/pcn.12394. From the Tehran University of Medical Sciences, Iran. Funded by Tehran Medical University. The study authors declared no competing interests.

Common Drug Trade Names: fluvoxamine—*Luvox*; riluzole—*Rilutek*

*See Reference Guide.

C-Reactive Protein and Antipsychotic Drug Elevations

In a retrospective analysis of laboratory data, up to 5-fold increases in serum concentrations of antipsychotic drugs were observed in patients whose C-reactive protein (CRP) levels indicated inflammation or infection.

Background: CRP is an acute-phase inflammatory marker that rises rapidly in response to inflammation or infection and returns rapidly to normal. CRP was the marker of interest because it is the most routinely measured inflammatory marker. The present study was conducted to examine the relationship of pathological CRP values and serum levels of 3 drugs metabolized by different CYP isoforms: clozapine, quetiapine, and risperidone.

Methods: The retrospective study was conducted in 105 psychiatric patients from a single center, who had ≥ 1 normal (< 5 mg/L) and 1 elevated (≥ 5 mg/L) CRP measurement, obtained at the same time as therapeutic drug monitoring of their antipsychotic. There were no eligibility restrictions based on age; gender; psychiatric diagnosis; somatic comorbidity; or body weight. Drug levels were adjusted for dose, and the metabolic ratios of each agent to its main metabolite were determined. Investigators calculated the threshold CRP level above which patients experienced a 100% increase in serum drug levels.

Results: In patients who received clozapine ($n=33$), elevated CRP levels were associated with a 48% increase in serum drug levels ($p<0.01$). In the risperidone group ($n=40$), elevated CRP was associated with a 58% increase in serum drug levels ($p<0.01$). In the quetiapine group, elevated CRP was associated with a nonsignificant 12% increase in drug concentration and the metabolic

ratio was not altered. The threshold CRP level to predict a 100% increase in drug levels was calculated at 25.5 mg/L for clozapine and 37.5 mg/L for risperidone.

Discussion: The study results suggest patients with elevated inflammatory markers may experience up to a 5-fold increase in clozapine or risperidone drug levels, enough to cause toxicity without a dosage increase. Age-related increases in drug sensitivity, as well as increased susceptibility to infection, may make this particularly concerning for elderly patients. Adverse effects of the increased drug concentrations were not evaluated in the present study, limiting the clinical usefulness of the results. However, the authors recommend therapeutic drug monitoring when CRP levels are found to be elevated.

Hefner G, Shams M, Unterecker S, Falter T, et al: Inflammation and psychotropic drugs: the relationship between C-reactive protein and antipsychotic drug levels. *Psychopharmacology* 2016;233 (May):1695–1705. From the University Medical Centre, Mainz, Germany; and other institutions. **The study was conducted without funding. Two study authors disclosed financial relationships with commercial sources; the remaining 3 authors declared no competing interests.**

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

Risperidone vs. Clozapine in Refractory Schizophrenia

In a 29-week, head-to-head comparison with risperidone, clozapine was associated with fewer study withdrawals for lack of efficacy and greater improvement in psychotic symptoms in patients with moderately refractory schizophrenia.

Methods: The study, conducted in 1995–1999, enrolled patients with partial or poor response to ≥ 1 prior first-generation antipsychotic used at an effective dose for ≥ 6 weeks. To maximize generalizability, the investigators recruited 2 groups of patients. One group met conventional, narrow clinical trial exclusion criteria, with none of the following: prior treatment with clozapine or risperidone for ≥ 3 weeks, a history of poor compliance, recent drug or alcohol abuse or dependence, and ongoing treatment with mood stabilizers or antidepressants. The second group had ≥ 1 of the criteria that would have otherwise led to exclusion. Patients received treatment for 29 weeks with randomly assigned clozapine or risperidone, flexibly dosed to targets of 500 mg/day and 6 mg/day, respectively. Doses could be increased to maximums of 800 mg/day clozapine or 16 mg/day risperidone. Primary outcomes were time to discontinuation for lack of efficacy and a $\geq 20\%$ improvement in Brief Psychiatric Rating Scale (BPRS) score.

Results: A total of 107 patients were randomized. Three-fourths were included under the broad criteria. Most patients had previously received risperidone, and about half had tried clozapine. By week 29, about half of patients in both treatment groups had discontinued treatment. The rate of discontinuation for lack of efficacy was higher with risperidone than clozapine (38% vs. 15%, respectively; $p=0.01$). Seven patients (13%) in the clozapine group stopped treatment because of adverse effects.

Rates of improvement in BPRS psychotic symptoms were numerically higher with clozapine using various cutoffs, but differences were not statistically significant. Remission (defined as $\geq 20\%$ improvement in BPRS plus no psychotic symptom rated as more than mild) occurred in 26% of clozapine-treated and 24% of risperidone-treated patients. Scores on the Clinical Global Impression–Improvement (CGI–I) scale were significantly better with clozapine ($p<0.01$), and asociality ratings on the Scale for the Assessment of Negative Symptoms were lower ($p<0.01$). For all BPRS and CGI measures, psychopathology decreased to a significantly greater degree with higher medication doses; these improvements were greater with clozapine than with risperidone.

Discussion: Previous trials comparing clozapine and risperidone did not find differences in efficacy between the drugs; however, treatment durations (4–14 weeks) were substantially

shorter than the present study. Based on these results, the authors suggest that clozapine should not be reserved only for patients with the most severe, refractory schizophrenia, but should be considered in those who have experienced partial responses with other antipsychotics.

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

Editor's Note: Although patients underwent weekly blood draws as part of the treatment protocol, the study report did not include information on the incidence of neutropenia or other blood dyscrasias.

Schooler N, Marder S, Chengappa K, Petrides G, et al: Clozapine and risperidone in moderately refractory schizophrenia: a 6-month randomized double-blind comparison. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.13m08351. From the Zucker Hillside Hospital, Glen Oaks, NY; and other institutions. **Funded by the NIMH. Seven study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

Common Drug Trade Names: clozapine—*Clozaril*; risperidone—*Risperdal*

*See Reference Guide.

Behavioral Adverse Effects of Bipolar-Disorder Drugs

Drug-related behavioral and emotional adverse effects can have important clinical implications. Despite the fact that data indicates many drugs commonly used in bipolar disorder are associated with these effects in patients with other psychiatric diagnoses, little-to-no information is available on their prevalence in bipolar disorder.

Methods: A systematic literature review was undertaken to identify published studies or descriptions of behavioral adverse events in neuropsychiatric patients and healthy control subjects. Medications were limited to those used to treat bipolar disorder according to current guidelines (e.g., SSRIs, antipsychotics, anticonvulsants). The review included both English- and Spanish-language articles published before September 2015, as well as unpublished material. The review excluded neurocognitive, motor, and autonomic adverse effects; effects on vigilance and appetite; switches to mania; and impulsivity.

Results: Four types of behavioral adverse effects of SSRIs—apathy/emotional blunting, inability to cry, sexual dysfunction, and decision-making modifications—were identified in the literature, both in patients with neuropsychiatric disorders and in healthy comparison subjects. Emotional blunting and apathy have been reported in patients with unipolar major depressive disorder and may be independent of the therapeutic effect of these drugs. Research in subjects with depression and in healthy volunteers suggests apathy may be the result of alterations in emotional processing interfering with the recognition of basic emotions such as happiness; sadness; fear; disgust; and surprise. Case reports suggest SSRIs are also associated with inability to cry in situations that would ordinarily bring forth tears—even in patients without apathy. SSRIs are well known to diminish sexual desire, perhaps as a consequence of emotional blunting due to impaired dopaminergic neurotransmission. There have been sparse reports that SSRIs may cause changes or difficulties in decision making. The literature search uncovered no study of any of the aforementioned effects in patients with bipolar disorders.

Antipsychotics are associated with 3 types of behavioral side effects: neuroleptic-induced deficit syndrome/emotional detachment; obsessive-compulsive symptomatology; and decision-making modifications. A syndrome of dysphoria-apathy-apragmatism and loss of creativity, called "neuroleptic dysphoria" among other terms, has been described in healthy volunteers and extensively studied in patients with schizophrenia. The syndrome has also been self-reported by patients with bipolar disorder. Several studies in schizophrenia suggested a causal and dose-related relationship between second-generation antipsychotics and obsessive-compulsive symptoms. Only case reports support the association in patients with bipolar disorder. No clinical studies that evaluated this effect in bipolar disorder were found.

Decision-making modification has been reported in patients with schizophrenia, but whether it is related to the medications or the illness is unclear, and no data were found regarding the issue in patients with bipolar disorder.

Lithium has been associated with an amotivational syndrome in several studies of euthymic patients with bipolar disorder, but whether as an adverse effect or a consequence of mood stabilization is controversial. Lamotrigine has been associated with emergence of tic disorders and obsessive-compulsive disorder in bipolar disorder. There is no information on behavioral effects of valproic acid in patients with bipolar disorder.

Discussion: Although bipolar disorder is more prevalent than schizophrenia and treated with a wider variety of drugs, the issue of behavioral and emotional side effects has been neglected in this patient population. The lack of information on many of these effects extends to patients with major depressive disorder. According to the authors, there are no reasons to expect these effects would not also develop in patients with bipolar disorder, and there is an urgent need to measure these effects so they can be considered in prescribing decisions. Patients taking these medications should also be made aware of potential behavioral adverse effects, which may otherwise go unnoticed and may contribute to biased or distorted judgement.

Szmulewicz A, Samame C, Caravotta P, Martino D, et al: Behavioral and emotional adverse events of drugs frequently used in the treatment of bipolar disorders: clinical and theoretical implications. *International Journal of Bipolar Disorder* 2016; doi 10.1186/s40345-016-0047-3. From Favaloro University, Buenos Aires, Argentina; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

Common Drug Trade Names: lamotrigine—*Lamictal*; valproic acid—*Depakene, Depakote*

Opioids and Depression Risk

Patients taking long-term opioid analgesics are at increased risk of new-onset depression, according to an analysis of 3 large databases.

Background: Depression often co-occurs with chronic non-cancer pain and is known to be associated with opioid use and possibly with opioid resistance and misuse. The present study was undertaken to extend the generalizability of the association between opioid use and depression previously demonstrated by these investigators in veterans and to evaluate the contributions of duration of use and dosage.

Methods: The investigators analyzed electronic medical records data from the Veterans Health Administration (VHA) and from 2 large regional health systems in Texas (Baylor Scott & White Health [BSWH]) and Michigan (Henry Ford Health System [HFHS]). The analysis included adult patients with no opioid use and no diagnosis of depression prior to the start of follow-up, who were given a prescription for an opioid during follow-up, and who did not have cancer or HIV. Patients were followed until the onset of depression or the end of study—2002–2012 for the VHA and 2005–2012 for the private health systems. New-onset depression was defined as ≥ 2 outpatient diagnoses within a 12-month period or a single inpatient diagnosis. The opioid exposure categories were 1–30 days, 31–90 days, and >90 days. Opioid dosages were converted to morphine equivalents.

Results: The sample consisted of about 71,000 veterans and nearly 37,000 patients from the 2 private health systems. Minorities of each sample received opioid analgesics for >30 days (7–22%). In each of the 3 samples, rates of depression increased with longer duration of opioid use. (See table, next page.) Because bias by indication could affect the association between opioid use and new-onset depression, hazard ratios* were calculated based on propensity scores* weighted for a large number of covariates including pain scores and the presence of 5 common painful conditions: arthritis; back pain; headache; musculoskeletal pain; and neuropathy; as well as medical and psychiatric diagnoses. Based on the VHA data, which is the

most complete in terms of covariates, depression can be expected to develop in 1 in 12 patients receiving opioid medication for >90 days. Incidence of depression was not associated with opioid dosage.

Association between duration of opioid use and new-onset depression during follow-up			
Exposure Duration	% of Patients	Depression Onset	Hazard Ratio (fully weighted)
VHA patients			
1–30 days	78%	11.6%	—
31–90 days	12%	13.6%	1.18
>90 days	10%	14.4%	1.35
BSWH patients			
1–30 days	93%	8.4%	—
31–90 days	6%	10.6%	1.29
>90 days	1%	19%	1.88
HFHS patients			
1–30 days	89%	10.7%	—
31–90 days	7%	14.8%	1.33
>90 days	4%	19.3%	2.05

Post-hoc analysis of the VHA sample indicated that for the vast majority of patients (93%), new-onset depression developed after the end of the incident opioid use. The mean lag time between stopping opioids and depression onset was 3.4 years.

Discussion: The study authors suggest that long-term opioid use may lead to hyperalgesia and subsequently to depression. It is also possible that consequences of chronic opioid analgesic use, such as low testosterone and opioid misuse, could be involved in new-onset depression.

Scherrer J, Salas J, Copeland L, Stock E, et al: Prescription opioid duration, dose, and increased risk of depression in 3 large patient populations. *Annals of Family Medicine* 2016;14 (January/February):54–62. From St. Louis University School of Medicine, MO; and other institutions. **Funded by the NIMH; and the VHA. The authors declared no competing interests.**

*See Reference Guide.

Longer-Acting Depot Paliperidone for Schizophrenia

A new 3-month injectable formulation of paliperidone had efficacy and tolerability similar to the 1-month formulation in a randomized noninferiority trial. No new safety concerns emerged with the longer-acting formulation, which recently received FDA approval for maintenance treatment of schizophrenia.

Methods: Study subjects, aged 18–70 years, met DSM-IV criteria for schizophrenia, had baseline Positive and Negative Syndrome Scale (PANSS) scores between 70 and 120, and were experiencing a worsening of pre-existing symptoms. Except for stable antidepressants, all previous psychotropic medications were discontinued, and patients were stabilized with open-label, once-a-month paliperidone (PP1M). Previous medications reflected those commonly used in the 26 participating countries: mostly second-generation antipsychotics, with first-generation agents in 23% of patients. After 17 weeks of open-label treatment, those who were clinically stable and met improvement criteria were randomly assigned to continue taking PP1M or to switch to the 3-month formulation (PP3M), with a placebo injection in months when they did not receive active medication. The primary efficacy outcome was the percentage of patients who remained relapse-free after 48 weeks. Relapse was defined as hospitalization for schizophrenia symptoms, a $\geq 25\%$ increase in PANSS score, an increase in selected PANSS items, or deliberate self-injury, violent behavior, and/or suicidal or homicidal ideation with aggressive behavior. Remission was defined as simultaneous ratings of mild or less on all selected PANSS items.

Results: Of 1429 patients who received open-label paliperidone, 8% did not benefit from the medication and 8% withdrew consent; 1016 (71%) went on to randomized treatment, and 995 were included in the efficacy analysis. A total of 83% of patients completed the study, including those who relapsed.

The new paliperidone formulation met statistical criteria for noninferiority to PP1M. Relapse rates were 8% with PP3M and 9% with PP1M. Secondary efficacy outcomes were also equivalent with the 2 formulations. About half of patients experienced a $\geq 20\%$ improvement in PANSS total score in the double-blind phase, beyond improvements that occurred during open-label treatment. Nearly 60% of patients in both groups achieved remission.

Pharmacokinetic exposures (e.g., peak and trough plasma concentrations) did not differ between the 2 formulations. Weight gain was the most frequent adverse event and increases averaged 5–7 lbs. in each group.

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

Savitz A, Xu H, Gopal S, Nuamah I, 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. From Janssen Research & Development, LLC, Raritan, NJ; and the Medical University, Innsbruck, Austria. **Funded by Janssen Research & Development. All study authors disclosed financial relationships with commercial sources including Janssen Research and Development.**

Common Drug Trade Names: paliperidone, extended-release, 1-month—*Invega Sustenna*; paliperidone, extended-release, 3-month—*Invega Trinza*

*See Reference Guide.

Vortioxetine: Brand Name Change

Prescribing and dispensing errors have been reported due to confusion of the brand names for the SSRI vortioxetine (*Brintellix*) and the antiplatelet agent ticagrelor (*Brilinta*). As a result, the FDA has approved a brand name change for vortioxetine, which will now be sold as *Trintellix*. No other changes will be made to the label or packaging or to the drug itself.

FDA MedWatch Alert: Brintellix (vortioxetine): Drug safety communication—brand name change to Trintellix, to avoid confusion with antiplatelet drug Brilinta (ticagrelor). Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm498607.htm>.

Escitalopram in Body Dysmorphic Disorder

In a randomized, placebo-controlled withdrawal trial, treatment with escitalopram (*Lexapro*) produced acute response in the majority of patients with body dysmorphic disorder. Continuation therapy prevented relapse over 6 months.

Background: SRIs are often prescribed to treat body dysmorphic disorder, but there have been few controlled studies of this or any other type of medication as acute treatment and no studies of continuation therapy.

Methods: Study participants were 100 adults who met DSM-IV criteria for body dysmorphic disorder of at least moderate severity for ≥ 6 months. Patients were excluded if their body-image concerns were accounted for primarily by an eating disorder or if weight concerns were predominant. In study phase 1, all patients received open-label escitalopram, with a target dosage of 30 mg/day, for 14 weeks. Treatment responders—those with a $\geq 30\%$ decrease in Yale-Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS) at the end of acute treatment—were eligible to enter phase 2, in which subjects were randomly assigned to continue taking escitalopram for an additional 6 months or to a taper to placebo. Relapse, the primary study endpoint, was defined as a $\geq 50\%$ loss of improvement from baseline in BDD-YBOCS score, a BDD-YBOCS score of >20 (indicating full-criteria body dysmorphic

disorder), and a rating of "much worse" or "very much worse" on the Clinical Global Impression (CGI) scale for body dysmorphic disorder. The 7-point Psychiatric Status Rating Scale (PSRS) for Body Dysmorphic Disorder was used throughout the study to evaluate whether patients met diagnostic criteria for the disorder or were in full or partial remission.

Results: Of the 100 enrolled study patients, 74 completed phase-1 treatment (1 patient withdrew because of increased suicidal ideation, and 4 discontinued because of adverse effects), 60 patients met response criteria, and 19 achieved full remission (PSRS score of 1 or 2). Mean BDD-YBOCs scores decreased from 33 at baseline to 17 at the last phase-1 visit, and patients' scores on the Hamilton Rating Scale for Depression and measures of beliefs, function, and quality of life all improved significantly. A total of 65 patients were much or very much improved according to CGI global improvement ratings. Response to treatment did not differ between patients with delusional or non-delusional body dysmorphic disorder.

A total of 58 patients were randomly assigned to continuation with escitalopram or placebo. By the end of treatment phase 2, relapse had occurred in 18% of the escitalopram group and 40% of the placebo group. Time to relapse was significantly longer in the escitalopram group (hazard ratio,* 2.72; p=0.049). Among the 28 patients who continued escitalopram in phase 2, average BDD-YBOCS scores decreased by an additional 4 points and 10 patients showed a further decrease in the PSRS score.

Discussion: These results indicate that escitalopram is effective in body dysmorphic disorder and that continuing treatment after response can prevent relapse. In this study, mean escitalopram dosages were 26.2 mg/day at the end of acute treatment and 28.7 mg/day at conclusion of the continuation phase. Results of this and other studies suggest that relatively high doses of SRIs (similar to those recommended in OCD) may be needed to treat body dysmorphic disorder.

Phillips K, Keshaviah A, Dougherty D, Stout R, et al: Pharmacotherapy relapse prevention in body dysmorphic disorder: a double-blind, placebo-controlled trial. *American Journal of Psychiatry* 2016; doi 10.1176/appi.ajp.2016.15091243. From Rhode Island Hospital, Providence; and other institutions. **Funded by the NIMH. Four study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

Propensity Score Matching: Selection bias can be problematic when using observational data, making causal relationships difficult to establish. Propensity score matching is 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.

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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Olanzapine-Associated DRESS

The FDA has issued a warning regarding the potential for olanzapine (*Zyprexa*), and other agents that contain the drug, to cause drug reaction with eosinophilia and systemic symptoms (DRESS). This rare but serious and potentially fatal skin reaction may begin as a rash that can spread to all parts of the body. The rash is accompanied by an elevated eosinophil level. Other symptoms may include fever, swollen lymph nodes, and other inflammation. DRESS can result in damage to the heart, liver, lungs, kidneys, and pancreas. Patients who experience these symptoms while taking olanzapine should seek medical attention at once. There is no specific treatment for DRESS. If suspected in patients taking olanzapine, the medication should be stopped immediately and supportive care should be administered. Systemic corticosteroids can be considered in cases with extensive organ involvement.

This warning is a result of an FDA review of 23 cases of DRESS associated with olanzapine that were reported to the FDA Adverse Event Reporting System since 1996. The FDA will now require manufacturers to add a warning about DRESS to the prescribing information for olanzapine-containing products.

FDA MedWatch Alert: Olanzapine: Drug Safety Communication - FDA Warns About Rare But Serious Skin Reactions. Available at <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm500123.htm>.

Unintended Consequence of Citalopram Risk Mitigation

According to a retrospective study, dosage reductions due to the lowered safety limit for citalopram (*Celexa*) were associated with a significantly increased rate of hospitalization for depression and self-injury in U.S. Department of Veterans Affairs (VA) patients. Hospitalizations for cardiac arrhythmias, the hazard that the dose reduction was intended to avoid, were unaffected.

Background: In 2011, the FDA issued a safety communication that daily citalopram doses should not exceed 40 mg because of increased risk of QT-interval prolongation. Given the low

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incidence of this adverse effect and the frequent clinical use of high citalopram dosages for difficult-to-treat mental-health problems, the present study was conducted to determine whether the cardiac benefits of the warning outweighed the consequences of worsening depression.

Methods: Investigators analyzed electronic medical records from the VA's nationwide database. The analysis included nearly 36,000 patients (mean age, 58 years; 92% men) who were taking citalopram at dosages of >40 mg/day in the 3 weeks before the FDA warning was issued. Citalopram prescriptions filled for up to 1 year after the FDA warning were examined, and outcomes were compared between patients with a dosage reduction and those who continued on high-dose therapy. The primary study outcome was time to first all-cause hospitalization or death. The study also used 2 composite secondary endpoints: all-cause death or hospitalization with a principal diagnosis of depression or self-inflicted injury, and all-cause death or hospitalization with arrhythmias, cardiac arrest, syncope, or sudden cardiac death. Results were analyzed with a multivariable regression that included 109 baseline variables.

