You can now easily search the 2015 issues of Psychiatry Drug Alerts and/or use the Index at the end of this collection to find a topic. Save a copy on your device for handy reference or visit http://www.alertpubs.com/Psychonlinecontent.html as needed.

Use Ctrl F on your keyboard to search the document OR click on the issue date below to jump to that month's issue or an article title to go directly to the article.

January 2015
New Adult ADHD Treatment in Development ......................... 1
Biomarker for Antidepressant Response ................................. 1
Antiinflammatory Drugs for Depression ................................ 2
Cannabinoid for Nightmares in PTSD ................................. 3
Paliperidone for Schizoaffective Disorder ......................... 4
Bipolar Depression Treatments: Benefits and Harms ............. 5
Cariprazine for Acute Mania .............................................. 6
Changes to Pregnancy and Lactation Labeling .................... 7
Memantine for Bipolar Disorder ........................................... 7

February 2015
Pioglitazone in Bipolar Depression ........................................ 9
ADHD Medications and Pregnancy Outcomes ..................... 10
Bipolar Disorder Treatment in Pregnancy ..................... 11
Safety of SRIs in Breastfeeding ......................................... 12
Antipsychotic Safety in Breastfeeding ................................ 12
Duloxetine for OCD ......................................................... 13
Adjunctive Pregabalin for Generalized Anxiety Disorder ... 14
Acute Antidepressant Effects of Nitrous Oxide .................... 15

March 2015
Lisdexamfetamine for Binge Eating Disorder ..................... 17
Quetiapine for Generalized Anxiety Disorder ..................... 18
Vortioxetine and Cognitive Deficits .................................. 19
Antidepressants and Cognitive Decline .............................. 20
SSRI plus Stimulant in Geriatric Depression ....................... 21
Long-Term Renal Safety of Lithium .................................... 21
Brexpiprazole in Acute Schizophrenia ............................... 22
Antidepressant Fracture Risks Compared ......................... 23
### September 2015
- Clozapine Monitoring Changes ................................................... 65
- Investigational Aripiprazole Depot Formulation ..................... 65
- Depot Aripiprazole vs. Paliperidone .......................................... 66
- Effects of Long-Term Lithium ..................................................... 67
- Lurasidone: Long-Term Weight Effects ................................. 68
- Flibanserin for Hypoactive Sexual Desire Disorder ................. 69
- Adjunctive Brexpiprazole in Depression .................................. 69
- Medication Changes After Hospital Discharge ........................ 71

### October 2015
- Clozapine and Anemia ............................................................... 73
- Pharmacotherapy for Pathological Hoarding ......................... 74
- New Options for Schizophrenia & Bipolar Disorder ............... 75
- Asenapine Dosing ................................................................. 75
- Brexpiprazole Efficacy in Acute Schizophrenia ...................... 76
- IV Clomipramine for Resistant OCD .................................. 77
- Antidepressants and Ischemic Stroke Mortality ..................... 78
- Dextromethorphan–Quinidine for Agitation in Alzheimer's... 79

### November 2015
- Aripiprazole Augmentation for Late-Life Depression ............. 81
- Atomoxetine Dosing in Adult ADHD ....................................... 82
- Genetic Marker for Schizophrenia Drug Response ............... 83
- Genetics and Antidepressant Response ................................ 84
- Timing of Sertraline for PMDD ............................................. 85
- Lurasidone for Bipolar Depression ....................................... 86
- Antipsychotic Comparison in First-Episode Schizophrenia ... 87

### December 2015
- Cariprazine for Manic Symptoms ......................................... 89
- Lisdexamfetamine in Binge Eating Disorder .......................... 90
- Investigational Antipsychotic: Efficacy and Tolerability ....... 91
- Transmucosal Ketamine for Resistant Depression ............... 92
- Antibiotics, Depression, and Anxiety .................................. 93
- Optimal Duration of Adjunctive Antipsychotics for Mania .. 94
- Antipsychotics and Hip Fracture .......................................... 95
- Chewable Methylphenidate ER ............................................ 96

---

**Index**
New Adult ADHD Treatment in Development

A novel dopamine and norepinephrine reuptake inhibitor (DNRI), dasotraline, appears to be an effective treatment for adults with ADHD, according to results of a placebo-controlled clinical study presented at the American College of Neuropsychopharmacology Annual Meeting. The agent, still in development, inhibits presynaptic dopamine and norepinephrine reuptake. It has a half-life suggestive of extended steady state plasma concentrations and therapeutic effects over a 24-hour dosing interval. In the first randomized, placebo-controlled trial, 4 weeks of dasotraline treatment, at dosages of 4 and 8 mg/day, improved ADHD Rating Scale–IV total scores as well as scores on both the inattentive and hyperactivity/impulsivity subscales. Results for the higher dose were statistically significant, while the lower dose was numerically but not statistically superior to placebo. The most common adverse effect leading to dasotraline discontinuation was insomnia (2.6% for the 4-mg dose and 10.8% for the 8-mg dose), followed by anxiety (2.6% and 1.8%, respectively), and panic attacks (0% and 2.7%). None of these adverse effects were recorded in the placebo group.

A second study is underway in an attempt to replicate these positive results. A clinical development program is also planned to assess the safety and efficacy of dasotraline in pediatric ADHD.


Biomarker for Antidepressant Response

C-reactive protein (CRP), an inflammatory biomarker, was a strong differential predictor of response to escitalopram versus nortriptyline in a randomized trial. The easy accessibility of CRP and its high predictive value suggest that if these results are replicated, it could be a clinically useful aid in antidepressant drug selection.

Methods: Data were analyzed from a subgroup of patients who participated in the Genome-Based Therapeutic Drugs for Depression (GENDEP) study, a European multicenter trial to compare...
treatment with escitalopram and nortriptyline. The analysis included 241 GENDEP participants who had CRP levels measured at baseline. In the GENDEP study, patients were randomly assigned to treatment for 12 weeks with open-label, protocol-guided escitalopram (mean dosage, 17 mg/day) or nortriptyline (mean dosage, 106 mg/day). The primary study outcome was the Montgomery-Asberg Depression Rating Scale (MADRS) total score.

**Results:** At baseline, measurement of CRP suggested low levels of systemic inflammation in 54% of patients, moderate levels in 26%, high levels in 15%, and levels suggesting acute inflammation in 4%. CRP was not correlated with depression severity or with any depressive symptom domains.

The 2 antidepressants were equally effective in the sample as a whole. Baseline CRP levels significantly interacted with antidepressant drug in predicting treatment outcome (p<0.001). The interaction was primarily due to the finding that escitalopram was less effective than nortriptyline for patients with high CRP levels. At low levels of systemic inflammation, escitalopram led to a 3-point greater MADRS improvement than nortriptyline. At moderate-to-high levels of inflammation, nortriptyline led to an improvement of 3 more points than escitalopram. The differential effects were similar when comparing Hamilton Rating Scale for Depression scores and even larger when comparing the self-reported Beck Depression Inventory. The interaction affected all 3 symptom dimensions: mood, cognitive, and neurovegetative. Levels of CRP explained 11% of the individual-level variance in the final MADRS score, greater than the clinical significance benchmark of 6.3% variance.

**Discussion:** The hypothesis of this study was based on the observations that inflammatory markers can predict response to a single antidepressant and that, in preclinical studies, the 2 antidepressant categories affect inflammation via different mechanisms. Among their multiple immunologic effects, there is evidence that norepinephrine reuptake inhibitors suppress cellular immunity and shift the balance toward humoral immunity, and serotonin reuptake inhibitors do the reverse. Although a tricyclic antidepressant, nortriptyline is also a norepinephrine reuptake inhibitor and has a superior efficacy record compared with more selective noradrenergic antidepressants.

Uher R, Tansey K, Dew T, Maier W, et al: An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. *American Journal of Psychiatry* 2014;171 (December):1278–1286. From Dalhousie University, Halifax, Canada; and other institutions. Funded by the European Commission; and other sources. Five study authors disclosed relationships with commercial sources; the remaining 6 authors declared no conflicts of interest.

**Drug Trade Names:** escitalopram—Lexapro; nortriptyline—Aventyl, Pamelor

### Antiinflammatory Drugs for Depression

A meta-analysis provides some support for the concept that antiinflammatory treatments may improve depression or depressive symptoms when used as monotherapy or as an add-on to SSRIs.

**Methods:** The analysis included all identifiable randomized controlled clinical trials of any antiinflammatory agent in adult patients with diagnosed depression or those with subclinical depressive symptoms measured with a clinician-rated scale or self-report questionnaire. Agents of interest were nonsteroidal antiinflammatory drugs (NSAIDs), cytokine inhibitors, and minocycline. The primary outcomes of interest were measures of symptom severity, expressed as a standard mean difference; response or remission as defined by each study; and serious gastrointestinal or cardiovascular adverse effects.

**Results:** A total of 14 randomized trials were conducted in 6262 patients and described in 10 publications. There were 10 trials of NSAIDs (6 as monotherapy, 4 as add-on treatment; all used
celecoxib), and 4 trials of cytokine inhibitor monotherapy. Most trials were 6–12 weeks in duration. Nine trials were conducted in patients with somatic comorbidity (e.g., osteoarthritis or psoriasis).

Antiinflammatory treatment was associated with an overall antidepressant effect size* of 0.34 (p=0.004). NSAIDs were associated with a pooled effect size of 0.27 (p=0.004), and cytokine inhibitors with an estimate that was somewhat larger but not statistically significant. Compared with placebo or other controls, antiinflammatory treatment was associated with higher likelihoods of response (odds ratio,* 2.41; p=0.02) and remission (odds ratio, 2.73; p=0.004). None of the NSAIDs were associated with adverse gastrointestinal or cardiovascular effects, but only a few trials provided information on these events. Cytokine inhibitors were not associated with increased infections.

**Discussion:** Most of the studies included in this analysis were small, the duration of observation was limited, and effect sizes were small to medium. All trials had a high risk of bias based on design, reporting features, and industry sponsorship. Despite these cautions, the authors say, the study provides proof of concept of clinically relevant effects of NSAIDs' depression response and remission.

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

Kohler O, Benros M, Nordentoft M, Farkouh M, et al: Effects of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 2014;71 (December):1381–1391. From Aarhus University Hospital, Denmark; and other institutions. Funded by Pfizer, manufacturer of Celebrex. The authors declared no conflicts of interest.

**Drug Trade Names:** celecoxib—Celebrex; minocycline—Dynacin, Minocin

*See Reference Guide.

---

**Cannabinoid for Nightmares in PTSD**

In a preliminary crossover study, nabilone (Cesamet), a synthetic endocannabinoid, was effective in relieving nightmares associated with combat-related PTSD.¹

**Methods:** Study participants were 10 men (mean age, 44 years) currently serving in the Canadian armed forces who had onset of PTSD at least 2 years in the past and who were experiencing distressing nightmares and difficulty falling and/or staying asleep. Patients were allowed to continue their current medication and psychotherapy during the study, provided there were no changes. They were assigned to receive double-blind nabilone and placebo for 7 weeks each, in random order, separated by a 2-week washout. Nabilone was flexibly dosed at 0.5–3 mg/day and taken 1 hour before bedtime. Symptoms were assessed using items on the Clinician-Administered PTSD Scale (CAPS). The primary outcome was change in score on the CAPS Recurring Distressing Dreams item.

**Results:** At baseline, all participants had experienced ≥1 distressing dream during the previous week. All patients completed nabilone therapy. A single patient was transferred for unrelated reasons before completing the placebo phase.

The mean baseline CAPS nightmare score was 6 in both groups at the start of each treatment period. Nabilone produced a significantly greater reduction in CAPS nightmare scores than placebo (3.6 points vs. 1 point; p=0.03). The 2 components of the score, Frequency and Intensity, were both reduced with nabilone (p=0.05 and p=0.06, respectively). Seven of 10 patients were rated as much or very much improved after nabilone treatment, compared with 2 of 9 after the placebo phase. Improvements with nabilone were also reflected by a significantly lower Clinical Global Impression-Improvement* score (1.9 after nabilone vs. 3.2 after placebo; p=0.05) and by significant improvement in the Well Being Questionnaire (p=0.04), compared
with a slight decline with placebo. Nabilone did not affect sleep quantity or quality. At the end of nabilone treatment, 4 patients reported no distressing dreams in the past week, compared with none of the patients in the placebo group.

Nabilone was well tolerated. There were no significant changes in blood pressure or heart rate, and no subject withdrew because of adverse effects. During nabilone treatment, dry mouth affected 6 patients, and headaches occurred in 4.

**Discussion:** Nabilone, approved for treating chemotherapy-induced nausea, does not produce a positive urine test for cannabis and has little or no street value. It was previously found to suppress nightmares and showed promising effects in an open-label study in a civilian population. Although the current results are positive, they require replication because of the small sample size.

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

---

**Paliperidone for Schizoaffective Disorder**

Oral paliperidone is the only agent with FDA approval for acute treatment of schizoaffective disorder. In a manufacturer-sponsored randomized trial, once-monthly injectable paliperidone was effective for relapse prevention.

**Methods:** Study participants were adults with an acute exacerbation of psychotic symptoms lasting between 4 days and 4 weeks; all had prominent mood symptoms at study entry. Patients first underwent a 13-week, open-label, flexible-dose titration of monthly injectable paliperidone as either monotherapy or added to existing antidepressant, mood stabilizer, or benzodiazepine therapy. All previous antipsychotic agents were withdrawn. Patients who met criteria for reduction of psychotic and mood symptoms then entered a 12-week stabilization period, with no dose adjustments. Those who remained clinically stable were randomized to double-blind treatment with either continued paliperidone or switched to injectable placebo, and then followed for 15 weeks. The primary study outcome was relapse, which the investigators defined using any of 5 criteria: psychiatric hospitalization; an intensification of care to avoid hospitalization; clinically significant suicidality or violence; worsening of selected core psychotic symptoms; and/or stable worsening of certain other symptoms or overall clinical status. Psychotic symptoms were measured with the Positive and Negative Syndrome Scale, and clinical status with the Clinical Global Impression–Severity (CGI-S) score.

**Results:** A total of 667 patients received lead-in treatment, of whom 334 (mean age, 39 years; 51% men) were stabilized and randomized to paliperidone or placebo. Most received stable paliperidone doses of 156 mg or 234 mg. Relapses occurred during the randomized study phase in 25 patients (15%) who received paliperidone and 57 (34%) who received placebo. Relapse was more than twice as common in the placebo group (hazard ratio,* 2.49; p<0.001). Relapse risk was lower with paliperidone both in patients who received the drug as monotherapy and in those in whom it was added to other medications. All types of relapse—psychotic, depressive, and manic—occurred less frequently with paliperidone than with placebo.

Personal and social functioning, a secondary outcome, measured with the Personal and Social Performance Scale, significantly favored paliperidone over placebo (p=0.014). At the start of
randomized treatment, more than 95% of patients had CGI-S scores reflecting mild or no illness. At the study endpoint, these favorable scores were observed in 84% of the paliperidone group and 65% of the placebo group.

The adverse-event profile of paliperidone was similar to that reported in acute-treatment studies. Only patients who could tolerate injectable paliperidone were included in the randomized phase, limiting the study’s ability to detect adverse events. The tolerability results from the open-label phase of this trial will be published separately.

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


*Drug Trade Names:* paliperidone—*Invega*; paliperidone IM—*Invega Sustenna*

*See Reference Guide.

## Bipolar Depression Treatments: Benefits and Harms

According to a review of the overall benefits and harms of treatments for acute bipolar depression, the olanzapine-fluoxetine combination and quetiapine monotherapy are useful in high-urgency situations, where efficacy rather than tolerability is the primary concern. In contrast, antidepressants have better tolerability that might mitigate their lesser efficacy in low-urgency situations. Lurasidone, the most recently approved bipolar-depression treatment, may have utility in a wide range of situations, independent of urgency.

### Methods:
The analysis, funded in part by Sunovion (the manufacturer of lurasidone), was based on large (sample size, >100), published, randomized, placebo-controlled trials of treatments for acute bipolar depression and a single meta-analysis of multiple antidepressants. The included studies reported response as ≥50% improvement on a depression rating scale. The present analysis evaluated benefit as the number needed to treat (NNT)* to yield 1 additional response, compared with placebo. Harm was evaluated as the number needed to harm (NNH)* for the adverse effect that was most common and clinically relevant for each particular treatment.

According to some, the goal of treatment should be a single-digit NNT and at least a double-digit NNH—that is, at least 10% more efficacy than placebo and no greater than a 10% greater risk of adverse effects.

<table>
<thead>
<tr>
<th>Benefits (NNTs) and Harms (NNHs) of Treatments for Acute Bipolar Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Olanzapine-Fluoxetine</td>
</tr>
<tr>
<td>Quetiapine</td>
</tr>
<tr>
<td>Olanzapine monotherapy</td>
</tr>
<tr>
<td>(U.S. trial)</td>
</tr>
<tr>
<td>Olanzapine monotherapy</td>
</tr>
<tr>
<td>(international trial)</td>
</tr>
<tr>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Lurasidone monotherapy</td>
</tr>
<tr>
<td>Adjunctive lurasidone</td>
</tr>
<tr>
<td>Adjunctive armodafinil</td>
</tr>
</tbody>
</table>

*NNT for Montgomery Asberg Depression Rating Scale (MADRS) response vs. placebo
**NNH for clinically relevant harm vs. placebo
Results: Both the olanzapine–fluoxetine combination and quetiapine monotherapy have single-digit NNT and NNH estimates. (See table). They have adequate efficacy, but their utility may be substantially limited by having an approximately equal likelihood of causing benefit and harm: weight gain for olanzapine–fluoxetine and sedation/somnolence for quetiapine. Lurasidone, approved in 2013 as monotherapy or an adjunct to mood stabilizers in acute bipolar depression, was found to have a favorable benefit-to-harm ratio that is not offset by a reduction in efficacy.

Among off-label treatments, olanzapine monotherapy shows a greater likelihood of harm than benefit. Lamotrigine and antidepressants show relatively weak efficacy but a low likelihood of harm. Armodafinil has had variable results in clinical trials.

Discussion: In terms of tolerability, the present findings should be interpreted cautiously as the calculated NNH refers to the adverse effect judged to be most clinically relevant (i.e., affected the most patients compared with placebo), thus the risk assessment does not include more serious adverse effects that have a low prevalence (e.g., skin rash with lamotrigine).

Ketter T, Miller S, Dell’Osso B, Calabrese J, et al: Balancing benefits and harms of treatments for acute bipolar depression. Journal of Affective Disorders 2014;169:S1:S24–S33. From Stanford University School of Medicine, CA; and other institutions. Funded by Teva Pharmaceuticals; and Sunovion Pharmaceuticals. All 6 study authors disclosed financial relationships with commercial sources, including 4 with Sunovion.

Drug Trade Names: armodafinil—Nuvigil; fluoxetine—Prozac; lamotrigine—Lamictal; lurasidone—Latuda; olanzapine—Zyprexa; olanzapine-fluoxetine—Symbyax; quetiapine—Seroquel

*See Reference Guide.

Cariprazine for Acute Mania

The investigational atypical antipsychotic cariprazine was effective and well tolerated in a randomized, controlled trial of patients with acute mania or mixed episodes of bipolar I disorder.¹

Background: Cariprazine is a dopamine D2 and D3 receptor partial agonist. Unlike other drugs of this class, cariprazine has strongly preferential binding to the D3 receptor, which is thought to play a role in regulating mood and cognition.

Methods: Subjects in this multicenter, parallel-group study were 312 adults, aged 18–65 years (65% men), with confirmed bipolar I disorder who were currently experiencing acute mania, with or without psychotic symptoms. Those experiencing their first episode or with rapid cycling were excluded. Participants were required to have a Young Mania Rating Scale (YMRS) total score of ≥20, with elevated scores on ≥2 of the following: irritability, speech, content, and disruptive/aggressive behavior. Following a 4–7 day inpatient washout of previous medications, patients received double-blind treatment with either cariprazine or placebo for 3 weeks. Cariprazine was flexibly dosed in the range of 3–12 mg/day. The primary efficacy endpoint was the YMRS score after 3 weeks of treatment, with response defined as a ≥50% decrease in score, and remission as a score of ≤12.

Results: About one-third of patients in each group discontinued treatment before completing the study. Discontinuations due to withdrawal of consent were more common with cariprazine (17% vs. 11%), and withdrawal for lack of efficacy occurred more frequently with placebo (10% vs. 4%). Premature discontinuation due to adverse effects was similar in both groups: 10% and 7% in the cariprazine and placebo groups, respectively.

In a last observation carried forward analysis,* cariprazine was associated with a larger mean decrease than placebo in YMRS score. The mean baseline score was 32 in each treatment group. At the 3-week evaluation, scores were decreased by 20 points with cariprazine versus 15 points
with placebo (p=0.0004; effect size,* 0.40). Cariprazine treatment also produced significantly
greater improvements in Clinical Global Impression-Severity (p=0.0027) and Improvement
scores (p=0.0004), and Positive and Negative Syndrome Scale scores (p=0.0035). Montgomery-
Asberg Depression Rating Scale scores were low at baseline and did not change differentially
with treatment. Response occurred in 59% of the cariprazine group, compared with 44% of the
placebo group (p=0.0097), and remission in 52% and 35%, respectively (p=0.0025).

Cariprazine was associated with higher rates of akathisia (22%) and extrapyramidal symptoms
(15%) than placebo (5% and 2%, respectively). The agent was not associated with increased
rates of weight gain; metabolic problems; QTc prolongation; prolactin increases; or sedation.

**Discussion:** The effect size for cariprazine in the present study, although modest, was compa-
rable to those calculated for other atypical antipsychotics in a meta-analysis of acute mania
treatments.\(^2\) In addition, the mean changes in weight and metabolic parameters were small,
suggesting cariprazine may have a favorable metabolic profile compared with other agents.
However, given the short treatment duration, this requires replication in longer-term studies.

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

double-blind, placebo-controlled, phase III trial. *Journal of Affective Disorders* 2015;174 (March):296–302. From
Massachusetts General Hospital, Boston; and other institutions. **Funded by Forest Laboratories, Inc.; and Gedeon
Richter Plc. All study authors disclosed financial relationships with commercial sources, including 7 of the 8 with
(March):21.


*See Reference Guide.

**Changes to Pregnancy and Lactation Labeling**

The FDA has updated its standards for how information about medication use during preg-
nancy and breastfeeding is presented in the labeling of prescription drugs and biological
products. The current system, which uses categories A, B, C, D, and X to classify the risks of
using prescription drugs during pregnancy, gives an over-simplified view of risk and will be
replaced by 3 detailed label subsections that describe risks in a real-world context. The 3
sections—Pregnancy, Lactation, and Females and Males of Reproductive Potential—will each
include a summary of the risk, a discussion of the data supporting the summary, and relevant
information to help physicians make prescribing decisions. When the final rule is in effect (June
30, 2015), newly approved drugs and biological products will be required to use the new format
immediately, while the changes for previously approved products will be phased in over time.