Results: Of the nearly 36,000 patients, 18,407 underwent citalopram dosage reduction to <40 mg/day following the warning. In a multivariate, propensity-score* matched analysis, the hazard ratio* for all-cause hospitalization or death in patients who had a dosage reduction was 4.1 ($p < 0.001$). This difference was driven entirely by a higher risk of hospitalizations, rather than deaths. The adjusted hazard ratio for the composite outcome of depression hospitalization, self-injury, or death was 2.0 in patients who underwent dosage reduction ($p < 0.001$). However, the hazard ratio for the arrhythmia-related secondary outcome (1.2) was not significantly lower in the patients who received a dosage reduction.

Discussion: Although citalopram can prolong the QT interval in a dose-dependent manner, the risk of ensuing death or hospitalization may have been too low to detect even in this large cohort of patients who had survived previous treatment with high-dose citalopram. Prior to the FDA warning, citalopram dosages >40 mg/day were frequently used for presumably difficult-to-treat cases. Given the seemingly low incidence of QT-related fatalities with citalopram dosages >40 mg/day, the unintended increases in self-injury and hospitalization due to worsening depression could offset the intended benefits of limiting citalopram dosage levels.

Rector T, Adabag S, Cunningham F, Nelson D, et al: Outcomes of citalopram dosage risk mitigation in a veteran population. *American Journal of Psychiatry* 2016; doi 10.1176/appi.ajp.2016.15111444. From the Minneapolis VA Health Care System, MN; and other institutions. **Funded by the VA. The authors declared no competing interests.**

*See Reference Guide.

Pimavanserin Approval

Following a priority review, the FDA has approved the atypical antipsychotic pimavanserin to treat hallucinations and delusions associated with psychosis in patients with Parkinson's disease.¹ Pimavanserin is the first agent granted approval for this indication, which has commonly been treated with off-label clozapine or quetiapine.² In a clinical trial, pimavanserin decreased frequency and severity of hallucinations and delusions in patients with Parkinson's disease without worsening motor symptoms.³ Common adverse effects in the trial included peripheral edema, nausea, and confusion. The agent will carry the same boxed warning as other atypicals regarding increased risk of death in elderly patients treated for dementia-related psychosis.

¹FDA news release (April 29, 2016): FDA approves first drug to treat hallucinations and delusions associated with Parkinson's disease. Available at <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm498442.htm>.

²Facts and Comparisons eAnswers: <http://online.factsandcomparisons.com>.

³Cummings J, et al: Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet* 2014;383 (February 8):533–540. See *Psychiatry Drug Alerts* 2014;28 (April):30–31.

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

Suicidal Behavior with Quinolones

Quinolone antibiotics were associated with suicidal behavior in a pharmacovigilance study of worldwide adverse-event reports.

Background: The reporting of several cases has raised concerns that exposure to quinolones may be associated with suicidal behavior. To investigate further, the present study examined data from the World Health Organization's VigiBase database, which collects spontaneous adverse event reports from health-care professionals, pharmaceutical companies, and patients in 110 countries.

Methods: All adverse event reports involving antibiotic exposure between December 1970 and January 2015 were included in the analysis. Odds ratios* for suicidal behavior were compared between quinolone users and users of other antibiotics. The 4 most frequently prescribed quinolones—ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin—were also analyzed separately. Results were adjusted for age and gender.

Results: Among nearly 1 million antibiotic-associated adverse events, there were 1627 reports of suicidal behavior. In quinolone users, 608 instances of suicidal behavior were reported, including 97 completed suicides. The majority of cases (93%) were reported after 2000, and most occurred in the U.S. and Europe (61% and 37%, respectively). Compared with other antibiotics, quinolones were associated with a higher risk of suicidal behavior (adjusted odds ratio, 2.78). Risks were significantly elevated for each of the 4 most commonly prescribed quinolones, with adjusted odds ratios ranging from 2.84 for moxifloxacin to 4.01 for ciprofloxacin. Compared with other antibiotics, quinolone exposure was also associated with higher rates of depression (odds ratio, 4.15) and completed suicide (odds ratio, 1.56).

Quinolone-related suicidal adverse events were equally distributed across gender. The mean age of patients with suicidal behavior was 40 years, and half of cases occurred in patients aged 45–64 years. In patients aged <17 years, risk of suicidal behavior was slightly elevated and risk of completed suicide was significantly elevated (odds ratio, 8.96).

Discussion: It is unclear whether suicidal behavior is an independent adverse effect or secondary to these drugs' potential psychiatric effects. Quinolones inhibit GABA-mediated inhibitory neurotransmission, possibly leading to anxiety; and they cause neuroexcitation, perhaps by activating NMDA receptors. Some quinolones have been shown to decrease serotonin levels in the brain and induce oxidative stress. These drugs may also alter expression of microRNAs, which may be linked to depression.

Samyde J, Petit P, Hillaire-Buys D, Faillie J-L: Quinolone antibiotics and suicidal behavior: analysis of the World Health Organization's adverse drug reactions database and discussion of potential mechanisms. *Psychopharmacology* 2016; doi 10.1007/s00213-016-4300-3. From CHU Montpellier University Hospital and the University of Montpellier, France. This study was conducted without funding. The authors declared no competing interests.

Common Drug Trade Names: ciprofloxacin—*Cipro*; levofloxacin—*Levaquin*; moxifloxacin—*Avelox*; ofloxacin—*Floxin*

*See Reference Guide.

New Longer-Acting Risperidone

In a randomized controlled trial, a new once-monthly injectable risperidone was significantly superior to placebo in patients with acute schizophrenia.

Background: Currently available long-acting risperidone requires twice monthly intramuscular injection. Sustained-release RBP-7000 uses the ATRIGEL delivery system, which is a sterile, polymeric solution of a biodegradable poly(DL-lactide-co-glycolide), or poly-L-lactic acid

copolymer, dissolved in a biocompatible solvent. The risperidone in RBP-7000 is both dissolved and suspended in the ATRIGEL polymeric solution. Following subcutaneous injection, the solution solidifies, creating a biodegradable implant that delivers risperidone for 28 days.

Methods: Study subjects were 354 adults, aged 18–55 years (77% men), who had been experiencing an acute exacerbation of schizophrenia for ≤8 weeks and had a Positive and Negative Syndrome Scale (PANSS) total score of 80–120. Subjects with a history of clozapine treatment for resistant schizophrenia were excluded. Eligible subjects were admitted to an inpatient unit, and any current oral antipsychotics were tapered. Following a low-dose challenge of oral risperidone to determine tolerability, patients were randomized to receive subcutaneous injections of RBP-7000 at either 90 or 120 mg or placebo on days 1 and 29. Concomitant lorazepam for anxiety/agitation was permitted for the first 2 weeks and then tapered. Propranolol was administered if extrapyramidal symptoms developed. Efficacy was assessed periodically beginning after the first injection and up to day 57 using the PANSS and the Clinical Global Impression–Severity (CGI-S) Scale* in the intent-to-treat population, which comprised 337 patients who received ≥1 injection of assigned medication.

Results: A total of 337 patients completed the study, with similar proportions of withdrawals in all groups. Withdrawal of consent was the most frequent reason for study dropout. Adverse effects were the reason for withdrawal in few patients (1.4%).

Both RBP-7000 doses were significantly superior to placebo at reducing PANSS total scores (see table) at all time points. Differences were evident beginning at day 15. Both RBP-7000 doses produced significant improvements in PANSS positive symptom and general psychopathology scores, but only the 120-mg dose improved negative symptom scores. CGI-S scores were also significantly reduced with both active medication doses, compared with placebo.

Efficacy Measures for RBP-7000 vs. Placebo			
	Baseline	Endpoint	Significance vs. Placebo
PANSS Total Scores			
Placebo	94.1	84.9	—
90 mg RBP-7000	95.5	80.1	p=0.0004
120 mg RBP-7000	94.9	78.4	p<0.0001
PANSS Positive Symptom Scores			
Placebo	25.4	22.6	—
90 mg RBP-7000	26	21.2	p=0.0003
120 mg RBP-7000	25.9	20.8	p<0.0001
PANSS Negative Symptoms Scores			
Placebo	22.6	20.4	—
90 mg RBP-7000	23.5	20.7	p=ns
120 mg RBP-7000	22.6	19.4	p=0.03
CGI-S Scores			
Placebo	4.8	4.3	—
90 mg RBP-7000	4.8	3.9	p=0.0002
120 mg RBP-7000	4.8	3.9	p<0.0001

Nearly 70% of study subjects reported ≥ 1 adverse event. The most common were headache (24% for placebo vs. 15% and 17% for 90 and 120 mg RBP-7000, respectively); injection-site pain (20% for placebo vs. 16% and 22% in the RBP-7000 groups, respectively); and weight gain (3.4% for placebo vs. 13.0% for each RBP-7000 group). There were no treatment-related serious adverse effects. Rates of extrapyramidal symptoms were low (9–11%), and there were no significant differences across groups. There were no clinically relevant changes in metabolic measures or ECG parameters in any group. Prolactin levels were increased with active treatment.

Discussion: The magnitude of improvement with RBP-7000 in this study is similar to that previously demonstrated with long-acting (twice-monthly) risperidone. In addition, tolerability appears to be similar. These results suggest RBP-7000 may be a viable option for long-acting treatment of schizophrenia, with the added benefit of fewer injections compared with currently available formulations. Additional study is needed to replicate these results in broader patient samples.

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

Nasser A, Henderson D, Fava M, Fudala P, et al: Efficacy, safety, and tolerability of RBP-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. *Journal of Clinical Psychopharmacology* 2016;36 (April):130–140. From Indivior Inc., Richmond VA; and other institutions. **Funded by Indivior Inc. All 7 study authors disclosed financial relationships with commercial sources including Indivior.**

Common Drug Trade Names: clozapine—*Clozaril*; lorazepam—*Ativan*; propranolol—*Inderal*; risperidone—*Risperdal*; risperidone, long-acting (twice-monthly) injectable—*Risperdal Consta*

*See Reference Guide.

Longer-Acting Risperidone and Quality of Life

In a safety and efficacy trial, a new subcutaneous once-monthly injectable risperidone formulation, RBP-7000, was associated with greater improvement than placebo in some measures of health-related quality of life (HRQoL).

Methods: Patient-reported outcomes were analyzed from a conventional phase-III trial comparing RBP-7000, 90 or 120 mg once monthly, with placebo. (See previous article for details.) Study participants with acute exacerbations of schizophrenia were admitted for the duration of the study, and all antipsychotic medications were withdrawn. Patients then received monthly injections of study medication for 2 months. Patient-reported outcome measures, used at baseline and upon study completion, included: The EuroQol-5D-5L, a measure of HRQoL with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression); the Visual Analogue Scale (VAS) of self-rated health (scale from 0 to 100); the Subjective Well-being under Neuroleptic Treatment Scale—short version (SWN-S), a 20-item instrument with 5 subscales (mental functioning, self-control, emotional regulation, physical functioning, and social integration); the Medication Satisfaction Questionnaire, consisting of a single item scored from 1 to 7; and the Preference of Medicine Questionnaire, rating preference for the present antipsychotic compared with the most recent pre-study agent.

Results: The 120-mg dose of RBP-7000 was associated with greater improvement than placebo in the VAS of self-rated health ($p=0.02$). Patients receiving the higher dose also had significantly greater improvement than the placebo group in SWN-S physical functioning, social integration, and total score. Improvements with the 90-mg dose were larger than with placebo but did not reach statistical significance. At screening, about one-third of patients were satisfied with their medication. At study end, 73% of patients taking the higher dose and 74% taking the lower dose were satisfied with their medication, compared with 51% of the placebo group ($p=0.0009$ and $p=0.0006$, respectively). Significantly more patients in the RBP-7000 groups than the placebo group reported they preferred the study medication to the previous treatment (54% vs 22%).

Discussion: Studying patients in an institutional setting may have limited the ability to perceive changes in HRQoL. Complete evaluation of HRQoL requires long-term exposure to normal daily activities, and improvements in an outpatient population could be greater.

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

Isitt J, Nadipelli V, Kouassi A, Fava M, et al: Health-related quality of life in acute schizophrenia patients treated with RBP-7000 once monthly risperidone: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. *Schizophrenia Research* 2016; doi 10.1016/j.schres.2016.03.020. From Indivior Inc., Richmond, VA; and Massachusetts General Hospital/Harvard Medical School, Boston. **Funded by Indivior Inc. All study authors disclosed financial relationships with commercial sources, including Indivior.**

*See Reference Guide.

Buprenorphine Implant for Opioid Dependence

The FDA had granted approval for the first buprenorphine implant (*Probuphine*) to be used as maintenance treatment for opioid dependence. The implant will provide a low dose of buprenorphine over 6 months and should be used in patients whose treatment is already stable with low-to-moderate oral doses. Potential advantages of this new formulation include improved convenience, as well as the impossibility of lost, forgotten, or stolen doses. *Probuphine* should only be used as part of a treatment program that also includes counseling and psychosocial support.

Probuphine consists of four, 1-inch-long rods that are implanted under the skin on the inside of the upper arm. If continued treatment is needed after 6 months, new implants may be inserted in the opposite arm for 1 additional course of treatment. Common adverse effects reported with *Probuphine* include implant-site pain, itching, and redness, as well as headache, depression; constipation; nausea; vomiting; back pain; toothache; and oropharyngeal pain. *Probuphine* labels will carry a boxed warning about the possibility of implant migration, protrusion, expulsion, and nerve damage resulting from the implant itself or from the removal procedure. Because the implants contain a significant amount of drug that could be expelled or removed, the potential exists for accidental exposure or intentional misuse and abuse. Patients should be seen within 1 week of implantation and not less than monthly thereafter. *Probuphine* must be prescribed and dispensed under a Risk Evaluation and Mitigation Strategies (REMS) program.

FDA News Release: FDA approves first buprenorphine implant for treatment of opioid dependence. Available at <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm503719.htm>.

Symptom-Specific Effects of Sertraline and Duloxetine

In a randomized trial, sertraline and duloxetine had similar overall antidepressant efficacy but differed in their effects on individual depressive symptoms.

Methods: Study participants (n=63; mean age, 41 years; 60% women) met DSM-IV-TR criteria for major depressive disorder and had no other Axis I or II diagnosis. They were randomly assigned to double-blind treatment with flexibly-dosed sertraline or duloxetine for 6 weeks. Duloxetine was started at 20 mg/day and increased in weekly increments to a mean of 55 mg/day (range, 20–60 mg/day). Sertraline was started at 50 mg/day and also increased weekly to a mean of 146 mg/day (range, 50–200 mg/day). Antidepressant response was measured with the Hamilton Rating Scale for Depression (HAM-D). Improvements in 17 individual symptoms were compared between the groups. The Clinical Global Impression–Improvement (CGI-I) Scale* was a secondary outcome measure.

Results: A total of 54 patients completed the 6 weeks of treatment and were included in the analysis. All patients who withdrew from the study did so because of adverse effects: loss of

appetite, gastric disturbance, and sexual problems in 4 sertraline patients and gastric disturbance, dizziness, and decreased appetite in 5 duloxetine patients.

At 6 weeks, sertraline and duloxetine had similar effects overall; mean HAM-D scores decreased significantly in both groups from 27 to 17 with sertraline and from 28 to 19 with duloxetine ($p < 0.001$ for both compared with baseline). CGI-I ratings were 1.5 and 1.3, respectively. The 2 drugs had similar effects on most of the individual depression symptoms. However, significant between-group differences were seen regarding efficacy on several individual items. Sertraline was significantly more effective at relieving agitation, anxiety (both psychological and somatic), and hypochondriasis ($p < 0.001$ for all vs. duloxetine). Duloxetine had significantly stronger effects on psychomotor retardation, somatic symptoms, and sexual problems ($p < 0.001$ for all vs. sertraline).

Discussion: The differing activity profiles of the 2 antidepressants may underlie their differential effects on specific symptoms. Duloxetine is a dual inhibitor of norepinephrine and serotonin reuptake and may also have analgesic effects via increasing the activity of these neurotransmitters in the CNS. Besides depression, it is also effective for somatic pain, diabetic neuropathy, and fibromyalgia. Sertraline is purely a serotonin reuptake inhibitor and is also efficacious in treating obsessive thoughts, such as those associated with hypochondriasis.

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

Mowla A, Dastgheib S, Jahromi L: Comparing the effects of sertraline with duloxetine for depression severity and symptoms: a double-blind, randomized controlled trial. *Clinical Drug Investigation* 2016; 10.1007/s40261-016-0399-6. From Shiraz University of Medical Sciences, Iran. **Funded by the university. The authors declared no competing interests.**

Common Drug Trade Names: duloxetine—*Cymbalta*; sertraline—*Zoloft*

*See Reference Guide.

Clozapine-Associated Heat Stroke

A 60-year-old man with treatment-resistant schizophrenia had received successful treatment for >20 years with 600 mg/day clozapine and 1000 mg/day valproic acid with no adverse effects. On the 7th day of an extended heat wave (environmental temperatures, 95–108 degrees), he presented for a regularly scheduled appointment and appeared stable with unremarkable blood counts. Several hours later, he collapsed and was admitted to the hospital with tachycardia, tachypnea, and a significantly elevated axillary temperature (107 degrees), but no rigidity. His score on the Glasgow Coma Scale was 9, and he was placed on a mechanical ventilator. Neuroleptic malignant syndrome (NMS), viral meningitis, pneumonia, and sepsis were suspected, and the psychotropics were stopped. Laboratory tests showed markedly elevated creatine kinase (CK) levels and sodium/potassium levels well below normal ranges. Within 24 hours, the patient regained consciousness, his breathing normalized, and his axillary temperature fell to <100.4 degrees. Clozapine was restarted on hospital day 6, and the patient was transferred to an air-conditioned psychiatric ward, where he remained for several days before being transferred back to a non-air conditioned medical ward. Four days after the transfer, while taking 125 mg/day clozapine, hyperthermia developed again along with increased CK activity. Symptoms resolved completely with rehydration and relocation to a cooled room.

Although neuroleptics are known to affect temperature regulation, this appears to be only the second case of heat stroke reported with clozapine. Symptoms of heat stroke can mimic those of NMS (e.g., altered mental status, increased CK, elevated body temperature). However, despite the similarities in presentation, treatment options for heat stroke and NMS are

markedly different. Heat-related illness should be considered when patients present with these symptoms, particularly when environmental temperatures are unusually hot.

Hoffmann M, Oliveira L, Lobato M, Belmonte-de-Abreu P: Heat stroke during long-term clozapine treatment: should we be concerned about hot weather? *Trends in Psychiatry and Psychotherapy* 2016;38 (January/March):56–59. From Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. **One study author disclosed financial relationships with commercial sources; the remaining 3 authors declared no competing interests.**

Common Drug Trade Names: clozapine—*Clozaril*; valproic acid—*Depakene, Depakote*

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.

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.

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: Selection bias can be problematic when using observational data, making causal relationships difficult to establish. Propensity score matching is 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.

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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SSRI Augmentation with Statins

According to results of a population-based study, the combination of SSRI and statin therapies is associated with fewer psychiatric hospital contacts than SSRI therapy alone.¹

Background: The addition of antiinflammatory agents, including aspirin and COX-2 inhibitors, is a promising strategy to improve response to antidepressant drugs. Statins have direct anti-inflammatory effects that are not mediated by their cholesterol-lowering effects.

Methods: Danish national patient registries were used to identify a study cohort of all patients who had filled ≥ 1 SSRI prescription between 1997 and 2012 but had no SSRI use in the prior year ($n=872,216$). Follow-up started on the day a patient filled the index SSRI prescription. Additional registry data were then used to identify patients within the cohort who also filled an initial prescription for a statin ($n=113,108$). Study outcomes were psychiatric hospital contacts for any reason and contacts specifically due to depression. (These were chosen as a marker for worsening mental illness.) Additional study outcomes were suicidal behavior (attempted or completed suicide) and all-cause mortality.

Results: Citalopram was the most frequently used SSRI, accounting for nearly 60% of prescriptions; simvastatin accounted for nearly all statin use; and the citalopram–simvastatin combination was the only one with a sufficiently large sample to be analyzed separately. Concomitant statin users were, on average, about 10 years older than users of SSRIs only.

Adjusted hazard ratios* for psychiatric hospital contacts for any reason and for depression in patients taking concomitant SSRIs were 0.75 and 0.64, respectively, compared with patients taking only SSRIs. The combination was not associated with significantly higher rates of suicidal behavior (hazard ratio, 0.85) or overall mortality (hazard ratio, 1.04). Effects of the most common combination, citalopram–simvastatin, were superior to citalopram alone (hazard ratios of 0.72 for any cause contact and 0.66 for depression contact).

The results support a recent review, which concluded that combining agents from the 2 classes is almost certain to be safe.² The only exception is fluvoxamine, which inhibits the hepatic

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enzymes that metabolize statins. An exploratory analysis as part of the present study found that the combination of any SSRI with lovastatin was associated with increased mortality, but this finding was based on 4 deaths that could not be investigated more closely.

¹Kohler O, Gasse C, Petersen L, Ingstrup K, et al: The effect of concomitant treatment with SSRIs and statins: a population-based study. *American Journal of Psychiatry* 2016; doi 10.1176/appi.ajp.2016.15040463. From Aarhus University Hospital, Risskov, Denmark. **Source of funding not stated. Two study authors disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

²Andrade C: Selective serotonin reuptake inhibitor drug interactions in patients receiving statins. *Journal of Clinical Psychiatry* 2014;75:e95–e99. See *Psychiatry Drug Alerts* 2014;28 (April):26–27.

Common Drug Trade Names: citalopram—*Celexa*; fluvoxamine—*Luvox*; lovastatin—*Mevacor*; simvastatin—*Zocor*

*See Reference Guide.