FDN issues final rule on changes to pregnancy and lactation labeling information for prescription drug and biological

**Memantine for Bipolar Disorder**

Preliminary clinical studies suggest that memantine, approved for treatment of Alzheimer’s
dementia, may be effective in preventing both phases of bipolar disorder and in reducing
manic-like symptoms associated with other disorders. Memantine was effective in reducing
symptoms of acute mania in a 3-week open-label trial in 33 patients and as an add-on therapy
in 2 small naturalistic trials lasting 6 and 12 months. In another small study of treatment-
resistant bipolar disorder, memantine decreased the duration of illness, the duration of new
episodes, recurrence frequency, and symptom severity over 3 years. In contrast, however,
2 small placebo-controlled studies showed no or limited efficacy of memantine added to
lamotrigine or valproate. A multicenter, randomized, controlled trial is currently underway
of adjunctive treatment with memantine or lamotrigine in patients with bipolar I disorder resistant to lithium or other standard treatments.

Evidence suggests that NMDA receptor stimulation mediates the development of dopamine D2 receptor sensitization, an underlying phenomenon of mood alterations. Antidepressant-induced manic episodes are associated with D2 receptor sensitization, followed by reduced sensitivity when the drug is withdrawn. This drug-induced phenomenon may be more than merely iatrogenic; it may intensify a spontaneous underlying process. In animal models, the NMDA receptor blocker memantine prevents antidepressant-induced increased sensitivity to D2 receptor stimulants and the subsequent desensitization and depressive-like behavior. Memantine may also act by blocking extracellular NMDA receptors, thereby preventing the excitotoxic effects of mania and the neurodegeneration that may underlie the depressive phase of the disorder. This mechanism is shared by lithium, a mainstay in the treatment of bipolar disorder.


Drug Trade Names: lamotrigine—Lamictal; memantine—Namenda; valproate—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.

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 one group has half the risk of the other group.

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

Number Needed to Harm (NNH): 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.

Number Needed to Treat (NNT): 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 >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 have been posted at www.alertpubs.com.

Contributing Editors: Kate Casano, MSHyg; Bennett Silver, MD
Consulting Editor: Steven J. Schleifer, MD, Rutgers–New Jersey Medical School
Executive Editor: Trish Elliott Associate Editor: Tara Hausmann Assistant Editor: Kasey Madara
Founding Editor: Michael J. Powers

*Off-Label Drug Use Statement:* Some drugs discussed for specific indications in *Psychiatry Drug Alerts* articles may not be approved for labeling and advertising for those indications by the United States Food and Drug Administration.
Pioglitazone in Bipolar Depression

In a group of patients with bipolar depression and no significant metabolic disorder, adding pioglitazone (Actos) to lithium produced earlier response and a higher rate of remission.

Background: The oral antidiabetic pioglitazone has incidentally been found to have antidepressant effects in patients with concomitant diabetes or metabolic syndrome and major depression or bipolar disorder. The present randomized controlled trial was undertaken to evaluate the antidepressive effects of adjunctive pioglitazone in patients receiving lithium for bipolar depression.

Methods: Study subjects (n=48; 15 women) had a DSM-IV-TR diagnosis of bipolar I disorder and were experiencing a current depressive episode that had not responded to a trial of lithium plus an antidepressant. Patients were required to have stable, therapeutic levels of lithium for ≥2 consecutive weeks before starting 6 weeks of double-blind, randomly assigned placebo or pioglitazone (15 mg/day for 1 week, followed by an increase to 30 mg/day). Response was defined as a ≥50% reduction in the Hamilton Rating Scale for Depression (HAM-D) score without a switch to mania or hypomania; early improvement was defined as a ≥20% reduction on the HAM-D within the first 2 weeks; and remission as a final score of ≤7.

Results: Of the 48 patients, 4 withdrew before receiving treatment and the remaining 44 completed the trial. The average illness duration was about 4.5 years, and patients had experienced an average of 4 previous depressive episodes. HAM-D scores averaged about 23 points at baseline and decreased by about 14 points with pioglitazone and 12 points with placebo (mean difference, 2.27; p=0.006). A total of 19 patients experienced response with pioglitazone and 16 with placebo, a statistically nonsignificant difference. Early improvement was observed in all 22 patients in the pioglitazone group and in 17 of 22 (77%) in the placebo group (p=0.048). Five patients experienced remission with pioglitazone, and 1 with placebo (23% vs. 5%), but the difference was not statistically significant. Treatment had no effect on fasting blood glucose, hemoglobin A1c, body weight, or hepatic enzymes. No patient experienced hypoglycemia, and no patient switched to mania or hypomania.
**Discussion:** Preclinical studies suggest the antidepressant effects of pioglitazone are mediated at least partly through the nitric oxide pathway and PPARγ (peroxisome proliferator-activated nuclear receptor gamma) receptors. The present results support the hypothesis that the pathophysiology of depressive disorders extends beyond the monoamine pathways. However, because participants were not tested for insulin resistance, it is possible the antihypoglycemic effects of pioglitazone may have played a role in patients' early response to treatment.

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

Zeinoddini A, Sorayani M, Hassanzadeh E, Arbabi M, et al: Pioglitazone adjunctive therapy for depressive episode of bipolar disorder: a randomized, double-blind, placebo-controlled trial. *Depression and Anxiety* 2015; doi 10.1002/da.22340. From Tehran University of Medical Sciences, Iran; and other institutions. Funded by Tehran University. The authors declared no conflicts of interest.

*See Reference Guide.*

### ADHD Medications and Pregnancy Outcomes

In a population-based cohort study, treatment with ADHD medications was associated with increased rates of some adverse pregnancy outcomes, but these were largely explained by the effects of ADHD itself.

**Methods:** Registry data were analyzed from a cohort of nearly 1 million pregnancies in Danish women over a 12-year period. The data included all diagnoses of ADHD and all prescriptions for methylphenidate or atomoxetine that were filled beginning 30 days before the estimated date of conception, until birth, stillbirth (weeks 22–28), or spontaneous abortion (before week 22). Adverse pregnancy outcomes included low birth weight (<5.5 lbs.), preterm birth (before 37 weeks), small size for gestational age (<10th percentile), Apgar scores <10 at 5 minutes, and major congenital malformations.

**Results:** The study population included 186 women who were taking ADHD medications and 275 with ADHD who did not use medications. Compared with those without ADHD, women with ADHD were younger, less well educated, lower-income, and more likely to be single and nulliparous; they also had higher rates of concomitant medication, comorbidity, and smoking. Women with ADHD had about a 55% increased risk of spontaneous abortion compared with those without ADHD, after adjustment for maternal age, education, cohabitation, comorbidity, and comedication. This association was present regardless of medication use. Women taking ADHD medication had a significantly higher adjusted proportion of newborns with low Apgar scores than comparison women (adjusted relative risk,* 2.06), but unmedicated women with ADHD did not (relative risk, 0.99). Unmedicated women with ADHD, but not medicated women, had elevated adjusted rates of preterm births compared with controls. Other study outcomes occurred too infrequently in women taking ADHD medications to be analyzed statistically: preterm birth, small for gestational age, low birth weight, and congenital malformations.

**Discussion:** Animal studies have shown methylphenidate associated with high rates of congenital anomalies, but this finding has not been replicated in humans. A few human studies suggest ADHD medications may be associated with adverse pregnancy outcomes. Confounding by indication—the contribution of risk from the underlying disease—is a persistent challenge in pharmacoepidemiological studies. The present study indicates that at least part of the increase in spontaneous abortion associated with ADHD medications may be due to the disorder itself, while low Apgar scores appear to be a direct effect of the drugs.

Bro S, Kjaersgaard M, Parner E, Sorensen M, et al: Adverse pregnancy outcomes after exposure to methylphenidate or atomoxetine during pregnancy. *Clinical Epidemiology* 2015;7:139–147. From Aarhus University and Aarhus University Hospital, Denmark. Funded by the Danish Epilepsy Foundation. The authors declared no competing interests.

**Drug Trade Names:** atomoxetine—Strattera; methylphenidate—Ritalin and others

*See Reference Guide.*
Bipolar Disorder Treatment in Pregnancy

During pregnancy both untreated bipolar disorder and pharmacotherapy for the disorder pose risks to mother and baby. According to a comprehensive literature review, there are no risk-free treatment options, and decisions about pharmacotherapy should move beyond simply whether or not to treat, and should encompass ways to minimize potential harms.

Episodes of mania or depression recur during pregnancy in 25–30% of women with bipolar disorder. There is no evidence that pregnancy protects women with bipolar disorder from a recurrence of mood episodes, and the postpartum period is a time of high risk. A diagnosis of maternal bipolar disorder is associated with a small but statistically significant increase in risk of pregnancy complications including placental abnormalities, antepartum hemorrhages, and toxicities related to substance use. Maternal bipolar disorder is also linked to neurocognitive and psychiatric impairments in the offspring. Uncontrolled bipolar disorder is associated with behavioral risks including substance use, poor adherence to prenatal care, disruptions in family and social support structures, and suicide.

Controlled studies and published treatment guidelines generally support the use of effective maintenance treatment with mood stabilizers during pregnancy. Valproate appears to be associated with the highest risk of teratogenicity, neonatal adverse events, and neurodevelopmental difficulties. Risk increases with the valproate dose and with concomitant use of other anticonvulsants. Congenital malformation rates are lower with lithium and carbamazepine, and rates with lamotrigine are similar to background rates in the general population. There has so far not been convincing evidence that carbamazepine, lamotrigine, or lithium is associated with neurodevelopmental difficulties.

The efficacy and safety of atypical antipsychotics in pregnancy have not been well studied, and the risk of major congenital malformations is unclear. The major risks associated with these agents appear to be excessive weight gain, maternal diabetes, and gestational diabetes. In addition, all atypical antipsychotics carry an FDA warning about the possibility of extrapyramidal symptoms and withdrawal syndromes in newborns exposed during the third trimester.

Practice guidelines for the treatment of bipolar disorder during pregnancy generally agree on several points: the need to discuss reproductive and obstetric risks long before a pregnancy is planned; maximizing nonpharmacologic treatments, social supports, and regularity of sleep; use of monotherapy; avoidance of valproate in the first trimester; and use of ECT.

| Reproductive Safety of Mood Stabilizers in Bipolar Disorder |
|-----------------|----------------------------------|
| Drug            | Major Reproductive Safety Concerns |
| Lithium         | Major congenital malformation rate: 2.8%  
                 | Neonatal adaptation syndrome has been reported, with risk increasing with higher maternal lithium levels |
| Valproate       | Highest major congenital malformation rate among mood stabilizers: 5–11%  
                 | Fetal risks may be dose-dependent and are increased when used with other anticonvulsants  
                 | Reported neonatal toxicity syndromes |
| Carbamazepine   | Major congenital malformation rate: 2–6%  
                 | Other adverse neonatal events also reported |
| Lamotrigine     | Risk of major congenital malformations and other adverse neonatal outcomes is unclear  
                 | No evidence of increased risk of adverse neurodevelopmental outcomes |
for severe or refractory symptoms. Guidelines also disagree on some points: whether lithium should be continued or avoided and the degree to which atypical antipsychotic treatment is prioritized.


Drug Trade Names: carbamazepine—Epitol, Tegretol; lamotrigine—Lamictal; valproate—Depakene, Depakote

*See Reference Guide.*

Safety of SRIs in Breastfeeding

When antidepressant treatment is required in a breastfeeding woman, the SRIs with the most favorable neonatal safety profile appear to be paroxetine and sertraline, according to a systematic literature review.

**Methods:** A comprehensive literature search was undertaken to identify articles that reported data on the use during breastfeeding of any of the 6 available SSRIs or 2 SNRIs. The studies reported effects of exposure during breastfeeding on selected pharmacokinetic indices of newborn exposure (e.g., relative infant dose, milk-to-plasma ratio, infant plasma concentrations) short-term outcomes (until 6 months postpartum), and long-term outcomes.

**Results:** A total of 104 studies were included in the analysis: 14 with citalopram; 8 with escitalopram; 21 with fluoxetine; 11 with fluvoxamine; 17 with paroxetine; 22 with sertraline; 3 with duloxetine; and 8 with venlafaxine. About one-third of those included were case reports. According to the review, only 2 cases of mild, transient adverse events were identified in the 228 infants exposed to paroxetine and 1 of the 279 infants exposed to sertraline. Exposure indices were within acceptable limits for both drugs. Moderately severe short-term effects and reduced growth curves have been reported with fluoxetine. The incidence of short-term adverse effects appears to be somewhat increased with citalopram and escitalopram, but data are limited. Very little is known about the safety of fluvoxamine, duloxetine, and venlafaxine.

**Discussion:** The neonatal safety of antidepressant use during breastfeeding remains controversial, in part because the available exposure literature includes primarily case reports and studies with small sample sizes, with reliability limited by methodological differences. In addition, the studies concentrate on measurements of exposure, such as the relative infant dose, milk drug concentration, or neonatal plasma drug concentration, rather than on the clinical relevance of exposure.

Orsolini L, Bellantuono C: Serotonin reuptake inhibitors and breastfeeding: a systematic review. *Human Psychopharmacology, Clinical and Experimental 2015;30:4–20.* From the United Hospital of Ancona and the Polytechnic University of Marche, Italy. Source of funding not stated. The authors declared no conflicts of interest.

Drug Trade Names: citalopram—Celexa; duloxetine—Cymbalta; escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox; paroxetine—Paxil; sertraline—Zoloft; venlafaxine—Effexor

Antipsychotic Safety in Breastfeeding

No antipsychotic is considered entirely safe for use during breastfeeding. However, the agents are excreted into breast milk at varying concentrations and, according to a review of the limited available literature, some may be safer than others.

**Background:** On the basis of teratogenic risk, most antipsychotics are labeled as pregnancy category C;* exceptions include clozapine and lurasidone, which are labeled as category B.* These pregnancy ratings do not help guide decisions about use after birth for mothers who breastfeed. Agents with breast milk concentrations of >10% of the maternal serum level constitute significant infant exposure, which could pose dangers to the infant’s health.
**Methods:** A comprehensive literature search was undertaken to identify reports of antipsychotic use during breastfeeding. A total of 60 English-language articles were identified that were published between 1960 and May 2014 and evaluated an antipsychotic available in the U.S. Both first- and second-generation antipsychotics were considered.

**Results:** Among the first-generation antipsychotics, perphenazine, trifluoperazine, and haloperidol can be detected in breast milk but do not cause clinically apparent adverse effects in the infants. Chlorpromazine has been associated with infant drowsiness and lethargy after exposure in breast milk. Haloperidol, when administered with chlorpromazine, has reportedly caused developmental delays in 12–18-month-old children. There are no data regarding the safety of fluphenazine, loxapine, pimozide, thioridazine, or thiothixene in breastfeeding.

The second-generation agents aripiprazole, clozapine, olanzapine, quetiapine, and risperidone have all been detected in breast milk. There have been no adverse-effect reports for aripiprazole exposure in breastfed infants. Although olanzapine, quetiapine, and risperidone also appear to have no adverse effects, exposed infants should be monitored carefully for sedation, extrapyramidal symptoms, and seizures. Periodic plasma-level monitoring is recommended for olanzapine-exposed infants, and those exposed to quetiapine should be followed for potential developmental delays. Clozapine is rarely prescribed for lactating women because of the potential for bone marrow suppression. In addition, clozapine in breast milk has been associated with sedation; decreased suckling; restlessness and irritability; seizures; and cardiovascular instability in exposed infants. No data exist for the safety in lactation of the newer antipsychotics asenapine, iloperidone, lurasidone, paliperidone, and ziprasidone.

**Discussion:** Although this review suggests several agents may be safe for use in breastfeeding, it should be noted that even with acceptable milk concentrations (<10%) of medications that appear to be safe for neonates, developmental delays remain a possibility with exposure. A registry-based or large-scale retrospective study could clarify the developmental effects of these antipsychotic agents.


**Drug Trade Names:** aripiprazole—Abilify; asenapine—Saphris; clozapine—Clozaril; haloperidol—Haldol; iloperidone—Fanapt; loxapine—Loxitan; lurasidone—Latuda; olanzapine—Zyprexa; paliperidone—Invega; pimozide—Orap; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

*See Reference Guide.

**Duloxetine for OCD**

In a small, manufacturer-sponsored, open-label study, the SNRI duloxetine (Cymbalta) produced significant symptom reductions in a group of patients with obsessive-compulsive disorder.

**Methods:** Study subjects (n=20) were adults with a diagnosis of OCD confirmed by structured clinical interview at a specialized OCD clinic. Mean patient age was 30 years (range, 18–55 years), and 11 patients (55%) were women. Participants were recruited by clinical referral and advertisement. All patients began treatment with 30 mg/day duloxetine. One week later, if the patient was free of intolerable adverse effects, the dosage was increased to 60 mg/day for an additional 2 weeks, and then to 120 mg/day for the remaining 12 study weeks. The duloxetine dosage could be reduced to 60 mg/day if the higher dosage was intolerable. The primary efficacy measures were the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the Clinical Global Impression–Improvement (CGI-I)* scale. Full response was defined as a ≥25% reduction in Y-BOCS score and a CGI-I score of <3. Quality of life along with depressive and anxiety symptoms were secondary outcomes.
**Results:** In the intent-to-treat analysis, statistically significant decreases in Y-BOCS scores were evident beginning at week 6. The mean baseline Y-BOCS score of 27.5 was reduced to 20.5 at study end (p<0.001; effect size,* 1.2). The mean CGI-I score at the final study visit was 2.7, indicating minimal-to-much improvement. A total of 7 patients (35%) met full response criteria. Significant reductions were also found in Beck Depression Inventory (BDI) scores, but not in Beck Anxiety Inventory (BAI) scores. Quality-of-life scores were significantly improved (p=0.045).

Of the 20 patients enrolled, 12 completed the study as designed. Of the noncompleters, 2 were lost to follow-up, 1 refused medication, and 5 discontinued study treatment because of adverse effects. Although no serious adverse events were reported, nausea developed in 50% of patients, fatigue affected 41%, and sexual dysfunction occurred in 23%. In a separate completer analysis, 7 patients (58%) achieved full response, 2 achieved partial response (i.e., either Y-BOCS or CGI-I criteria), and 3 patients met neither of the response criteria.

**Discussion:** SRIs are first-line treatment for OCD. Although there has been little research on SNRIs for this condition, duloxetine was studied in the present trial because its additional noradrenergic effects could provide added benefit over the serotonergic-only effects of SRIs. Although limited by small sample size and unblended treatment, these results suggest that duloxetine may be an effective treatment for patients with OCD. Additional research, in the form of large-scale randomized controlled trials, appears to be warranted.


*See Reference Guide.

---

**Adjunctive Pregabalin for Generalized Anxiety Disorder**

Patients with generalized anxiety disorder (GAD) partially responsive to SSRI therapy showed evidence of greater clinical improvement with adjunctive pregabalin than with other approaches, according to a retrospective analysis of data from a naturalistic manufacturer-sponsored study. Although pregabalin cost more than other options, reduced costs in other health-care areas compensated for the difference.

**Methods:** The present report is a post-hoc analysis of a 6-month, multicenter, observational study of adults with anxiety disorder. The study included patients with GAD who had experienced partial response, defined as a Hamilton Rating Scale for Anxiety (HAM-A) score of >16 and a Clinical Global Impression–Severity* (CGI-S) score of >3, to first-line SSRIs. Patients received treatment at their psychiatrists’ discretion with either pregabalin augmentation or "usual care" (i.e., switching to a different SSRI or augmentation with a different anxiolytic). Patients in the pregabalin group could also be taking concomitant benzodiazepines for a limited period of time. Study outcomes were evaluated after 6 months and included clinician-reported outcomes of anxiety (rated with the HAM-A), illness improvement (rated with the CGI-Improvement scale)*, depression (with the Montgomery-Asberg Depression Rating Scale [MADRS]), and patient-reported outcomes of sleep, disability, and quality of life. In addition, 6 months of health-care cost data were also analyzed.

**Results:** A total of 486 patients (325 women) were given pregabalin and 239 (159 women) received another treatment. Mean patient age was 47 years in the pregabalin group and 45 years in the usual care group. The groups were well matched demographically, but those who received pregabalin had greater severity of anxiety, depression, and overall illness at baseline than those who received usual care.
Adjunctive pregabalin was associated with greater improvements than usual care in anxiety, depression, and illness severity. (See table.) Pregabalin resulted in numerically greater improvement in all HAM-A domains, which was statistically significant for anxious mood, tension, fears, and intellectual, somatic, gastrointestinal, and autonomic symptoms. Secondary patient-reported outcomes also improved in both treatment groups after 6 months, but with statistical superiority for pregabalin in sleep problems ($p<0.001$), disability ($p<0.0001$), and global health status ($p<0.001$).

Health-care resource utilization included the costs of drug treatment, medical visits and hospitalizations, and nonpharmacological care such as support groups or psychosocial therapy. Compared with baseline, both treatment groups had significant reductions in health care costs during the 6 months of adjunctive therapy. Overall costs during those 6 months were similar in the 2 groups. Increased drug costs in the pregabalin group were compensated for by reductions in the number of visits and hospitalizations.

**Discussion:** The lack of treatment randomization is an important limitation of this study, which could result in selection bias and affect the outcome. While of interest, the study results must be interpreted cautiously and randomized controlled trials are needed to replicate the findings.

Alvarez E, Olivares J, Carrasco J, Lopez-Gomez V, et al: Clinical and economic outcomes of adjunctive therapy with pregabalin or usual care in generalized anxiety disorder patients with partial response to selective serotonin reuptake inhibitors. *Annals of General Psychiatry* 2015; doi 10.1186/s12991-014-0040-0. From the Universitat Autonoma de Barcelona, Spain; and other institutions. **Funded by Pfizer. All 5 study authors declared financial relationships with commercial sources.**

*See Reference Guide.*

### Acute Antidepressant Effects of Nitrous Oxide

In a preliminary study, nitrous oxide had rapid, marked antidepressant effects in patients with refractory depression.

**Methods:** Participants in this proof-of-concept study were 20 patients (12 women) with DSM-IV-TR major depressive disorder, a baseline score of $>18$ on the 21-item Hamilton Rating Scale for Depression (HAM-D), failure of $\geq 2$ adequate trials of an antidepressant during the current episode, and $\geq 3$ lifetime failed drug trials. Each patient received randomized nitrous oxide or placebo, and then after 1 week was crossed over to the alternate treatment. Nitrous oxide was administered at a maximum concentration of 50% with oxygen, a dosage empirically based on its use in dentistry and obstetrics. The placebo was 50% nitrogen in oxygen. Patients received treatment via a face mask for 1 hour, and then were monitored for 2 hours in a recovery area. For each treatment session, the HAM-D was administered at baseline, after 2 hours, and after 24 hours. The primary outcome was change from baseline to 24 hours in the HAM-D score.

**Results:** Participants (mean age, 48 years) had an average 19-year history of major depression, with an average of 8 failed treatments. The initial mean HAM-D score of 23.5 indicated severe depression. Patients were taking an average of 2 antidepressants during the current episode, and these were continued unchanged during the study. Treatment with nitrous oxide was interrupted briefly in 2 patients and ended prematurely in 3 for transient emotional discomfort, regurgitation, claustrophobia, or nausea and vomiting. Patients received an average of 56 minutes of nitrous oxide at a mean concentration of 44%. All patients completed 60 minutes of placebo.
At the 2-hour assessment, the mean HAM-D score decreased by 4.8 points with nitrous oxide to 18.7, followed by an additional decrease to 18 at 24 hours. Average scores decreased by about half that amount after placebo treatment (p<0.001 for nitrous oxide vs. placebo). Among the individual HAM-D items, depressed mood, guilt, suicidal ideation, and psychic anxiety showed the greatest improvement with nitrous oxide. At 24 hours, 4 patients met response criteria (HAM-D decrease of ≥50%) with nitrous oxide and 1 with placebo. A total of 3 patients met remission criteria (HAM-D score ≤7) with nitrous oxide, and no patient remitted with placebo. Because of a significant crossover effect in patients who received nitrous oxide as their initial treatment (i.e., observed carryover effect—patients who received active treatment first had lower scores when starting placebo), the investigators conducted an additional analysis comparing only the results of the first active or placebo treatment. The results were essentially the same as the full analysis.

Nagele P, Duma A, Kopec M, Gebara M, et al: Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial. Biological Psychiatry 2014; doi 10.1016/j.biopsych.2014.11.016. From Washington University School of Medicine, St. Louis, MO. Funded by Washington University School of Medicine. Three study authors disclosed relationships with commercial sources; the remaining 9 authors declared no conflicts of interest.

**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.

**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.

**Pregnancy Category B:** Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

**Pregnancy Category C:** Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

**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 have been posted at www.alertpubs.com.

---

**DELIVERY OF YOUR NEWSLETTER**

The U.S Postal Service continues to be very slow to deliver our newsletters. Did you know that you can receive an email copy of Psychiatry Drug Alerts (in addition to your print copy) as much as 2–3 weeks before your print copy arrives? If you are not signed up to receive Psychiatry Drug Alerts by email, simply send an email to kasey@alertpubs.com with the word "email" in the subject line. As always, M.J. Powers & Co. will never share your email address with a third party.

---

Contributing Editors: Kate Casano, MSHyg; Bennett Silver, MD
Consulting Editor: Steven J. Schleifer, MD, Rutgers–New Jersey Medical School
Executive Editor: Trish Elliott Associate Editor: Tara Hausmann Assistant Editor: Kasey Madara
Founding Editor: Michael J. Powers

**Off-Label Drug Use Statement:** Some drugs discussed for specific indications in Psychiatry Drug Alerts articles may not be approved for labeling and advertising for those indications by the United States Food and Drug Administration.
Lisdexamfetamine for Binge Eating Disorder

In a manufacturer-sponsored, multicenter, placebo-controlled trial, lisdexamfetamine (Vyvanse) was associated with reduced binge eating behavior and weight loss in patients with moderate-to-severe binge eating disorder.¹

Methods: Study subjects (n=255; 82% women) were adults, aged 18–55 years (mean age, 39 years), who met DSM-IV-TR criteria for binge eating disorder and had no other eating disorder, ADHD, or other psychiatric illness. Patients were randomly assigned to receive placebo or fixed-dose lisdexamfetamine 30, 50, or 70 mg/day, with weekly stepped 20-mg titration for the 2 higher doses. The primary efficacy endpoint was change from baseline to week 11 in the number of binge eating days per week, determined by clinician interviews and confirmed by patients’ binge eating diaries.

Results: The mean number of binge eating days per week at baseline was 4.5 in all groups. Lisdexamfetamine at the 2 higher doses, but not the lowest dose, was associated with a significantly greater reduction than placebo in the number of binge eating episodes (-4.1 vs. -3.3; p≤0.008) and a higher rate of response, defined as cessation of binge eating for 4 consecutive weeks (42–50% vs. 21%; p≤0.01). Results for several other secondary outcomes, including Clinical Global Impression–Improvement ratings, self-rated abnormal eating behavior, and obsessions and compulsions related to binge eating, all significantly favored lisdexamfetamine, particularly at the higher doses.

Body weight was assessed as a safety variable. Lisdexamfetamine was associated with weight loss, which averaged 9.5 pounds for the 3 dosages. The safety profile of lisdexamfetamine was consistent with the experience in adults with ADHD. One patient in the study died after taking an overdose of methamphetamine. This was believed to be unrelated to study medication, but it should be noted that lisdexamfetamine is a controlled substance and carries a black box warning about the potential for abuse and dependence.

Discussion: Pathologic overeating is believed to be related to dopaminergic and noradrenergic dysfunction. Lisdexamfetamine is a prodrug of dextroamphetamine, which inhibits...
reuptake of dopamine and norepinephrine and elicits release of monoamine neurotransmitters. Antidepressants also affect these systems and reduce the frequency of binge eating behaviors, but they do not produce weight loss.

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

**Editor’s Note:** Under the FDA’s priority review program, which provides expedited review of agents intended to treat serious diseases or to provide a significant improvement over available therapies, lisdexamfetamine received approval for the treatment of binge eating disorder in January 2015. The agent is dispensed with a medication guide warning about risks including cardiac complications and psychotic symptoms.


*See Reference Guide.

---

**Quetiapine for Generalized Anxiety Disorder**

In 2009, the Psychopharmacologic Drugs Advisory Committee of the FDA denied AstraZeneca’s application for a generalized anxiety disorder (GAD) monotherapy indication for quetiapine XR (*Seroquel*), not because the agent was ineffective, but because safety data were lacking. According to a literature review, quetiapine may play an important role in the treatment of GAD.

**Methods:** A literature search identified all published studies (n=9) of quetiapine for the primary management of GAD in adults. These included 3 studies of acute monotherapy, 1 of maintenance monotherapy, and 5 of acute adjunctive therapy. Most studies evaluated the sustained-release (XR) formulation, which appears to be identical in efficacy and tolerability to the immediate-release (IR) formulation.

**Results:** The 3 acute monotherapy trials were all placebo-controlled, and 2 also included an SSRI as an active comparator. The trials were large, with over 800 to nearly 1000 participants, and lasted 10 weeks—probably too little time to observe the full effects of quetiapine or SSRI treatment, and certainly not long enough to provide sufficient information on adverse effects. Quetiapine produced significant improvement in the Hamilton Anxiety Rating Scale (HAM-A), the common primary endpoint of the 3 trials. In some studies, improvement occurred as early as treatment day 4. The 150-mg/day dosage appears to offer the best response and remission rates, 62–71% and 37–43%, respectively. The 50-mg and 300-mg/day dosages were also significantly superior to placebo, but the highest dose did not offer superior efficacy to 150 mg.

In the study of maintenance monotherapy, 432 patients receiving open-label quetiapine were randomly assigned to either continue their established dose or switch to placebo. All 3 doses of quetiapine were associated with prolonged time to an "anxiety event," defined as a recurrence of significant anxiety symptoms or use of off-study anxiety medications. Anxiety events occurred in 10% of patients receiving quetiapine and 39% of the placebo group, and median times to recurrence of anxiety were 107 and 69 days, respectively. The trial was terminated prematurely as a result of meeting a predetermined number of anxiety events, and the long-term safety could not be investigated.

In the augmentation trials, quetiapine was added to traditional anxiolytic, SSRI, or SNRI therapy. The trials varied in background therapy, duration (8–18 weeks), design (2 were open-label and uncontrolled), GAD severity, comorbidity, and reported outcomes. Because of this
heterogeneity, it is difficult to draw conclusions about the efficacy of adjunctive quetiapine in GAD. The 3 controlled trials did not report any advantage of quetiapine over placebo in response or remission rates. Remission occurred in 48% and 72% of patients in the 2 open-label studies.

Adverse effects of quetiapine were those already reported in the product labeling. There is little information on adverse effects specific to patients with GAD, and further observation is required because patients' tolerance of antipsychotic medications may vary based on psychiatric diagnosis.

Kreys T-J, Phan S: A literature review of quetiapine for generalized anxiety disorder. Pharmacotherapy 2015;35 (February): 175–188. From California Northstate University, Elk Grove; and the University of Georgia, Albany. This review was conducted without funding. The authors declared no conflicts of interest.

Vortioxetine and Cognitive Deficits

In a manufacturer-sponsored controlled trial, vortioxetine was associated with statistically significant but modest improvement in cognitive function in patients with major depression.

Background: Mood disorders are often accompanied by impairments in cognitive function. The present study was conducted to explore the effect of vortioxetine on specific cognitive domains, following earlier reports suggesting positive effects on cognitive function.

Methods: Study subjects were 602 adults, aged 18–65 years, from 80 centers in the U.S. and Europe. Participants were experiencing a current depressive episode in the context of recurrent major depressive disorder and reported cognitive problems such as difficulty concentrating, slow thinking, and difficulty learning or remembering new things. Patients were randomly assigned to 8 weeks of treatment with either vortioxetine, placebo, or duloxetine, the latter as an active control for antidepressant effects. Vortioxetine was administered at 10 or 20 mg/day at the clinician's discretion. The primary efficacy measure was the Digital Symbol Substitution Test (DSST), which measures multiple cognitive domains: executive function, processing speed, attention, spatial perception, and visual scanning. A major secondary endpoint was the Perceived Deficits Questionnaire (PDQ), a patient-reported measure of cognitive function.

Results: About 85% of each treatment group completed the 8-week study. The group receiving vortioxetine showed a larger improvement than the placebo group on the DSST (p=0.019), with an effect size* of 0.25. Duloxetine and vortioxetine had similar effects on the DSST; however, duloxetine was numerically but not statistically superior to placebo. A path analysis* showed that 76% of the effect of vortioxetine on the DSST was direct, rather than secondary to relief of depression.

Both vortioxetine and duloxetine were associated with improvement in the PDQ domains of attention/concentration and planning/organization (p≤0.001 for both drugs). Patients taking the 2 active medications had overall improvement in depression on the Clinical Global Impression scale and the Montgomery-Asberg Depression Rating Scale. Vortioxetine was associated with improvement on the Trail-Making Tests of processing speed and executive function, but not on several of the study's other secondary cognitive measures. Patients who received vortioxetine showed a statistically significant improvement on the University of San Diego Performance-Based Skills Assessment (p<0.001), while the duloxetine group did not.

Discussion: Cognitive performance has not been measured in a consistent manner in studies of antidepressant treatment. The present study used a measure that was believed to capture the main aspects affected by depression: verbal learning, verbal memory, attention, executive function, and working memory.
Although duloxetine was also associated with improvement in some cognitive measures, significant improvements occurred in fewer areas than with vortioxetine, and path analysis showed these changes were the result of duloxetine's antidepressant effects. Conclusions about the relative efficacy of the drugs for depression-related cognitive dysfunction cannot be drawn from this study.

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


Drug Trade Names: duloxetine — Cymbalta; vortioxetine — Brintellix

*See Reference Guide.

### Antidepressants and Cognitive Decline

In a large, nationally representative sample of older adults followed for 6 years, antidepressant use did not modify the well-established association between depression and cognitive decline.

**Methods:** The Health and Retirement Study is an ongoing study of U.S residents, aged >50 years at enrollment in 1992. Alternate-year interviews of participants include assessments of depression and cognitive function. Prescription drug data were also available beginning in 2005. The sample for the present analysis (n=3714) consisted mostly of people who were aged ≥65 years in 2007, community-dwelling, and able to participate in cognitive-function tests. Cognitive function was tested on 4 occasions between 2004 and 2010, using a 27-point scale based on a battery of memory and computational tests. Cognitive function was classified as normal, impaired function, or dementia based on these scores. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) Scale.

**Results:** At baseline, 12% of the study participants were taking an antidepressant. Depressive symptoms were associated with reduced baseline cognitive function, but there was no difference in cognitive function at baseline between those taking or not taking antidepressants. During the 6-year follow-up, both users and nonusers of antidepressants experienced a decline in cognitive function, which did not differ between the groups. In an analysis that was adjusted for socio-demographic variables, functional impairment, comorbidity, depressive symptom burden, and the anticholinergic activity of the antidepressant, rates of cognitive decline still did not differ between users and nonusers of antidepressants. (See table.)

**Discussion:** Because antidepressant use does not appear to protect against cognitive decline in older patients with depression, adding nonpharmacological approaches that may be associated with cognition (e.g., social engagement, physical activity) should be considered for these patients.

Saczynski J, Rosen A, McCammon R, Zivin K, et al: Antidepressant use and cognitive decline: the Health and Retirement Study. *American Journal of Medicine* 2015; doi 10.1016/j.amjmed.2015.01.007. From the University of Massachusetts Medical School, Worcester; and other institutions. *Funded by the National Institute on Aging and other sources. The authors declared no conflicts of interest.*
SSRI plus Stimulant in Geriatric Depression

In elderly patients with chronic depression, the combination of citalopram and methylphenidate resulted in a more robust antidepressant response than either agent alone.

**Methods:** This randomized trial was carried out in 143 older adults (average age, 70 years; 78 women) with a current episode of unipolar major depression and no or minimal cognitive impairment. Patients were seen in the clinic, weekly for 4 weeks of methylphenidate titration, and then every 2 weeks until the 16-week endpoint. Methylphenidate was dosed flexibly at 5–40 mg/day, depending on response and tolerability, with response defined as a Clinical Global Impression–Improvement (CGI-I)* rating of 1 or 2. Citalopram was dosed flexibly in the same manner, in the 20–60-mg/day range. Patients in the 2 monotherapy groups received a placebo for the alternate drug. The primary outcome measure was change from baseline on the Hamilton Rating Scale for Depression (HAM-D). Remission was defined as a HAM-D score of ≤6. The rate of HAM-D reduction by the fourth week of treatment (based on the methylphenidate titration schedule) was also evaluated. Neuropsychological tests of cognitive function were carried out at baseline and study end.

**Results:** Patients had a history of 3–4 depressive episodes on average, with a mean duration of nearly 4 years for the present episode. About 40% met criteria for treatment resistance, with failure of ≥2 adequate trials of antidepressants from different classes.

By 16 weeks, combination therapy was associated with a significantly larger average reduction in HAM-D score than citalopram alone (p=0.02) or methylphenidate alone (p=0.005). During the first 4 weeks of treatment, combination therapy was associated with greater improvement than citalopram monotherapy (p=0.03), but not methylphenidate alone. Efficacy did not differ significantly between the monotherapy groups. After week 4, improvement was significantly more rapid with combination therapy than with methylphenidate (p=0.04); improvement was not more rapid with combination therapy than with citalopram. By week 16, remission occurred in 62% of the combination therapy group, compared with 42% of patients who received citalopram alone (p=ns), and 29% of the methylphenidate group (p=0.003).

CGI-I scores of 1 or 2 were noted in 84% of the combined therapy group, 57% of the citalopram group, and 39% of the methylphenidate group (p=0.001 for the combined group vs. each monotherapy). Cognitive outcomes of treatment were variable, with greater improvement in some areas of cognitive function observed in the 2 groups receiving citalopram. The treatment groups did not differ in any measure of tolerability or adverse effects.

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

Lavretsky H, Reinlieb M, St. Cyr N, Siddarth P, et al: Citalopram, methylphenidate, or their combination in geriatric depression: a randomized, double-blind, placebo-controlled trial. American Journal of Psychiatry 2015; doi 10.1176/appi.ajp.2014.14070889. From the University of California, Los Angeles. Funded by the NIH. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no conflicts of interest.

*See Reference Guide.

Long-Term Renal Safety of Lithium

Results of a longitudinal study in a large, unselected population suggest lithium therapy may be associated with kidney damage that could later lead to end-stage renal disease (ESRD).1

**Methods:** Data were analyzed from 630 patients (average age at treatment initiation, 46 years) treated at a single Swedish regional hospital. The study subjects began lithium treatment between 1981 and 2010 and received treatment for ≥10 years cumulatively. If a patient had a 365-day period without any positive lithium measurements, treatment was considered long-term nonadherent.
discontinuous and that time period was subtracted from the cumulative treatment total. Serum creatinine levels closest in time to the first and last lithium measurements were considered as initial and final creatinine levels. Those with initially abnormal levels were excluded. The age- and gender-adjusted glomerular filtration rate (GFR) was estimated, and used to classify patients according to the stages of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative. (See table.)

**Results:** Patients showed a continuous yearly increase in average serum creatinine beginning with the first year of treatment. After ≥10 years on lithium, 45% of patients had a ≥30% increase in serum creatinine level. One-third of patients had an abnormally low estimated GFR after ≥10 years on lithium, and almost 5% had Stage 4 or 5 chronic kidney disease (CKD; 27 and 2 patients, respectively).

**Discussion:** Previous research by these investigators found risk for ESRD in lithium treated patients to be greater than in the general population (relative risk,* 7.8). However, it is not clear whether there is a safe level of renal function for continuation of lithium treatment. More than half of patients in the present study had virtually unchanged creatinine levels throughout treatment, despite similar lithium treatment duration and initial creatinine concentrations. This suggests that other factors such as concomitant illnesses and individual vulnerability, which could not be evaluated in the present study, may influence risk.

**Brexpiprazole in Acute Schizophrenia**

The investigational second-generation antipsychotic brexpiprazole, designed to minimize adverse effects, was effective in a multi-dose phase III trial in patients hospitalized with an acute exacerbation of schizophrenia.

**Background:** Brexpiprazole was designed with a serotonin and dopamine activity profile that would theoretically result in a low potential for some of the most concerning side effects of second-generation antipsychotics, including prolactin elevation and extrapyramidal symptoms.

**Methods:** This trial was conducted at 64 centers in 8 countries, with a little more than one-third of patients from U.S. centers. Study participants had a diagnosis of schizophrenia and were suffering an acute exacerbation of psychotic symptoms with marked deterioration of function, warranting inpatient admission or continued hospitalization. After a washout of concomitant antipsychotic drugs, patients were randomly allocated to receive double-blind 1, 2, or 4 mg/day brexpiprazole or placebo for 6 weeks. Change from baseline in the Positive and Negative Syndrome Scale (PANSS) was the primary efficacy outcome. Change from baseline in the Clinical Global Impression–Severity (CGI-S)* scale score was the key secondary endpoint.

---

1 Aiff H, Attman P-O, Aurell M, Bendz H, et al: Effects of 10 to 30 years of lithium treatment on kidney function. Journal of Psychopharmacology 2015; doi 10.1177/026988115573808. From the University of Gothenburg, Sweden; and other institutions. **Funded by the Elsa and Henrik Sjobring Memorial Foundation; and other sources. The authors declared no conflicts of interest.**


*See Reference Guide.*
Results: A total of 674 patients (251 women) received randomized treatment, and 68% completed the study. The rate of study completion was similar in all treatment groups. Patients were markedly ill at study entry, with a mean CGI-S score of nearly 5 and a mean PANSS total score of 95.

The 4-mg brexpiprazole dose was associated with a significantly greater improvement in PANSS total score than placebo; at week 6, scores were 75 and 81.5, respectively (p<0.0022). Average reductions in PANSS scores with the 4-mg dose were a clinically meaningful 20–30%. The 2 lower doses were associated with numerically larger improvements than placebo, but the difference was not statistically significant. Patients who received the 4-mg dose also had a significantly greater reduction in CGI-S scores relative to placebo (1.2 points vs. 0.81 points;  p=0.0015). Multiple secondary endpoints also supported the efficacy of 4 mg brexpiprazole; again, the lower doses were numerically but not statistically superior to placebo.

No treatment-emergent adverse events met the criteria for common adverse events, defined as an incidence ≥5% and at least twice the rate of placebo. Most serious adverse events were related to the underlying course of schizophrenia (e.g., aggression, psychosis); for these the incidence was lower with brexpiprazole than with placebo (≤2.5% vs. 5.4%). Brexpiprazole was associated with moderate weight gain, which averaged >3 lbs. after 6 weeks of treatment with the 4-mg dose.

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


*See Reference Guide.

Antidepressant Fracture Risks Compared

SNRI and SSRI antidepressants are associated with a similar risk of fracture, according to results of a cohort study of patients aged ≥50 years.

Background: Fracture risks associated with SSRIs and older antidepressant classes are well documented, but less is known about SNRIs. Antidepressants are known to increase fractures in older patients by causing dizziness and falls upon initiation. Drugs that affect serotonin downregulate osteoblast activity, decreasing bone mineral density; norepinephrine-inhibiting drugs can increase bone resorption thus reducing bone density. This study was conducted to determine whether initiating an SNRI would result in a lower fracture risk than starting an SSRI.

Methods: Combined data from commercial managed care plans throughout the U.S. were gathered using the PharMetrics Claims Database and then used to retrospectively identify a cohort of patients, aged ≥50 years, who filled a new prescription for an SSRI or an SNRI between 1998 and 2010. Patients who had received any other antidepressant in the previous 12 months were excluded. The outcome of interest was fracture of the hip, humerus, radius, or ulna in the 360 days after starting therapy. Patients were removed from follow-up when they switched antidepressants, even within the same class, or when they added a second antidepressant. The analysis was weighted for the propensity of patients to be given a prescription for an SNRI rather than an SSRI.

Results: The analysis included >335,000 patients given a prescription for an SSRI and 61,000 given an SNRI. In the primary analysis, rates of fracture per 1000 patient-years within the first 360 days of treatment did not differ between the 2 drug classes: 7.5 for SNRIs and 6.7 for SSRIs (hazard ratio,* 1.03 for SNRIs vs. SSRIs). Rates did not differ between drug classes in analyses with different follow-up times, ranging from the initial month to the first 5 years following
Fracture rates associated with the 2 drug classes were the same in patients without a depression diagnosis. However, in those with depression, SNRIs were associated with a slightly, nonsignificantly elevated risk (hazard ratio, 1.31).

**Discussion:** Although the underlying mechanism for fracture risk differs between the SSRIs and SNRIs, results of this research suggest that actual risks are similar in both classes. The suggestion that depression status may modify the effect of SNRIs on fracture requires further investigation.

Lanteigne A, Sheu Y-H, Sturmer T, Pate V, et al: Serotonin-norepinephrine reuptake inhibitor and selective serotonin reuptake inhibitor use and risk of fractures: a new-user cohort study among US adults aged 50 years and older. CNS Drugs 2015; doi 10.1007/s40263-015-0231-5. From Harvard School of Public Health, Boston, MA; and other institutions. *Funded by the NIMH. One study author declared potentially relevant financial relationships; the remaining 6 authors declared no conflicts of interest.*

*See Reference Guide.

**Reference Guide**

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

**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.

**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 one group has half the risk of the other group.

**Path Analysis:** A method employed to determine whether or not a multivariate set of nonexperimental data fits well with a particular (a priori) causal model.

**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 have been posted at www.alertpubs.com.
Olanzapine-Associated Deaths

The FDA has concluded its investigation into the unexplained deaths of 2 patients who received intramuscular injections of olanzapine pamoate (Zyprexa Relprevv). The patients died 3–4 days after receiving appropriate doses of the drug, and both were found to have very high olanzapine blood levels after death. Results of the FDA study were inconclusive, and the possibility that the deaths were caused by rapid, delayed entry of the drug into the bloodstream could not be ruled out. However, the investigation also suggested that much of the drug-level increase may have occurred after death, which could explain the extremely high blood levels after appropriate drug dosing. The FDA is not recommending any changes to the prescribing information for Zyprexa Relprevv.