Lurasidone and Quality of Life

Patients with symptomatic schizophrenia who were switched from another antipsychotic to lurasidone experienced improvements in health-related quality of life over 30 weeks of observation.

Background: In patients with schizophrenia, health-related quality of life has been shown to be inversely associated with relapse and hospitalization rates and with medication nonadherence. Long-term improvements in health-related quality of life could improve patient outcomes.

Methods: A 6-week multisite clinical trial enrolled clinically stable but symptomatic patients with schizophrenia or schizoaffective disorder who had experienced at least a partial response to their prior medication but were considered for a drug switch because of insufficient efficacy or safety/tolerability concerns. Lurasidone was flexibly dosed in the range of 40–120 mg/day, and those who completed the 6-week core trial continued to the extension phase, during which lurasidone was continued at the same dose. For the present analysis, health-related quality of life was measured at baseline and after 6 and 30 weeks using 2 patient-rated instruments: the Personal Evaluation of Transitions in Treatment (PETiT) and the 12-item Short Form Survey (SF-12). The PETiT is a disease-specific questionnaire with 30 items grouped into 2 domains relevant to schizophrenia: adherence-related attitude and psychosocial functioning, the latter further subdivided into 4 subdomains. The SF-12 is a widely used generic instrument measuring patient perceptions of physical and mental health.

Results: Of 198 patients who completed the core trial, 148 entered the 24-week extension study. PETiT scores were available at both baseline and the 30-week endpoint for 95 patients, and SF-12 results were available at both time points for 97. In addition to the main analysis, results were analyzed separately by prior drug category: quetiapine (24% of patients), aripiprazole (22%), risperidone (20%), ziprasidone (13%), and olanzapine (9%).

The mean baseline PETiT score of 34.9 was significantly improved at both the core-study and extension endpoints (39.5 after 6 weeks and 39.1 at 30 weeks; $p < 0.001$ for both endpoints). Lurasidone was associated with significant improvement in both the adherence-related attitude and psychosocial functioning domains ($p < 0.001$ for both) and in the subdomains of activity, cognitive function, and dysphoria (all $p < 0.001$), but not social functioning. Significant improvement occurred between baseline and 6 weeks for all prior medication groups except olanzapine, possibly because too few patients took olanzapine for there to be statistical significance. Patients switched from quetiapine or aripiprazole maintained their improvement up to the extension study endpoint.

Patients who met symptom response criteria ($\geq 20\%$ decrease in Positive and Negative Syndrome Scale score) showed the greatest improvement in PETiT scores from the core study baseline to both the extension study baseline and endpoint (8.4 vs. 8.0). Patients considered non-responders

experienced only modest improvement in PETiT total score from core baseline to extension study baseline; their health-related quality of life continued to improve over the course of the extension study (3.5 vs. 4.1).

According to the SF-12, both physical and mental health domains showed significant improvement from the study baseline to the end of treatment. When outcomes were analyzed by prior antipsychotic, mental health status showed the largest improvement in patients switched from aripiprazole or ziprasidone, and physical health status remained stable irrespective of the prior medication.

Discussion: This study is one of few investigating the long-term effects of an antipsychotic medication switch on health-related quality of life. The results should be interpreted with caution because there was no control group.

Awad G, Ng-Mak D, Rajagopalan K, Hsu J, et al: Long-term health-related quality of life improvements among patients treated with lurasidone: results from the open-label extension of a switch trial in schizophrenia. *BMC Psychiatry* 2016; doi 10.1186/s12888-016-0879-5. From the University of Toronto and Humber River Hospital, Canada; and Sunovion Pharmaceuticals, Inc., Marlborough, MA, and Fort Lee, NJ. **Funded by Sunovion Pharmaceuticals Inc. Five study authors disclosed financial relationships with Sunovion; the remaining author declared no competing interests.**

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

Basimglurant for Resistant Depression

Adjunctive treatment with basimglurant, an investigational orally administered glutamate receptor subtype inhibitor, was not superior to placebo in a randomized trial in major depressive disorder; however, it did improve several patient-rated secondary study outcomes.¹ According to an accompanying editorial,² a high placebo response rate may have interfered with the ability of the trial to demonstrate antidepressant efficacy.

Background: Evidence indicates a pathophysiologic role for cortical glutamatergic pathways in major depression. In addition, antidepressant effects of ant glutamatergic drugs, such as ketamine, have been demonstrated. Basimglurant is an inhibitor of the postsynaptic metabolic glutamate subtype 5 receptor, a mechanism it shares with ketamine. In preclinical trials, the agent showed robust antidepressant and anxiolytic effects. The present study evaluated a modified-release oral formulation of basimglurant that provides a 5-hour time-to-peak concentration and was designed to improve safety and tolerability.

Methods: Study participants, aged 18–70 years, were experiencing a current major depressive episode not responsive to ≥ 6 weeks of ongoing treatment with an SSRI or SNRI. Patients whose current episode had been unresponsive to 2–3 antidepressant trials were also included, but those with > 3 failed trials were excluded. Study subjects were randomly assigned to 6 weeks of adjunctive double-blind treatment with 0.5 mg or 1.5 mg basimglurant or placebo. The primary efficacy endpoint was change from baseline in the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) total score. Secondary outcomes included the Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR16), the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF), and the patient-rated MADRS.

Results: A total of 333 patients were enrolled and received treatment. About 90% of the patients had recurrent depression, and most (82%) reported failure of a single treatment in the current episode. About two-thirds of the patients were women, and the mean age was 47 years. Nearly 80% were receiving background treatment with an SSRI, including sertraline (n=95), citalopram (n=49), escitalopram (n=52), paroxetine (n=36), and fluoxetine (n=32). Between 87% and 90% of each group completed randomized study treatment.

The mean baseline MADRS score was 31 in each treatment group and was reduced to 15–17 at week 6, with no significant differences among the treatment groups. Rates of response ($\geq 50\%$ decrease in clinician-rated MADRS total score) and remission (final clinician-rated MADRS score ≤ 10) were higher with the 1.5-mg dose of basimglurant than placebo (50% vs. 40% for response [$p=ns$]; 36% vs. 22% for remission [$p=0.03$]).

Patient-reported outcomes showed significantly greater improvements with the higher dose of basimglurant. Scores on the QIDS-SR16 decreased from a mean of 14 at baseline to 6.8 with 1.5 mg basimglurant and to 8.3 with placebo ($p=0.009$). Q-LES-Q-SF scores improved from a mean of 32 at baseline to 46 and 43, respectively ($p=0.02$). Patient-rated MADRS scores were decreased by a similar proportion to clinician-rated scores, but the difference between the higher basimglurant dose and placebo reached statistical significance ($p=0.04$).

Basimglurant was well tolerated. Dizziness, the main adverse event, occurred in nearly one-fourth of patients receiving the higher dose but was usually transient. Two patients receiving basimglurant had suicidal ideation, but no clear association with the agent was noted. Another 2 basimglurant-treated patients experienced mania, which resolved upon discontinuation.

Discussion: Although basimglurant was not significantly superior to placebo at reducing clinician-rated symptoms, significant positive effects were shown on patient-reported outcomes. In light of the large placebo response rate, which may have affected the ability of between-group differences to reach statistical significance, the trend for greater patient-reported improvements, and the good tolerability of basimglurant, additional study appears to be warranted.

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

¹Quiroz J, Tamburri P, Deptula D, Banken L, et al: Efficacy and safety of basimglurant as adjunctive therapy for major depression: a randomized clinical trial. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.0838. From Roche Innovation Center, Basel, Switzerland; and other institutions. **Funded by F. Hoffmann-La Roche Ltd. All study authors disclosed financial relationships with commercial sources, including F. Hoffmann-La Roche Ltd.**

²Sanacora G: What are we learning from early-phase clinical trials with glutamate targeting medications for the treatment of major depressive disorder [editorial]. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.0780. From Yale University, New Haven, CT. **The author disclosed financial relationships with commercial sources.**

Common Drug Trade Names: citalopram—*Celexa*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; ketamine—*Ketalar*; paroxetine—*Paxil*; sertraline—*Zoloft*

*See Reference Guide.

Brexpiprazole: Long-Term Tolerability and Safety

According to an analysis of combined data from its registration trials, brexpiprazole (*Rexulti*) has a relatively favorable tolerability and safety profile compared with other atypical antipsychotics.

Background: Pharmacologic profiles of the receptor activity of second-generation antipsychotics vary and likely underlie the differences in adverse effects. Approved in July 2015 for treatment of schizophrenia and as an adjunctive treatment for major depressive disorder, brexpiprazole has a receptor activity profile that predicts a reduced potential for activation, extrapyramidal symptoms (EPS), sedation, and weight gain.

Methods: Data were examined from 5 manufacturer-sponsored studies of brexpiprazole in patients with schizophrenia: a 6-week flexible-dose phase II trial; 2 additional 6-week fixed-dose phase III trials; and 2 flexible-dose, uncontrolled, 52-week open-label extension studies that included both patients who completed the short-term studies and new patients. The present analysis was based on pooled data from these trials. The short-term studies comprised 1256 patients who received brexpiprazole and 463 who received placebo. The open-label extension studies comprised 1059 patients who all received brexpiprazole.

Results: Rates of short-term study completion were 65% and 60% with brexpiprazole and placebo, respectively, and rates of discontinuation due to adverse events were 13% for placebo and 9% for brexpiprazole. In these studies, most adverse events occurred with a similar frequency in both the brexpiprazole and placebo groups. No brexpiprazole-associated treatment-emergent adverse events had an incidence of >5% and occurred with twice the frequency of placebo. However, the incidence of akathisia was increased in patients receiving >4 mg brexpiprazole in the phase II trial; as a result, this dose was not tested in the phase III studies. Akathisia usually occurred early in treatment (peak incidence, 8–11 days after initiating treatment) and was associated with discontinuation rates of <1%. No patient experienced tardive dyskinesia. Rates of sedation and somnolence (see table) were low. Mean weight gain was <0.5 lb. with placebo and nearly 2.5 lbs. with brexpiprazole. Clinically-relevant weight gain (>7%) occurred in 10% of actively-treated patients. The number needed to harm* (NNH) for weight gain ≥7% (40) was higher than that previously reported with aripiprazole (NNH, 20), risperidone (NNH, 12), olanzapine (NNH, 6), and quetiapine (NNH, 6). In the long-term studies, 34% of patients completed 52 weeks of treatment and 15% withdrew because of adverse events. Rates of akathisia and other EPS were low and similar to those in the short-term studies. Clinically-relevant weight gain occurred more frequently with long-term treatment (18% vs. 10%). During long-term brexpiprazole treatment, 6 patients reported suicidal ideation, 1 attempted suicide, and 1 completed suicide (total suicidality incidence, <1%). Changes in metabolic parameters were small, and prolactin changes were not clinically meaningful.

Incidence of selected adverse events in brexpiprazole short- and long-term studies			
	Placebo	Brexpiprazole (6 weeks)	Brexpiprazole (52 weeks)
Insomnia	13.2%	11.2%	8.0%
Agitation	7.8%	6.8%	5.2%
Sedation	0.6%	2.3%	0.9%
Somnolence	2.6%	2.5%	2.4%
Akathisia	4.5%	5.8%	4.6%
Weight Gain ≥7%	4.8%	9.9%	18.2%
Metabolic Syndrome	0.8%	1.2%	3.1%

Discussion: Taken together, the results of these studies indicate that brexpiprazole is well tolerated and has a favorable safety profile in terms of several important adverse effects associated with other available second-generation antipsychotics.

Kane J, Skuban A, Hobart M, Ouyang J, et al: Overview of short- and long-term tolerability and safety of brexpiprazole in patients with schizophrenia. *Schizophrenia Research* 2016; doi 10.1016/j.schres.2016.04.013. From the Zucker Hillside Hospital, Glen Oaks, NY; Otsuka Pharmaceutical Development and Commercialization Inc., Princeton, NJ; and H. Lundbeck A/S, Copenhagen, Denmark. **Funded by Otsuka; and Lundbeck. All study authors disclosed financial relationships with commercial sources, including Otsuka or Lundbeck.**

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

*See Reference Guide.

Relative Hyponatremia Risk with Antidepressants

Hyponatremia is a well-known adverse effect of antidepressants. According to results of a large registry-based study, most commonly used antidepressants are associated with increased risk of hyponatremia, particularly in the elderly. The results also suggest that drugs like mirtazapine or SNRIs may be a safer choice for older patients.

Methods: The study was carried out using Danish population data, which included a patient registry and linked prescription and laboratory records. The population consisted of all persons born before 1998 and living in northern Denmark between 1998 and 2012. The analysis included exposure to the most commonly prescribed antidepressants in Denmark: tricyclics (amitriptyline, clomipramine, nortriptyline), SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), SNRIs (duloxetine, venlafaxine), and noradrenergic and specific serotonergic antidepressants (NaSSAs; mirtazapine, mianserin). The primary outcome was hyponatremia, defined as a plasma sodium level of <135 mEq/L. Severe hyponatremia, sodium level of <130 mEq/L, was a secondary outcome. Results of the analysis were adjusted for relevant comorbidities and the use of antiepileptic drugs or diuretics, which influence sodium levels. To avoid bias from the antidepressant choice influencing the number of sodium measurements, an analysis was carried out using only the first sodium measurement after starting treatment.

Results: The study population included >600,000 individuals, of whom 15.5% started treatment with an antidepressant during the study years. Hyponatremia occurred during antidepressant use in 8.9% of the total sample (n=6476).

Citalopram had the highest risk of hyponatremia (incidence rate ratio [IRR],* 7.8 relative to no antidepressant use; see table), followed by paroxetine. Among drug classes, odds ratios* were highest for SSRIs and TCAs, intermediate for SNRIs, and lowest for the NaSSAs. Mianserin was the only antidepressant not associated with a significant elevation in risk.

Discussion: It is assumed that the mechanism of antidepressant-induced hyponatremia is increased secretion of or renal sensitivity to antidiuretic hormone, but the exact cause is unknown. This mechanism is consistent with the 2-week time frame observed in the study. Mild hyponatremia is clinically important for several reasons, not least because it can be associated with instability and falls, reduced cognitive function, osteoporosis, and increased morbidity and mortality.

Adjusted Incidence Rate Ratios for Hyponatremia with Specific Antidepressants	
Drug	IRR
Citalopram	7.8
Paroxetine	6.18
Fluoxetine	5.61
Nortriptyline	5.26
Clomipramine	4.93
Sertraline	4.53
Escitalopram	3.74
Amitriptyline	3.36
Mirtazapine	2.95
Venlafaxine	2.90
Duloxetine	2.05
Mianserin	0.90

Leth-Moller K, Hansen A, Torstensen M, Andersen S, et al: Antidepressants and the risk of hyponatremia: a Danish register-based population study. *BMJ Open* 2016; doi 10.1136/bmjopen-2016-011200. From Nykøbing Falster Hospital, Denmark; and other institutions. **Funded by the Regional Research Foundation, Region Zealand, Denmark. Two study authors disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

Common Drug Trade Names: amitriptyline—*Elavil*; citalopram—*Celexa*; clomipramine—*Anafranil*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; mianserin (not available in U.S.)—*Norval*; mirtazapine—*Remeron*; nortriptyline—*Pamelor*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor*

*See Reference Guide.

Citalopram Neuropsychiatric Effects in Dementia

A randomized controlled trial found citalopram (*Celexa*) reduced agitation in patients with Alzheimer's disease.¹ The present secondary analysis of data from that study showed several additional positive neuropsychiatric effects, but also a negative effect on severity of nighttime behavior disturbances.²

Methods: Citalopram was compared with placebo in a double-blind multicenter trial in patients with probable Alzheimer's disease who had mini-mental state examination scores

between 5 and 28, as well as clinically significant agitation, occurring frequently and with at least moderate severity. Participants (n=186) received 9 weeks of randomized treatment with either placebo or citalopram, titrated over 3 weeks to a target dosage of 30 mg/day. The present analysis examined the effect of treatment on secondary endpoints, as rated on the Neuropsychiatric Inventory (NPI), which examines 12 symptom domains, including agitation/aggression. The NPI was administered to each patient's primary caregiver at baseline and at weeks 3, 6, and 9.

Results: A total of 169 patients were assessed at study end. Besides agitation/aggression, which was required for study inclusion, the most common neuropsychiatric symptoms present at baseline were irritability/lability (84%); anxiety (65%); apathy/indifference (61%); aberrant motor behavior (52%); disinhibition (51%); depression/dysphoria (51%); and delusions (42%). Hallucinations were rare and/or mild, in part because the study excluded patients with psychosis requiring antipsychotic medication.

By week 9, citalopram was associated with lower rates of delusions, anxiety, and irritability/lability. (See table.) At baseline, nighttime behavior disturbances were present in 43% and 49% of the citalopram and placebo groups, respectively. At week 9, incidence was reduced to 24% and 36% (a nonsignificant difference). However, severity of these symptoms was increased significantly with citalopram (p=0.03). Emergence of new neuropsychiatric symptoms during treatment was uncommon but occurred more frequently with placebo than citalopram: delusions (10% vs. 4%) and anxiety (34% vs. 18%). Remission of NPI symptoms that were present at baseline occurred more often with citalopram than placebo for delusions (41% vs. 15%), anxiety (43% vs. 20%), and irritability/lability (39% vs. 14%).

Presence of NPI symptoms after 9 weeks of treatment with citalopram or placebo				
NPI Symptom Domain	Citalopram Group	Placebo Group	Odds Ratio*	Significance
Delusions	26%	42%	0.40	p=0.03
Anxiety	42%	65%	0.43	p=0.01
Irritability/Lability	57%	73%	0.38	p=0.01

Discussion: While the results of this analysis suggest that citalopram may be beneficial for a range of neuropsychiatric symptoms in patients with Alzheimer's disease, the study was not statistically powered to evaluate outcomes other than agitation. The results need to be replicated before firm conclusions can be drawn. In addition, the citalopram dosage used in the study was higher than that now recommended for patients aged >60 years (average age of study participants was 78 years), and according to the primary study results, that dosage was associated with cognitive worsening and delayed cardiac repolarization.

¹Porsteinsson A, et al: Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA* 2014;311 (February 19):682–691. See *Psychiatry Drug Alerts* 2014;27 (April):29–30.

²Leonpacher A, Peters M, Drye L, Makino K, et al: Effects of citalopram on neuropsychiatric symptoms in Alzheimer's dementia: evidence from the CitAD study. *American Journal of Psychiatry* 2016;173 (May):473–480. From Johns Hopkins University School of Medicine, Baltimore, MD; and other institutions. **Funded by the National Institute on Aging; and other sources. Nine study authors disclosed financial relationships with commercial sources; the remaining 8 authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

Incidence Rate Ratio: The number of new cases of a condition in a defined (specified) group or population expressed as a ratio. For example, if there are 1000 people and a condition develops in 14 of them, the incidence rate is 14 per 1000 or 1.4%.

Number Needed to Harm: A measure of how many patients need to be exposed to a risk factor to cause harm in 1 patient that would not otherwise have been harmed. Lower NNH indicates more attributable risk.

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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Pharmacotherapy for Binge Eating Disorder

Lisdexamfetamine, second-generation antidepressants, and therapist-led cognitive behavioral therapy (CBT) all have positive effects in adults with binge eating disorder (BED), according to a systematic review and meta-analysis.

Background: Current guidelines from the American Psychiatric Association (APA) and the National Institute for Health and Care Excellence (NICE) differ in terms of their recommendations for treating BED. The APA recommends a team approach, with CBT as the primary treatment and medication as an adjunctive therapy. In contrast, NICE recommends a CBT-based self-help approach but also endorses medication monotherapy as sufficient treatment for some patients. The present review updates and extends a previous review of eating-disorder treatments published in 2006.

Methods: A comprehensive literature search identified randomized controlled trials conducted in adults with BED diagnosed according to DSM-IV or DSM-5 criteria. Treatments that were compared included standard medical and psychological interventions, as well as self-help and complementary and alternative medicine. Primary outcomes of interest were behavioral, psychological, and physical benefits; and treatment-related harms. The review included only studies with low or medium risk of bias. Treatment-outcome pairs with too few studies to combine in a meta-analysis were reviewed qualitatively.

Results: A total of 34 trials were included in the review: 25 placebo-controlled trials of a medication or a combination treatment, and 9 wait list-controlled trials of psychological interventions. Medications included the anticonvulsants topiramate and lamotrigine, the stimulant lisdexamfetamine, the dietary supplement chromium picolinate, various SSRI antidepressants, and others. The psychological trials evaluated forms of BED-focused CBT (including self-help CBT), psychodynamic interpersonal psychotherapy, dialectical behavior therapy, and behavioral weight-loss treatment. Trial durations ranged from 6 weeks to 6 months. Only 5 trials conducted post-treatment follow-up assessments.

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According to the meta-analysis, compared with placebo, abstinence from binge eating was achieved by more patients who received lisdexamfetamine (15% vs. 40%; risk ratio,* 2.6), the only FDA-approved pharmacotherapy for BED, and second-generation antidepressants (24% vs. 40%; risk ratio, 1.7). The number of binge eating episodes per week was also reduced to a greater degree with lisdexamfetamine and antidepressants than placebo. Eating-related obsessions and compulsions were also reduced with lisdexamfetamine and second-generation antidepressants. Although pre-treatment levels of comorbid depression were low to moderate, second-generation antidepressants also significantly reduced Hamilton Rating Scale for Depression scores. Lisdexamfetamine treatment resulted in average weight losses in the range of 5–6% of body weight. Antidepressants were not associated with weight loss. Medication adverse effects were consistent with those documented with lisdexamfetamine and antidepressants in non-BED populations. Therapist-led CBT also increased abstinence from binge eating; compared with 11% of wait listed patients, 59% of CBT patients achieved abstinence (risk ratio, 4.95).

In qualitative analyses of studies not included in the meta-analysis, partially therapist-led CBT, guided self-help CBT, and topiramate increased abstinence and reduced binge-eating frequency; therapist-led CBT and structured self-help CBT also reduced binge frequency. Topiramate, therapist-led CBT, and guided self-help CBT also improved eating-related psychological outcomes.