Antipsychotics and Ventricular Arrhythmia

Use of antipsychotic medications was associated with a >50% increase in the incidence of ventricular arrhythmia or sudden cardiac death in an epidemiologic study from Taiwan.¹

Methods: Data spanning 2000–2009 were analyzed from the Taiwanese National Health Insurance Research Database. Study subjects were individuals who were hospitalized or treated in the emergency department for episodes with ICD-9 codes indicating paroxysmal ventricular tachycardia, ventricular fibrillation or flutter, cardiac arrest, instantaneous death, and sudden death <24 hours from symptom onset. Antipsychotic drug exposure was defined as ≥1 day of use in the 14 days preceding the event. In a case-crossover design, the rate of use during this period was compared with use in the control period—i.e., the 15–28 days prior to the episode. To test the hypothesis that these effects were related to a drug’s potency in blocking the human ether-à-go-go-related gene (hERG) potassium ion channel, drugs were classified as high or low blockers of this pathway. The analysis was adjusted for healthcare utilization and for use of other medications.
Results: More than 17,700 patients experienced ventricular arrhythmia or sudden cardiac death. Of these, 5625 patients had received an antipsychotic in the 14 days prior to the event; about two-thirds of these were second-generation agents. Antipsychotic use was associated with an adjusted 1.53-fold increase in risk (odds ratios,* 1.66 and 1.36 for first- and second-generation agents, respectively; p<0.05). Among second-generation agents, risk was significantly elevated for quetiapine, risperidone, and sulpiride, with odds ratios ranging from 1.26 to 1.39 (p<0.05 for each).

Patients with a shorter duration of antipsychotic use had an increased risk of ventricular arrhythmia/sudden death, compared with those using the drugs for >28 days. Risk was not dose-related and not associated with patient age, gender, serious medical comorbidity, or underlying psychiatric illness. Drugs with high hERG potassium channel blockade were associated with increased incidence of arrhythmia/sudden death, compared with those with low blockade (adjusted odds ratio, 1.24; p<0.05).

Discussion: The excess risks found in this study are smaller than those reported in earlier research. The difference may be due in part to higher rates of underlying cardiovascular disease in white Western populations, according to an editorial.2 The role of antipsychotic-related hERG potassium channel blockade does not appear to have been previously studied. Most medications that cause QT interval prolongation, a marker for risk of Torsades de pointes, also block the hERG pathway. This study indicates that drugs with a greater blocking effect also increase risk of ventricular arrhythmia. The lower risk of ventricular arrhythmia/sudden death with second-generation antipsychotics, compared with first-generation agents, may be a reflection of the recent increase in awareness and caution in drug approvals and prescribing.

*See Reference Guide.
analysis, mixed features were defined as severity scores of ≥2 on ≥2 of the instrument’s 11 items. The primary efficacy outcome measures were the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression, Bipolar—Severity of Illness (CGI-BP-S) depression score.

**Results:** Included in the present analysis were 485 patients, 272 (56%) of whom met criteria for mixed features. Members of this group resembled previously described populations of patients with mixed features: They were more likely than those with pure depression to be women (61% vs. 52%) and white (71% vs. 59%), and to have a history of rapid cycling (9% vs. 3%). They also had earlier onset of bipolar disorder (by about 2.5 years on average) and higher levels of anxiety.

Both doses of lurasidone were significantly superior to placebo at reducing depression. Mean MADRS scores were about 30 in all groups; these decreased by 16 points in lurasidone-treated patients with mixed features and by 15 points in those without, compared with 11 points in placebo-treated patients with and without mixed features. Effect sizes* were similar for change from baseline in MADRS (0.48 for both lurasidone-treated subgroups), and the CGI-BP-S (0.57 for patients with mixed features, 0.49 for those without). Results were similar for secondary outcome measures of response, remission, anxiety, function, and quality of life. An analysis using the alternative definition of mixed features had a similar result. Improvement in depression in patients with mixed features was not influenced by the baseline severity of these features (i.e., baseline YMRS). Emergent mania or hypomania occurred in 2.2% of the lurasidone group and in 3.2% of the placebo group.

**Discussion:** Few studies have examined the effects of mixed features on treatment response in bipolar depression. This analysis provides preliminary evidence that lurasidone may be effective in this patient group.

1McIntyre R, Cucchiaro J, Pikalov A, Kroger H, et al: Lurasidone in the treatment of bipolar depression with mixed (subsyndromal hypomanic) features: post hoc analysis of a randomized placebo-controlled trial. *Journal of Clinical Psychiatry* 2015; doi 10.4088/JCP.14m09410. From the University of Toronto, Canada; and Sunovion Pharmaceuticals Inc., Fort Lee, NJ. **Funded by Sunovion Pharmaceuticals Inc.** All 5 study authors declared financial relationships with commercial sources including Sunovion Pharmaceuticals.


*KSee Reference Guide.*

### Ketamine for Suicidal Ideation

Preliminary evidence suggests that ketamine may be a promising rapidly-acting treatment for suicidal ideation.

**Methods:** A literature search identified all available English-language peer-reviewed articles describing studies of any design that directly assessed suicidal ideation as an outcome. A total of 9 publications met criteria: 3 each of case reports, uncontrolled studies, and randomized controlled trials. In 3 of the studies, suicidal ideation was a secondary outcome and was assessed using a selection of items from larger depression rating scales, the Hamilton Rating Scale for Depression (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), or Beck Depression Inventory (BDI).

**Results:** In the largest study, 57 patients with treatment-resistant depression were randomly assigned to receive ketamine or midazolam (control). Suicidal ideation was assessed with composite subscales of the BDI and the MADRS and with the Quick Inventory of Depressive Symptomatology-Self Report. Patients who received ketamine had larger reductions in composite suicidality scores at 24 hours than the control group (p=0.01). They also had
significant reductions in explicit but not implicit suicidality. In another placebo-controlled trial, suicidality was assessed as a secondary outcome in 15 patients with bipolar depression, treated in a randomized crossover design. Ketamine was associated with significant reductions in 3 composite measures of suicidality based on the HAM-D, MADRS, and BDI. Improvements were noted as early as 40 minutes after infusion and lasted for 2–10 days. A third controlled study, also with a crossover design, showed that ketamine reduced HAM-D symptoms of suicidal ideation over 72 hours in 8 patients with unipolar depressive disorder.

The 3 open-label studies were also primarily focused on depression. In 1 study, a subset of 13 patients, out of 26 with treatment-resistant depression, had significant suicidal ideation at baseline. Evaluated 24 hours post-infusion, only 2 continued to have MADRS suicidal ratings above the threshold of concern. In another study of 33 patients with major depressive disorder, suicidal ideation was the primary treatment outcome. Patients experienced significant improvement on 4 measures of suicidal ideation — HAM-D, MADRS, BDI, and the Beck Scale for Suicide Ideation — with scores reaching 0 within an average of 2 hours after infusion. In 14 patients who presented to an emergency department with suicidal ideation, ketamine was associated with dramatic reductions in the MADRS suicidality item and with subjective relief of suicidal thoughts lasting ≥10 days.

**Discussion:** Ketamine is considered safe, but it can cause adverse effects such as transient dissociation and hallucinations, and there is some potential for abuse. To date there are no data addressing whether ketamine has prevented suicide attempts or deaths by suicide. Further research should be based on more targeted study designs and should investigate optimal dosing and administration as well as any long-term adverse effects.

Reinstatler L, Youssef N: Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature. *Drugs in R&D* 2015; doi 10.1007/s40268-015-0081-0. From the Medical College of Georgia at Georgia Regents University and Charlie Norwood VA Medical Center, Augusta, GA. This review was conducted without funding. The authors declared no conflicts of interest.

**Partial NMDA Agonism in Resistant Depression**

In a proof-of-concept study, the investigational N-methyl-D-aspartate receptor glycine site functional partial agonist, GLYX-13, showed promising effects in treatment-resistant depression, without the psychotomimetic side effects produced by ketamine and some other experimental NMDA receptor modulators.

**Methods:** Participants in this multicenter U.S. trial were adults, aged 18–65 years, with major depressive disorder not responsive to treatment with existing antidepressants. To explore different dosages of GLYX-13, patients were recruited prospectively into dosage cohorts. The first 80 participants were randomly assigned to receive a single injection with 1 of 3 doses of the experimental drug — 1, 5, or 10 mg/kg — or placebo. A second cohort was planned to investigate a higher or lower dose, depending on the results with the first cohort. Based on results of the first cohort, the second cohort received a single injection of 30 mg/kg or placebo. Antidepressant response was evaluated with the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Bech-6, a brief depression inventory suitable for multiple tests during the first 24 hours after drug administration. Participants were followed for 14 days.

**Results:** A total of 116 patients with an average age in the mid-40s received randomly assigned treatment: placebo (n=33); 1 mg/kg GLYX-13 (n=25); 5 mg/kg GLYX-13 (n=20); 10 mg/kg GLYX-13 (n=17); and 30 mg/kg GLYX-13 (n=21). Mean baseline HAM-D scores were 26 in the placebo group and 25–26 in each of the GLYX-13 groups.

There was a large placebo response: a mean 45% reduction in HAM-D scores. Even so, the 3 lower doses of GLYX-13 were associated with rapid HAM-D reductions. These were statistically
superior to placebo (p<0.05) for the 5 and 10 mg/kg doses, but not the 1 mg/kg dose. The higher doses of GLYX-13 were significantly superior to placebo beginning at the last observation on day 1 and remained superior through days 3 and 7, but not at 14 days. Effect sizes* ranged from 0.56 on day 1 to 0.39 at day 7 with the 5-mg/kg dose; and from 0.37 on day 1 to 0.60 on day 7 with the 10-mg/kg dose. The 30-mg/kg dose had no antidepressant effect.

Results of analysis using the Bech-6 score showed GLYX-13 was significantly superior to placebo beginning 2 hours after injection. Rates of response and remission were high in the placebo group and higher, but not statistically, in the groups receiving GLYX-13.

Adverse events were limited to dizziness in 10% of patients who received GLYX-13. Dizziness had onset from minutes to hours after injection, and it is not clear whether it was related to medication. There were no psychotomimetic effects and no increase in suicidality.

Discussion: Proof-of-concept studies are generally conducted to identify candidate drugs for further development. Many small studies have indicated NMDA receptor modulators can produce rapid antidepressant effects. The evidence from this study suggests that these agents can be effective without producing psychotomimetic effects if they are used at low doses or if they are partial NMDA receptor agonists. The large placebo effect in this trial may be explained by the use of an injected placebo or patients' expectations based on their knowledge of ketamine. As a result of this and another study, GLYX-13 is entering phase III development.

Preskorn S, Macaluso M, Mehra V, Zammit G, et al: Randomized proof of concept trial of GLYX-13, an N-methyl-d-aspartate receptor glycine site partial agonist, in major depressive disorder nonresponsive to a previous antidepressant agent. Journal of Psychiatric Practice 2015;21 (March):140–149. From the University of Kansas School of Medicine, Wichita; and other institutions including Naurex, Inc. Funded by Naurex, Inc. All study authors declared financial relationships with commercial sources.

*See Reference Guide.

Agomelatine–Bupropion for Resistant Depression

Results of a preliminary chart-review study suggest the combination of agomelatine and bupropion may be an effective option for SSRI-resistant depression.

Background: Combination antidepressant therapies are recommended as an option in treatment-resistant depression, but efficacy results have been mixed. The 2 agents used in this study have distinct receptor activity: 5-HT2C antagonism and melatonergic agonism for agomelatine and norepinephrine/dopamine reuptake inhibition for bupropion; both have mild side-effect profiles.

Methods: A chart review from a hospital in Germany, where agomelatine is commercially available, identified 15 adults with treatment-resistant depression who had received naturalistic treatment between 2010 and 2011 with flexibly-dosed agomelatine and bupropion. Despite adequate doses of agents from ≥1 antidepressant class for >6 weeks each, the patients all had a Beck Depression Inventory (BDI) score of >14 and their ineffective therapy was discontinued before agomelatine and bupropion were started. A comparison group of 15 inpatients, matched for age, gender, and stage of treatment resistance, who received antidepressant monotherapy, were also identified. As part of routine clinical care, depressive symptoms were measured every week with the BDI. The primary outcome for comparison was change from baseline in the BDI, with response defined as a >50% decrease in the score and remission as a score <13.

Results: The 2 treatment groups were well matched on baseline depressive symptom severity, level of treatment resistance, and other factors. Before hospital admission,
patients had received SSRI monotherapy for ≥6 weeks. At discharge, average dosages were about 50 mg/day for agomelatine and 325 mg/day for bupropion. In the monotherapy group, 10 patients received a different SSRI, 3 received venlafaxine, and 2 received mirtazapine.

After 6 weeks of treatment, both groups showed significant improvement in BDI scores. The combined-antidepressant group improved somewhat more than the monotherapy group (mean BDI reduction, 20 vs. 12.5 points; p=ns; effect size,* 0.7). Response occurred in 11 patients with combined therapy and 8 in the monotherapy group (73% vs. 53%). This difference was not statistically significant but resulted in a number needed to treat (NNT)* of 5 for 1 additional response with agomelatine–bupropion. Remission occurred in 9 patients receiving combination therapy and in 6 on monotherapy (60% vs. 40%; p=ns; NNT, 4). Treatment response and remission were not related to the degree of treatment resistance.

Combination treatment was associated with transient headache in 4 patients and increased motor activity/agitation in 3. Neither treatment had adverse metabolic effects.

Suhs K-W, Correll C, Eberlein C, Pul R, et al: Combination of agomelatine and bupropion for treatment-resistant depression: results from a chart review study including a matched control group. Brain and Behavior 2015; doi 10.1002/brb3.318. From Hannover Medical School, Germany; and other institutions. Source of funding not stated. The authors declared no conflicts of interest.

Drug Trade Names: agomelatine (not available in the U.S.)—Valdoxan; bupropion—Wellbutrin; mirtazapine—Remeron; venlafaxine—Effexor

*See Reference Guide.

Long-Acting Paliperidone for Relapse Prevention

A new 3-month formulation of paliperidone palmitate (Invega Sustenna) was superior to placebo at preventing relapse of schizophrenia in patients who previously received treatment with 1-month paliperidone.1 According to results of a manufacturer-sponsored trial, the new formulation allows patients to maintain therapeutic paliperidone levels with fewer injections, potentially removing a barrier for some with limited access to treatment.

Methods: Participants in this multinational study were adults with schizophrenia for ≥1 year. Those whose symptoms were clinically stable on other long-acting injectable antipsychotics were eligible to participate. After oral tolerability testing and transition to open-label paliperidone, patients received treatment for 4 months with 117–234 mg once-monthly injected paliperidone, followed by a single injection of open-label 3-month paliperidone. The dosage for 3-month paliperidone was 3.5 times the maximum tolerated monthly dosage. After 3 months, participants were randomly assigned to either continue receiving 3-month paliperidone or to switch to placebo, in a double-blind fashion. The primary efficacy outcome was time from randomization to the first relapse in the double-blind phase. Relapse was defined by a complex set of criteria that included hospitalization, increases in scores on the Positive and Negative Syndrome Scale; increases in certain target symptoms; and suicidal, self-injurious, or aggressive behavior.

Results: The study was stopped after an interim analysis found a significant difference in relapse rates between 3-month paliperidone and placebo. At this point, a total of 283 patients were available for analysis. Those who received placebo had >3 times the rate of relapse (hazard ratio,* 3.45; p<0.001). The median time from randomization to relapse was 274 days for placebo and could not be calculated for the paliperidone group. By the interim analysis, relapse had occurred in 23% of the placebo group and 7% of the group receiving 3-month paliperidone. The effect of paliperidone was consistent with regard to patient age, gender, race, body mass index, and geographic region.
The most common adverse events during treatment with 3-month paliperidone were anxiety (6%), insomnia (5%), weight gain (4%), and headache (3%). Smaller proportions of patients had hyperkinesia or parkinsonism. Steady-state paliperidone levels during the 3-month maintenance and double-blind phases were consistent with the known steady-state exposure to once-monthly paliperidone. No new safety concerns emerged with the new formulation.

**Editor’s Note:** In January 2015, the FDA granted Priority Review for the 3-month formulation of paliperidone palmitate, which makes it likely to receive consideration in 6, instead of the usual 10, months.²

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


*See Reference Guide.*

## Antipsychotics and Gray Matter

Second-generation antipsychotics may be associated with less cortical gray matter loss than first-generation or mixed antipsychotic regimens, according to a meta-analysis of longitudinal MRI studies.

**Background:** Loss of gray matter volume is known to be present at the time of schizophrenia onset, to progress over the disease course, and to be associated with exposure to antipsychotic drugs. The present analysis was conducted to investigate the possible impact of different antipsychotic classes and other moderating factors.

**Methods:** A systematic literature search identified all peer-reviewed longitudinal magnetic resonance imaging (MRI) studies of gray matter volume changes in patients with schizophrenia and healthy control subjects. Studies of patients at risk for schizophrenia were excluded, as were those that employed morphometry rather than MRI.

**Results:** A total of 18 studies were included in the meta-analysis; the complete sample comprised 1155 patients with schizophrenia and 911 healthy controls. Sufficient data were available to analyze gray matter changes in 4 different regions of interest: whole brain, frontal lobe, temporal lobe, and parietal lobe. Of these, schizophrenia was associated with an increased loss of whole brain and parietal gray matter volumes (p<0.001 for both regions). Decreases in frontal lobe and temporal lobe gray matter were not statistically different from controls. Effect sizes for the changes in cortical volume were small to moderate but consistent in the studies, which had low heterogeneity and little evidence of publication bias.

Studies in which patients received treatment with first-generation or mixed antipsychotic regimens showed significant decreases in all 4 regions of interest. In patients who received treatment only with second-generation agents, there was no decrease in whole brain or parietal lobe gray matter and small nonsignificant increases in the frontal and temporal lobes. In these patients, there was no association between the cumulative atypical antipsychotic dose and whole brain gray matter volume changes. However, compared with patients who had received ≥1 first-generation agent, higher mean daily doses between scans was associated with less loss of whole brain gray matter volume over time in patients who received only second-generation treatments. With first-generation or mixed treatments, whole brain gray matter loss was associated with higher cumulative exposure to antipsychotics and...
mean daily doses. Other factors, including patient age, severity of illness, duration of MRI follow-up, and substance use, were not moderators of longitudinal change in gray matter volumes.

**Discussion:** Only studies directly comparing randomly assigned first- and second-generation drugs can definitively resolve the question of their differential effects. Three studies included in this analysis had a randomized design; a subgroup analysis of the 3 supports the conclusions of the main study. Explanations for the drug classes’ differential effects are speculative and include a possible neuroprotective effect of second-generation drugs, neurotoxicity of first-generation agents, and a lower capacity of older drugs to interfere with the natural pathophysiologic course of schizophrenia.

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

Vita A, De Peri L, Deste G, Barlati S, et al: The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: does the class matter? A meta-analysis and meta-regression of longitudinal magnetic resonance imaging studies. *Biological Psychiatry* 2015; doi 10.1016/j.biopsych.2015.02.008. From the University of Brescia; and the Spedali Civili Hospital, Italy. Funded by a grant from the Lombardia Region; and other sources. Two study authors disclosed potentially relevant financial relationships; the remaining 3 authors declared no conflicts of interest.

*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 one 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.

**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 have been posted at www.alertpubs.com.

Contributing Editors: Kate Casano, MSHyg; Bennett Silver, MD
Consulting Editor: Steven J. Schleifer, MD, Rutgers–New Jersey Medical School
Executive Editor: Trish Elliott  Associate Editor: Tara Hausmann  Assistant Editor: Kasey Madara
Founding Editor: Michael J. Powers

**Off-Label Drug Use Statement:** Some drugs discussed for specific indications in *Psychiatry Drug Alerts* articles may not be approved for labeling and advertising for those indications by the United States Food and Drug Administration.

**Statement of Editorial Policy:** All of the information and opinions presented in each *Psychiatry Drug Alerts* article are strictly those contained in the cited article unless otherwise noted. Reader comments are welcome by mail, by telephone (973-898-1200) 8:30–4:00 Eastern time Monday–Friday, or by e-mail (psych@alertpubs.com).
Generic Abilify Approved

The first generic version of Abilify (aripiprazole) has received FDA approval for the treatment of bipolar disorder and schizophrenia. Generics will be marketed by several manufacturers and will carry the same Boxed Warnings regarding increased risk of death with off-label use in elderly patients with dementia-related psychosis and the risk of suicidal behavior and thinking in children, adolescents, and young adults.

FDA News Release: FDA approves first generic Abilify to treat mental illness. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

Generic Olanzapine Bioequivalence

Patients with schizophrenia who were switched from brand-name olanzapine (Zyprexa) to the same dose of a generic formulation had significantly lower serum drug concentrations after ≥4 weeks. Although symptom control was not affected in this study, the changes in serum concentration are concerning, particularly with antipsychotics, most of which have a narrow therapeutic index.

Methods: Study participants were 25 consecutive outpatients (mean age, 41 years; 13 women) stabilized on branded olanzapine, who were switched to the same dose of a generic produced by a single manufacturer. Patients with recent changes in medications, including potentially interacting comedications, were excluded from the study. Serum concentrations of olanzapine were measured during treatment with the brand-name drug and again ≥4 weeks after the switch. On both occasions, blood samples were drawn in the morning before the first daily olanzapine dose (≥12 hours after the previous evening administration). Symptoms were assessed at the same times using the Positive and Negative Syndrome Scale (PANSS).

Results: Patients had a mean illness duration of 18 years and were receiving a mean olanzapine dosage of 12 mg/day (range, 5–20 mg/day). The mean olanzapine concentration during treatment with the branded drug was 27.7 ng/mL (range, 6–61 ng/mL). After the switch, the mean concentration was significantly lower at 22.6 ng/mL (p<0.01; range 5–56 ng/mL).
PANSS scores did not change between the 2 assessments. No patient experienced a relapse, required a dosage adjustment, or reported a new adverse effect after switching.

**Discussion:** There have been several reports of second-generation antipsychotics losing efficacy or causing adverse effects after a switch to a generic, but few systematic studies. The lower olanzapine blood levels in the present study might be of concern after a longer period of treatment than 4 weeks. The study authors recommend generic substitution as an indication for therapeutic drug monitoring in psychiatry.


**Alternative Routes of Drug Administration**

Many available antidepressants and antipsychotics have the potential for formulation in non-traditional dosage forms, but only a few are available for administration other than by the oral or injectable routes, according to a review. The development of alternative formulations would allow clinicians to treat psychiatric patients who cannot take oral medications, such as those with difficulty swallowing or with gastrointestinal (GI) abnormalities, or requiring bowel rest. Intravenous or intramuscular (IM) dosage forms are not available for all medications and may not be the best choice in certain situations. A literature search for case reports, clinical trials, and reviews describing alternate routes of administration of antidepressant and antipsychotic drugs was undertaken to summarize the existing evidence.

**Inhalation.** Absorption by inhalation is rapid and results in high bioavailability. The first-generation antipsychotic loxapine is the only psychotropic medication available in an inhaled form, and, because of the risk of bronchospasm, only through a Risk Evaluation and Mitigation Strategy program. In clinical trials, inhaled loxapine was rapidly effective in controlling agitation.

**Intranasal.** There are currently no approved intranasal antidepressants or antipsychotics. A small pharmacokinetic study of haloperidol in healthy volunteers found peak concentrations were similar with intranasal and IM delivery. Peak concentrations were achieved in half the time with intranasal delivery (15 vs. 30 minutes). Bioavailability of intranasal haloperidol was <50% of IM delivery.

**Buccal.** The buccal route provides sustained drug delivery and is suitable for medications with a long half-life and wide therapeutic range. There are no commercially available buccal antidepressants or antipsychotics, but there is a case report of buccal amitriptyline administration in a patient with depression and short-bowel syndrome and a feasibility study of buccal selegiline for depression. Amitriptyline levels were generally maintained in the therapeutic range with a 75-mg/day buccal dosage, and the patient’s depressive symptoms were reduced. Buccal administration of orally disintegrating selegiline resulted in an increase in brain monoamine oxidase-A inhibition similar to that with transdermal delivery.

**Sublingual.** Administration via the sublingual route results in more rapid and less sustained drug absorption than buccal administration. The antipsychotic asenapine is the only commercially available sublingual dosage form, but successful sublingual administration of haloperidol and olanzapine have been described for the management of agitation in terminally ill patients. Sublingual liquid fluoxetine was used successfully in 2 patients with GI complications.

**Transdermal.** Selegiline is the only antidepressant commercially available in a transdermal dosage form. Transdermal delivery avoids GI exposure and the food-associated risks of monoamine oxidase inhibition in the gut. Transdermal administration of other antidepressants
(e.g., fluoxetine, doxepin) has been described in a few case reports, with mixed results in achieved serum levels. Transdermal delivery of haloperidol or chlorpromazine did not result in detectable serum levels.

**Rectal.** Although there are no commercially available rectal antidepressants or antipsychotics, rectal administration of antidepressants has been described in a small number of patients who were unable to receive oral therapy because of bowel obstruction or other severe GI complications. In 2 cases, trazodone and amitriptyline were compounded as suppositories; while clinical improvement was noted, serum drug levels were not measured. In addition, doxepin capsules inserted rectally (without a suppository base) have reportedly produced serum levels in the therapeutic range. Fluoxetine, compounded with sterile water and administered as an enema, produced measurable but subtherapeutic levels in 1 patient but increased dosages were not tolerated due to abdominal cramping. In healthy volunteers, bioavailability of rectally administered fluoxetine capsules was found to be 15% relative to oral dosing.

**Discussion:** Despite the variety of available oral and injectable antidepressant and antipsychotic medications, few commercially marketed products for administration via other routes exist. However, because of their small molecular size, lipophilicity, and other physicochemical properties, most of the available antipsychotics and about half of the available antidepressants could be suitable candidates for development in nasal, sublingual, transdermal, or other dosage forms. According to the literature, studies of inhaled, intranasal, buccal, sublingual, transdermal, and rectal routes of administration suggest there is potential for future drug development, which could allow for the treatment of psychiatric diseases in patients who cannot or will not take oral or injectable forms of medication. Other advantages of these delivery routes could include rapid action, the ability to discontinue drug delivery by removing a partially absorbed dose, and avoidance of first-pass GI or hepatic metabolism.

Kaminsky B, Bostwick J, Guthrie S: Alternate routes of administration of antidepressant and antipsychotic medications. *Annals of Pharmacotherapy* 2015; doi 10.1177/1060028015583893. From the University of Michigan, Ann Arbor. This review was conducted without funding. The authors declared no conflicts of interest.

**Drug Trade Names:** amitriptyline—Elavil, Endep; asenapine—Saphris; fluoxetine—Prozac; haloperidol—Haldol; loxapine, inhaled—Adasuve; olanzapine—Zyprexa; selegiline, transdermal—Emsam; trazodone—Oleptro

---

**SNRI for SSRI Partial Response**

Adjunctive therapy with an investigational selective norepinephrine reuptake inhibitor was safe and well tolerated in a long-term study of patients with major depressive disorder (MDD) that was partially responsive to SSRIs.

**Methods:** This multinational uncontrolled study was conducted to investigate long-term safety of flexibly-dosed open-label edivoxetine, added to patients' background SSRIs. Participants were 608 patients (mean age, 48 years; 75% women) with MDD, confirmed by structured interview, and a partial response to >6 weeks of SSRI therapy. Participants received adjunctive edivoxetine, flexibly dosed at 12–18 mg/day, for 54 weeks. The mean duration of SSRI therapy at study entry was 21 weeks, and individual SSRI use was fairly well distributed across available agents with an indication for MDD. Background SSRI therapy remained unchanged throughout the study.

**Results:** A total of 67% of enrolled patients completed 14 weeks of adjunctive treatment, and 54% completed the full 54-week trial; 17% of study patients discontinued the trial because of adverse events. The most common adverse events leading to discontinuation included hypertension (2%), urinary retention (1%), and constipation, dizziness, and tachycardia (0.8% for each). Other frequent treatment-emergent adverse events that did not lead to discontinuation
included nausea; hyperhidrosis; constipation; headache; dry mouth; dizziness; vomiting; and insomnia. These events affected 6–15% of patients, and at least half of each type of event resolved by 8 weeks of treatment. Serious adverse events—mania and hypertension—in 2 patients were believed to be treatment related. Adjunctive edivoxetine was associated with significant increases in systolic BP (range, 0–2.3 mm Hg), diastolic BP (range, 1.9–3.3 mm Hg), and heart rate (range, 5.9–8.4 bpm). These changes were numerically small and plateaued during treatment. However, about 2% of patients had larger sustained BP elevations, which is in keeping with other antidepressants with norepinephrine effects. Increases in the QTc interval (>450 ms in men or >470 ms in women) were observed in 1.4% of patients.

Clinically significant weight gain occurred in 6% of patients and weight loss in 12%. Five study participants had emergent serious suicidal ideation and 1 made a serious suicide attempt, but suicidal ideation improved in 88% of patients who had these thoughts at baseline. Edivoxetine was associated with improvement on a standardized measure of sexual function. Existing sexual dysfunction improved categorically in about the same proportion of patients as had new onset of sexual dysfunction.

Discussion: Development of edivoxetine for MDD was halted after disappointing acute efficacy results, however, safety data from this trial may be useful to clinicians considering prescribing other SNRIs in the context of already established SSRI therapy.


Antipsychotics and Insight

Patients with first-episode schizophrenia had significant improvement in insight during the first 3 months of antipsychotic treatment, over and above the reduction in other psychosis symptoms.

Methods: This study was a secondary analysis of data from the European First-Episode Schizophrenia Trial (EUFEST), which compared the effectiveness of 5 different antipsychotics in 498 patients. Participants in EUFEST were experiencing a first-episode of schizophrenia, schizoaffective disorder, or schizophreniform disorder, had untreated psychosis for ≤2 years, and had received antipsychotic medication for ≤2 weeks in the previous year. Insight was measured using a single 7-point item (G12) on the Positive and Negative Syndrome Scale (PANSS). Depression was assessed with the Calgary Depression Scale for Schizophrenia (CDSS), designed to assess the severity of depression in patients with psychotic symptoms. The present analysis was limited to 455 adults (average age, 26 years; about 40% women) who had at least a minimal impairment in insight at study entry (PANSS insight item score, ≥2). Patients received treatment for 1 year in a single-blind fashion with randomly assigned, flexibly dosed amisulpride, haloperidol, olanzapine, quetiapine, or ziprasidone.

Results: At baseline, patients with schizoaffective disorder had significantly better insight than the other diagnostic groups (p<0.001). Insight was poorest in those with schizophreniform disorder. In all 3 groups, insight improved during the first 3 months of treatment (p<0.001; effect size,* 0.47) and then plateaued afterward. The pattern of improvement was similar for all 5 medications studied, although quetiapine was associated with less improvement than the other drugs. Mean insight ratings improved from about 4 at baseline to <3 after 3 months of treatment, approaching normal levels. Changes in insight were not completely explained by overall symptom reduction. At baseline, better insight was significantly, but modestly, correlated with better mood. Long-term changes in insight and mood were uncorrelated.
Discussion: Although poor insight has a negative effect on functioning and treatment adherence, it is rarely reported as an outcome of clinical trials of antipsychotics. Outcomes in the present study suggest that first-episode patients with poor insight may benefit more from medication than psychosocial interventions, which have been shown to have only limited effects on insight. The authors suggest that it may not be necessary to offer too many additional interventions that target insight during the first year, instead focusing on psychosocial rehabilitation and resuming of social roles.


**Drug Trade Names:** amisulpride—not available in U.S.; haloperidol—*Haldol*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; ziprasidone—*Geodon*

*See Reference Guide.*

## Treatment Algorithm for Postpartum Mania

Use of a 4-step treatment algorithm resulted in remission in a large majority of women with postpartum psychosis or mania.

**Background:** Although postpartum psychosis is a severe and potentially life-threatening disorder, the literature contains little research and few standardized treatment recommendations.

**Methods:** Subjects in this uncontrolled, open-label study were 64 women receiving inpatient treatment for postpartum psychosis at a mother–baby psychiatry unit that specializes in severe postpartum psychopathology. All women had new-onset psychosis (including depressive disorder with psychotic features, psychotic disorder NOS, brief psychotic disorder, or mania) within 4 weeks of delivery and received treatment based on an algorithm developed at the institution. The treatment algorithm consisted of 4 steps:

**Step 1.** Lorazepam at bedtime for 3 days to determine if restoration of sleep will ameliorate symptoms.

**Step 2.** After 3 days of nonresponse, add an antipsychotic medication—primarily haloperidol, but atypicals if haloperidol is not tolerated—for 2 weeks.

**Step 3.** After 2 weeks of nonresponse, initiate adjunctive lithium for 12 weeks.

**Step 4.** After 12 weeks without symptom resolution, taper all 3 medications and recommend ECT.

Patients were evaluated clinically every week until 9 months postpartum. Remission was defined as the absence of psychotic, manic, and depressive symptoms for ≥1 week, based on scores on the Young Mania Rating Scale (YMRS), the Edinburgh Postnatal Depression Scale, and the Clinical Global Impression–Bipolar Disorder scale. Lorazepam was discontinued after complete symptom remission. Patients who achieved remission with Step 2 were advised to continue antipsychotic monotherapy until 9 months postpartum. In those who met response criteria with Step 3, antipsychotics were tapered and lithium monotherapy was recommended until 9 months. All maintenance medication was tapered in women who were clinically stable at 9 months.

**Results:** Full clinical remission occurred in all but 1 of the 64 patients: 4 during lorazepam monotherapy (Step 1), 12 with lorazepam plus antipsychotic (Step 2), and 47 with triple therapy (Step 3). No patient received ECT.
Sustained remission was evident at 9 months in 51 patients (80%). Relapse occurred a median of 54 days after remission and consisted mostly of depressive episodes. No patient who achieved remission with lorazepam monotherapy experienced a relapse. Among patients who progressed beyond Step 1, relapse was significantly less likely in patients receiving lithium maintenance than in those who received an antipsychotic. Relapse occurred in 6 of the 12 receiving maintenance antipsychotics and in 6 of the 47 who received lithium maintenance (odds ratio,* 6.8 for antipsychotics vs. lithium; p=0.01). Sustained remission was more likely in primiparous women and in those with an affective psychosis.

**Discussion:** Women who present with postpartum psychosis should be questioned about thoughts of self-harm or harm of the child and screened for potential medical causes of psychosis. The results of the present study support inpatient treatment of these patients using the 4-step treatment algorithm. The study authors also recommend attention to mother–baby interaction and support for the father.

Bergink V, Burgerhout K, Koorengevel K, Kamperman A, et al: Treatment of psychosis and mania in the postpartum period. *American Journal of Psychiatry* 2015;172 (February):115–123. From Erasmus Hospital, Rotterdam, the Netherlands. **Source of funding not stated. The authors declared no conflicts of interest.**

*See Reference Guide.*

### Parenteral Neuropeptide for Alzheimer's Disease

A neurotrophic supplement, Cerebrolysin, has positive effects on cognition in patients with Alzheimer's disease, according to a meta-analysis.1

**Background:** Cerebrolysin is a biotechnologically prepared peptide that stimulates neurotrophic regulation in the central nervous system.2 It is used in many countries, but not the U.S., for treatment of ischemic and hemorrhagic stroke, traumatic brain injury, dementia (i.e., vascular dementia, Alzheimer’s disease), and other cognitive disorders and to prevent cognitive decline after brain injuries. Cerebrolysin is administered by injection or infusion.

**Methods:** All randomized, double-blind, parallel-group, placebo-controlled trials of Cerebrolysin for the treatment of mild-to-moderate Alzheimer’s disease were identified by literature search. The included studies were ≥4 weeks in duration and used a variety of primary cognitive efficacy endpoints, such as the Alzheimer’s Disease Assessment Scale–cognitive subscale and the mini-mental state examination. To compensate for the variety of outcome measures, mean changes in cognitive function were standardized and the effect size* estimated using the standardized mean difference (SMD).*

**Results:** In 6 trials, patients received 30 mg/day Cerebrolysin in 20 infusions over the first 4 weeks; 1 study had an additional treatment cycle that started 8 weeks after the end of the first; and 1 study extended treatment with 2 weekly injections for a further 8 weeks. Data on cognitive function was available for 763 patients at 4 weeks and for 519 patients at 6 months. After 4 weeks, there was a 0.4-point SMD for measures of cognitive function in favor of Cerebrolysin over placebo (p=0.003). The 6-month follow-up showed a difference of similar size, but without statistical significance. Cerebrolysin produced significantly more global clinical change than placebo, with odds ratios* of 3.32 (p=0.02) at 4 weeks and 4.98 (p=0.015) at 6 months. The number needed to treat* for 1 patient to benefit was 3 at both time intervals. Global benefit was estimated as a combined effect of global clinical change and cognitive function. At both follow-up time points, the effect size of Cerebrolysin was >0.57, indicating more than a small superiority to placebo (p=0.0006 for 4 weeks and 0.0010 for 6 months).

Cerebrolysin and placebo were associated with similar rates of adverse events. Patients who received Cerebrolysin had slightly higher rates of headache, vertigo, and hyperhidrosis. Rates
of discontinuation due to adverse effects were similar in the Cerebrolysin and placebo groups: 34% and 35%, respectively.

**Discussion:** Compared with meta-analyses of other Alzheimer's-disease treatments, this study places the effect size of Cerebrolysin between the smaller effects of memantine and the larger effects of donepezil. However, further study is needed to determine the effects of Cerebrolysin on functioning and behavior.

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

1Gauthier S, Proano J, Jia J, Froelich L, et al: Cerebrolysin in mild-to-moderate Alzheimer's disease: a meta-analysis of randomized controlled clinical trials. *Dementia and Geriatric Cognitive Disorders* 2015; doi 10.1159/000377672. From the McGill Center for Studies in Aging, Montreal, Canada; and other institutions including EVER Neuro Pharma GmbH, Unterach, Austria. **Source of funding not stated. Four study authors disclosed potentially relevant financial relationships; the remaining 2 authors declared no conflicts of interest.**


**Drug Trade Names:** donepezil—Aricept; memantine—Namenda

*See Reference Guide.

### Cariprazine: New Option in Acute Mania

In a phase III clinical trial, cariprazine, a candidate atypical antipsychotic, was effective and well tolerated as treatment of acute mania in bipolar I disorder.1 Effect sizes* for cariprazine were impressive, according to an editorial, but the value it may add to existing treatments is uncertain.2

**Background:** Cariprazine is currently under review by the FDA. It is a potent D2 and D3 receptor partial agonist with preferential binding to D3 receptors, a unique pharmacologic profile. The D3 receptor is believed to be involved in mood regulation and may be a novel target for mania treatment.

**Methods:** Study participants were patients with bipolar I disorder, manic or mixed type, with a current Young Mania Rating Scale (YMRS) score of ≥20. After a 1-week drug-free washout, patients were randomly assigned to cariprazine or placebo. Cariprazine was flexibly dosed within the 2 dosage categories of low (3–6 mg/day) and high (6–12 mg/day). The primary study outcome, assessed after 3 weeks of treatment, was change from baseline in the YMRS total score. Response was defined as a YMRS reduction of ≥50%, and remission as a final score of ≤12. Change in the Clinical Global Impression–Improvement (CGI-I)* score was a secondary outcome.

**Results:** A total of 497 patients with an average age around 42 years (264 men) were randomized, and about 75% completed the study. The 2 dosages of cariprazine had equal efficacy and were superior to placebo in reducing the YMRS total score, improving overall disease severity, and inducing response and remission. (See table.) Cariprazine was associated with statistically significant improvement in each of the 11 individual items of the YMRS. In both cariprazine groups, the number needed to treat (NNT)* estimate was 5 for response and 7 for remission.

<table>
<thead>
<tr>
<th><strong>Efficacy Outcomes</strong></th>
<th>Baseline YMRS</th>
<th>3 Week YMRS</th>
<th>P Value vs. Placebo</th>
<th>Effect Size*</th>
<th>YMRS Response</th>
<th>YMRS Remission</th>
<th>CGI-I Score at 3 Weeks</th>
<th>P Value vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Dose Cariprazine</td>
<td>33</td>
<td>15</td>
<td>p&lt;0.001</td>
<td>0.62</td>
<td>61%</td>
<td>45%</td>
<td>2.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>High-Dose Cariprazine</td>
<td>33</td>
<td>14</td>
<td>p&lt;0.001</td>
<td>0.60</td>
<td>59%</td>
<td>44%</td>
<td>2.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>33</td>
<td>20</td>
<td>——</td>
<td>——</td>
<td>38%</td>
<td>29%</td>
<td>2.9</td>
<td>——</td>
</tr>
</tbody>
</table>
Akathisia was the only frequent (>5%) adverse event occurring more often with both doses of active medication than with placebo. Cariprazine was not associated with adverse metabolic or cardiac effects, although that treatment duration was likely too short to observe these effects.

**Editorial.** Remission is an important outcome in bipolar mania because patients with residual symptoms have an increased rate of relapse. The remission rate with cariprazine is less than optimal, and an analysis using a proposed stricter YMRS cutoff of 8 points yields a modest remission rate of 25%. The effect size and NNT of cariprazine place it among the best-performing atypicals, but valid comparison of different agents' effects is difficult. Assuming cariprazine is approved for treating mania, cost will be a major barrier to its use, now that many atypicals are available as generics.

1 Calabrese J, Keck P Jr, Starace A, Lu K, et al: Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *Journal of Clinical Psychiatry* 2015;76 (March):284–292. From Case Western Reserve School of Medicine, Cleveland, OH; and other institutions including Forest Research Institute, Jersey City, NJ; and Gedeon Richter, Plc., Budapest, Hungary. **Funded by Forest Laboratories and Gedeon Richter.** All 8 study authors disclosed relationships with commercial sources, including Forest and Gedeon Richter.

2 Tohen M: Cariprazine in bipolar disorders [editorial]. *Journal of Clinical Psychiatry* 2015;76 (March):e368–e370. From the University of New Mexico Health Sciences Center, Albuquerque. **The author disclosed relationships with commercial sources.**

*See Reference Guide

---

**Reference Guide**

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

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

**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.

**Standardized Mean Difference:** The difference between 2 normalized means—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.

---

Contributing Editors: Kate Casano, MSHyg; Bennett Silver, MD
Consulting Editor: Steven J. Schleifer, MD, Rutgers–New Jersey Medical School
Executive Editor: Trish Elliott  Associate Editor: Tara Hausmann  Assistant Editor: Kasey Madara
Founding Editor: Michael J. Powers

**Off-Label Drug Use Statement:** Some drugs discussed for specific indications in *Psychiatry Drug Alerts* articles may not be approved for labeling and advertising for those indications by the United States Food and Drug Administration.
Dasotraline for Adult ADHD

The investigational dual dopamine and norepinephrine reuptake inhibitor (DNRI) dasotraline was superior to placebo in a randomized trial in adults with ADHD.

**Background:** Both dopamine and norepinephrine have been implicated in the pathophysiology of ADHD. Dasotraline is a novel compound that acts as a potent dopamine and norepinephrine transporter inhibitor and a weaker inhibitor of serotonin transporters.

**Methods:** The multicenter U.S. trial was conducted in patients, aged 18–55 years, with a primary diagnosis of ADHD, moderate-or-greater symptom severity, and ≥1 prior medication trial. After screening and a washout of any prior medications, patients were randomly assigned to 4 weeks of daily treatment with 4 or 8 mg/day dasotraline or placebo. The 2 doses were chosen based on target plasma concentrations and dopamine receptor occupancy. The primary outcome measure was the ADHD Rating Scale–IV (ADHD-RS-IV) with adult prompts.

**Results:** The analysis included 331 patients with a mean age of 34 years (59% men). After 4 weeks, the 8-mg dasotraline dose was statistically superior to placebo for the primary study outcome and many secondary outcomes. The lower dose was numerically but not statistically superior to placebo for most outcomes. In the primary evaluation, 8 mg dasotraline was associated with an average 14-point improvement in the ADHD-RS-IV total score, compared with 10 points for placebo (p=0.019; effect size,* 0.41). This dasotraline dose was superior to placebo with regard to the hyperactivity/impulsivity subscale (p=0.027) and the inattention subscale (p=0.016) of the ADHD-RS-IV. Both doses resulted in larger improvement than placebo in the mean Clinical Global Impression–Severity score: 1.1 points in each dosage group versus 0.7 points. Rates of response (≥30% reduction in ADHD-RS-IV total score) were 52% with 8 mg dasotraline and 38% with placebo (p=0.029; number needed to treat,* 8).

Nearly 30% of the 8-mg dasotraline group, 10% of the 4-mg group, and 2% of the placebo group discontinued treatment because of adverse events. The most frequent adverse events were insomnia, decreased appetite, nausea, anxiety, and dry mouth. Patients lost an average of...
nearly 6.5 lbs. after 8 weeks of the higher dasotraline dose. With regard to the abuse potential of dasotraline, there was no evidence of drug liking, misuse, or diversion.

**Discussion:** Effect sizes for dasotraline in this study were similar to those reported for methylphenidate (*Ritalin*), also a dual dopamine/norepinephrine transporter inhibitor, but smaller than those reported for amphetamine-based medications. However, because of its long elimination half-life, dasotraline requires approximately 2 weeks to reach steady state and it is possible that a longer duration of treatment may have produced stronger effects. These study results support the concept that ADHD symptoms can be improved by providing constant, steady-state inhibition of dopamine and norepinephrine reuptake.

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


*See Reference Guide.

---

### More on Psychotropic Mortality in Dementia

Results of a large study based on Veterans Administration (VA) data suggest that antipsychotics prescribed for behavioral disturbances of dementia may carry a higher mortality risk than previously reported. Risk is dose-related and appears to differ among the agents.

**Background:** First- and second-generation antipsychotics carry a black box warning about increased mortality when used in patients with behavioral disturbances of dementia, but precise mortality estimates are needed for decision-making.

**Methods:** The study cohort consisted of patients treated in the VA system over an 11-year period. Patients were aged ≥65 years, had a diagnosis of dementia, and received an initial prescription for 1 of the following antipsychotics: haloperidol, olanzapine, quetiapine, or risperidone. The analysis also included valproic acid and antidepressants other than tricyclics and monoamine oxidase inhibitors. Each patient receiving 1 of these drugs was matched with a control, also with dementia, who was similar in age, race, comorbidity, and other factors, but not receiving treatment with any of the study medications. The primary outcome of interest was death within 180 days of the prescription.