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

Brownley K, Berkman N, Peat C, Lohr K, et al: Binge-eating disorder in adults: a systematic review and meta-analysis. *Annals of Internal Medicine* 2016; doi 10.7326/M15-2455. From the University of North Carolina at Chapel Hill; and other institutions. **Funded by the Agency for Healthcare Research and Quality; and the Swedish Research Council. Four study authors disclosed financial relationships with commercial sources; the remaining 3 authors declared no competing interests.**

Common Drug Trade Names: lamotrigine—*Lamictal*; lisdexamfetamine—*Vyvanse*; topiramate—*Topamax*

*See Reference Guide.

SSRIs and Acute Angle-Closure Glaucoma

In a population-based study, patients taking SSRIs had a nearly 6-fold increase in risk of acute angle-closure glaucoma, a potentially blinding ocular emergency.

Methods: This case-control study used national health-insurance data for a representative sample of 1 million Taiwanese beneficiaries. Case patients (n=1465) were those aged 20–84 years in whom acute angle-closure glaucoma developed between 2000 and 2011. Up to 4 age- and gender-matched controls without the disorder were selected for each case patient (n=5712). Immediate SSRI use was defined as use within 7 days of acute angle-closure glaucoma onset (or the case's index date, for corresponding controls), and nonimmediate use was defined as a prescription within 8–30 days. Patients who had filled a prescription >1 month before the index date were excluded from the study. The analysis was adjusted for the comorbidities of diabetes; hypertension; hyperlipidemia; coronary artery disease; anxiety; and depression.

Results: Rates of SSRI use were higher in case patients with acute angle-closure glaucoma than in controls. Of the 1465 case patients, 10 were immediate SSRI users, compared with 5 of the 5712 control patients (0.68% vs. 0.09%). A total of 6 case patients and 23 control patients (4.2% vs. 2.1%) were nonimmediate SSRI users. In addition, compared with patients who had never used an SSRI, immediate SSRI users had an elevated risk of acute angle-closure glaucoma, after adjusting for comorbidities (odds ratio,* 5.8; p<0.01). Risk appeared to be dose-related. Of the 10 cases associated with immediate SSRI use, all occurred in patients aged >60 years; 4 involved fluoxetine, 3 sertraline, 2 escitalopram, and 1 citalopram; 8 of the

10 patients were women. Compared with no SSRI use, nonimmediate SSRI use was not associated with acute angle-closure glaucoma.

Discussion: Previous reports of SSRI-related acute angle-closure glaucoma often described younger patients, and paroxetine was often implicated. Glaucoma risk factors—i.e., female gender; advancing age; ethnicity; glaucoma family history; hyperopia; and cataracts—should be considered before patients are given an SSRI.

Chen H-Y, Lin C-L, Lai S-W, Kao C-H: Association of selective serotonin reuptake inhibitor use and acute angle-closure glaucoma. *Journal of Clinical Psychiatry* 2016;77 (June):e692–e696. From China Medical University, Taichung, Taiwan. Funded by the Taiwan Ministry of Health and Welfare; and other sources. The authors declared no competing interests.

Common Drug Trade Names: citalopram—*Celexa*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; paroxetine—*Paxil*; sertraline—*Zoloft*

*See Reference Guide.

Brexpiprazole for Depression with Irritability

In an exploratory study, adjunctive brexpiprazole (*Rexulti*) improved irritability in patients with depression who continued to experience at least mild symptoms despite antidepressant medication.

Background: Irritability and anger attacks affect one-third to one-half of patients with major depressive disorder. The hypothesis that brexpiprazole has potential to improve irritability is based on its mechanistic profile: It is a partial agonist of serotonin 5-HT_{1A} and dopamine D₂ receptors, mechanisms which have been shown to reduce aggression in animals.

Methods: Study participants (n=54; mean age, 42 years) were patients with major depressive disorder who had an inadequate response (<50% reduction in depressive symptoms) with their current antidepressant. Current episode duration was required to be >10 weeks, and patients must have received monotherapy with an SSRI or SNRI for ≥6 weeks. Participants were also required to have irritability, defined as a score of ≥2 on the irritable-mood item of the clinician-rated Inventory of Depressive Symptomatology (IDS-C). Following a 2-week lead-in with unchanged background medication, all patients received open-label brexpiprazole, titrated to a target dosage of 3 mg/day, added to stable background medication. Outcomes were measured after 6 weeks of treatment and again 4 weeks after brexpiprazole discontinuation.

Results: The 54 enrolled patients had a median episode duration of 6 months and a median of 5 lifetime depressive episodes. On average, patients were experiencing moderate-to-severe depression. Four patients were withdrawn from treatment, 2 as a result of adverse events. The majority of patients (80%) completed treatment with the maximum brexpiprazole dosage.

Mean scores on the IDS-C irritability item decreased from 2.2 at baseline to 1.0 at 6 weeks (p<0.0001). There were also highly significant decreases in patient-reported symptoms, including irritability (Sheehan Irritability Scale), impulsiveness (Barratt Impulsiveness Scale), and anger-hostility (Kellner Symptom Questionnaire; p<0.0001 for all 3 instruments). Of 17 patients who reported anger attacks at baseline on the Anger Attacks Questionnaire, 15 no longer reported these attacks after treatment; 5 patients who had reported no anger attacks at baseline had new anger attacks during treatment.

Depressive symptoms improved over the 6 weeks of treatment, with mean Montgomery-Asberg Depression Rating Scale (MADRS) scores decreasing from 29 to 14 (p<0.0001). A total of 24 patients (48%) met MADRS response criteria (≥50% score reduction), and 17 (34%) met remission criteria (response plus a final score ≤10). Symptoms of irritability, anger-hostility, and depression worsened after brexpiprazole discontinuation, although not

to baseline levels. Reported adverse effects of treatment were considered mild to moderate. However, akathisia developed in 20% of patients and 11% experienced headache.

Discussion: The positive effects of adjunctive brexpiprazole on irritability and anger, as well as depressive symptoms, in this preliminary study suggest that controlled trials are warranted.

Fava M, Menard F, Davidsen C, Baker R: Adjunctive brexpiprazole in patients with major depressive disorder and irritability: an exploratory study. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.15m10470. From Massachusetts General Hospital, Boston; and other institutions. **Funded by H. Lundbeck A/S; and Otsuka Pharmaceutical Development & Commercialization, Inc. All study authors declared financial relationships with commercial sources, including Lundbeck and/or Otsuka.**

Treating Opioid Dependence in Pregnancy

Methadone has been the standard of care for opioid dependence in pregnancy. However, a review of the limited available evidence suggests buprenorphine may be equally safe and effective.

A literature search identified 5 head-to-head comparisons of methadone and buprenorphine in pregnant women. Of these, 3 employed a randomized design, 1 compared a subset of patients from a single participating site in the largest, multicenter, randomized trial with a clinical population, and the last used a retrospective design to evaluate buprenorphine plus naloxone versus methadone.

Overall, methadone and buprenorphine were found to have similar efficacy and safety. Neonatal abstinence syndrome (NAS) developed in 40% of the buprenorphine-group infants and in 54% of the methadone-group infants. The total amount of morphine used to treat NAS and the duration of NAS symptoms were slightly lower in the buprenorphine group, but the difference reached significance only in a single large randomized trial. Length of infant hospital stay was 7–11 days with buprenorphine, compared with 8–18 days with methadone. No differences were found with other neonatal or maternal outcomes.

At present, methadone is the only FDA-approved treatment for opioid addiction during pregnancy. Buprenorphine has several advantages, including not requiring daily visits to a methadone treatment center, fewer drug interactions, and a better tolerability profile. However, acceptability of buprenorphine was the most common reason for its high discontinuation rate (33% of patients in the largest study, compared with 18% of the methadone group) and should be taken into account when choosing treatment. Patient dissatisfaction is likely the result of the drug's longer induction phase, its partial agonist activity, and the need for patients to be in mild-to-moderate withdrawal when starting therapy.

Noormohammadi A, Forinash A, Yancey A, Crannage E, et al: Buprenorphine versus methadone for opioid dependence in pregnancy. *Annals of Pharmacotherapy* 2016; doi 10.1177/1060028016648367. From the VA Outpatient Clinic, Corpus Christi, TX; and other institutions. **This review was conducted without funding. The authors declared no competing interests.**

Common Drug Trade Names: buprenorphine—*Buprenex*; buprenorphine–naloxone—*Suboxone, Zubsolv*; methadone—*Dolophine, Methadose*

Lithium and Hypothyroidism Risk

In a population-based study, thyroid abnormalities were found with a high frequency in patients with bipolar disorder, regardless of treatment. These abnormalities may be a feature of the underlying disease, and it is possible that they may be found more often in patients taking lithium because they are more likely to have their thyroid function tested.

Background: In addition to the long-known association of hypothyroidism with lithium, emerging literature suggests there is also increased risk with other bipolar-disorder treatments.

Methods: Claims data from commercially insured patients in the U.S. were analyzed to compare the incidence of thyroid abnormalities in patients taking lithium versus other bipolar-disorder treatments. The study cohort comprised >1.2 million adults with bipolar disorder insured between 2003 and 2013. The analysis was limited to patients aged 18–65 years who were prescribed monotherapy after at least 1 year of no drug treatment, who did not have hypothyroidism at baseline, and who received ≥ 1 thyroid-function test during monotherapy. A total of 9 monotherapy agents were considered: lithium; carbamazepine; lamotrigine; oxcarbazepine; valproate; aripiprazole; olanzapine; quetiapine; and risperidone. Follow-up was ended when monotherapy stopped.

Results: The analysis included nearly 25,000 patients, with a mean age of 40 years; 65% were women. Lamotrigine, lithium, quetiapine, and valproate were each used in 12–29% of patients, and the other drugs were prescribed less frequently. Follow-up of the sample ranged from 1 day to 9 years, with a mean of about 9 months.

During follow-up, hypothyroidism developed in 1850 patients (7.5%). The incidence was significantly higher for lithium than for most other drugs ($p < 0.05$ for all agents except quetiapine and carbamazepine). However, patients receiving lithium were administered thyroid-function tests about 2–3 times more often than patients taking other drugs. After correcting for this bias and for other factors such as age and gender, lithium still was associated with the highest risk of hypothyroidism, but the difference in incidence from other drugs was smaller and no longer statistically significant for quetiapine. The 4-year risks of hypothyroidism were: 8.8% for lithium; 8.3% for quetiapine; 7.1% for lamotrigine; 7.0% for valproate; 6.7% for carbamazepine; 6.5% for risperidone; 6.4% for olanzapine; and 6.3% for oxcarbazepine.

Discussion: Results of this analysis suggest that the perception of hypothyroidism risk with lithium, compared with other agents, may be overestimated by observation bias as lithium-treated patients received thyroid tests more than twice as often as those receiving other therapies. Currently, only lithium and quetiapine have testing recommendations in their product labels. Because thyroid abnormalities appear to occur with high frequency in patients with bipolar disorder regardless of treatment, patients receiving any treatment should be regularly tested to prevent adverse effects of thyroid disorders.

Lambert C, Mazurie A, Lauve N, Hurwitz N, et al: Hypothyroidism risk compared among nine common bipolar disorder therapies in a large US cohort. *Bipolar Disorders* 2016;18 (May):247–260. From the University of New Mexico Health Sciences Center, Albuquerque; and other institutions. **Funded by the Reagan-Udall Foundation for the FDA; and other sources. One author disclosed relationships with commercial sources; the remaining 9 authors declared no competing interests.**

Common Drug Trade Names: aripiprazole—*Abilify*; carbamazepine—*Tegretol*; lamotrigine—*Lamictal*; olanzapine—*Zyprexa*; oxcarbazepine—*Trileptal*; quetiapine—*Seroquel*; risperidone—*Risperdal*; valproate—*Depakene, Depakote*

Neuropsychiatric Safety of Smoking-Cessation Products

In a large safety trial mandated by the FDA and funded by the drug manufacturers, varenicline and bupropion were not associated with increased risk of neuropsychiatric adverse events compared with nicotine patches or placebo. The drugs were safe and effective for smoking cessation in patients with or without psychiatric disorders.

Background: The present multinational postmarketing trial was undertaken as a result of concern about reports of neuropsychiatric events, such as suicidality and aggression, as well as the limitations and potential biases of earlier studies supporting the safety of smoking-cessation agents.

Methods: Study participants, aged 18–75 years ($n=8144$; mean age, 47 years; 44% men), smoked ≥ 10 cigarettes per day and were motivated to quit. Nearly half of participants had a diagnosis

of a psychiatric disorder—i.e., mood disorder (including bipolar disorder); anxiety disorder; schizophrenia or schizoaffective disorder; or borderline personality disorder. Those with alcohol and other drug-use disorders, as well as those who were clinically unstable or at high risk of suicidal behavior, were excluded. Within non-psychiatric and psychiatric cohorts, participants were randomly assigned to treatment, with about 1000 patients per group. Among the psychiatric cohort, treatment groups were balanced by illness category. Randomly assigned treatments were targeted to: 1 mg varenicline b.i.d.; 150 mg sustained-release bupropion b.i.d.; nicotine patches (21 mg/day); or placebo. In a triple-dummy design, all patients took 2 pills a day and used active or inactive patches. Participants set a quit date 1 week after randomization, received treatment for 12 weeks, and had an additional 12 weeks of follow-up. Neuropsychiatric adverse events were ascertained by self-report, clinical observation, and a semi-structured interview for psychiatric symptoms. Smoking cessation was defined as self-reported, continuous abstinence for study weeks 9–12, confirmed by low exhaled carbon monoxide.

Results: More than three-fourths of the study cohort completed treatment, and dropout rates were similar across groups. Among patients with psychiatric illness, the majority had a mood disorder (71%) or an anxiety disorder (19%). Half were taking psychotropic medications at baseline. One-third of the psychiatric cohort had a history of suicidal ideation, and 13% had a history of suicidal behavior.

The overall incidence of the composite neuropsychiatric outcome (see table) was 3.7% with placebo, 3.9% with nicotine patches, 4% with varenicline, and 4.5% with bupropion. Between-group differences were not significant. The rate, combined across all treatments, was higher in the psychiatric cohort than in the non-psychiatric cohort (5.8% vs. 2.1%; $p < 0.0001$). Among the non-psychiatric cohort, varenicline was associated with a lower risk of adverse events than placebo, and bupropion did not differ from placebo. In the psychiatric cohort, there were no significant differences among treatments and placebo. Rates of severe aggression or suicidal behavior ranged from 0 to $< 0.1\%$ in the groups. There was 1 completed suicide, in a placebo-treated patient in the non-psychiatric cohort.

Patients who received varenicline had the highest rate of smoking cessation (34% for weeks 9–12 and 22% for weeks 9–24), significantly higher than the other treatments. Bupropion and the nicotine patch had similar efficacy and were both superior to placebo.

Components of the primary neuropsychiatric composite outcome
Anxiety
Depression
Feeling abnormal
Hostility
Agitation
Aggression
Delusions
Hallucinations
Homicidal ideation
Mania
Panic
Paranoia
Psychosis
Suicidal behavior
Suicidal ideation
Completed suicide

Discussion: The study did not find longitudinal changes in mood, anxiety, or suicidality using validated questionnaires or conventional adverse-event assessments. The results are consistent with either a modest increase or no increase in neuropsychiatric events in both psychiatric and non-psychiatric cohorts. Efficacy of the medications was similar in both patient groups, although rates of smoking cessation were somewhat lower in the psychiatric cohort. The study observations are broadly generalizable but do not apply to patients with unstable mental illness or substance-use disorders.

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

Anthenelli R, Benowitz N, West R, St Aubin L, et al: Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016; doi 10.1016/S0140-6736(16)30272-0. From the University of California, San Diego; and other institutions. **Funded by Pfizer and GlaxoSmithKline. All study authors disclosed financial relationships with commercial sources including Pfizer and/or GlaxoSmithKline.**

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

*See Reference Guide.

Quetiapine Monotherapy in PTSD

In a randomized trial, quetiapine (*Seroquel*) was superior to placebo as monotherapy for military posttraumatic stress disorder. Although improved, patients who received quetiapine remained symptomatic and likely would have required additional treatment.

Background: SSRIs are the only agents FDA-approved for treating PTSD, but atypical antipsychotics are often used as well, either adjunctively or as monotherapy. Current practice guidelines support atypical antipsychotics as second-line therapy, but data on their use are limited. The pharmacological profile of quetiapine suggests potential efficacy for a range of PTSD symptoms, particularly re-experiencing and hyperarousal symptoms.

Methods: The NIMH-funded study, conducted at 2 VA medical centers, enrolled veterans, aged 18–65 years, with PTSD according to DSM-IV criteria. Those with schizophrenia, schizoaffective disorder, bipolar disorder, or dementia were excluded. Other psychotropic medications were discontinued, and patients underwent a 1-week placebo lead-in to rule out placebo response before receiving 12 weeks of randomized medication. Quetiapine was flexibly dosed, to a target of 400 mg/day (allowed range, 50–800 mg/day). The Clinician-Administered PTSD Scale (CAPS) was the primary outcome measure.

Results: A total of 80 patients (mean age, 53 years; 5 women) were randomly assigned to treatment. Mean baseline CAPS total scores were 75 and 71 in the quetiapine and placebo groups, respectively. The quetiapine group had a larger decrease from baseline in the CAPS total score than the placebo group (21.5 vs. 5 points; $p=0.02$; effect size,* 0.49). However, patients remained symptomatic despite quetiapine treatment, with a mean endpoint CAPS total score of 54. Quetiapine was associated with larger decreases than placebo in CAPS re-experiencing score (effect size, 0.54; $p=0.0004$) and in CAPS hyperarousal score (effect size, 0.56; $p=0.007$). Treatment-related decreases in the third subscale, avoidance/numbing, were more modest and not statistically significant. Quetiapine was also associated with significant improvement in scores on the Hamilton Rating Scales for Depression (effect size, 0.64; $p=0.02$) and Anxiety (effect size, 0.41; $p=0.01$), and the Positive and Negative Syndrome Scale (PANSS) global psychopathology (effect size, 0.50; $p=0.005$) and positive symptom scores (effect size, 0.32; $p=0.002$). Quetiapine was not associated with significant improvement in sleep or in PANSS negative symptoms.

Discussion: While these results are encouraging, they will need to be replicated in additional studies. Considering that patients remained symptomatic after treatment in this study, additional pharmacotherapy may be necessary in a clinical setting.

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

Villareal G, Hamner M, Canive J, Robert S, et al: Efficacy of quetiapine monotherapy in posttraumatic stress disorder: a randomized, placebo-controlled trial. *American Journal of Psychiatry* 2016; doi: 10.1176/appi.ajp.2016.15070967. From Raymond G. Murphy VA Medical Center, Albuquerque, NM; and other institutions. **Funded by the AstraZeneca. Two study authors disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

*See Reference Guide.

Escitalopram in Depression and Heart Failure

In patients with heart failure and depression, escitalopram did not influence mortality or cardiovascular morbidity, nor did it improve depressive symptoms to a greater degree than placebo.¹

Methods: Study subjects were adults attending outpatient heart-failure clinics who were screened for depression and underwent a DSM-IV structured clinical interview to confirm major depression diagnosis. Subjects were randomly assigned to receive 10–20 mg/day escitalopram or placebo for up to 24 months while receiving optimal heart-failure care. The primary endpoint

was death from any cause or the first occurrence of hospitalization. Secondary outcomes included depression, anxiety, and health-related quality of life. The study was terminated prematurely based on a determination of futility.

Results: The efficacy analysis was based on 372 patients, who participated for a median of about 18 months. Death or hospitalization occurred in 63% of the escitalopram group and 64% of the placebo group ($p=ns$). There were no statistically significant differences between groups in any time-to-event outcome, including cardiovascular or non-cardiovascular death or hospitalization for different causes, or in subgroups analyzed separately.

Montgomery Asberg Depression Rating Scale scores at 12 weeks were similar in the escitalopram and placebo groups. Depression and anxiety decreased to a similar extent in both groups, and cardiomyopathy-related quality of life at 12 months was significantly better in the placebo group. An exploratory analysis suggested that remission of depression or marked improvement did not reduce the risk of death or hospitalization.

Discussion: Depression is common in patients with cardiovascular disease and is associated with poorer clinical outcomes. Results of previous randomized studies in patients with coronary artery disease suggest that antidepressants may improve depression but do not affect the cardiovascular prognosis. Until now, a 12-week study of sertraline was the only randomized antidepressant trial in patients with heart failure; results of this study were also negative.² In the present study, escitalopram levels, obtained at weeks 6 and 12 and again at 6 and 12 months, were in the therapeutic range, indicating that the results likely confirm a lack of therapeutic efficacy in this sample.

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

¹Angermann C, Gelbrich G, Stork S, Gunold H, et al: Effects of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *JAMA* 2016;315 (June 28):2683–2693. From the University Hospital Würzburg, Germany; and other institutions. **Funded by the German Ministry of Education and Research; and Lundbeck AS Denmark. Ten study authors disclosed potentially relevant financial relationships; the remaining 8 authors declared no competing interests.**

²O'Connor C, et al: Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *Journal of the American College of Cardiology* 2010;56:692–699.

Common Drug Trade Names: escitalopram—*Lexapro*; sertraline—*Zoloft*

*See Reference Guide.

Reference Guide

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.

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.

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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Raloxifene for Refractory Schizophrenia

Adjunctive treatment with the selective estrogen receptor modulator (SERM) raloxifene (*Evista*) reduced illness severity in women with refractory schizophrenia in a placebo-controlled trial.

Background: Estradiol has been shown to have many positive effects in the brain, including enhanced neurogenesis, antiinflammatory effects, and enhanced dopamine release. Estradiol therapy has been shown to improve schizophrenia in women but has undesirable systemic effects. Raloxifene has mixed estrogen receptor agonistic and antagonistic activity, depending on its location in the body.