**Results:** The study cohort consisted of >45,000 matched pairs of medication users and nonusers. Haloperidol was associated with the highest mortality of any study medication (nearly 21%), followed by risperidone and olanzapine (14% each), valproic acid (12%), and antidepressants (8%). Risk was significantly higher (2–4%) in antipsychotic users versus nonusers (p<0.01). The numbers needed to harm* (NNH) ranged from 26 for haloperidol to 50 for quetiapine. (See table.) Antidepressant users had a slightly greater risk than nonusers (<1%; p<0.01), and the difference was not statistically significant for users versus nonusers of valproic acid.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Crude death rate</th>
<th>Risk difference: users vs. nonusers</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>20.7%</td>
<td>3.8</td>
<td>26</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>13.9%</td>
<td>2.5</td>
<td>40</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>11.8%</td>
<td>2.0</td>
<td>50</td>
</tr>
<tr>
<td>Risperidone</td>
<td>13.9%</td>
<td>3.7</td>
<td>27</td>
</tr>
</tbody>
</table>
Patients who received high-dose haloperidol had significantly higher mortality than those who received lower doses (p=0.02). After controlling for dose, olanzapine was associated with a 1.5% increase in mortality over quetiapine, and risperidone with a 1.7% increase over quetiapine.

**Discussion:** Mortality estimates were lower in previous research that was based on randomized controlled trials completed in 6–12 weeks. The present study, with its longer observation period, may be a more accurate reflection of risk in the community. Although the analysis was adjusted for multiple clinical characteristics, the clinical complexity of these patients may not have been entirely captured. As a result, it is possible that some of the increased mortality risk among the medication users could be related to the symptom or behavior for which the medication was prescribed.

Maust D, Kim H, Seyfried L, Chiang C, et al: Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry* 2015;72 (May):438–445. From the University of Michigan, Ann Arbor; and other institutions. Funded by the NIMH; and other sources. Two study authors disclosed potentially relevant financial relationships; the remaining 5 authors declared no conflicts of interest.

**Drug Trade Names:** haloperidol—Haldol; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal; valproic acid—Depakene, Depakote

---

**Augmentation in Treatment-Resistant Depression**

Results of a network meta-analysis suggest that quetiapine and aripiprazole are the best evidence-based agents for augmentation therapy in treatment-resistant depression.¹

**Background:** Of the several secondary strategies for treatment-resistant depression, augmentation has the advantages of eliminating the transition period between antidepressants and of building on any partial response the patient has had with the initial antidepressant. However, head-to-head comparisons of augmentation strategies are scarce.

**Methods:** A systematic literature search identified all controlled trials of augmentation strategies in broadly-defined treatment-resistant depression (≥1 historical treatment failure, plus ≥1 failure in the current episode). Studies of patients with bipolar depression or depression with psychotic features and single-gender studies were excluded. The primary endpoints of the meta-analysis were response (≥50% reduction in the depression measurement scale used by the study) and remission (posttreatment scores below a cutoff). Acceptability was measured as the rate of all-cause discontinuation of the augmenting agent, and tolerability as discontinuation because of adverse effects.

**Results:** Studies of 11 agents in comparison with placebo or another active medication met criteria for inclusion in the analysis: aripiprazole (n=4); bupropion (n=4); buspirone (n=5); lamotrigine (n=3); lithium (n=13); methylphenidate (n=2); olanzapine (n=4); pindolol (n=5); quetiapine (n=8); risperidone (n=5); and thyroid hormone (n=6; T3 and T4 were grouped for the analysis). The analysis included 48 trials with >6600 patients (mean age, 44 years; about two-thirds women). Randomized treatment lasted 2–14 weeks (mean duration, 6 weeks). The trials were of generally good quality, and there was no indication of bias by manufacturer sponsorship.

Of the 11 agents studied, 4 were statistically superior to placebo in inducing response. These were quetiapine (odds ratio OR for response, 1.92) followed by aripiprazole (OR, 1.85) thyroid hormone (OR, 1.84), and lithium (OR, 1.56).

For remission, 6 agents were significantly superior to placebo, with the highest odds ratio for thyroid hormone (2.94), followed by risperidone (2.17), quetiapine (2.08), buspirone (1.86), aripiprazole (1.83), and olanzapine (1.79). There was no difference in acceptability between any
active agents compared with each other or with placebo. However, quetiapine, olanzapine, aripiprazole, and lithium were significantly less well tolerated than placebo.

Discussion: Considering the primary efficacy endpoint of the meta-analysis, the authors conclude that aripiprazole and quetiapine are the best augmentation agents. Because of prescreening and ongoing monitoring requirements and the potential for tachycardia and other adverse effects, the study authors do not consider thyroid hormone an acceptable option. However, an accompanying commentary highlights the tolerability issues of quetiapine and aripiprazole. The odds ratios for discontinuation for these agents were substantially greater than for response (3.85 and 2.51, respectively, vs. 1.92 and 1.85). It further points out that the odds ratio for response with thyroid hormone (1.84) was comparable to the atypicals, while its tolerability was better (odds ratio, 1.36).

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

1 Zhou X, Ravindran A, Qin B, Giovane C, et al: Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. *Journal of Clinical Psychiatry* 2015;76 (April):e487–e498. From the First Affiliated Hospital of Chongqing Medical University, China; and other institutions. Funded by the National Basic Research Program of China. Two study authors declared financial relationships with commercial sources; the remaining 11 authors declared no conflicts of interest.

2 Shelton R: What are the comparative benefits and harms of augmentation treatments in major depression [commentary]? *Journal of Clinical Psychiatry* 2015;76 (April):e531–e533. From The University of Alabama at Birmingham. Funded by Pamlab, Inc. The author declared financial relationships with commercial sources, including Pamlab.

Drug Trade Names: aripiprazole—Abilify; bupropion—Wellbutrin; buspirone—BuSpar; lamotrigine—Lamictal; methylphenidate—Ritalin; olanzapine—Zyprexa; pindolol—Visken; quetiapine—Seroquel; risperidone—Risperdal

*See Reference Guide.

Adjunctive Hormonal Therapy in Schizophrenia

In a randomized trial, adjunctive treatment with the second-generation selective estrogen receptor modulator (SERM) raloxifene (Evista) improved measures of cognition and memory in men and women with schizophrenia.

Background: Abnormalities of prefrontal cortical and hippocampal function contribute to cognitive deficits in schizophrenia. Sex hormones are known to have beneficial effects at these sites. Despite promising preliminary evidence, there have been few studies of hormones to improve cognitive function in schizophrenia. While raloxifene has been observed to improve schizophrenia psychopathology in elderly women, as well as cognition in elderly patients of both genders, no previous clinical trials have evaluated the drug in younger populations.

Methods: Study participants were 93 patients, aged 18–51 years, who had a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder and had been receiving antipsychotic medication for ≥1 year before enrollment. In addition to their antipsychotic, patients received randomly assigned adjunctive 120 mg/day raloxifene or placebo for 6 weeks, followed by a 1-week washout, and then a crossover to the alternate study treatment. Patients were assessed at baseline and weeks 6 and 13 for cognitive performance, schizophrenia symptoms, emotional status, and quality of life. The primary study outcome was cognitive performance.

Results: Because there were significant carryover effects between the 2 treatment periods, the primary analysis was conducted using only the first treatment interval, with the 40 patients receiving raloxifene (22 men) and 39 receiving placebo (27 men). Levels of leutinizing hormone and follicle stimulating hormone did not generally show clinically relevant changes between baseline and week 6. Patients taking raloxifene showed statistically significant improvement from baseline in tests of immediate verbal memory, delayed verbal memory, and attention/processing speed (p≤0.001 for all 3 measures). Relative to the
placebo group, patients who received raloxifene had significantly larger improvement in immediate verbal memory, attention/processing speed, and verbal fluency (p<0.05 for all 3). The 2 treatment groups did not differ with regard to changes in schizophrenia symptoms or emotional or functional measures.

Of the 40 patients who initially received raloxifene, 16 (40%) showed clinically reliable change (≥20% improvement) in ≥1 cognitive measures, compared with 15% of the placebo group. The number needed to treat* to achieve improved cognition in 1 patient over 6 weeks was 4.

**Discussion:** Although previous research has shown symptom reductions with raloxifene in postmenopausal women, the results of this study do not support a generalized positive effect of the drug on schizophrenia symptoms. They do, however, suggest that adjunctive treatment can improve cognition and memory.

Weickert T, Weinberg D, Lenroot R, Catts S, et al: Adjunctive raloxifene treatment improves attention and memory in men and women with schizophrenia. *Molecular Psychiatry* 2015;20 (June):685–694. From the University of New South Wales, Kensington, Australia. Funded by the University of New South Wales School of Psychiatry; and other sources. The authors declared no conflicts of interest.

*See Reference Guide.

### Atypical Antipsychotics: Safety in Pregnancy

Women who require antipsychotic treatment are at higher risk for certain adverse maternal and perinatal outcomes. However, results of a large population-based cohort study suggest that the medications themselves may not be the cause.

**Background:** There have been few studies of the pregnancy risks associated with atypical agents, which have a different adverse-effect profile than older drugs—notably, metabolic syndrome and venous thromboembolism. The present study was conducted using high dimensional propensity score matching, a technique designed to nearly eliminate confounding and that would allow for the separation of risks due to antipsychotic drugs from risks due to other differences between women who use atypical antipsychotics and the general population.

**Methods:** The study cohort consisted of all women who gave birth to a singleton infant in the province of Ontario, Canada, between 2003 and 2012 and who obtained subsidized prescription drug coverage. (About 70% of all pregnant women with a psychotic disorder in Ontario have this coverage.) Antipsychotic medication exposure was defined as the filling of ≥2 consecutive prescriptions for an atypical antipsychotic between conception and delivery, with ≥1 filled during the first or second trimester. Women who received antipsychotic medication were matched with unexposed women using a high-density propensity score based on 500 covariates related to the likelihood of exposure to antipsychotic drugs. In 2 separate analyses, exposed women were compared with the matched cohort and to the entire remaining cohort of unexposed, unmatched pregnancies. The primary outcomes of interest were gestational diabetes, any of the hypertensive disorders of pregnancy, and venous thromboembolism, arising within pregnancy, hospitalization, or the first 6 postpartum weeks. Infant outcomes of interest were preterm birth (<37 weeks) and extremes of birth weight.

**Results:** During the study period, there were >52,600 singleton live births or stillbirths in women eligible for prescription drug coverage. Out of about 1200 antipsychotic users in the cohort, 1021 were successfully matched with a control subject. Several maternal and neonatal adverse outcomes were more frequent in antipsychotic-exposed women than in the entire unmatched cohort (see table), but none of the primary outcomes differed between exposed women and propensity-matched controls. The study did not show a significantly increased rate of neonatal adaptation syndrome, a secondary outcome, in exposed pregnancies.
**Selected Maternal and Neonatal Outcomes in Women Exposed to Antipsychotics and the Unmatched Cohort**

<table>
<thead>
<tr>
<th></th>
<th>Unmatched Cohort</th>
<th>High-Dimensional Propensity Score Matched Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency in exposed women</td>
<td>Frequency in unexposed women</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>7.7%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>5.2%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>14.8%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>3.7%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Neonatal adaptation syndrome</td>
<td>13.3%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

**Discussion:** These findings suggest that although women exposed to antipsychotics during pregnancy have increased rates of some adverse outcomes, this occurrence is attributable to factors other than antipsychotic use.

Vigod S, Gomes T, Wilton A, Taylor V, et al: Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study. BMJ 2015; doi 10.1136/bmj.h2298. From the University of Toronto; and the Institute for Clinical Evaluative Sciences (ICES) Toronto, Canada. Funded by the Canadian Institutes of Health Research; and ICES. Two study authors disclosed potentially relevant financial relationships; the remaining 3 authors declared no conflicts of interest.

*See Reference Guide.

**Antidepressants in Pregnancy and Pulmonary Hypertension**

Use of SSRIs in late pregnancy was associated with increased risk of persistent pulmonary hypertension (PPHN) of the newborn, according to results of a cohort study.

**Background:** PPHN of the newborn is associated with substantial morbidity and mortality, and as many as 20% of affected infants will not survive. Those who do may have serious long-term consequences including chronic lung disease, seizures, and neurodevelopmental problems. The FDA issued an advisory in 2006 on PPHN associated with fetal SSRI exposure, but withdrew the warning when later studies had conflicting findings.

**Methods:** The study cohort included nearly 4 million women enrolled in Medicaid who gave birth to live infants between 2000 and 2010. Approximately 129,000 women (3.4%) received antidepressant treatment during the last 90 days of pregnancy. The primary outcome was confirmed PPHN in exposed newborns within 30 days of birth.

**Results:** About 102,000 women took an SSRI, and about 27,000 used a non-SSRI antidepressant. Women who took antidepressants were more likely to be older and white; to smoke; to have chronic illnesses or obesity; to use other psychotropic medications; and to have greater health care use.

Overall, the incidence of PPHN was 31 per 10,000 infants exposed to an antidepressant and 21 per 10,000 unexposed infants, with similar risk increases in infants exposed to SSRIs or other antidepressants. The unadjusted odds ratio* for PPHN was 1.51 for SSRIs and 1.40 for non-SSRI antidepressants. Various adjustments and alternative analyses tended to diminish but
not eliminate the excess risk. Restricting the outcome to primary PPHN, without cardiac malformations or pulmonary hypoplasia, in full-term infants reduced the odds ratios to 1.28 for SSRIs and to 1.14 for non-SSRIs.

**Discussion:** The initial FDA warning on SSRI-associated PPHN was based on the findings of a single study. The negative results that followed and led to the withdrawal of the warning tended to come from small studies, raising the possibility of false negative findings. The present study is the largest to date and used advanced methods of analysis to mitigate the confounding effects of underlying psychiatric illness. The results confirm previous observations; but the increase in risk of PPHN was smaller than that suggested by earlier research.

Huybrechts K, Bateman B, Palmsten K, Desai R, et al: Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *JAMA* 2015;313 (June 2):2142–2151. From Brigham and Women's Hospital, Boston, MA; and other institutions. Funded by the Agency for Healthcare Research and Quality. The authors declared no conflicts of interest.

**Personalized Prescribing for Depression**

Emerging evidence suggests that antidepressant prescribing can be personalized by aligning the pharmacological actions of different drugs with depression symptoms and symptom clusters, according to a review. A complete baseline assessment could help to provide a patient-specific profile that can be matched to treatments based on an understanding of the neural systems and targets they engage.

The goal of treating depression is not only a full remission of symptoms, but also restoration of function and quality of life. Many clinical studies define remission as low scores on standardized symptom rating scales, but improvement in mood alone should not be mistaken for remission. The same symptoms that most impair function are those that commonly persist despite treatment: cognitive dysfunction, fatigue, and sleep-wake disturbances.

Unique mechanisms comprising multiple malfunctioning neural circuits may underlie each depressive symptom. (See table for neurotransmitter and symptom associations.) Brain regions with functional impairment in depression are modulated by monoaminergic neurotransmission. Aberrant dopamine and norepinephrine signaling adversely affect motivation, and abnormalities in various serotonergic subsystems form, at least in part, the basis for anhedonia, guilt, and other negative-affect symptoms. Serotonin and norepinephrine also have descending spinal pathways that mediate physical fatigue and associated somatic symptoms.

Cognitive impairment—i.e., a diminished ability to think, or indecision—is a core feature of depression. Numerous neurotransmitters are involved in cognition. The use of dopamine agonists, such as pramipexole, as add-on therapy has been shown to improve cognition. Also potentially useful are agents that enhance glutamatergic transmission, such as

<table>
<thead>
<tr>
<th>Depressive Symptom Cluster</th>
<th>Neurotransmitter Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite and weight change</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Guilt and feelings of worthlessness</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>Serotonin, Dopamine, and Norepinephrine</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Serotonin, Dopamine, and Norepinephrine</td>
</tr>
<tr>
<td>Psychomotor disturbance</td>
<td>Serotonin, Dopamine, and Norepinephrine</td>
</tr>
<tr>
<td>Apathy</td>
<td>Dopamine and Norepinephrine</td>
</tr>
<tr>
<td>Executive dysfunction</td>
<td>Dopamine and Norepinephrine</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Dopamine and Norepinephrine</td>
</tr>
</tbody>
</table>
as ketamine and memantine. Vortioxetine acts via serotonin to modulate GABAergic neurons that influence glutamatergic circuits.

Fatigue is another persistent symptom that interferes with recovery from depression; it may also be an adverse effect of some antidepressant medications. Dual-mechanism antidepressants may offer advantages over SSRIs in reducing fatigue and should be prescribed in patients with baseline fatigue. Add-on therapy, such as with stimulants, atomoxetine, or low doses of atypical antipsychotics, may alleviate fatigue by improving nighttime sleep.

Most patients with depression have disturbance of the sleep/wake cycle. Insomnia is also a side effect of some common antidepressant medications. Trazodone and doxepin are 2 agents with sleep-promoting effects, due to antagonism of serotonin and histamine respectively. When sleep problems emerge during antidepressant treatment, switching to another agent or adding a hypnotic may be beneficial.

Saltiel P, Silvershein D. Major depressive disorder: mechanism-based prescribing for personalized medicine. Neuropsychiatric Disease and Treatment 2015;11:875–888. From New York University School of Medicine, NY. Writing assistance was funded by Takeda Pharmaceuticals. Both study authors declared financial relationships with commercial sources.

Drug Trade Names: atomoxetine—Strattera; memantine—Namenda; pramipexole—Mirapex; trazodone—Desyrel; vortioxetine—Brintellix

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.

Network Meta-Analysis: A study design that can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common. For example, if in a clinical trial comparing treatment A with treatment B, option A is determined to be superior, and a separate trial in similar patients found option B superior to a third agent, option C, a network meta-analysis of these two trials would allow a researcher to conclude that treatment option A is more effective than option C, even though the 2 options have never been directly compared.

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.

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.

Contributing Editors: Kate Casano, MSHyg; Bennett Silver, MD
Consulting Editor: Steven J. Schleifer, MD, Rutgers–New Jersey Medical School
Executive Editor: Trish Elliott Associate Editor: Tara Hausmann Assistant Editor: Kasey Madara
Founding Editor: Michael J. Powers

Off-Label Drug Use Statement: Some drugs discussed for specific indications in Psychiatry Drug Alerts articles may not be approved for labeling and advertising for those indications by the United States Food and Drug Administration.
Brexpiprazole Approval

The FDA has announced approval of the new second-generation antipsychotic brexpiprazole (Rexulti) for the treatment of schizophrenia in adults and as an add-on to antidepressants in adults with major depression. Efficacy of brexpiprazole was demonstrated in 2 clinical trials in >1300 patients with schizophrenia and in 2 trials of >1000 patients with major depression. As with other agents in its class, brexpiprazole will carry boxed warnings about increased risk of death in elderly patients with dementia-related psychosis as well as increased risk of suicidal thinking and behavior in children, adolescents, and young adults.

Brexpiprazole was designed with a serotonin and dopamine activity profile that would theoretically result in a low potential for some of the most concerning side effects of second-generation antipsychotics, including prolactin elevation and extrapyramidal symptoms. The most common adverse effects of brexpiprazole in clinical trials were weight gain and inner restlessness.

1FDA News Release: FDA approves new drug to treat schizophrenia and as an add-on to an antidepressant to treat major depressive disorder. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

Quetiapine Abuse

Although antipsychotics are not generally considered drugs of abuse, quetiapine (Seroquel) was associated with a 90% increase in emergency department visits between 2005 and 2011, about half for misuse or abuse and one-fourth to one-third for suicide attempts.

Background: Concern about quetiapine misuse has emerged from the existence of street names and markets for the drug, reports of patients feigning symptoms to obtain it, and reports of intravenous or intranasal use. Quetiapine has reportedly been used to self-medicate insomnia and anxiety, to get drunk without the hangover, as a sedative after using stimulants or crack cocaine, to zone out, and to substitute for other drugs.
Methods: Data were collected from the Drug Abuse Warning Network (DAWN), a surveillance system of emergency department visits that acts as an indirect measure of drug use, abuse, and misuse. DAWN data are based on a sample of 250–350 hospitals, depending on the year, and come from abstracting of emergency department records. The present report examined visits in patients aged ≥12 years for 3 types of drug-related problems: adverse events, suicide attempts, and misuse and abuse—the latter defined as use by a person for whom the drug was not prescribed, or use not according to medical instructions, such as in larger amounts or more often.

Results: The nationally representative estimate of quetiapine-related visits increased from about 35,600 in 2005 to 67,500 in 2011. The number of visits for misuse or abuse increased from about 19,000 to 32,000, and visits for suicide attempts increased from about 8600 to 16,000. Quetiapine accounted for about half of all visits involving an antipsychotic agent and 62% of visits involving an atypical. Proportions of visits for suicide attempts were the same: quetiapine accounted for 52% of antipsychotics and 62% of atypicals. Among patients taking drug combinations, quetiapine was typically used with anxiolytics, sedatives, or hypnotics for both misuse/abuse and suicide attempts. Alcohol was involved in about one-third of misuse/abuse or suicide visits, and illicit drugs in about one-fourth.

Discussion: It is possible that the increasing rate of quetiapine misuse may be the result of its greater availability; it is among the most widely prescribed antipsychotics. Regardless of the reasons, the data from DAWN suggest that concerns about the misuse and abuse of quetiapine are warranted. Clinicians should be particularly cautious when prescribing quetiapine for patients with comorbid mental health and substance abuse issues or when quetiapine is used in substance abuse/dependence.

Celecoxib in OCD

Adjunctive celecoxib was effective in a preliminary placebo-controlled trial in patients with obsessive-compulsive disorder who received treatment with fluvoxamine. This result provides support for the idea that inflammation may play a role in the pathogenesis of OCD.

Background: Increasing evidence suggests inflammatory processes and immune dysregulation contribute to the pathogenesis of OCD. Celecoxib is a cyclooxygenase-2 (COX-2) inhibitor; COX-2 is known to promote inflammation and pain, and its inhibition prevents glutamate-mediated neuronal death and suppresses proinflammatory cytokines.

Methods: Study participants were adults, aged 18–60 years, with moderate-to-severe OCD as evidenced by Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores of ≥21. Patients were free of all psychotropic medications for the 6 weeks before enrollment, and upon entry began treatment with 100 mg/day fluvoxamine for 4 weeks and then 200 mg/day for an additional 6 weeks. They also received, by random assignment, 200 mg celecoxib b.i.d. or placebo. Efficacy was assessed with the Y-BOCS at weeks 4 and 10. Partial response was defined as a 25% reduction in Y-BOCS score, complete response as a 35% reduction, and remission as a score <16.

Results: The 50 study participants had a mean age of about 32 years, had been ill for an average of nearly 6 years, and had a mean baseline Y-BOCS score of 30; 38% of patients were women. By week 10, patients who received celecoxib had significantly greater reductions in mean Y-BOCS total scores than the placebo group (14.7 vs. 9.4; p=0.006; effect size,* 0.81). Average scores were significantly reduced on both the obsession (p=0.005; effect size, 0.84)
and compulsion (p=0.04; effect size, 0.61) subscales. Celecoxib was also associated with higher rates of partial response, complete response, and remission. (See table.) For nearly all efficacy outcomes, the celecoxib group differed significantly from placebo at week 4 and at week 10; a clear difference in efficacy was seen as early as 2 weeks. Rates of overall and individual adverse events did not differ between celecoxib and placebo.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Celecoxib (n=25)</th>
<th>Placebo (n=25)</th>
<th>Significance</th>
<th>Odds Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>23</td>
<td>10</td>
<td>p=0.0001</td>
<td>17.25</td>
</tr>
<tr>
<td>Complete response</td>
<td>22</td>
<td>9</td>
<td>p=0.0001</td>
<td>13.03</td>
</tr>
<tr>
<td>Remission</td>
<td>15</td>
<td>8</td>
<td>p=0.047</td>
<td>3.18</td>
</tr>
</tbody>
</table>

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


**Drug Trade Names:** celecoxib—Celebrex; fluvoxamine—Luvox

*See Reference Guide.

**Vortioxetine: Effective Doses in Depression**

Results of 2 similar randomized controlled trials suggest that 20 mg/day vortioxetine (*Brintellix*) may be superior to placebo in patients with recurrent major depressive disorder; but 5-, 10-, and 15-mg doses may not. These trials extend results of previous vortioxetine clinical trials, although most have reported efficacy at doses of 5–10 mg.

**Methods:** In both studies, participants were adults, aged 18–75 years, with a primary diagnosis of recurrent major depressive disorder and a current episode of at least moderate severity. In the first study, patients were randomly assigned to placebo or either 10 or 20 mg/day vortioxetine; the second trial randomized patients to placebo or either 10 or 15 mg/day vortioxetine. Both trials had an 8-week treatment duration, and the primary efficacy endpoint was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS), with response defined as a ≥50% decrease in score. The second trial used centralized raters, rather than site-specific raters, in an attempt to improve the accuracy of ratings.

**Results:** In study 1, a total of 462 patients received randomized treatment, of whom about 17% discontinued prematurely, most for reasons unrelated to treatment efficacy or tolerability. The mean baseline MADRS score was 32, indicating moderate-to-severe depressive symptoms. At the end of treatment, 20 mg/day vortioxetine was superior to placebo for both the primary outcome and for the response rate. Mean MADRS scores decreased to 21.2 with placebo, compared with 19.3 with 10 mg vortioxetine (p=0.058; ns) and 18 with 20 mg vortioxetine (p=0.002). MADRS response was achieved by 28% of the placebo group, compared with 34% of the 10-mg vortioxetine group (p=ns) and 39% of the 20-mg vortioxetine group (p=0.044). Other secondary outcomes—the Clinical Global Impression-Improvement (CGI-I) scale, Hamilton Anxiety Rating Scale, MADRS remission rate, and the Sheehan Disability Scale—showed slightly greater numeric improvements with 20 mg/day vortioxetine, but none reached statistical significance.

In study 2, a total of 469 patients received randomized treatment. Similar to the first study, 18% discontinued prematurely, most for reasons unrelated to treatment efficacy or tolerability. The
mean baseline MADRS score was similar to the previous study at nearly 34, also indicating moderate-to-severe depressive symptoms. After 8 weeks, neither the 10- nor the 15-mg dose of vortioxetine differed from placebo in MADRS score reduction. Reductions averaged 13–14 points in all treatment groups. Secondary study outcomes – MADRS response and remission and CGI-I – were numerically, but not significantly, better with both vortioxetine doses than with placebo. However, in the subgroup of patients with severe depression (MADRS >34), the 15-mg dose did produce significantly greater MADRS reductions than did placebo (-18 points vs. -12 points; p=0.034).

Vortioxetine adverse effects in both studies were consistent with those reported in previous studies, primarily nausea, headache, diarrhea, and dizziness.

**Editorial.** The 2 studies described were conducted in the U.S., as were 2 previous studies that failed to show efficacy for a 5-mg dose. These results contrast with prior trials conducted outside the U.S., in which dosages as low as 5 mg/day were superior to placebo in treating depression. Four prior published studies of vortioxetine with an active comparator resulted in 2 positive, 1 negative, and 1 failed trial.

According to the editorial, these results should not be surprising, given that about half of all trials of FDA-approved antidepressants have not demonstrated superiority over placebo. In the case of vortioxetine, inconsistent study results are less likely to arise from trial design characteristics and more likely to be caused by the characteristics of study participants or how the study procedures were conducted. The use of centralized raters in the second trial did not improve signal detection as it was intended to do. Trials with a high placebo response rate tend to leave little room for the active drug to demonstrate superiority; but placebo response was generally low in the present studies. Unmeasured characteristics of a U.S. study population may partly explain the inconsistency.

1Jacobsen P, Mahableshwarkar A, Serenko M, Chan S, et al: A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. *Journal of Clinical Psychiatry* 2015;76 (May):575–582. From Takeda Development Center Americas, Deerfield, IL; and the University of Texas Southwestern Medical Center, Dallas. **Funded by Takeda Pharmaceutical Company, Ltd.; and H. Lundbeck A/S.** All 5 study authors disclosed financial relationships with commercial sources, including Takeda.


3Dunlop B, Rapaport M: Antidepressant signal detection in the clinical trials vortex [editorial]. *Journal of Clinical Psychiatry* 2015;76 (May):e657–e658. From Emory University School of Medicine, Atlanta, GA. **One study author disclosed financial relationships with commercial sources, including Takeda; the remaining author disclosed no relevant financial relationships.**

### Augmentation vs. Switching for Depression

In a randomized trial in patients with major depression showing partial response to an initial antidepressant, augmentation with aripiprazole (*Abilify*) was superior to antidepressant switching.

**Background:** Aripiprazole is 1 of only 2 drugs approved as augmenting agents for major depressive disorder. Both switching and augmentation have been shown to be effective and this study appears to be the first to directly compare atypical-antipsychotic augmentation with switching strategies.

**Methods:** Study participants had a confirmed diagnosis of unipolar major depression (DSM-IV-TR) and continued to have a Hamilton Rating Scale for Depression (HAM-D) score of ≥14 despite receiving an adequate dose of their current antidepressant for ≥6 weeks. The study excluded patients with first-episode depression and those currently receiving cognitive...
behavioral therapy or other psychotherapy. Patients were randomly assigned to receive either augmentation with flexible-dose aripiprazole (started at 2 or 5 mg/day and increased to a maximum of 15 mg/day) or were switched to another antidepressant chosen by their treating physician. The primary endpoint was change from baseline to 6 weeks in the Montgomery-Asberg Depression Rating Scale (MADRS) score as measured by a blinded rater.

**Results:** A total of 96 patients (average age, 49 years; 77% women) were included in the analysis. The most common initial antidepressant drug class in both treatment groups was SSRIs, followed by SNRIs. A wide variety of switching strategies was used, the most common being switch to an SSRI (n=24), including 10 patients who were switched from 1 SSRI to another. Nine patients were switched from an SSRI to an SNRI.

Baseline HAM-D scores of 23 in both treatment groups indicated moderate-to-severe symptoms. Aripiprazole augmentation was significantly superior to switching for the primary study outcome and for multiple secondary endpoints. (See table.) Augmentation was also more effective as measured by the HAM-D, Iowa Fatigue Scale, and Sheehan Disability Scale. The 2 treatment options were equally well tolerated.

| Aripiprazole Augmentation vs. Antidepressant Switching: Efficacy Outcomes at 6 Weeks |
|---------------------------------|---------------------------------|----------|
| MADRS, mean change from baseline | Aripiprazole augmentation (n=50) | Antidepressant switch (n=46) | Significance |
| Response (<50% decrease in MADRS score) | -16.3 | -7.6 | p<0.0001 |
| Remission (MADRS score, ≤10) | 54% | 19% | p=0.005 |
| Clinical Global Impressment-Improvement score of 1 or 2 | 70% | 41% | p=0.007 |

**Discussion:** The present study, although limited by its short duration and small sample size, which did not permit comparison of different switching strategies, suggests augmentation may be a better strategy than switching medication in patients with partially responsive depression. While switching medications may also be effective, it may require a longer treatment period and it remains unclear whether switching between antidepressant classes or within-class switching is more effective.

**Study Rating**—17 (100%): This study met all criteria for a randomized controlled trial. However, it should be noted that only raters, not patients, were blinded to treatment assignment.


*See Reference Guide.*

**Single-Capsule Drug Combination for Alzheimer's Disease**

Results of 2 preliminary studies in healthy adults suggest a single-capule, fixed-dose combination of donepezil and memantine is bioequivalent to coadministered commercially available versions of the 2 drugs.1 Food intake and sprinkling the capsule contents on applesauce did not affect bioavailability of the combination pill.

**Background:** Patients with moderate-to-severe Alzheimer's disease take an average of 6 different medications each day, and medication nonadherence has been reported in about 40%
of patients with the disease. Nonadherence may be caused by forgetfulness, high caregiver burden, high pill burden, complex medication regimens, or swallowing difficulties. Combining 2 of the most commonly prescribed medications into a single, daily capsule has the potential to improve treatment adherence, and the ability to administer the drugs sprinkled on soft foods can further increase compliance and safety in patients who have difficulty swallowing.

**Methods:** The fixed-dose combination of 28 mg extended-release memantine and 10 mg donepezil, which received FDA approval in late 2014, was evaluated in 2 groups of healthy men and women, aged 18–45 years. Pharmacokinetics of the fixed-dose combination were compared with coadministered commercially available donepezil and memantine in 38 participants. Treatments were administered in a single dose, in a randomized crossover fashion, with a 21-day washout between tests. In the second study, 36 patients received 3 treatments in randomized order, again separated by a 21-day washout: an intact fixed-dose combination capsule taken while fasting, a capsule taken following a high-fat meal, and the capsule contents sprinkled on applesauce and taken while fasting.

**Results:** In the first trial, the fixed-dose combination was bioequivalent to the commercially available drugs, as indicated by the area under the concentration-time curve. Peak concentrations, time to peak, half-life, and plasma concentration-time profiles did not differ between treatments. In the second study, most pharmacokinetic parameters were similar for the 3 types of administration. For memantine, the half-life after administration of an intact capsule while fasting was significantly longer than the other 2 methods (24 vs. 14 hours). For donepezil, administration with a high-fat meal was associated with a later time-to-peak concentration. All 3 methods were bioequivalent. In both studies, adverse events were similar with all treatments; the most common being nausea; dizziness; feeling hot; vomiting; headache; and abdominal discomfort.


**Drug Trade Names:** donepezil—Aricept; donepezil-memantine—Namzaric; memantine—Namenda

### Bipolar Depression Treatments Compared

According to a meta-analysis, carbamazepine, older antidepressants, olanzapine–fluoxetine, lurasidone, and quetiapine show a favorable combination of efficacy and tolerability in patients with bipolar depression. Newer antidepressants, valproate, lamotrigine, lithium, olanzapine, aripiprazole, and ziprasidone have less favorable profiles.

**Methods:** A literature review was undertaken to identify all published randomized trials of treatments for acute bipolar depression in adults. A total of 22 studies, comprising 33 drug-placebo comparisons, were included. There were 10 trials of anticonvulsants, 8 of antidepressants, 14 of antipsychotics, and 1 of lithium. Clinical efficacy was expressed as the number needed to treat* (NNT) for response over placebo, with response usually defined as ≥50% reduction in a depressive symptom rating. Tolerability was defined by the number needed to harm* (NNH) for a specific adverse effect of each type of drug: switch to mania/hypomania for antidepressants; excessive sedation, akathisia, or a ≥7% weight gain for antipsychotics; non-serious rash for lamotrigine; dizziness for carbamazepine; nausea for valproate; and tremor or nausea for lithium. Favorable NNT values are considered those <10, with lower values indicating better efficacy. Favorable NNH values are those >10, with higher values indicating better tolerability. The risk–benefit ratio was expressed as the ratio of NNH to NNT (with higher values better).
Results: Overall pooled NNT values did not differ statistically among the 4 drug categories but were lowest (best) for anticonvulsants and highest for lithium. NNH estimates were highest (best) for antidepressants and lowest for antipsychotics. There was considerable variability in risks and benefits of individual agents within drug classes. (See table.)

Antidepressants had the best combination of substantial efficacy and high tolerability. Overall risk of mood switching with antidepressants was 17%, compared with 8% for placebo. Older antidepressants were more effective than newer ones, but newer antidepressants had a very high NNH of >1000.

Anticonvulsants also had good efficacy but highly variable tolerability. Carbamazepine ranked best in terms of NNT. The NNH was unfavorable for carbamazepine, valproate, and lamotrigine.

Lithium was evaluated in only 1 trial, where it was an active control for quetiapine. It had relatively poor efficacy and the best tolerability of any individual agent investigated, but an unfavorable risk–benefit ratio.

Efficacy of atypical antipsychotics was highly variable. Aripiprazole, olanzapine, and ziprasidone had unfavorable NNT values. NNH estimates were unfavorable for most antipsychotics, with lurasidone having the best tolerability and the highest risk–benefit ratio. Olanzapine–fluoxetine had nearly equal NNT and NNH values.

Discussion: Although these results suggest that the newer antidepressants have the best risk–benefit profile, the conclusion is based on limited evidence—possibly due to exaggerated fears of inducing manic mood switches or an oversimplified view of bipolar depression. Because there are few treatment options for bipolar depression, off-label experimentation with various agents is widespread.

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

<table>
<thead>
<tr>
<th>Drug Class/Agent</th>
<th>NNT</th>
<th>NNH</th>
<th>Risk–Benefit Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants Overall</td>
<td>5.75</td>
<td>104</td>
<td>18.1</td>
</tr>
<tr>
<td>Older Agents (i.e., imipramine, phenelzine)</td>
<td>4.52</td>
<td>13.6</td>
<td>3.01</td>
</tr>
<tr>
<td>Newer Agents (i.e., fluoxetine, paroxetine, bupropion)</td>
<td>7.43</td>
<td>1080</td>
<td>145</td>
</tr>
<tr>
<td>Anticonvulsants Overall</td>
<td>5.06</td>
<td>19</td>
<td>3.75</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3.44</td>
<td>8.8</td>
<td>2.56</td>
</tr>
<tr>
<td>Valproate</td>
<td>4.4</td>
<td>4.92</td>
<td>1.12</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>5.76</td>
<td>23.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Antipsychotics Overall</td>
<td>8.25</td>
<td>4.89</td>
<td>0.59</td>
</tr>
<tr>
<td>Olanzapine–fluoxetine</td>
<td>3.89</td>
<td>3.98</td>
<td>1.02</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>5.24</td>
<td>20.2</td>
<td>3.85</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>5.62</td>
<td>4.18</td>
<td>0.74</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>11.3</td>
<td>3.99</td>
<td>0.35</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>45.1</td>
<td>3.67</td>
<td>0.08</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>77.4</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lithium</td>
<td>15</td>
<td>38</td>
<td>2.53</td>
</tr>
</tbody>
</table>

Vazquez G, Holtzman J, Tondo L, Baldessarini R: Efficacy and tolerability of treatments for bipolar depression. Journal of Affective Disorders 2015;183 (September):258–262. From McLean Hospital, Belmont, MA; and other institutions. Funded by the Aretaean Foundation of Rome; and other sources. The authors declared no conflicts of interest.

Drug Trade Names: aripiprazole—Abilify; carbamazepine—Carbatrol, Epitol, Tegretol; lamotrigine—Lamictal; lurasidone—Latuda; olanzapine—Zyprexa; olanzapine–fluoxetine—Symbbyax; quetiapine—Seroquel; valproate—Depakene, Depakote; ziprasidone—Geodon

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

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

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.

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.

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.
Brintellix, Brilinta Name Confusion

The FDA has released a drug safety communication regarding prescribing and dispensing errors involving the antidepressant Brintellix (vortioxetine) and the antiplatelet agent Brilinta (ticagrelor). The primary reason for the errors appears to be the similarity of the drugs’ brand names. Prescribers can reduce the risk of these errors by including the generic name as well as the indication for treatment on all prescriptions for these agents. Patients should be reminded to check their prescriptions to ensure the proper medication was dispensed.

Brintellix (vortioxetine) and Brilinta (ticagrelor): drug safety communication-name confusion. Available at www.fda.gov/Safety/MedWatch.

Nicotinic Receptor Agonist for Cognitive Impairment

Encenicline, an investigational α7 nicotinic acetylcholine receptor agonist, had positive effects on cognition in a randomized phase II trial in patients with schizophrenia.

Background: Cognitive impairment affects nearly all patients with schizophrenia, but there are currently no FDA-approved treatments. Encenicline, also in development for treatment of Alzheimer's disease, acts by increasing cholinergic neurotransmission and the release of glutamate and dopamine in the prefrontal cortex.

Methods: Study participants (n=307) were adults, aged 18–55 years, with schizophrenia or schizoaffective disorder. Participants were required to have an illness duration of ≥3 years and to be clinically stable while receiving an atypical antipsychotic (unchanged) for the duration of study treatment. Patients with more than moderate severity of positive symptoms or with formal thought disorders based on Brief Psychiatric Rating Scale scores were excluded. Following a 14-day placebo run-in, patients were randomly assigned to 12 weeks of daily treatment with 0.27 or 0.9 mg encenicline or placebo. The primary efficacy outcome measure was the CogState Overall Cognition Index (OCI), based on 7 computerized tasks and 2 paper-and-pencil tasks from the Neuropsychological Test Battery.
**Results:** For most of the individual tasks that comprise the OCI, results were numerically superior with both encenicline doses than with placebo. The lower encenicline dose was significantly superior to placebo for the primary endpoint of improved general cognitive function (p=0.034; effect size,* 0.257), while the 0.9-mg dose was not (effect size, 0.093). In contrast, the 0.9-mg dose, but not the lower dose, produced significantly greater improvement than placebo in Positive and Negative Syndrome Scale (PANSS) Cognition Impairment domain and negative symptoms subscale scores and the Schizophrenia Cognition Rating Scale, with effect sizes in the range of 0.1–0.4. Encenicline was generally safe and well tolerated. It was not associated with weight gain or worsening of schizophrenia symptoms.

**Discussion:** The positive effects of encenicline on cognition, along with its favorable safety profile, suggest that further studies with larger populations, longer durations, and higher doses appear to be warranted. The disparate dose response results on the different cognitive measures may be related to the sensitivity of each measure, but this will also require further study.

Keefe R, Meltzer H, Dgetluck N, Gawryl M, et al: Randomized, double-blind, placebo-controlled study of encenicline, an alpha-7 nicotinic acetylcholine receptor agonist as a treatment for cognitive impairment in schizophrenia. *Neuropsychopharmacology* 2015; doi 10.1038/npp.2015.176. From Duke University Medical Center, Durham, NC; and other institutions including FORUM Pharmaceuticals, Boston, MA. **Funded by FORUM Pharmaceuticals. All 8 study authors disclosed financial relationships with commercial sources, including 7 with FORUM Pharmaceuticals.**

*See Reference Guide.

---

**Antidepressant/NSAID Interaction**

According to results of a population-based study, the addition of nonsteroidal antiinflammatory drugs to antidepressants increases early risk of intracranial hemorrhage.¹

**Methods:** Data were extracted from the Korean national health insurance database, and all patients who had received a new prescription for an antidepressant between 2010 and 2013 were identified. Patients with a recent diagnosis (within 1 year) of cerebrovascular disease and those aged >99 years were excluded from the analysis. Combined drug use was defined as a prescription for an NSAID within the first 30 days following prescription of an antidepressant. Patients were assigned propensity scores* for adding NSAIDs to antidepressants, and those given prescriptions for both drugs were matched by propensity score to those receiving only an antidepressant. The primary study outcome was hospitalization for an intracranial hemorrhage within 30 days of the first antidepressant prescription.

**Results:** After propensity score matching, the cohort consisted of >4 million people. NSAID prescription was associated with a 60% increase in intracranial hemorrhage within the 30 days following antidepressant prescription (hazard ratio,* 1.6; p<0.001). Risk was higher in men than women (hazard ratio, 2.6 and 1.2, respectively). There was no statistically meaningful difference in risk among antidepressant drug classes, nor was risk associated with age, concomitant medications, or subtype of intracranial hemorrhage.

**Discussion:** Antidepressants and NSAIDs are not known to increase intracranial hemorrhage risk when used alone, but they have been shown separately to increase risk of gastrointestinal bleeding. Serotonergic antidepressants and NSAIDs both interfere with platelet function. Elevation of norepinephrine levels may also be associated with risk of intracranial hemorrhage. These study results indicate that patients who receive combined antidepressants and NSAIDs require special attention.

**Editorial.**² The findings from this study raise concern because conditions that require antidepressant and NSAID treatment often coexist. Although the study evaluated only prescription NSAID use, nonprescription NSAID use is common, and over-the-counter

---

¹See Reference Guide.
medications are not usually considered in prescribing decisions. Nonprescription NSAID use is usually shorter term than prescription treatment, but risk was shown in this study to be increased within 30 days, and risk with long-term combined treatment could be considerably higher.


Mercer S, Payne R, Nicholl B, Morrison J: Risk of intracranial haemorrhage linked to co-treatment with antidepressants and NSAIDs [editorial]. *BMJ* 2015; doi 10.1136/bmj.h3745. From the University of Glasgow; and the University of Cambridge, U.K. The authors declared no competing interests.

*See Reference Guide.*

### Antipsychotic Dose Reduction in Late Life

Positron emission tomography (PET) scans suggest the therapeutic window of dopamine D$_{2/3}$ receptor occupancy may be reduced in late-life schizophrenia, potentially allowing for reduced drug dosages. According to the results of an observational study, antipsychotic dose reduction is feasible in older patients with stable schizophrenia and can result in fewer adverse effects and better control of psychotic symptoms.

**Methods:** Study participants were patients, aged ≥50 years, with clinically stable schizophrenia or schizoaffective disorder who had been receiving the same dose of olanzapine or risperidone for 6–12 months. Those with late-life onset of psychosis (after age 50 years) were not included. Patients underwent a PET scan to determine dopamine D$_{2/3}$ receptor occupancy at baseline. Each patient’s antipsychotic dose was then reduced gradually to up to 40% of the baseline dose or the lower limit of the recommended range. Clinical assessments and PET scans were performed again at least 2 weeks after the final target dose was reached. Patients were monitored for 3–6 months, and the dose was increased if there was clinical deterioration. Schizophrenia symptoms were measured with the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), and Targeted Inventory of Problems in Schizophrenia (TIP-Sz), among other assessments. Adverse effects were also assessed using standardized measures.

**Results:** A total of 35 patients (mean age, 60 years; range 50–79 years) were enrolled in the study. They had been ill with schizophrenia for most of their adult lives. A total of 22 patients received treatment with olanzapine and 13 with risperidone. Two patients had clinical deterioration before the dose reduction was completed. For the remaining 33 patients, dose reduction took an average of 2 weeks. Four patients experienced deterioration during the follow-up period (6–19 weeks after starting taper). Five of the 6 who experienced deterioration were re-stabilized with a dose increase, and 1 continued to have symptomatic fluctuation. A total of 29 patients had successful dose reduction and remained clinically stable during follow-up. Overall, the group had small but significant improvements in the PANSS (p=0.02), BPRS (p=0.03), and TIP-Sz (p=0.046). Total scores on the Barnes Akathisia Scale (p=0.03), the Simpson-Angus Scale (p<0.001), and other measures of adverse effects decreased after the dose reduction. Of 22 patients who had extrapyramidal symptoms at baseline, 12 experienced resolution of these symptoms at follow-up. Hyperprolactinemia that was initially present in 13 patients had resolved in 5 by follow-up.