Methods: Study participants were peri- or postmenopausal women, aged 40–70 years, with schizophrenia or schizoaffective disorder and a Positive and Negative Syndrome Scale (PANSS) total score of ≥ 60 while receiving stable doses of antipsychotic medication. The women were randomly assigned to receive 12 weeks of adjunctive treatment with either 120 mg/day raloxifene or placebo. The primary outcome was change from baseline in the PANSS total score. Clinical response, a secondary outcome, was defined as a $\geq 20\%$ reduction in PANSS score.

Results: A total of 54 women (mean age, 53 years) were randomized and began treatment. Of these, 46 (85%) completed the 12-week study. Withdrawals were for various circumstantial reasons that did not include adverse effects.

Mean baseline PANSS total scores did not differ between treatment groups: 80 and 77 in the raloxifene and placebo groups, respectively. By week 12, the women taking raloxifene had a significantly larger reduction in the PANSS total score than the placebo group (10 points vs. 4 points; $p=0.02$), as well as a larger reduction in the PANSS general psychopathology subscale (5.5 vs. 2 points; $p=0.02$). There were no significant differences between groups in the PANSS positive or negative symptom subscale changes, or in Montgomery-Asberg Depression Rating Scale scores or a battery of cognitive function tests. Clinical response was observed in 11 of 26 women receiving raloxifene and in 4 of 30 receiving placebo.

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(42% vs. 13%; $p=0.01$; hazard ratio, * 5.79). Sex hormone levels appeared unaffected by raloxifene, and there were no notable adverse effects of treatment.

Discussion: There have been previous reports of positive effects of raloxifene in women with schizophrenia, but this is the first large study in women with refractory illness. There is some suggestion that its effects are dose-specific (a high dose of raloxifene was used in this study), symptom-specific, and gender-specific; requiring additional investigation. Potential risks of treatment should be noted; thromboembolic events and fatal stroke have been observed in large, controlled trials in women with or at high risk of cardiovascular disease.

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

Kulkarni J, Gavrilidis E, Gwini S, Worsley R, et al: Effect of adjunctive raloxifene therapy on severity of refractory schizophrenia in women: a randomized clinical trial. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1383. From Monash University, Melbourne, Australia; and other institutions. **Funded by the Australian National Health and Medical Research Council. Four study authors disclosed potentially relevant relationships with commercial sources; the remaining 6 authors declared no competing interests.**

*See Reference Guide.

Raloxifene and Negative Symptoms

Clinical trials of the effects of the selective estrogen receptor modulator (SERM) raloxifene (*Evista*) on negative symptoms in women with schizophrenia have had inconsistent results. Results of a post-hoc exploratory analysis from 1 of these studies suggests that genetic variants may partially explain the failure to replicate study results.

Methods: This pharmacogenetic study was conducted as a secondary aim of a raloxifene clinical trial in postmenopausal women with schizophrenia and prominent negative symptoms. Patients were continued on stable doses of their background antipsychotic medication and were randomly assigned to treatment with 60 mg/day raloxifene or placebo for 24 weeks. The primary outcome of the genetic analysis was change from baseline in the negative symptom subscale of the Positive and Negative Syndrome Scale. Positive symptoms and general psychopathology were explored as secondary outcomes. Genotyping was performed for 3 single-nucleotide polymorphisms (SNPs) located in the estrogen receptor 1 (ESR1) gene and for 1 additional SNP in the UDP-glucuronosyltransferase 1A8 (UGT1A8) gene, which is involved in the major metabolic pathway of raloxifene.

Results: A total of 65 women (mean age, 62 years) participated in the study. None of the ESR1 SNP variants was associated with a differential response of negative symptoms to raloxifene. However, women who had a specific UGT1A8 genotype were more likely than others to show improvement in negative symptoms when receiving treatment with raloxifene ($p=0.04$). These women were homozygous for the C allele in the rs1042597 SNP of UGT1A8. One of the ESR1 gene SNPs, rs2234693, was associated with a larger response of positive symptoms to raloxifene ($p=0.04$).

Discussion: Because estrogens are known to improve psychotic symptoms, raloxifene and other SERMs are under investigation as potential treatments. Results of previous studies suggest they may improve positive and negative symptoms, general psychopathology, and cognition. Other studies have shown no effects on negative symptoms. It is possible that genetic variants in UGT1A8 may influence the bioavailability of raloxifene, leading to the inconsistent results.

Labad J, Martorell L, Huerta-Ramos E, Cobo J, et al: Pharmacogenetic study of the effects of raloxifene on negative symptoms of postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. *European Neuropsychopharmacology* 2016; doi 10.1016/j.euroneuro.2016.08.006. From the Autonomous University of Barcelona, Spain; and other institutions. **Funded by the Stanley Medical Research Institute. The authors declared no competing interests.**

Pherine Nasal Spray for Social Anxiety

A nasal spray containing a novel substance that targets chemosensory neurons was effective for as-needed treatment of social anxiety symptoms in a pilot study. The active ingredient is a pherine, an odorless synthetic molecule that induces rapid activation of specific brain areas, distinct from olfactory targets that can modulate autonomic and behavioral responses.

Background: FDA-approved medications for social anxiety disorder (i.e., paroxetine, sertraline, and venlafaxine) require sustained treatment and have limited benefits for many patients. The events/social encounters that cause distress for patients with social anxiety disorder are predictable; making an effective, rapidly-acting treatment that could be taken as needed before such an event a particularly attractive option.

Methods: The study was conducted in adults who met DSM-IV criteria for social anxiety disorder, generalized type, with symptoms of at least moderate severity. Subjects had no other significant psychiatric conditions and were not taking psychotropic medications. During a 2-week baseline period, study participants were encouraged to enter into distressing social and performance situations as much as possible and to record their anticipatory and peak symptoms using the Subjective Units of Distress Scale (SUDS). Those who had ≥ 6 occasions of significant distress during the baseline period then began 4 weeks of double-blind crossover treatment using the study investigational drug PH94B, or a placebo. They were instructed to use the medication ≤ 4 times daily, 15 minutes before an anticipated stressful situation but after they began to experience anticipatory anxiety. The primary study outcome was change from baseline in mean peak scores on the SUDS, which range from 0 to 100.

Results: A total of 22 patients participated in the study. Patients (50% women) had a mean age of 40 years and social anxiety onset at a mean age of 10 years. Participants administered a mean of 19 doses of active PH94B and 21 doses of placebo per 2-week period. No patient used more than 4 doses per day. Distressing situations recorded in the diaries ranged widely, and included job interviews, business presentations, and driving classes.

Mean peak SUDS scores were between 65 and 70 at baseline and they decreased by 16 points in patients receiving the active nasal spray, compared with 8 points in the placebo group ($p=0.006$; effect size, * 0.66). In patients switched from PH94B to placebo, mean peak SUDS scores worsened after the switch but did not return to baseline levels. Those who received placebo first showed a modest initial improvement, which increased when they were switched to active medication. Average baseline scores on the Liebowitz Social Anxiety Scale (LSAS) indicated patients were severely ill. In the first 2 weeks of treatment, patients who received PH94B had a larger (although nonsignificant) improvement in LSAS score than the placebo group ($p=0.07$), but the effect size was large (0.81). For the sample as a whole, differences between treatments in the LSAS were small, possibly because of a carryover effect of active medication in those who received it before placebo. It is

Common Adverse Effects of Treatment		
	PH94B	Placebo
Ear, nose, throat symptoms	1	2
Palpitations	1	0
Tachycardia	0	1
Lightheadedness	1	0
Headache	3	1
Insomnia	1	0
Panic	0	1
Sadness	1	1
Irritability	1	0
Decreased appetite	0	1
Flu-like symptoms	1	1

also possible that the significant positive effects of the medication on avoidance, which are reflected on the LSAS avoidance subscale, could have led patients to participation in more and more challenging situations. After the first 2 weeks, 7 of the patients receiving PH94B and 1 of those receiving placebo rated themselves as treatment responders. Clinical Global Impression–Severity ratings show a similar pattern, with between-group differences limited to the first 2 study weeks. Adverse effects were reported by 9 patients (see table on previous page); all were mild or moderate. Of the 22 patients, 21 completed the full 2 weeks of each treatment.

Discussion: While these results are positive, they cannot be considered definitive and will need to be replicated in larger studies.

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

Liebowitz M, Hanover R, Draine A, Lemming R, et al: Effect of as-needed use of intranasal PH94B on social and performance anxiety in individuals with social anxiety disorder. *Depression and Anxiety* 2016; doi 10.1002/da.22546. From the Medical Research Network, LLC, New York, NY; and other companies including Pherin Pharmaceuticals, Los Altos, CA. **Funded by Pherin Pharmaceuticals. All 6 study authors disclosed financial relationships with commercial sources.**

Common Drug Trade Names: paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor*

*See Reference Guide.

Early Lurasidone Dose Escalation in Schizophrenia

In a manufacturer-sponsored controlled trial, patients with a weak response to 80 mg/day lurasidone (*Latuda*) after 2 weeks demonstrated greater improvement after prompt dose escalation than patients continuing at the initial dose.

Background: Early nonresponse to antipsychotics is a robust predictor of poor short-term outcomes in patients with schizophrenia. Strategies to overcome poor response include augmentation, switching, and dose escalation. The present study was undertaken to evaluate early lurasidone dose escalation to the upper limit of the recommended range.

Methods: Study participants were 412 patients with schizophrenia of ≥ 6 months' duration who were experiencing a symptom exacerbation. Participants were required to have a Positive and Negative Syndrome Scale (PANSS) total score of ≥ 80 ; at least moderate scores for ≥ 2 PANSS items—delusions, conceptual disorganization, hallucinations, or thought disturbances; and a Clinical Global Impression–Severity (CGI–S) rating of at least "moderately ill." Patients were initially randomized to 3 treatment groups in a 1:2:1 ratio: 20 mg/day lurasidone, 80 mg/day lurasidone, and placebo. After 2 weeks, patients assigned to 80 mg lurasidone were classified as either early responders (≥ 20 decrease from baseline in the PANSS total score) or nonresponders ($< 20\%$ PANSS improvement). Nonresponders were then re-randomized to either continue at the 80-mg dose or to have an increase to 160 mg/day. The primary efficacy endpoint was change from baseline to week 6 in PANSS total score. The CGI–S score was the key secondary endpoint.

Results: After 2 weeks of treatment with 80 mg/day lurasidone, 98 patients (50%) were classified as early nonresponders and underwent re-randomization. Among this group, the average decrease in PANSS total scores from baseline to 6 weeks was significantly greater for those who had dose escalation compared with those who continued on the 80-mg dose (17 vs. 9 points; $p < 0.05$; effect size,* 0.52). CGI–S scores decreased by 1 point with dose escalation and by 0.6 in the comparison group ($p = \text{ns}$; effect size, 0.4). Overall response occurred in 74% of early nonresponders receiving dose escalation and in 60% of those continuing on the original dose ($p = \text{ns}$; number needed to treat,* 7).

Early nonresponders who underwent dose escalation reported a higher incidence of anxiety; abdominal discomfort; akathisia; insomnia; and somnolence compared with those who continued on the 80-mg dose. However, between-group differences in adverse effects were small and not significant. Dropout rates were similar in the early nonresponder groups (16–18%) regardless of re-randomized lurasidone dose.

Discussion: The effects of lurasidone dose escalation in this study were consistent with previous observations of a dose-response effect and with the drug's known mechanisms of action. Serum drug concentrations are correlated with dopamine D₂ receptor occupancy, and doses greater than 80 mg/day may be required to reach threshold levels of D₂ receptor occupancy in some patients. A substantial percentage of patients considered nonresponders at week 2 went on to achieve response without dose escalation. Consequently, the increased probability of response with dose escalation must be weighed against the moderate increase in adverse effects associated with the dose increase.

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

Loebel A, Silva R, Goldman R, Watabe K, et al: Lurasidone dose escalation in early nonresponding patients with schizophrenia: a randomized, placebo-controlled study. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.16m10698. From Sunovion Pharmaceuticals Inc., Fort Lee, NJ; and other institutions. **Funded by Sunovion. All study authors disclosed financial relationships with commercial sources, including Sunovion.**

*See Reference Guide.

Adjunctive Liraglutide and Alzheimer's Progression

In patients with Alzheimer's disease, treatment with the GLP-1 analog liraglutide (*Victoza*) prevented the predicted decline of brain glucose metabolism, a marker for disease progression. Treatment did not affect cognition or amyloid deposition.

Background: Liraglutide is a GLP-1 receptor agonist used to treat type 2 diabetes. Common pathophysiological mechanisms for type 2 diabetes and Alzheimer's disease include deficient insulin and GLP-1 signaling and beta-cell toxicity. GLP-1 receptor agonists cross the blood-brain barrier and have been reported to be neuroprotective of several neurodegenerative disorders in animal models.

Methods: Study subjects were 38 patients with Alzheimer's disease, recruited from dementia clinics. Patients were required to be aged 50–80 years, able to give informed consent, and have mini-mental state examination scores of 18–21. Those with diabetes were excluded. In addition to existing medications (including cholinesterase inhibitors), participants were randomly assigned to treatment with liraglutide (maintenance dose, 1.8 mg injected daily) or placebo for 26 weeks. Outcomes included beta-amyloid deposition and glucose metabolic rate, measured by PET scan, and cognitive function, measured using the Brief Cognitive Status Exam from the Wechsler Memory Scale.

Results: Participants had a mean age of about 65 years. By chance, the treatment groups were somewhat unbalanced; members of the group receiving liraglutide were older on average, were more likely to be female, and had a significantly longer mean duration of Alzheimer's disease—30 vs. 15 months ($p < 0.05$). Four patients did not complete liraglutide treatment, but only 1 for a drug-related reason: nausea and anorexia. The patients who received liraglutide lost >10 pounds on average during the first 3 months, after which their weight stabilized. Fasting plasma glucose levels were lower during the study in the group receiving liraglutide.

Measures of amyloid deposits in different brain regions showed increases during the study, to a similar extent in both groups. In the placebo group, measures of glucose metabolism had

statistically significant decreases over the course of treatment in the precuneus ($p=0.009$); the parietal, temporal, and occipital lobes ($p=0.04$, 0.046 , and 0.009 , respectively); and the cerebellum ($p=0.04$). There were small, nonsignificant increases in glucose metabolism in the liraglutide group. Cognitive outcomes did not differ between the 2 groups.

Discussion: Current treatments for Alzheimer's disease target neurotransmission without addressing neurodegeneration or neuronal metabolism. Liraglutide potentially affects neurodegeneration, neuronal performance, and neuroinflammation, suggesting it could reduce intracerebral amyloid deposition and improve glucose metabolism in the CNS of patients with Alzheimer's disease, which would then improve cognition. In the present study, liraglutide prevented the decline of brain glucose consumption but had no effect on amyloid accumulation or cognition, possibly because the study lacked the statistical power to show positive effects of liraglutide on these outcomes.

Gejl M, Gjedde A, Egefjord L, Moller A, et al: In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. *Frontiers in Aging Neuroscience* 2016; doi 10.3389/fnagi.2016.00108. From Aarhus University, Denmark; and other institutions. **Funded by Novo Nordisk Scandinavia; and Aarhus University. Three study authors declared financial relationships with commercial sources; the remaining 10 authors declared no competing interests.**

Canadian Depression Guidelines: Pharmacotherapy

The Canadian Network for Mood and Anxiety Treatments (CANMAT) has updated its guidelines for the use of pharmacotherapy, psychological therapies, neurostimulation, and complementary and alternative treatment of unipolar major depression in adults. The pharmacotherapy update is based on meta-analyses and systematic reviews published between 2009 and 2015 and includes information on recently introduced drugs, meta-analyses of the relative efficacy of antidepressants, adjunctive versus switching strategies, and management of the new DSM-5 entity persistent depressive disorder.

Most second-generation antidepressants are recommended as first-line treatments for depression of at least moderate severity, including SSRIs; SNRIs; agomelatine; bupropion; and mirtazapine. Antidepressants are not recommended as first-line treatment for mild depression unless the patient has not had a response with nonpharmacologic interventions, there is a history of response to an antidepressant, or the patient prefers a drug to the alternatives. A number of comparative meta-analyses have shown little difference in efficacy among agents, although some appear to have modest superiority: escitalopram, mirtazapine, sertraline, and venlafaxine. However, studies only show a 5–6% differential in efficacy among all antidepressants. There is no evidence to support any particular agent in older patients, those with anxiety, or those with a longer duration of illness; nor does evidence provide any medication selection guidance in patients with different depressive subtypes.

Several new antidepressants have been introduced since the CANMAT 2009 guideline was released. Levomilnacipran, an SNRI, has greater selectivity for noradrenaline compared with other agents in its class. Vilazodone is a multimodal agent that must be taken with food and titrated according to a fixed schedule in order to avoid GI side effects. Both levomilnacipran and vilazodone are endorsed as second-line therapies. Vortioxetine, another multimodal antidepressant, may have additional beneficial effects on cognition and is included as a first-line treatment option.

The guideline recommends that prior to prescribing, assessment should be made of suicidality, bipolarity, and depression symptom specifiers or dimensions; for treatment preferences; and for antidepressant medication history including each drug's dose, duration, response, and side effects. Once given an antidepressant prescription, patients should be reassessed for

tolerability, safety, and early efficacy within 2 weeks. Pharmacogenetic testing for drug selection or routine therapeutic drug monitoring is not recommended. If an initial course of treatment is not successful, the decision between adding an adjunctive medication and switching should be individualized based on clinical factors. There is little evidence supporting selection of a specific adjunctive agent to target specific residual symptoms.

The DSM-5 has added a new diagnosis, persistent depressive disorder, which subsumes the DSM-IV categories of dysthymic disorder and chronic major depressive disorder. A single meta-analysis supported the efficacy of most of the drugs in depression lasting ≥ 2 years. However, some experts have argued that this disorder requires a chronic disease management approach, with greater relative emphasis on improving function and quality of life and greater use of psychotherapy and nondrug treatments.

Kennedy S, Lam R, McIntyre R, Tourjman S, et al: Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3: pharmacological treatments. *Canadian Journal of Psychiatry* 2016; doi 10.1177.0706743716659417. From the University of Toronto, Canada; and other institutions. **Funded with internal CANMAT funds. Twelve study authors declared financial relationships with commercial sources; 2 authors declared financial relationships with noncommercial sources; and 4 authors declared no competing interests.**

Common Drug Trade Names: agomelatine (not available in U.S.)—*Valdoxan*; bupropion—*Wellbutrin*; escitalopram—*Lexapro*; levomilnacipran—*Fetzima*; mirtazapine—*Remeron*; sertraline—*Zoloft*; venlafaxine—*Effexor*; vilazodone—*Viibrid*; vortioxetine—*Trintellix*

Antipsychotics and Birth Defects

According to results of a large population-based study, with the possible exception of risperidone, use of antipsychotic medications early in pregnancy is not associated with increased risk of congenital malformations.¹

Methods: Data were analyzed from >1.3 million pregnant women who gave birth in 2000–2010 and who were covered by Medicaid. Women exposed to known teratogens or with evidence of chromosomal abnormalities were excluded. Exposure to an antipsychotic was based on filling a prescription during the first 90 days of pregnancy, the relevant period for organogenesis. The overall incidence of congenital malformations and that of 13 specific malformation groups were analyzed, with separate comparisons for first- and second-generation antipsychotics. Following propensity score* stratification, congenital malformations were compared among the offspring of the 733 first-generation antipsychotic-exposed women, 9258 second-generation antipsychotic-exposed women, and unexposed women. Final comparisons were adjusted for a broad range of potential confounders including age, race, smoking, multiple gestation, indication for antipsychotic use, comorbid conditions, concomitant medication use, and general markers of the burden of illness.

Results: The most frequently used second-generation antipsychotic was quetiapine (n=4221), followed by aripiprazole (n=1756), risperidone (n=1566), olanzapine (n=1394), and then ziprasidone (n=697). Overall, rates of congenital malformations were higher among exposed infants than those who were not exposed—38 per 1000 with first-generation antipsychotics and 45 per 1000 with second-generation antipsychotics, compared with 33 per 1000 with no exposure. However, after adjustment for multiple confounding factors, neither relative risk (RR)* for overall malformations nor cardiac malformations were increased with first-generation agents (RRs, 0.9 and 0.75, respectively) or with second-generation antipsychotics (RRs, 1.05 and 1.06, respectively). Among individual agents, only risperidone showed significantly increased risk for both overall and cardiac malformations (RR, 1.26 for both).

Discussion: These results support prescribing antipsychotic medication in pregnant women as it is justified by the need to minimize the overall impact of the disease, which is greater

than that of the drug.² The risperidone association could be due to chance or unmeasured confounding factors and it should not yet be viewed not as causal, but rather as a potential safety signal requiring further investigation. It is also possible that prolactin elevation or its treatment might be a link.

¹Huybrechts K, Hernandez-Diaz S, Paterno E, Desai R, et al: Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1520. From Brigham and Women's Hospital Boston, MA; and other institutions. **Funded by the NIMH; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 8 authors declared no competing interests.**

²Wisner K, Jeyong H, Chambers C: Use of antipsychotics during pregnancy: pregnant women get sick—sick women get pregnant [editorial]. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1538. From Northwestern University Feinberg School of Medicine, Chicago, IL; and other institutions. **Two authors disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

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

*See Reference Guide.

Reference Guide

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 is the treatment.

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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Mood Stabilizers, Antipsychotics, and Breastfeeding

In women taking mood stabilizers or antipsychotics for bipolar disorder, the benefits of breastfeeding generally outweigh the risks, according to a systematic literature review. However, precautions should include choosing medications with an adequate safety record, reducing exposure by combining breast milk with other sources of nutrition, and avoiding or restricting breastfeeding in premature newborns.

The postpartum period is one of high risk for new onset of bipolar disorder or for relapse, especially in women who have discontinued medication. Almost all drugs used to treat bipolar disorder are secreted into breast milk, and the risk of toxicity from these drugs could be significant. The literature was reviewed for all evidence of the effects on breastfed newborns of drugs commonly used to treat bipolar disorder. Data were collected from 56 studies—mainly case reports, case series, and small open-label studies.

General Considerations. Drugs with a high percentage of plasma protein binding are the least likely to enter breast milk. Availability is often reported as the milk/plasma (M/P) ratio—i.e., the ratio of the concentration of drug in the milk to that in the plasma. Drugs with an M/P ratio >1 may be present in milk at high concentrations. However, a high M/P ratio may not be a problem if maternal plasma levels are low. Another factor to consider is the relative infant dose, the ratio of the weight-based dose in milk to the weight-adjusted dose received by the mother. A ratio of <10% is generally considered safe. Premature and newborn infants are at greater risk to develop high plasma drug concentrations because of their immature hepatic and renal systems. Infants who are exclusively breast fed for long periods of time develop higher concentrations than those in whom breast milk is alternated with supplemental foods. The mother should take her medication immediately after breastfeeding and not before.

Specific Agents. The consensus on lithium, use of which was previously discouraged in breastfeeding women, has changed based on recent case series showing low serum levels in

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exposed infants and no clinically apparent adverse effects. Lithium levels of about one-fourth of maternal levels have been reported in breastfeeding newborns. If lithium is used, monitoring of maternal and infant lithium levels, as well as infant hydration, weight gain, muscle tone, and renal and thyroid function should be conducted.

Data on antiepileptic mood stabilizers in breastfeeding, although scarce, suggest that they are safe to use under close observation. Case reports and open-label studies have found few adverse effects of valproate, carbamazepine, and oxcarbazepine. Lamotrigine is considered "moderately safe" based on wide variability of M/P ratios and infant plasma concentrations and elevated platelet counts; there were no reports of serious adverse effects.

Among the second-generation antipsychotics, quetiapine and olanzapine are considered safe, based on numerous reports of low plasma concentrations in exposed infants. Evidence suggests the same is probably true for most other second-generation antipsychotics, but the data are extremely limited. First-generation antipsychotics are not recommended because of a lack of data.

Pacchiarotti I, Leon-Caballero J, Murru A, Verdolini N, et al: Mood stabilizers and antipsychotics during breastfeeding: focus on bipolar disorder. *European Neuropsychopharmacology* 2016; doi 10.1016/j.euroneuro.2016.08.008. From the University of Barcelona, Spain; and other institutions. **Funded by the Spanish Ministry of Economy and Competitiveness; and other sources. Nine study authors disclosed financial relationships with commercial sources; the remaining 9 authors declared no competing interests.**

Common Drug Trade Names: carbamazepine—*Tegretol*; lamotrigine—*Lamictal*; olanzapine—*Zyprexa*; oxcarbazepine—*Trileptal*; quetiapine—*Seroquel*; valproate—*Depakene, Depakote*

Metabolic Effects of Injectable Aripiprazole

Aripiprazole lauroxil, the long-acting injectable form of the antipsychotic, was associated with low risk of weight gain, adverse metabolic effects, and prolactin increases, according to a secondary analysis of safety data from a phase III clinical trial.¹

Methods: The multicenter trial was carried out in hospitalized adults with an acute relapse of schizophrenia. Participants were required to have an illness duration of ≥ 2 years and to have had a prior beneficial response to an antipsychotic. After receiving a test dose of aripiprazole or placebo, patients received an initial injection of 441 mg or 882 mg aripiprazole lauroxil or placebo. Patients randomized to aripiprazole lauroxil also received 15 mg/day oral aripiprazole for 3 weeks. Two additional doses of study medication were given 29 and 57 days after randomization. Efficacy results of the study were previously reported.²

Results: A total of 622 patients received ≥ 1 dose of study medication. Patients had a mean age of about 40 years, two-thirds were men, and 40% were black or African American. Baseline body mass index averaged 27–28 kg/m²; about one-third of the patients were overweight and another third were obese at the start of treatment.

Mean body weight increased by < 2 lbs in the groups receiving active medication and did not change in the placebo group. About 9–10% of the groups receiving aripiprazole lauroxil and 6% of the placebo group gained $\geq 7\%$ of their initial body weight. There were no clinically relevant changes from baseline in glucose, HbA_{1c}, or lipid parameters. In the aripiprazole lauroxil groups, mean total cholesterol, LDL cholesterol, and triglyceride levels decreased by 5–8%. Both doses of aripiprazole lauroxil, but not placebo, were associated with mean decreases in prolactin; these reductions occurred in both men and women and were judged to be clinically meaningful. Of the patients with high baseline prolactin levels, 61% and 42% of those in the low- and high-dose aripiprazole groups, respectively, had levels in the normal range at the last assessment.

Metabolic changes were reported as an adverse event in 6 patients receiving aripiprazole lauroxil (increases in glucose or triglycerides, hyperlipidemia, and 1 case of hypoglycemia probably unrelated to medication) and in 2 patients in the placebo group. Weight increase was reported as an adverse event in 11 patients (<3%) receiving aripiprazole lauroxil.

Discussion: These results suggest aripiprazole lauroxil limits weight gain and other risks commonly encountered with antipsychotic treatment. The metabolic safety and tolerability of this agent is similar to that reported in studies of the oral form of aripiprazole.

¹Nasrallah H, Newcomer J, Risinger R, Du Y, et al: Effect of aripiprazole lauroxil on metabolic and endocrine profiles and related safety considerations among patients with acute schizophrenia. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.15m10467. From St. Louis University School of Medicine, MO; Florida Atlantic University, Boca Raton; and Alkermes, Inc., Waltham, MA. **Funded by Alkermes, Inc. All study authors disclosed financial relationships with commercial sources, including Alkermes.**

²Meltzer H, et al: A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *Journal of Clinical Psychiatry* 2015;76 (August):1085–1090. See *Psychiatry Drug Alerts* 2015;29 (September):65–66.

Common Drug Trade Names: aripiprazole—*Abilify*; aripiprazole lauroxil—*Aristada*

Hormonal Contraception and Depression Risk

Women using hormonal contraceptives had an increased incidence of depression in a population-based longitudinal study. Risk varied with different types of contraceptive and was especially pronounced in adolescents.

Methods: The Danish Sex Hormone Register Study is an ongoing cohort study of all women living in Denmark. The present analysis included women who were aged 15–34 years between 2000 and 2013. Those with a diagnosis of depression before 2000 or their 15th birthday were excluded, as were women with other psychiatric diagnoses and those with contraindications to hormonal contraceptives. Users of any type of prescription hormonal contraceptive were compared with non-users of any contraceptive. The study used 2 outcome measures for depression onset: first prescription of an antidepressant medication and a diagnosis of depression on discharge from an inpatient or outpatient psychiatric hospital.

Results: The study population included >1 million women followed for a mean of 6.4 years. More than 55% of women used a hormonal contraceptive during this period. A total of about 133,000 received a prescription for an antidepressant, and 23,000 received a discharge diagnosis of depression.

In users of hormonal contraceptives, the incidence of first use of an antidepressant was 2.2 per 100 person-years and of a depression diagnosis was 0.3 per 100 person-years. In non-users, the corresponding rates were 1.78 and 0.28 per 100 person-years. Relative risks* for antidepressant prescriptions differed according to contraceptive type. (See table.) Relative risks for a discharge diagnosis were slightly lower or similar.

Relative Risk of Antidepressant Prescription in Women Using Hormonal Contraception Compared with Non-Users	
Contraceptive Type	Relative Risk
Combined oral	1.2
Progestin-only	1.3
Transdermal patch (norelgestromin)	2.0
Vaginal ring (etonogestrel)	1.6
Implant	2.1
Levonorgestrel intrauterine system	1.4
Medroxyprogesterone acetate depot	2.7

Relative risks of depression decreased with increasing age for most commonly used contraceptives. Risks were highest in adolescents aged 15–19 years, with a relative risk of 1.8 for combined oral contraceptives and parallel elevations for other types. Adolescents using non-oral types had 3 times the risk, compared with nonusers in their age group.

Risks increased with increasing duration of contraceptive use, peaking at 6 months of use and then declining to background levels after about 4 years.

Discussion: Results of this study are consistent with the hypothesis that progesterone is involved in the etiology of depression. Progesterone dominates combined contraceptives. The high rates of depression in women using the transdermal patch and vaginal ring are probably a function of the dose rather than the route of administration. Risk of depression was also particularly high in women using progestin-only products. Progesterone metabolites influence the GABA receptor complex, the major inhibitory system in the CNS, and progestins, particularly if exogenous, increase levels of monoamine oxidase, which degrades serotonin.

Skovlund C, Mørch L, Kessing L, Lidegaard O: Association of hormonal contraception with depression. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.2387. From the University of Copenhagen, Denmark. **Funded by the University of Copenhagen; and the Lundbeck Foundation. Two study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

Common Drug Trade Names: ethinyl estradiol–norelgestromin patch—*Evra*; etonorgestrel–ethinyl estradiol vaginal ring—*NuvaRing*; levonorgestrel implant—*Norplant*; levonorgestrel intrauterine device—*Liletta, Mirena*; medroxyprogesterone acetate, depot—*Depo-Provera*

*See Reference Guide.

Medical Marijuana in Psychiatry

The rapidly changing legal status of medical marijuana gives rise to an urgent need to investigate its use for psychiatric indications, according to a literature review. At present, the quality of evidence supporting its use is very low.

Background: In addition to crude marijuana, 2 oral pharmaceutical cannabinoids are available in the U.S., dronabinol, approved for cachexia in HIV/AIDS, and nabilone, approved for nausea and vomiting associated with chemotherapy. Another, nabiximols, is available in Canada and some European countries as a nasal spray for treatment of multiple sclerosis. At present, no cannabinoid is FDA-approved for treatment of a psychiatric disorder.

Methods: A literature search was undertaken to identify all research articles on medical marijuana for psychiatric indications, beginning in 1980 and including conference proceedings. A total of 13 articles were identified that described medical marijuana use in Tourette's disorder, posttraumatic stress disorder (PTSD), and Alzheimer's disease.

Results: Two small, randomized, placebo-controlled trials of dronabinol in patients with Tourette's disorder have shown positive effects on some but not all measures of tic severity. Observational studies and case reports indicate many patients report improvement in tic severity with use of the oral agents or marijuana. The existing studies in Tourette's are flawed by small sample size, inconsistent results across multiple measures, possible selection bias, and other problems.

Studies of marijuana in PTSD include a randomized crossover trial of nabilone in 10 male soldiers, 2 retrospective chart reviews of nabilone in adult male offenders and in patients with nightmares, and an open-label study of adjunctive nabilone in patients with PTSD. There have also been 2 unpublished studies and a number of anecdotal reports. Marijuana appears to reduce nightmares and improve sleep in PTSD. The existing evidence is sparse

and its quality is limited by small samples and weak experimental designs, but emerging data on the effects of the endocannabinoid system on extinction learning may provide a basis for future hypothesis-driven clinical trials.

There are no randomized controlled trials of marijuana in Alzheimer's disease, but the handful of existing prospective studies show improvement in some measures of agitation and aggression with use of oral agents. These studies are limited by small sample size, lack of control groups, lack of blinding, and inconsistent results using different outcome measures. There is some evidence that the endocannabinoid system is involved in Alzheimer's disease. It is possible that the purported calming effect of marijuana is the result of nonspecific sedation. Since cannabinoids impair cognitive function in domains already affected by Alzheimer's disease, future studies should weigh their purported benefits against this impairment.

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

Wilkinson S, Radhakrishnan R, D'Souza D: A systematic review of the evidence for medical marijuana in psychiatric indications. *Journal of Clinical Psychiatry* 2016;77 (August):1050–1064. From Connecticut Mental Health Center, New Haven; and other institutions. **Funded by the VA; the NIMH; and other sources. All 3 study authors disclosed financial relationships with commercial sources.**

Common Drug Trade Names: dronabinol—*Marinol*; nabilone—*Cesamet*; nabiximols (not available in U.S.)—*Sativex*

*See Reference Guide.

Antimanic vs. Antipsychotic Drugs in Bipolar Disorder

Results of a population-based comparative effectiveness study suggest that lithium and valproate are superior to second-generation antipsychotics as initial therapy for manic episodes.

Background: Results of randomized controlled trials, conducted in carefully selected patients and under strict conditions, indicate that second-generation antipsychotics are equivalent to or superior in efficacy to conventional antimanic agents. However, little is known about their comparative effectiveness in real-world settings, an important issue due to the cardiometabolic effects of some second-generation agents, as well as their higher costs.

Methods: Using nationwide claims data from the Department of Veterans Affairs (VA), spanning 2003–2010, efficacy was compared between second-generation antipsychotics and conventional antimanic agents in nearly 28,000 patients with bipolar disorder type I, type II, or NOS, who were started on either class of drug or both. The analysis was limited to the 5 most common second-generation antipsychotics: aripiprazole; olanzapine; quetiapine; risperidone; and ziprasidone. Antimanic agents included lithium, valproate, and carbamazepine or oxcarbazepine. The primary outcome measure was hospitalization for any cause during the year following the first prescription. The analysis was adjusted for an extensive list of covariates.

Results: Study participants had an average age of 45 years, and 17% were women. Patients with psychosis were more likely than others to receive a second-generation antipsychotic, and those with substance use disorders, psychosis, antidepressant use, and prior hospitalization were more likely to receive combination therapy, but the analysis was adjusted for these differences.

Compared with patients receiving second-generation antipsychotic monotherapy, rates of all-cause hospitalization were significantly lower in those receiving lithium (odds ratio [OR],* 0.82) or valproate (OR, 0.85). The combination of a second-generation antipsychotic plus valproate was associated with a higher likelihood of all-cause hospitalization than second-generation antipsychotics alone (OR, 1.32). Comparative rates of mental health hospitalization paralleled these results, while rates of medical-surgical hospitalization were

similar among the treatment groups. Compared with second-generation antipsychotics, time to hospitalization was significantly shorter for lithium (hazard ratio [HR],* 0.86; $p < 0.0004$) and valproate (HR, 0.87; $p < 0.0001$).

An exploratory head-to-head analysis of second-generation antipsychotics, using risperidone as the reference treatment, showed that aripiprazole was associated with a significantly lower likelihood of all-cause hospitalization (HR, 0.69). The other drugs—olanzapine, quetiapine, and ziprasidone—did not differ from risperidone.

Discussion: Although the study is subject to the limitations of observational study designs, the results suggest that lithium or valproate, rather than second-generation antipsychotics, could be considered for initial antimanic treatment in bipolar disorder.

Bauer M, Miller C, Li M, Bajor L, et al: A population-based study of the comparative effectiveness of second-generation antipsychotics vs older antimanic agents in bipolar disorder. *Bipolar Disorders* 2016; doi 10.1111/bdi.12425. From the VA Boston Healthcare System, MA; and other institutions. **Funded by the VA. The authors declared no competing interests.**

Common Drug Trade Names: aripiprazole—*Abilify*; carbamazepine—*Tegretol*; olanzapine—*Zyprexa*; oxcarbazepine—*Trileptal*; quetiapine—*Seroquel*; risperidone—*Risperdal*; valproate—*Depakene, Depakote*; ziprasidone—*Geodon*

*See Reference Guide.

Escitalopram for Body Dysmorphic Disorder

In a placebo-controlled relapse-prevention trial in patients with body dysmorphic disorder, 6 months of continued treatment with the SSRI escitalopram (*Lexapro*) significantly delayed the time to relapse.

Methods: Study participants were adults who had been experiencing DSM-IV body dysmorphic disorder for ≥ 6 months and who had a Yale-Brown Obsessive Compulsive Scale modified for body dysmorphic disorder (BDD-YBOCS) total score of ≥ 24 as well as Clinical Global Impression–Severity (CGI-S) ratings of at least "moderately ill." All patients received treatment with open-label escitalopram for 14 weeks (phase 1), with a target dosage of 30 mg/day. Response was defined as a $\geq 30\%$ reduction in the BDD-YBOCS on at least 2 consecutive assessments and through the last visit. Patients who experienced response with escitalopram were randomly assigned to 6 additional months of treatment, either with their final escitalopram dosage or with placebo after an escitalopram taper. Relapse was defined as a loss of $\geq 50\%$ of previous improvement on the BDD-YBOCS, plus a final score > 20 (which corresponds to meeting full diagnostic criteria) and a CGI-Improvement rating of "much worse" or "very much worse." The primary study outcome was time to relapse after the start of phase 2.

Results: Of 100 patients who received escitalopram in phase 1, 60 completed treatment and achieved response after a median of 8 weeks and at a median final escitalopram dosage of 26 mg/day. Response rates did not differ significantly between the 26 patients with delusional beliefs and the 74 without these beliefs.

Of the 60 responders, 58 entered the randomized withdrawal phase. Time to relapse was significantly longer with continued escitalopram than with placebo (hazard ratio,* 2.72; $p = 0.049$). By the end of phase 2, 18% of the escitalopram group and 40% of the placebo group had experienced a relapse. One-third of the escitalopram-treated patients experienced further decreases in psychiatric symptoms during phase 2.

Discussion: Results of the few previous pharmacotherapy studies in body dysmorphic disorder, all with small sample sizes, suggest SRIs are effective, a result confirmed in phase 1

of the present trial. No dose finding studies have been conducted, but the results of the present study and others suggest relatively high SRI doses may be necessary to treat body dysmorphic disorder.

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

Phillips K, Keshaviah A, Dougherty D, Stout R, et al: Pharmacotherapy relapse prevention in body dysmorphic disorder: a double-blind, placebo-controlled trial. *American Journal of Psychiatry* 2016;173 (September):887–895. From Brown University, Providence, RI; and other institutions. **Funded by the NIMH. Four study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

*See Reference Guide.

Sertraline and Post-TBI Depression

In a placebo-controlled trial, low-dose sertraline (*Zoloft*) prevented depression when started within a few weeks following traumatic brain injury.

Methods: Study participants were adults, aged 18–85 years (40% women), who had a closed TBI of any severity. They were required to be free of depression at baseline and to have complete recovery of posttraumatic amnesia within 4 weeks of the injury. Those with a history of mood disorder were required to be in full remission for at least the previous year, and those already taking antidepressants were excluded. Participants were randomly assigned to receive 100 mg/day sertraline or placebo for 24 weeks. The primary study outcome was onset of a depressive episode identified using the Mini-International Neuropsychiatric Interview.

Results: Of >1000 patients with a TBI who were screened for the study, about half met eligibility criteria. The most common reason for exclusion was a diagnosis of drug/alcohol use disorder. Of about 500 eligible patients, 80% refused to participate, including 120 who were unwilling to add another drug to the ones they were already taking and 30 who would not consent to potential placebo treatment and started antidepressant therapy outside the study. The remaining 94 patients (46% women; average age, 50–55 years) were enrolled, most within 3–4 weeks after the TBI. According to Glasgow Coma Scale ratings, the injury was mild in nearly 80% of the patients and severe in 10%.

Nearly half of all patients did not complete 24 weeks of treatment. Withdrawal rates were similar across groups, and all patients who received any randomized treatment were included in the analysis. Depression developed in 27 patients (29%) during the 24 weeks of follow-up. Incident depression was significantly less likely to occur in sertraline-treated patients for whom the number needed to treat* to prevent 1 depressive episode was 5.9 ($p=0.03$). Given that SSRIs can enhance neuroplasticity, neuropsychiatric tests for attention, memory, and executive function were administered to patients who did not develop a mood disorder. No differences were found between the sertraline and placebo groups.

Discussion: These observations suggest sertraline may be effective in preventing depression when administered early after a brain injury. Given the study's limitations, including small sample size and the predominance of mild TBI, the results should be viewed as preliminary until they can be replicated.

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

Jorge R, Acion L, Burin D, Robinson R: Sertraline for preventing mood disorders following traumatic brain injury; a randomized clinical trial. *JAMA Psychiatry* 2016;73 (October):1041–1047. From Baylor College of Medicine, Houston, TX; and other institutions. **Funded by the NIH. Two study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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 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.

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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Adjunctive Rivastigmine and Cognition in Schizophrenia

The cholinesterase inhibitor rivastigmine (*Exelon*), FDA approved for treatment of dementia, improved cognition in patients with schizophrenia already receiving conventional, first-generation antipsychotic medication.

Background: Evidence suggests that alterations in the cholinergic system may underlie cognitive deficits in schizophrenia. The present study was conducted to clarify previous, mixed reports of the efficacy of cholinesterase inhibitors on positive and negative symptoms, as well as cognitive deficits, in patients with schizophrenia.

Methods: Study subjects (n=46; mean age, 45 years) were male inpatients with a DSM-5 diagnosis of schizophrenia, present for ≥ 2 years. Because atypical antipsychotics have beneficial effects on the symptoms of interest (e.g., cognitive, depressive, and negative symptoms), only patients taking first-generation neuroleptics were enrolled. Additional psychotropic medications and psychosocial interventions were not permitted. The patients received treatment with double-blind, randomized, adjunctive rivastigmine (maximum dosage, 12 mg/day) or placebo for 12 weeks. The primary study outcome measures were the Positive and Negative Syndrome Scale and the mini-mental state examination (MMSE).

Results: A total of 10 patients (5 in each group) withdrew from the study prematurely because of gastrointestinal problems or reluctance to participate. Among the remaining 36 patients, the mean MMSE score increased from 24 at baseline to 27 at 12 weeks in the rivastigmine group ($p < 0.001$), while remaining unchanged in the placebo group. Differences in MMSE scores between the groups was evident beginning at week 6. Rivastigmine treatment did not affect positive or negative symptoms of schizophrenia. However, average scores on the Clinical Global Impression-Improvement scale (CGI-I) showed significant improvement from baseline with rivastigmine (from 3.03 to 2.66; $p < 0.05$) but remained unchanged with placebo. Effect sizes* for rivastigmine on the MMSE and CGI-I were 0.8 and 0.5, respectively. Rivastigmine was associated with few adverse effects—i.e., nausea in 2 patients, and vomiting, dizziness, and diarrhea in 1 patient each. Rates were comparable to those in the placebo group.

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Discussion: Current antipsychotic medication is only partially effective against negative symptoms and cognitive decline. Reduced muscarinic and nicotinic receptors in the central cholinergic system may contribute to cognitive impairment in schizophrenia. In Alzheimer's disease, cholinesterase inhibitors produce modest cognitive improvement, slow the progression of memory loss, and reduce apathy, depression, and hallucinations. Current understanding of biological mechanisms suggests that cholinesterase inhibitors have the potential for treating visual hallucinations. While positive, the results of this study are limited by low statistical power, short treatment duration, small sample size, exclusion of female participants, and the possibly limited utility of measuring cognition with the MMSE in patients with schizophrenia.

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

Shafti S, Khoei A: Effectiveness of rivastigmine on positive, negative, and cognitive symptoms of schizophrenia: a double-blind clinical trial. *Therapeutic Advances in Psychopharmacology* 2016;6 (October):308–316. From Razi Psychiatric Hospital, Tehran, Iran. **This study was conducted without external funding. The authors declared no competing interests.**

*See Reference Guide.

SSRI Metabolic Alterations in Psychosis

In a cross-sectional study of patients with schizophrenia or bipolar disorder, SSRIs were associated with small, dose-related adverse metabolic changes. The clinical implications of these alterations are likely to be minimal.

Background: Antidepressants as a group do not adversely affect metabolic parameters in patients with depression, but several studies have reported associations of SSRIs with various aspects of the metabolic syndrome, particularly total and LDL cholesterol. Antidepressants are often prescribed in bipolar disorder or schizophrenia, which themselves are associated with metabolic disturbances. However, the metabolic effects of SSRIs have not previously been studied in this population.

Methods: Study data were extracted for a cohort of patients enrolled in the ongoing University of Norway's Thematically Organized Psychosis study at the University of Oslo. Participants were aged 18–65 years and met DSM-IV criteria for schizophrenia or bipolar disorder. Exposure to SSRIs was defined in 2 ways: by multiples of defined daily dose (10 mg escitalopram; 20 mg citalopram, fluoxetine, and paroxetine; and 50 mg sertraline) and by serum concentrations related to the central laboratory reference range of each drug. The primary outcome of the present analysis was the serum concentration of total cholesterol. Secondary outcomes were other lipid and anthropometric measures. Metabolic syndrome was defined as the measurement of ≥ 3 of the 5 following variables beyond cutoffs defined by the National Cholesterol Education Program Adult Treatment Program-III: waist circumference, HDL cholesterol, triglycerides, glucose, and blood pressure.

Results: Of 1301 eligible patients, 280 (22%) used SSRIs, primarily escitalopram ($n=154$; 55%). Few patients ($n=8$; <3%) received paroxetine. Most patients (about 75%) were also taking antipsychotic drugs.

For each multiple of defined daily antidepressant dose, total cholesterol was increased by nearly 4 mg/dL on average ($p=0.032$). Compared with patients not using SSRIs, those with a serum SSRI level in the middle of the reference range had higher average levels of total cholesterol (14.6 mg/dL; $p=0.002$). Among secondary outcome measures, the SSRI serum concentration was significantly associated only with triglycerides in the adjusted analysis ($p<0.001$). A mid-range SSRI serum concentration was associated with a 2-fold increased risk of metabolic syndrome, relative to patients not taking an SSRI (adjusted odds ratio, * 2.10; $p=0.008$). Adverse metabolic effects have previously been reported for fluoxetine and paroxetine, but removing these SSRIs from the analysis did not affect the results.

Discussion: Although these results extend previous findings of adverse metabolic effects of SSRIs, the absolute size of the alterations found in this study was small and not likely to be clinically concerning. It should be noted that because SSRIs may inhibit the metabolism of antipsychotic drugs, they could enhance these drugs' metabolic effects. However, based on their observations, the study authors consider these effects to be negligible.

Fjukstad K, Engum A, Lydersen S, Dieset I, et al: Metabolic abnormalities related to treatment with selective serotonin reuptake inhibitors in patients with schizophrenia or bipolar disorder. *Journal of Clinical Psychopharmacology* 2016; doi 10.1097/JCP.0000000000000582. From Levanger Hospital, Norway; and other institutions. **Funded by a co-organization of St. Olav's University Hospital and Norwegian University of Science and Technology; and other sources. One study author disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

Common Drug Trade Names: escitalopram—*Lexapro*; fluoxetine—*Prozac*; paroxetine—*Paxil*

*See Reference Guide.

Benign Neutropenia and Clozapine Safety

Clozapine may be used safely in patients with benign ethnic neutropenia (BEN) and pre-existing benign low neutrophil counts with other causes, according to a retrospective chart review. This observation supports the FDA's recent decision to permit low absolute neutrophil counts (ANCs) in patients with BEN, which may lead to less frequent monitoring and more widespread use of the drug.

Background: It has been suggested that the inflexibility of the original, pre-2015 FDA guidelines for monitoring clozapine created a significant impediment to use of the drug, especially in patients of African or Middle Eastern descent. People from these parts of the world can carry a genetic mutation that protects them from malaria, but homozygotes also have ANCs that are lower than heterozygotes or non-carriers. These ANC values fall into the neutropenic range, as defined by norms in European populations, but do not indicate immunocompromise.

Methods: Records were reviewed for patients (n=26; mean age, 34 years at clozapine initiation) with treatment-resistant psychotic disorders and preexisting benign neutropenia who received clozapine in 2001–2014 at a single hospital/research center. Patients were monitored using modified guidelines (see table) that were individualized on the basis of each patient's ANC history. For the most part, green, amber, and red alert thresholds were 500 cells/ μ L lower than conventional guidelines. Patients who did not report African or Middle Eastern ancestry were also included in the review; 19 self-identified as African-American and 7 as Caucasian. ANCs had been monitored for a median of 230 days before clozapine initiation and for 1 year afterward. The primary outcome was the difference in ANC values after initiation of clozapine.

Absolute neutrophil count (ANC) thresholds		
	Present Study	New FDA Guidelines
Severe neutropenia	<500 cells/ μ L	<500 cells/ μ L
Moderate neutropenia	<1500 cells/ μ L	<1000 cells/ μ L
Mild neutropenia	<2000 cells/ μ L	<1500 cells/ μ L

Results: Within-patient ANCs were somewhat more variable after clozapine initiation, and individual mean values were significantly higher after clozapine initiation than before (2630 cells/ μ L vs. 2130 cells/ μ L; $p < 0.001$). However, the median ANC values did not differ from pre-clozapine values. There were no cases of severe neutropenia, and no patient was discontinued from clozapine for falling below their assigned threshold. After clozapine initiation, fewer patients had ANC values that prompted twice-weekly monitoring (4.2% vs. 1.8%; $p = 0.04$) and fewer had ANC values requiring temporary discontinuation (0 vs. 1.9%; $p < 0.001$). Of the 26 patients, 4 discontinued clozapine: 2 for reasons unrelated to medication and 2 because of

thrombocytopenia (preexisting in 1 patient and possibly clozapine-related in the other). Because of the patients with thrombocytopenia, the investigators recommend including the platelet count with regular CBC monitoring in patients with benign neutropenia.

Richardson C, Davis E, Vyas G, DiPaula B, et al: Evaluation of the safety of clozapine use in patients with benign neutropenia. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.15m10315. From the University of Maryland, Baltimore; and other institutions. **Funded by the NIMH; and other sources. One study author disclosed a financial relationship with a commercial source; the remaining 6 authors declared no competing interests.**

Antidepressants and Falls in Older Women

Prescribers may avoid SSRIs and tricyclic antidepressants in frail elderly patients out of concern that these agents increase risk of falls. However, an analysis of data from a clinical trial suggests that other antidepressants, with the possible exception of bupropion, may not be any safer with regard to falls.

Methods: Data from a 2-year clinical trial of a bisphosphonate in frail women, aged ≥ 65 years, living in long-term care facilities were analyzed to determine the risk of recurrent falls with antidepressant use. Participating women ($n=181$; mean age, 85 years) had a history of osteoporosis or vertebral/hip fracture and a life expectancy of ≥ 2 years. Rates of recurrent falls (i.e., ≥ 2 within 6 months) were compared among groups of women receiving SSRIs or TCAs, other antidepressants, or no antidepressant. The "other" category included duloxetine, venlafaxine, mirtazapine, trazodone, and bupropion. Because bupropion is the only one of these agents with low effect on serotonin, a separate analysis was carried out excluding bupropion-treated patients.

Results: The majority of participants (72%) were cognitively intact, while 28% were moderately-to-severely cognitively impaired. At baseline, 33% of women were taking an SSRI or tricyclic, and 18% were taking another antidepressant, including 5 women (3%) receiving bupropion. Depression/anxiety was the most common indication for antidepressant use.

A total of 18% of the study women had recurrent falls during the first 6 months of follow-up, and 16% during the second 6 months. After adjustment for cognitive status, comorbidity, anxiety/depression symptoms, and other medications that may increase falls, women receiving non-SSRI/non-tricyclics had a 2-fold increased incidence of recurrent falls compared with women not receiving any antidepressant (adjusted odds ratio,* 2.14; $p=0.05$). It should be noted that average prescribed doses of non-SSRI/non-tricyclic antidepressants were 67–73% higher than for the minimum effective geriatric dose for depression. SSRI/tricyclics were associated with a smaller increase that was not statistically significant (adjusted odds ratio, 1.46). There was no meaningful change in the odds ratios when the analysis was controlled for the use of bisphosphonate.

When the women taking bupropion were removed from the "other" category, risk for recurrent falls was further increased (adjusted odds ratio, 2.73; $p=0.01$). Bupropion was associated with a 60% lower risk of fractures than no antidepressant use, but the number of exposed women was too small to determine statistical significance.

Discussion: These observations are consistent with findings of previous research associating non-SSRI/non-tricyclics with increased rates of hip fracture.

Naples J, Kotlarczyk M, Perera S, Greenspan S, et al: Non-tricyclic and non-selective serotonin reuptake inhibitor antidepressants and recurrent falls in frail older women. *American Journal of Geriatric Psychiatry* 2016; doi 10.1016/j.jagp.2016.08.008. From the University of Pittsburgh and the VA Pittsburgh Healthcare System, PA. **Funded by the National Institutes on Aging; and other sources. One study author disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

Common Drug Trade Names: bupropion—*Wellbutrin*; duloxetine—*Cymbalta*; mirtazapine—*Remeron*; trazodone—*Oleptro*; venlafaxine—*Effexor*

*See Reference Guide.

Dextromethorphan: Rapid Effect in Resistant Depression

A 51-year-old man presented with recurrent, severe, nonpsychotic unipolar major depression and concomitant generalized anxiety disorder, each with the full spectrum of symptoms.¹ Fluoxetine plus psychotherapy had been prescribed for his first depressive episode many years earlier. Depression remitted for 6–7 months, but he experienced a relapse despite medication adherence. The initial episode eventually remitted spontaneously. More than 20 years later, he had a second episode and subsequently experienced a clinical course of responses, remissions, and relapses while receiving multiple trials and various dosages of citalopram, bupropion, and vortioxetine, alone and in combinations. Depressive symptoms remitted for a short time with 450 mg/day bupropion but returned and did not improve with an increase to 600 mg/day. Assuming a tolerance to bupropion, dextromethorphan was added in a 300-mg loading dose. After his first dose, the patient reported euthymia, with complete remission of depression within 6 hours. However, adverse effects (e.g., nausea, dizziness, blurred vision) developed, requiring a dose reduction to 30 mg b.i.d., which led to a return of depressive symptoms. Symptoms of depression and his anxiety disorder again resolved after the dextromethorphan was increased to 60 mg b.i.d. He remained symptom-free for about 3 weeks, before relapse again occurred without any evident stressors. He did not experience euphoria or mania while taking dextromethorphan.

The time course of improvement in this patient is similar to that observed with ketamine and not consistent with a conventional antidepressant response. Although the patient did not maintain remission, according to the Naranjo probability scale,* his response could "definitely" be attributed to dextromethorphan. This case adds to a previous report of antidepressant efficacy of dextromethorphan in 58 patients with bipolar disorder II and treatment-resistant depression.²

¹Lauterbach E: Treatment resistant depression with loss of antidepressant response: rapid-acting antidepressant action of dextromethorphan, a possible treatment bridging molecule. *Psychopharmacology Bulletin* 2016;46:53–58. From Mercer University School of Medicine, Macon, GA.

²Kelly T, et al: The utility of the combination of dextromethorphan and quinidine in the treatment of bipolar II and bipolar NOS. *Journal of Affective Disorders* 2014;16:333–335.

Common Drug Trade Names: bupropion—*Wellbutrin*; citalopram—*Celexa*; dextromethorphan—*Delsym*; fluoxetine—*Prozac*; vortioxetine—*Trintellix*

*See Reference Guide.

SSRIs, Tamoxifen, and Mortality

According to results of a large cohort study, SSRI-associated inhibition of CYP2D6, the enzyme that converts tamoxifen to its most important active metabolite, does not increase risk of death.¹

Methods: This study compared mortality in women concomitantly treated with tamoxifen and fluoxetine or paroxetine, which are potent inhibitors of CYP2D6, versus any of the other SSRIs, which are not potent inhibitors. The analysis included data from 5 large U.S. electronic health-care databases covering privately insured women and those insured by Medicare or Medicaid. The study cohort included all women simultaneously receiving tamoxifen and an SSRI between 1995 and 2013. The analysis was adjusted for a large number of covariates using propensity scores* for the probability of being prescribed fluoxetine or paroxetine instead of another SSRI.

Results: The study cohort comprised 6067 women who began using tamoxifen before starting an SSRI (of whom 2268 received fluoxetine or paroxetine) and 8465 who received the SSRI first (3531 who used the high-potency CYP2D6 inhibitors). The study women had a mean age of about 55 years at the start of follow-up, which lasted a median of 2.2 years. More than half had a diagnosis of stage 0 or I breast cancer.

Fluoxetine and paroxetine were not associated with increased mortality compared with the other SSRIs (hazard ratio,* 0.96). Mortality was not increased either in women who started tamoxifen before the SSRI (hazard ratio, 0.91) or in those who began SSRI treatment first (hazard ratio, 1.02). Results did not differ when the analysis was stratified by the length of concomitant exposure, when the analysis was limited to fluoxetine or paroxetine as individual agents, or when it included only women who had received a diagnosis of stage 0–IV breast cancer within 180 days before receiving a tamoxifen prescription.

Discussion: Tamoxifen is a prodrug that is converted to 2 active metabolites. It is possible that the lack of an effect of CYP2D6 inhibition may be attributable to the other metabolite, or to the usual practice of administering tamoxifen at much higher doses than are required to be clinically active. A previous study found increases in mortality with paroxetine but not fluoxetine, but in women who were on average 20 years older than those in the present study.² Menopausal status might affect the relationship among tamoxifen, CYP2D6 inhibition, and mortality. An important limitation of this study was the lack of information on breast cancer-specific mortality.

¹Donneyong M, Byov K, Bosco-Levy P, Dong Y, et al: Risk of mortality with concomitant use of tamoxifen and selective serotonin reuptake inhibitors: multi-database cohort study. *BMJ* 2016; doi: 10.1136/bmj.i5014. From Brigham and Women's Hospital and other institutions, Boston, MA. **Funded by the Agency for Healthcare Research and Quality. Two study authors declared financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

²Kelly C, et al: Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ* 2010; doi 10.1136/bmj.c693.

Common Drug Trade Names: fluoxetine—*Prozac*; paroxetine—*Paxil*; tamoxifen—*Nolvadex*

*See Reference Guide.

Relative Cardiac Safety of High-Dose SSRIs

Based on case reports of serious ventricular arrhythmias and thorough QT-interval studies showing prolongation, both citalopram and escitalopram carry FDA maximum-dose warnings. However, in a large cohort of high-dose SSRI users, risk of sudden cardiac death was no higher with citalopram or escitalopram than with other SSRIs.

Methods: Relative risks of sudden unexpected death were examined in a study cohort of patients who were Tennessee Medicaid enrollees and had filled prescriptions for a high-dose SSRI between 1998 and 2011. Excluded from the cohort were patients with a hospital discharge in the previous 30 days, those aged >75 years, those with cancer or other life-threatening diseases, and patients living in a nursing home. High dose was defined as >40 mg/day for citalopram, fluoxetine, and paroxetine, >20 mg/day for escitalopram, and >150 mg/day for sertraline. The primary study endpoint was sudden unexpected deaths, a composite of sudden cardiac deaths, other cardiovascular deaths, and deaths from unintentional medication overdose. Sudden cardiac deaths were deaths consistent with a ventricular tachyarrhythmia in the absence of a known non-cardiac condition; these deaths are considered an indicator of proarrhythmic medication effects. Other cardiovascular deaths were included in the endpoint to allow for misclassification of sudden cardiac deaths and medication overdoses were included because proarrhythmic effects of overdose can lead to death and can be difficult to distinguish postmortem from those due to arrhythmia. The analysis of relative mortality was adjusted for individual patient cardiovascular risk score, which was based on characteristics including other medications and comorbidity.

Results: The cohort consisted of >54,000 patients who filled nearly 560,000 prescriptions for high-dose SSRIs. The mean patient age was 47 years, 76% were women, and 10% were aged ≥60 years. Concomitant medication use was frequent, including antipsychotics (42%), benzodiazepines (58%), mood stabilizers (23%), and opioid analgesics (71%).

A total of 245 deaths occurred in the cohort, of which 145 were sudden unexpected deaths: 95 sudden cardiac deaths, 24 other cardiovascular deaths, and 26 deaths from unintentional overdose. There was some variation among drugs in the crude rates of sudden unexpected deaths, ranging from 27.2 per 10,000 person-years for sertraline to 84.9 per 10,000 person-years for paroxetine. (See table.)

Deaths per 10,000 person-years of treatment					
	Citalopram (n=9860)	Escitalopram (n=4185)	Fluoxetine (n=13,692)	Paroxetine (n=11,080)	Sertraline (n=15,403)
Sudden Unexpected Death	43.3	58.8	34.2	55.1	27.2
Sudden Cardiac Death	25	41.2	20.7	40.2	18.4
Other Deaths	21.6	11.8	32.4	29.8	23.2
All Deaths	64.9	70.6	66.6	84.9	50.3

After adjustment for a large number of covariates including demographic factors, concurrent medications, and comorbid conditions, the risk of sudden unexpected death did not differ between citalopram and any of the other SSRIs. Hazard ratios (HRs)* ranged from 0.89 for citalopram versus paroxetine to 1.53 for citalopram versus sertraline. Hazard ratios for escitalopram also did not differ significantly, ranging from 0.76 with paroxetine to 1.82 with sertraline. There were no significant pairwise differences between drugs for any of the other study outcomes or outcome groupings. In comparisons with all 3 other SSRIs pooled, citalopram was associated with a hazard ratio of 1.16 for sudden unexpected death and escitalopram with a hazard ratio of 1.37. Analyses were also conducted in patients thought to be at greatest risk for the adverse effects of QT prolongation—i.e., those aged ≥ 60 years and those with a high cardiovascular disease risk score. Again hazard ratios did not differ among the SSRIs.

Discussion: The FDA warnings against high-dose citalopram and escitalopram have been controversial, in part because of negative results from several epidemiologic studies. The present study appears to be the first to compare risk among high-dose users of a variety of SSRIs as opposed to high- versus lower-dose users of the same agent.

Ray W, Chung C, Murray K, Hall K, et al: High-dose citalopram and escitalopram and the risk of out-of-hospital death. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.15m10324. From Vanderbilt University, Nashville, TN. **Funded by National Heart, Lung, and Blood Institute; and other sources. The authors declared no competing interests.**

Common Drug Trade Names: citalopram—*Celexa*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; paroxetine—*Paxil*; sertraline—*Zoloft*

*See Reference Guide.

Negative Results for Investigational Alzheimer's Drug

In a randomized clinical trial, the investigational $\alpha 7$ nicotinic acetylcholine receptor agonist ABT-126 failed to show efficacy in patients with Alzheimer's disease. In view of the present results, phase III trials of the drug have been put on hold and the agent has been withdrawn from clinical development. Future development of this class of drugs is uncertain.

Methods: The trial was conducted in patients, aged 55–90 years, with mild-to-moderate Alzheimer's dementia. Patients were randomly assigned to 1 of 3 different doses of ABT-126, placebo, or the active control donepezil (*Aricept*), and received treatment for 24 weeks. After the first 100 patients were enrolled, subsequent patients were randomized with a higher probability to receive the more effective doses of ABT-126. In the second study phase, also 24 weeks, patients were randomly assigned to receive the most effective ABT-126 dose or placebo. The primary efficacy measure was change from baseline to week 24 in the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog).

Results: A total of 438 patients received treatment in the first study phase. The second-phase population included 124 patients who completed the first phase and 88 newly enrolled patients. No statistically significant improvement from baseline in ADAS-Cog score was observed in any of the ABT-126 dosage groups, relative to placebo. In contrast, the donepezil group showed significant improvement in ADAS-Cog scores, indicating the study design was adequate to show an effect. By the end of the second study phase, ABT-126 had some modest treatment effects, but these did not exceed those of donepezil.

Gault L, Lenz R, Ritchie C, Meier A, et al: ABT-126 monotherapy in mild-to-moderate Alzheimer's dementia: randomized double-blind, placebo and active controlled adaptive trial and open-label extension. *Alzheimer's Research and Therapy* 2016; doi 10.1186/s13195-016-0210-1. From AbbVie, Inc., Chicago, IL; and other institutions. **Funded by AbbVie, Inc. All study authors declared financial relationships with commercial sources.**

Reference Guide

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.

Naranjo Probability Scale: A 10-point scale used to determine the likelihood that an adverse reaction is caused by an implicated medication. Based on scores, associations are considered doubtful, possible, probable, or highly probable.

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.

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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Metformin and Weight Loss in Schizophrenia

In a pilot head-to-head comparison study of patients with schizophrenia, both metformin and topiramate produced weight loss in patients with obesity. Metformin, however, was associated with greater weight loss and with more lasting effects.

Methods: Study subjects (n=22) were inpatients with schizophrenia and a body mass index (BMI) of >27 kg m² and a waist circumference >90 cm in men and >80 cm in women. Only hospitalized patients were included to minimize variations in medication compliance and food availability. Patients were nondiabetic and receiving stable doses of antipsychotic medication that were held constant throughout the study. They were randomly assigned to open-label treatment with either 1000 mg/day metformin or 100 mg/day topiramate. Treatment was continued for 3 months, and participants were followed for an additional 9 months. Outcomes were reported at 1 and 4 months after the study medications were stopped. A control group consisted of 10 additional non-obese patients with schizophrenia.

Results: The mean baseline BMI in treated patients was 31, mean waist circumference was 101 cm, mean patient ages were 55 years and 48 years in the metformin and topiramate groups, respectively, and average durations of illness were 27–33 years. Patients in the metformin group lost on average 8.4 lbs by month 4 and 11 lbs by month 7 (p=0.009 and p=0.012, respectively). Average weight loss from baseline in the topiramate group was 6 lbs at week 4 and 4.5 lbs at week 7 (p=0.039 and p=0.099, respectively). Waist circumference decreased by about 7 cm with metformin and 4 cm with topiramate at the 7-month observation. Changes in both weight and waist circumference remained statistically significant at 7 months with metformin, but not with topiramate. The nonobese control group steadily gained weight throughout the study.

Levels of HDL cholesterol increased significantly in both treatment groups and were maintained at 7 months (p<0.04). LDL cholesterol decreased only in the patients who received metformin. Levels of leptin were decreased significantly in both groups only at the later time point.

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Discussion: Previous randomized controlled trials support the efficacy and safety of metformin and topiramate for treating obesity in patients with schizophrenia. This study may be the first head-to-head comparison. The results suggest metformin is the more effective of the 2 agents.

Peng P-J, Ho P-S, Tsai C-K, Huang S-Y, et al: A pilot study of randomized, head-to-head of metformin versus topiramate in obese people with schizophrenia. *Clinical Neuropharmacology* 2016; doi 10.1097/WNF:0000000000000188. From the National Defense Medical Center, Taipei, Taiwan. **Funded by the Civilian Administration Division, Tri-Service General Hospital. The authors declared no competing interests.**

Common Drug Trade Names: metformin—*Glucophage*; topiramate—*Topamax*

Quetiapine in PTSD

In a manufacturer-sponsored trial, quetiapine (*Seroquel*) monotherapy produced significant improvement in PTSD symptoms in a group of military veterans.

Background: Current guidelines recommend atypical antipsychotics as adjunctive therapies in PTSD. The unique pharmacologic profile of quetiapine, as well as evidence from other studies, suggest it may have particular efficacy across a range of PTSD symptoms, including anxious features, depression, and psychotic symptoms.

Methods: Patients who met DSM-IV criteria for chronic PTSD were recruited from 2 VA medical centers in 2004–2008. Participants were required to have a Clinician-Administered PTSD Scale (CAPS) score of ≥ 50 , and those with schizophrenia, bipolar disorder or dementia were excluded. After withdrawal of other medications and a placebo run-in, 80 patients (mean age, 52 years; 75 men) were randomly assigned to receive single-blind treatment with either quetiapine (target dosage 400 mg/day; range 50–800 mg/day) or placebo and received treatment for 12 weeks. The primary outcome measure was the CAPS total score. Secondary outcome measures included the Positive and Negative Syndrome Scale (PANSS), the Hamilton Rating Scale for Depression (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A), the Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I) scales,* and the Pittsburgh Sleep Quality Index (PSQI).

Results: Mean baseline CAPS total scores were 75 and 71 in the quetiapine and placebo groups, respectively. At 12 weeks, the change in CAPS total score was significantly larger with quetiapine than with placebo (22 vs. 5 points; $p=0.02$; effect size,* 0.49). However, at the study endpoint, the mean CAPS score in the quetiapine group was 54, still higher than the cutoff for study entry. Patients who received quetiapine also had larger decreases than the placebo group in the CAPS re-experiencing subscale ($p=0.0004$; effect size, 0.54) and the CAPS hyperarousal subscale ($p=0.007$; effect size, 0.56). Differences in CAPS avoidance/numbing were not statistically significant. Secondary outcomes also generally showed greater improvement with quetiapine than placebo. (See table.) Surprisingly, quetiapine did not improve sleep quality scores. Negative symptoms were also unaffected.

Selected Secondary Efficacy Outcomes with Quetiapine vs. Placebo						
	Quetiapine		Placebo		Significance	Effect Size
	Baseline	Endpoint	Baseline	Endpoint		
HAM-D	20.4	13.4	19.8	18.0	$p=0.02$	0.64
HAM-A	20.0	13.6	18.8	16.6	$p=0.01$	0.41
PSQI	11.0	7.7	10.4	8.6	$p=ns$	0.17
PANSS Global Psychopathology	34.8	29.0	34.7	32.5	$p=0.005$	0.50
PANSS Positive Symptoms	12.7	11.1	11.9	12.0	$p=0.002$	0.32
PANSS Negative Symptoms	14.3	13.1	13.7	13.4	$p=ns$	0.07

Adverse effects of quetiapine were mild and consistent with the known profile of the drug; the most commonly reported were dry mouth (16%), somnolence (13%), and sedation (7%). Quetiapine was not associated with weight gain or blood pressure changes. A total of 9 quetiapine-treated patients (21%) and 3 placebo-treated patients (8%) discontinued medication because of adverse effects.

Discussion: The magnitude and wide range of improvements with quetiapine in this study suggest it may be useful in treating PTSD. However, while the improvements with quetiapine were statistically significant, patients' considerable residual symptoms suggest additional interventions would likely be needed.

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

Villareal G, Hamner M, Canive J, Robert S, et al: Efficacy of quetiapine monotherapy in posttraumatic stress disorder: a randomized, placebo-controlled trial. *American Journal of Psychiatry* 2016;173 (December):1205–1212. From the Raymond G. Murphy VA Medical Center, Albuquerque, NM; and other institutions. **Funded by AstraZeneca. Two study authors disclosed financial relationships with commercial sources including AstraZeneca; the remaining 6 authors declared no competing interests.**

*See Reference Guide.

Adjunctive Asenapine for PTSD

In a pilot study, adjunctive asenapine improved residual symptoms of PTSD in patients receiving treatment with serotonergic antidepressants.

Background: Asenapine was investigated in the present study because some aspects of its pharmacologic profile distinguish it from other atypical antipsychotics. It has a higher affinity for serotonergic and alpha 1 and 2 adrenergic receptors, which are all implicated in PTSD; and its partial agonist activity at the 5HT_{1a} receptor may confer positive effects on mood and anxiety.

Methods: The study, conducted at a VA medical center, enrolled residential patients or outpatients with PTSD who had an inadequate response despite >8 weeks of treatment with citalopram, escitalopram, fluoxetine, mirtazapine, sertraline, or venlafaxine. Those taking fluvoxamine or paroxetine were excluded because of potential interactions with asenapine. Patients taking other psychotropic medications could opt for washout of these agents before enrollment. All study participants were started on 5 mg asenapine b.i.d, which was increased to 10 mg b.i.d. if tolerated and continued for 12 weeks.

Results: The 18 study participants (mean age, 48 years; 3 women) had been experiencing PTSD for an average of 19 years (range, 1–47 years). Traumatic events were mostly military related but also included a few cases of civilian trauma and sexual assault. Most patients (72%) also met criteria for major depressive disorder, and 50% had a substance use disorder, currently in remission.

On average, patients experienced a large, clinically meaningful decrease in PTSD symptoms, as measured using the Clinician-Administered PTSD Scale (CAPS). Mean scores decreased from 78 at baseline to 49 at week 4 and to 35 at week 12 ($p < 0.0001$). Responses extended to each of the 3 CAPS symptom clusters, with robust reductions in re-experiencing and hyperarousal and somewhat smaller effects on avoidance/emotional numbing. Remission, defined as a CAPS score of ≤ 45 , was achieved by 7 patients (39%), and 10 patients (56%) met criteria for response (CAPS decrease of $\geq 30\%$). Other rating scales showed clinically meaningful improvement in overall illness severity and depressive symptoms. Patients did not report improvement on the Quality of Life Enjoyment and Satisfaction Questionnaire.

A total of 15 patients completed ≥ 4 weeks of treatment, and 11 completed the 12-week study. Three patients who withdrew early did so because of adverse effects (i.e., agitation, sedation

syncope, and severe extrapyramidal symptoms (EPS). Treatment was not generally associated with weight gain or EPS. Sedation was the most common adverse event leading to discontinuation.

Discussion: This study group comprised patients with a wide spectrum of age, index trauma, symptom duration, and background antidepressant. However, because the patients had clinical depression and a high rate of residual PTSD symptoms, they may have been atypically refractory. Based on the present results, a larger, placebo-controlled trial appears to be warranted.

Pilkinton P, Berry C, Norrholm S, Bartolucci A, et al: An open label pilot study of adjunctive asenapine for the treatment of posttraumatic stress disorder. *Psychopharmacology Bulletin* 2016;46:8–17. From Tuscaloosa Veterans Affairs Medical Center, AL; and other institutions. **Funded by Merck, Sharp & Dohme Corp.; and Forest Research Institute, Inc. One study author disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

Common Drug Trade Names: asenapine—*Saphris*; citalopram—*Celexa*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; mirtazapine—*Remeron*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor*

Antidepressant Switching

According to results of a meta-analysis, there is no evidence from high-quality studies to support switching antidepressants in patients with major depression who do not experience response to initial antidepressant monotherapy.

Methods: The meta-analysis was based on a wide-ranging search for trials in which non-responding patients with unipolar major depression were randomly assigned to either continue their antidepressant at the same dosage or to switch to a new antidepressant. Nonresponse was defined as a <30% improvement on a standardized rating scale while receiving an antidepressant at standard or higher doses. The primary outcome was the standard mean difference* in depression symptom ratings between the switch and continuation arms of the studies. The investigators conducted a "broad" analysis, which included studies with a dose escalation of the continued drug, and a "strict" analysis, which was limited to studies where the initial antidepressant was continued unchanged.

Results: Four studies were included in the strict analysis, and an additional 4 in the broad analysis. Total patient populations were 459 in the strict analysis and 1627 in the broad analysis. Antidepressant switching strategies in the studies included: from another SSRI to duloxetine (n=3); from either venlafaxine or nortriptyline to fluoxetine (n=2); from fluoxetine to mianserin (n=1); from an SSRI to mirtazapine (n=1); and from desipramine to citalopram or vice versa (n=1). All studies used either the Hamilton Rating Scale for Depression or Montgomery-Asberg Depression Rating Scale to measure outcomes.

None of the 4 studies in the strict analysis found an advantage of switching, and 1 found that continuing the initial antidepressant was superior. In the broad analysis, 5 studies found no difference between strategies, 1 found that switching was superior to continuation, and 2 found that switching was inferior. The meta-analysis did not show a statistical difference between strategies. Conclusions of the meta-analysis did not change when secondary outcomes (response or remission rates) were examined or when the analysis was limited to the 4 studies with a low risk of bias.

Discussion: Despite a lack of supporting evidence, switching antidepressants is common in clinical practice. The published studies examined only a limited number of switching strategies, and the results cannot be generalized to other switching strategies. However, because nearly all antidepressants share a related mechanism of action, switching may not start a truly

new neuropharmacologic action, but may instead only prolong the wait for the drug to take effect. Pending more research, clinicians are advised to choose a second-stage strategy with better support, such as increasing the dosage of the current antidepressant, combining 2 antidepressants, or augmentation.

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

Bschor T, Kern H, Henssler J, Baethge C: Switching the antidepressant after nonresponse in adults with major depression: a systematic literature search and meta-analysis. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.16r10749. From Schlosspark-Hospital, Berlin, Germany; and other institutions. **This research was conducted without funding. The authors declared no competing interests.**

Common Drug Trade Names: citalopram—*Celexa*; desipramine—*Norpramin*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; mianserin (not available in the U.S.)—*Norval, Tolvan*; mirtazapine—*Remeron*; nortriptyline—*Pamelor*; venlafaxine—*Effexor*

*See Reference Guide.

Loss of Antidepressant Effectiveness

In patients with bipolar II disorder receiving medication for depression, the number of prior antidepressant trials was associated with stepwise reductions in the likelihood of response and remission, according to a secondary analysis of data from a clinical trial. The number of prior antidepressant trials was not related to the likelihood of relapse.

Methods: The clinical trial compared the antidepressant efficacy of venlafaxine (*Effexor*) monotherapy and lithium monotherapy in patients with bipolar II depression. Patients (n=129; mean age, 43 years; 73 women) received treatment with randomly assigned medication for 12 weeks, followed by optional continuation therapy in responders for 6 months. Information on prior medications was obtained from patient interviews and medical and pharmacy records. The analysis included only prior antidepressant trials judged to be adequate. Response was defined as a ≥50% reduction in Hamilton Rating Scale for Depression (HAM-D) score and a final Clinical Global Impression–Severity (CGI-S)* score of ≤3. Remission was defined as a final HAM-D score of ≤8 and a CGI-S score of ≤2.

Results: Study participants had undergone a mean of 2.7 prior antidepressant trials; 22 patients (17%) were medication-naïve, and 31 patients (24%) had undergone ≥5 previous trials. Patients who were white, had higher baseline HAM-D scores, and had more prior depressive episodes received a greater number of prior antidepressant trials. Those with interepisode recovery received fewer prior antidepressants. After taking these factors into account, the number of prior antidepressants was associated with lower rates of response to acute treatment (odds ratio,* 0.75; p<0.02) and lower rates of remission (odds ratio, 0.68; p=0.002). The stepwise reductions in these outcomes (see table) were similar in patients treated with venlafaxine or lithium. Specifically, an increase in the number of SSRI trials was associated with reduced likelihood of acute response (odds ratio, 0.75; p=0.02) and remission (odds ratio, 0.78; p=0.04). Loss of effectiveness was not associated with the number of prior mood stabilizer trials or trials of other drug classes.

Previous Trials	# of Patients	Response Rate	Remission Rate
0	22	64%	59%
1	23	70%	61%
2	20	55%	50%
3	19	47%	37%
4	14	36%	36%
5	15	33%	20%
6	16	38%	25%

Discussion: Patients' odds of experiencing response or remission during acute venlafaxine or lithium therapy was reduced by approximately 25% and 32%, respectively, with each increase in the number of prior antidepressant trials. A similar phenomenon has been observed in patients with unipolar depression in several previous studies. The loss of effectiveness appears to be especially common after repeated exposures to SSRIs. The cause of the stepwise loss of effectiveness is unclear but may be related to development of physiological adaptation of central neurotransmitter systems over time, leading to progressive tolerance. Similar adaptations have not been observed with psychotherapeutic interventions, which supports the association.

Amsterdam J, Lorenzo-Luaces L, DeRubeis R: Step-wise loss of antidepressant effectiveness with repeated antidepressant trials in bipolar II depression. *Bipolar Disorders* 2016;18 (November):563–570. From the University of Pennsylvania, Philadelphia; and Brown University, Providence, RI. **Funded by the NIMH; and the University of Pennsylvania. The authors declared no competing interests.**

SSRIs and Intracranial Hemorrhage

In a cohort study, SSRIs, and particularly those with strong serotonin reuptake inhibiting activity, were associated with increased risk of intracranial hemorrhage. Risk was greatest during the first month of use and in patients also taking oral anticoagulants.

Methods: Data were collected from the U.K.'s Clinical Practice Research Datalink, covering more than 12 million patients in primary care. The cohort consisted of all adult patients who received a first prescription for an antidepressant between 1995 and mid-2014 and who had no history of stroke or transient ischemic attack. Case patients were those who experienced an intracranial hemorrhage. For each case, up to 30 controls were matched for age, gender, year of cohort entry, and duration of follow-up. Antidepressant use was defined as current (within 30 days), past (ending 30–90 days before index date), or non-use. A separate analysis compared hemorrhage risk with antidepressants having strong or intermediate serotonin reuptake inhibition, relative to those with weak inhibition. Drugs with strong inhibition were clomipramine, duloxetine, fluoxetine, paroxetine, and sertraline.

Results: The cohort consisted of >1.3 million new users of antidepressants. The mean age at cohort entry was 48 years, and the mean follow-up was nearly 6 years. A total of 3036 patients experienced an intracranial hemorrhage during follow-up. About one-third of patients were taking antidepressants at the time of stroke, including 588 SSRI-treated patients and 364 treated with a TCA.

Relative Risk of Intracranial Hemorrhage Associated with Antidepressant Use		
Risk Category	Comparison Group	Relative Risk*
Current users of SSRIs	Current users of TCAs	1.17
	Non-users of antidepressants	1.35
First 30 days of SSRI use	First 30 days of TCA use	1.44
Strong SSRI inhibition	Weak SSRI inhibition	1.25
Anticoagulants plus strong SSRI inhibition	Anticoagulants plus strong SSRI inhibition	4.99

In the study's main comparison, current SSRI use was associated with an increased risk of intracranial hemorrhage compared with current use of TCAs. (See table.) Risk was greatest during the first 30 days of SSRI use; the difference was no longer statistically significant after 30 days. Hemorrhage incidence was increased in users of SSRIs with strong serotonin reuptake inhibition. These relationships were observed for both intracerebral and subarachnoid hemorrhage. The association was consistent in comparisons of SSRI users with patients not taking antidepressants as well as with users of TCAs. Among patients receiving anticoagulants, the

incidence of intracranial hemorrhage was 3-fold higher in current SSRI users than current users of TCAs, although this increase did not reach statistical significance. The effect was most pronounced in users of SSRIs with strong activity. Use of antiplatelet drugs did not influence risk.

Renoux C, Vahey S, Dell'Aniello S, Boivin J-F: Association of selective serotonin reuptake inhibitors with the risk for spontaneous intracranial hemorrhage. *JAMA Neurology* 2016; doi 10.1001/jamaneurol.2016.4529. From Jewish General Hospital and McGill University, Montreal, Canada. Funded by the Canadian Institutes of Health Research; and the Fonds de la Recherche en Sante du Quebec. The authors declared no competing interests.

Common Drug Trade Names: clomipramine—*Anafranil*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; paroxetine—*Paxil*; sertraline—*Zoloft*

*See Reference Guide.

Paroxetine vs. Cognitive Therapy for Social Anxiety

In a randomized trial, paroxetine (*Paxil*) was less effective than cognitive therapy as treatment for social anxiety disorder. Combining the 2 treatments did not offer any additional advantage over cognitive therapy alone.

Methods: Study subjects were adults, aged 18–65 years, with a primary diagnosis of social anxiety disorder, with or without avoidant personality disorder. Most other psychiatric diagnoses, including major depression, psychotic illness, body dysmorphic disorder, drug or alcohol dependence, and suicidality, were exclusion criteria. Participants (n=102; 50% women) were randomly assigned to 1 of 4 treatment arms: a 12-week program of cognitive therapy; 26 weeks of treatment with paroxetine and clinical management; a combination of cognitive therapy and paroxetine; or placebo pills with clinical management. All medications were administered in a blinded fashion. Paroxetine dosage followed the manufacturer's recommendations for social anxiety disorder (target range, 20–60 mg/day). Cognitive therapy followed a manualized program, with specific enhancements based on metacognitive therapy and providing additional work on regulating attention and reducing threat monitoring. Treatment efficacy was measured using the Fear of Negative Evaluation Questionnaire (FNE), administered at the end of treatment (12 weeks) and at 12 months.

Results: At the 12-week endpoint, average scores on the FNE improved in all 3 groups that received active treatment. Cognitive therapy was significantly superior to paroxetine and placebo but not combination treatment; the combined treatment was superior to placebo but not paroxetine; and paroxetine was not superior to placebo. (See table.) Effect sizes* relative to placebo at 12 weeks were 1.96 for cognitive therapy, 1.09 for the combination, and 0.59 for paroxetine alone. The proportion of patients who met an operationalized criterion for recovery (i.e., ≥6-point change in FNE score plus a final score of ≤15) at 12 weeks was 68% with cognitive therapy, 45% with combination treatment, 23% with paroxetine, and 4% with placebo (p=0.041

Contrasts in change from baseline in FNE scores in patients with social anxiety disorder				
Comparison	12 weeks post-baseline		12 months post-baseline	
	Mean FNE difference [±]	P value	Mean FNE difference [±]	P value
Cognitive therapy vs. combined	-4.1	NS	-4.5	NS
Cognitive therapy vs. paroxetine	-6.2	0.006	-6.1	0.009
Cognitive therapy vs. placebo	-9.0	<0.0005	-8.7	<0.0005
Combined vs. paroxetine	-2.1	NS	-1.6	NS
Combined vs. placebo	-5.0	0.038	-4.2	NS
Paroxetine vs. placebo	not stated	NS	-2.6	NS

[±]Negative number indicates difference in symptom reduction in favor of the first-mentioned treatment. Differences reflect adjusted means. Baseline FNE scores were in the range of 23 to 25 points.

for cognitive therapy vs. combined treatment). Changes in secondary outcomes of anxiety and interpersonal problems generally favored cognitive therapy. By the 12-month follow-up, the combined treatment was no longer superior to placebo and effect sizes were reduced to 1.20, 0.60, and 0.39, for cognitive therapy, combination treatment, and paroxetine, respectively.

Discussion: This study result and a few others challenge the typical assumption that SSRIs and cognitive therapy can be combined to good effect. Possible explanations for the apparent decrease in long-term efficacy in patients who received paroxetine include its effects during tapering, rebound effects, and persistent post-withdrawal disorders.

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

Nordahl H, Vogel P, Morken G, Stiles T, et al: Paroxetine, cognitive therapy or their combination in the treatment of social anxiety disorder with and without avoidant personality disorder: a randomized clinical trial. *Psychotherapy and Psychosomatics* 2016;85 (October):346–356. From the Norwegian University of Science and Technology, Trondheim, Norway; and other institutions. **Funded by the university. The authors did not include disclosure of potential conflicts of interest.**

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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.

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.

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.

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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