Baseline striatal dopamine D$_{2/3}$ receptor occupancy was 70% (range, 41–89%) at baseline and decreased to 66% (range, 49–84%) in the patients who had a successful dose reduction. Receptor occupancy did not differ between patients with or without extrapyramidal symptoms.
Discussion: In younger patients, striatal dopamine D2/3 receptor occupancy >65% is associated with good clinical response, and occupancy >80% is likely to result in extrapyramidal effects. Results of the present study suggest the efficacy threshold in older patients is 50%. There was no clear threshold for extrapyramidal effects, which were observed with receptor occupancy as low as 40%.

Graff-Gurrero A, Rajji T, Mulsant B, Nakajima S, et al: Evaluation of antipsychotic dose reduction in late-life schizophrenia: a prospective dopamine D2/3 receptor occupancy study. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2015.0891. From the Centre for Addiction and Mental Health, Toronto, Canada; and other institutions. Funded by the Canadian Institutes of Health Research; the NIH; and other sources. Six of the 11 study authors disclosed financial relationship with commercial sources.

Drug Trade Names: olanzapine—Zyprexa; risperidone—Risperdal

## Esmirtazapine for Insomnia

In a multicenter, placebo-controlled trial, esmirtazapine, the investigational maleic acid salt of the S(+) enantiomer of the antidepressant mirtazapine, improved sleep parameters in patients with chronic primary insomnia without producing residual morning effects.

**Background:** Mirtazapine has sleep-promoting properties believed to be due to its binding of serotonin 5-HT2 and histamine-1 (H1) receptors. The enantiomer esmirtazapine has a shorter half-life than the racemic compound, suggesting a smaller risk for residual sedative effects the next day. It has been shown in previous shorter-term studies to improve primary insomnia.

**Methods:** Study participants were adults, aged 18–65 years, with primary insomnia. Patients with recent or current depression were excluded. During 2 screening polysomnography evaluations, they were required to have an average total sleep time (TST) of <6.5 hours and a wake time after sleep onset (WASO) of ≥45 minutes. Patients were randomly assigned to esmirtazapine (3.0 or 4.5 mg) or placebo, to be taken 30 minutes before bedtime. The primary endpoint was WASO, measured at days 1, 15, and 36. Latency to persistent sleep, measured with polysomnography, was the key secondary endpoint. Rebound was assessed with polysomnography on 2 nights during the 1-week discontinuation period and with sleep diaries. Patients also completed the Withdrawal Symptom Questionnaire.

**Results:** In an intent-to-treat analysis of 398 patients (average age, 45 years; 66% women) who received treatment and underwent ≥1 assessment, esmirtazapine was associated with about a 50- to 55-minute decrease in WASO, compared with about 25 minutes for placebo (baseline range, 43–243 minutes). Both doses of esmirtazapine were superior to placebo at each of the 3 time points (p<0.0001). Esmirtazapine was also associated with significant improvement in sleep latency: about a 30-minute decrease versus about 15 minutes for placebo (baseline range, 10–205 minutes) at all 3 time points (p<0.006). Active treatment was also associated with an increase in total sleep time (baseline range, 193–398 minutes): about 80 minutes versus 35 minutes for placebo (p≤0.0001), fewer nighttime awakenings (p≤0.03), and more time spent in slow-wave sleep (p<0.05). Sleep diaries confirmed the polysomnographic data. There were no significant differences in efficacy between the 2 esmirtazapine doses.

There was no evidence of rebound or withdrawal effects when esmirtazapine was discontinued. Compared with baseline, all treatment groups including placebo showed improvement in tests of daytime alertness and in patient-reported energy levels and ability to work. The predominant adverse effects of esmirtazapine were somnolence and headache. Five patients stopped taking esmirtazapine because of somnolence. Four reported mild-to-moderate weight gain.

**Discussion:** Standard treatments for insomnia treatment include benzodiazepines, zolpidem, eszopiclone, and zaleplon. These agents exert their sleep-promoting activity via GABAergic
stimulation of the sleep system, and they often result in residual daytime sleepiness. In contrast, esmirtazapine, via its high-affinity for 5-HT₂A and H₁ binding, improves insomnia by inhibiting the wakefulness system, thus causing less residual sleepiness.

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

Ivgy-May N, et al: Esmirtazapine in non-elderly adult patients with primary insomnia: efficacy and safety from a randomized, 6-week sleep laboratory trial. *Sleep Medicine* 2015;16 (July):838–844. From Merck & Co., Kenilworth, NJ; and other institutions. Funded by Organon, a subsidiary of Merck. All study authors disclosed financial relationships with commercial sources.

**Drug Trade Names**: eszopiclone—**Lunesta**; mirtazapine—**Remeron**; zaleplon—**Sonata**; zolpidem—**Ambien**

*See Reference Guide.

**Adjunctive Pregabalin for GAD with Comorbid Depression**

Pregabalin (*Lyrica*) was effective when added to antidepressants in patients with resistant generalized anxiety disorder and severe depressive symptoms, according to a post-hoc analysis of data from an observational study.

**Background**: Initial treatment of GAD often does not produce response, and comorbid depression is common in patients with the disorder. Although pregabalin has been shown to be effective in GAD alone, the evidence base for treatment-resistant GAD with depression is limited.

**Methods**: More than 1800 patients with GAD were enrolled in a study whose primary aim was to examine the DSM-IV criteria for the disorder. Patients included in this post-hoc analysis (n=133; mean age, 47 years; 70% women) experienced persistent GAD symptoms or a suboptimal response to an antidepressant (taken for ≥6 months) as indicated by Hamilton Anxiety Rating Scale (HAM-A) scores of >16 and a Clinical Global Impression–Severity* (CGI-S) scores of >3. Participants were also required to have Montgomery-Asberg Depression Rating Scale (MADRS) scores of >35. Efficacy endpoints were change from baseline in the HAM-A and MADRS, anxiety response and remission (HAM-A reduction of ≥50% and a score of ≤7, respectively), and depression response and remission (MADRS reduction of ≥50% and a score of ≤12, respectively).

**Results**: At baseline, patients were severely symptomatic, with 86% rated as at least "markedly ill" with the CGI-S. More than half had major depressive disorder. The majority of patients received pregabalin in combination with other psychotropics: antidepressants plus benzodiazepines (57%), antidepressants alone (20%), benzodiazepines alone (4.5%), and other combinations (15.1%). Only 4 patients (3%) received pregabalin as monotherapy.

Patients experienced large improvements in anxiety and depression over the 6 months following the initiation of pregabalin (see table), with >50% decreases on average in all outcome scores and large effect sizes.* Patients had comparable decreases in psychic and somatic subscales of the HAM-A. There were large effects on all of the 10 individual depressive symptoms measured by the MADRS, including a 61% decrease in suicidal thoughts. Patients reported substantial positive effects on sleep and quality of life.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Baseline Score</th>
<th>Mean Score at 6 Months</th>
<th>Effect Size</th>
<th>Response Rate</th>
<th>Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAM-A</td>
<td>35.5</td>
<td>15.2*</td>
<td>3.4</td>
<td>63%</td>
<td>25%</td>
</tr>
<tr>
<td>MADRS</td>
<td>39.4</td>
<td>17.1*</td>
<td>5.0</td>
<td>59%</td>
<td>38%</td>
</tr>
<tr>
<td>CGI-S</td>
<td>5.2</td>
<td>3.1*</td>
<td>3.0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*p<0.0001 for change from baseline in all outcomes
**Discussion:** The mean daily pregabalin dosage in this study, 222 mg/day, is relatively low but within the range known to be effective in GAD (200–450 mg/day). The fact that pregabalin was combined with 2 other drugs in the majority of patients may account for the efficacy of the relatively low dose. This study is limited by its uncontrolled nature and by the requirement of only 1 previous adequate treatment trial. However, these positive results support additional, more rigorous research.


*See Reference Guide.

### Pregabalin Efficacy in GAD

In a head-to-head comparison, pregabalin and sertraline were similarly effective in patients with generalized anxiety disorder, but pregabalin was associated with more rapid response.

**Methods:** Study subjects were 107 adult outpatients (aged 20–60 years; 46% women) with GAD who sequentially received treatment at a psychiatric clinic. Participants were required to have a baseline Hamilton Anxiety Rating Scale (HAM-A) score of >20 and to be free of comorbid depression, alcoholism, personality disorders, or psychosis. Participants had not experienced remission with prior SSRI and/or SNRI treatment before they were randomized to 4 weeks with flexibly dosed sertraline or pregabalin. Change from baseline on the HAM-A was the primary study outcome.

**Results:** Average daily doses were 150 mg for sertraline and 225 mg for pregabalin. Both drugs were associated with significant reductions in anxiety. However, the mean HAM-A decreased rapidly within the first week in the pregabalin group, from 23.6 to 18.1. In contrast, the sertraline group demonstrated a decrease from 24 to 23.5 at 1 week. By week 2, the HAM-A score had decreased to 19.2 with sertraline. Both drugs significantly reduced scores on the psychic and somatic subscales of the HAM-A. At study end, Clinical Global Impression–Improvement ratings were "very much improved" in all but 1 patient in each treatment group.

Adverse events were mild, usually resolved within a few days, and did not cause any patient to discontinue treatment. Dizziness and somnolence were the most frequent adverse events with pregabalin, and nausea with sertraline. No patient in either group dropped out of the study.

**Discussion:** Along with SSRIs and SNRIs, pregabalin is recommended as first-line treatment of GAD in Europe. However, use for anxiety in the U.S. is off-label. Rapid onset of efficacy of pregabalin could potentially be important in GAD for improving both quality of life and medication compliance.


**Drug Trade Names:** pregabalin—Lyrica; sertraline—Zoloft; venlafaxine—Effexor

### MAO-B Inhibitor for Persistent Negative Symptoms

Results of a randomized trial suggest that rasagiline, a new selective MAO-B inhibitor, may improve persistent negative symptoms in patients with schizophrenia.

**Methods:** Study participants (n=57; mean age, 46 years; 77% men) were clinically stable in- or outpatients with schizophrenia or schizoaffective disorder with persistent moderate-to-severe negative symptoms despite ongoing antipsychotic therapy. Patients were required to
have no more than minimal positive, depressive, and extrapyramidal symptoms on stand-
ardized assessments. Participants were randomly assigned to receive 1 mg/day rasagiline
or placebo in addition to their background medications for 12 weeks. A total of 39% of the
rasagiline group and 38% of the placebo group were already receiving treatment with clozapine.
The primary outcome measure was the Scale for the Assessment of Negative Symptoms
(SANS) total score, which was assessed monthly.

**Results:** SANS total scores decreased by 2.8 points (from a baseline mean of 33) with rasagiline
and increased by 0.6 points (from a baseline mean of 34) with placebo (p=0.023; effect size,* 0.41).
This difference was largely driven by a decrease in the SANS avolition subscale in the rasagiline
group (p=0.002; effect size, 0.50 vs. placebo). The treatment groups did not differ with regard to
changes in SANS subscale scores. Similar numbers of patients in each group had a ≥20% reduc-
tion in SANS total score: 5 of 26 with rasagiline and 2 of 23 with placebo (19% vs. 9%). For the
avolition subscale, ≥20% reductions occurred in 12 rasagiline-treated patients and in 1 placebo-
treated patient (46% vs. 4%; p=0.0009). Rasagiline did not differ from placebo in effects on
positive symptoms, global illness severity, or neurocognitive test performance.

One patient experienced a severe adverse event possibly related to rasagiline: a panic attack
accompanied by command hallucinations to commit suicide. This event was considered
possibly related to the study drug; however, this patient had a history of hospitalizations for
panic attacks. Rasagiline did not differ from placebo with regard to extrapyramidal symptoms
or changes in body weight. Two rasagiline-treated patients discontinued treatment—one for
worsened OCD and one for positive-symptom exacerbation.

**Discussion:** MAO-B inhibitors increase endogenous dopamine levels without causing tyramine-
induced hypertensive crises like nonselective MAO inhibitors. Dopamine is believed to play
a role in brain reward mechanisms that are impaired in patients with negative symptoms.
The full effects of rasagiline took 12 weeks to emerge, which suggests the effects do not
merely reflect acute changes in dopamine levels. Abnormalities in cortical dopamine transmis-
sion are also believed to contribute to cognitive impairment, but the study did not support
the hypothesis that rasagiline would improve cognition.

**Study Rating*—16 (94%):** This study met most criteria for a randomized controlled trial.
However, the authors did not include discussion of potential study limitations.

*Buchanan R, Weiner E, Kelly D, Gold J, et al: Rasagiline in the treatment of the persistent negative symptoms of schizo-
phrenia. Schizophrenia Bulletin 2015;41 (July):900–908. From the University of Maryland School of Medicine, Baltimore.
Funded by the Stanley Medical Research Institute; and other sources. Three study authors disclosed financial rela-
tionships with commercial sources; the remaining 4 authors declared no competing interests.

Drug Trade Names: clozapine—Clozaril; rasagiline—Azilect

*See Reference Guide.

---

**SSRIs and Birth Defects**

An analysis of national birth-defects data confirmed associations between fluoxetine and
paroxetine use in early pregnancy and specific birth defects, but the drug-related increases in
absolute risk were small. There was no evidence to support potential associations with other
SSRIs, including sertraline, the most widely used SSRI in pregnant women.

**Methods:** The study was a bayesian analysis, in which data from previously published epidemi-
ologic studies were combined with data from the National Birth Defects Prevention Study
(NBDPS), a surveillance system operating in 10 U.S. states. The NBDPS is a case-control study
investigating 30 major birth defects in live-born infants, stillbirths, and induced abortions. The
present analysis included data from postnatal interviews of mothers, obtained in 1997–2009. For
the study, SSRI exposure was defined as any use of fluoxetine, paroxetine, sertraline, citalopram,
or escitalopram between 1 month before and 3 months after conception. A systematic review
identified 6 epidemiologic studies published before 2010 in which specific SSRI–birth defect combinations were reported. Data from the studies were combined using a meta-analysis to establish prior odds ratios* of each combination. The bayesian analysis combined these prior probabilities with data from the NBDPS.

**Results:** The NBDPS data included nearly 18,000 cases with birth defects and about 10,000 unexposed controls. Sertraline was the most commonly used SSRI, accounting for about 40% of use. Of the 5 SSRIs investigated in the bayesian analysis, no associations were confirmed between citalopram, escitalopram, or sertraline and any birth defect. However, fluoxetine use was associated with ventricular septal defects, right ventricular outflow obstruction, and craniosynostosis, and paroxetine was associated with anencephaly, atrial septal defects, right ventricular outflow obstruction, gastrochisis, and omphalocele. These defects, although uncommon, occurred about 2–3.5 times as often (see table) in pregnancies with early exposure to fluoxetine or paroxetine.

**Discussion:** This analysis confirms the need to investigate specific associations of SSRIs with birth defects, rather than combining the entire drug class or a heterogeneous group of birth defects. SSRIs differ chemically, and if any of them are teratogenic, this may be by a mechanism unrelated to serotonin reuptake inhibition. A strength of bayesian analysis is that it allows consideration of evidence both for and against previously reported associations from previously reported studies.

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Defect</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Right ventricular outflow obstruction</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Craniolgyosis</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Ventricular septal defects</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Anencephaly</td>
<td>3.3</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Atrial septal defects</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Right ventricular outflow obstruction</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Gastrochisis</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Omphalocele</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Reefhuis J, Devine O, Friedman J, Louik C, et al: Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports. BMJ 2015; doi 10.1136/bmj.h3190. From the CDC, Atlanta, GA; and other institutions. Funded by the CDC. The study authors declared no competing interests.

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

*See Reference Guide.

### Reference Guide

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

**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.

**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.

---

**Contributing Editors:** Kate Casano, MSHyg; Bennett Silver, MD
Consulting Editor: Steven J. Schleifer, MD, Rutgers–New Jersey Medical School
Executive Editor: Trish Elliott  Associate Editor: Tara Hausmann  Assistant Editor: Kasey Madara
Founding Editor: Michael J. Powers

**Off-Label Drug Use Statement:** Some drugs discussed for specific indications in Psychiatry Drug Alerts articles may not be approved for labeling and advertising for those indications by the United States Food and Drug Administration.
# PSYCHIATRY DRUG ALERTS

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole vs. Paliperidone</td>
<td>66</td>
</tr>
<tr>
<td>Brexpiprazole in Depression</td>
<td>69</td>
</tr>
<tr>
<td>Clozapine Monitoring</td>
<td>65</td>
</tr>
<tr>
<td>Depot Aripiprazole</td>
<td>65</td>
</tr>
<tr>
<td>Flibanserin for HSDD</td>
<td>69</td>
</tr>
<tr>
<td>Long-Term Lithium</td>
<td>67</td>
</tr>
<tr>
<td>Lurasidone Weight Effects</td>
<td>68</td>
</tr>
<tr>
<td>Medication Changes After Discharge</td>
<td>71</td>
</tr>
<tr>
<td>Reference Guide</td>
<td>72</td>
</tr>
</tbody>
</table>

## Clozapine Monitoring Changes

A new centralized clozapine risk evaluation and mitigation strategy (REMS) program has been created to replace the 6 individual registries previously maintained by individual manufacturers. All requirements for prescribing, dispensing, monitoring, and receiving clozapine products will now be incorporated into the single REMS program. (See www.clozapinerems.com.) Patients already receiving the medication will be automatically transferred to the new registry. The transition is scheduled to begin in October 2015.

In addition to the centralized registry, the FDA has also updated the monitoring requirements for neutropenia in patients receiving clozapine. Neutropenia will now be evaluated only by absolute neutrophil count (ANC), rather than in conjunction with white blood cell counts. This change is designed to allow patients with lower ANC to continue clozapine treatment and to allow for treatment of patients with benign ethnic neutropenia, who were not eligible to receive clozapine under the old REMS program. According to the FDA, the changes increase "prescribers' ability to make individualized treatment decisions if they determine that the risk of psychiatric illness is greater than the risk of recurrent severe neutropenia."


## Investigational Aripiprazole Depot Formulation

Aripiprazole lauroxil is an investigational, long-acting, injectable formulation with controlled-release technology, allowing multiple dose strengths and dosing intervals. The agent showed robust efficacy in a randomized, placebo-controlled trial in patients with acute exacerbation of schizophrenia.

**Methods:** Study subjects (n=596) were adult inpatients who had previously benefitted from antipsychotic treatment and who were having an acute exacerbation or relapse of <2 months' duration. Participants were required to have a Positive and Negative Syndrome Scale (PANSS)
total score of 70–120, significant positive symptoms, and a Clinical Global Impression–Severity* (CGI-S) scale score of ≥4. Patients were randomly assigned to injections on days 1, 29, and 57 with: 441 mg aripiprazole lauroxil (equivalent to 300 mg oral), 882 mg (equivalent to 600 mg), or placebo. A gluteal injection site was used because the larger aripiprazole lauroxil dose cannot be administered in the deltoid. Patients also received oral aripiprazole (Abilify) or placebo to provide coverage during the first 3 weeks after randomization. Inpatient treatment was required for ≥2 weeks, after which time patients could be discharged at the physicians’ discretion. The primary efficacy endpoint was change from baseline to day 85 in the PANSS total score. This outcome was analyzed in all patients who received ≥2 doses of study drug and had ≥1 primary efficacy evaluation.

Results: At baseline, patients were markedly-to-severely ill, with a mean PANSS total score of 93 and a mean CGI-S rating of 5. Two-thirds of patients received all 3 aripiprazole lauroxil injections, compared with only half of the placebo group (p=0.0005 for 441 mg vs. placebo and p<0.0001 for 882 mg vs. placebo).

Both doses of active medication were significantly more effective than placebo. Mean PANSS total score decreases were 21 and 22 points in the low- and high-dose aripiprazole lauroxil groups, compared with a 10-point reduction in the placebo group (p <0.001 for both dosages). The active medication differed statistically from placebo as early as day 8. Significantly more patients who received active treatment were rated "much" or "very much improved" on the CGI–Improvement scale (41–45% vs. about 20% for placebo; p<0.001 for both). A subgroup analysis according to illness severity suggested that the higher dose may provide additional benefit in patients with more severe schizophrenia symptoms.

The adverse-effect profile of aripiprazole lauroxil was similar to that associated with oral aripiprazole. Akathisia was the only notable adverse effect (occurring in ≥5% of patients). A single patient in the 882-mg dosage group experienced severe akathisia; akathisia of any severity occurred in about 12% of patients treated with aripiprazole lauroxil, more than twice the frequency as the placebo group.

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


*See Reference Guide.

Depot Aripiprazole vs. Paliperidone

In a head-to-head comparison, once-monthly injectable aripiprazole was superior to paliperidone in improving health-related quality of life in patients with schizophrenia, particularly in patients under age 36 years.

Methods: Subjects in this multinational study were patients, aged 18–60 years, with clinically stable schizophrenia who needed a change from current oral medication because of incomplete efficacy, poor tolerability, or lack of adherence. Patients were required to be rated as mildly to markedly ill on the Clinical Global Impression–Severity* scale and to have been receiving oral antipsychotics for ≥3 months. Treatment was open-label, but raters were blinded to treatment assignment. After a 3-week conversion to randomly assigned oral aripiprazole or paliperidone, patients who tolerated oral medication began once-monthly injections with 400 mg aripiprazole or flexibly dosed paliperidone (78–234 mg/month). The primary efficacy outcome was change from baseline to week 28 on the Heinrichs-Carpenter Quality-of-Life Scale (QLS), a 21-item instrument that measures 4 domains of quality of life.
**Results:** A total of 281 patients (60% men; average age, 42 years) received treatment; 183 completed the full study protocol: 68% of the aripiprazole group and 57% of the paliperidone group. Baseline QLS total scores were 66 and 63 in the aripiprazole and paliperidone groups, respectively. At week 28, aripiprazole was associated with larger average improvement in the QLS total score than paliperidone (7.5 vs. 2.8 points; p=0.036). Aripiprazole was statistically superior beginning at treatment week 8 and in all subsequent assessments. Subgroup analysis by age showed aripiprazole to be superior in patients aged ≤35 years, but not in older patients. Among the QLS subscales, aripiprazole was associated with superior improvement in intrapsychic foundations (p=0.039), but not the other domains (common objects and activities, interpersonal relations, and instrumental role).

The most frequent treatment-related adverse events were weight gain, psychotic disorder, and insomnia, all of which occurred less frequently with aripiprazole than paliperidone. Clinically significant weight gain (≥7% change from baseline) occurred in 11% of the aripiprazole group and 15% of the paliperidone group. Rates of extrapyramidal symptoms were low in both groups. No new safety concerns emerged.

**Discussion:** Aripiprazole and paliperidone are both effective as long-acting injectable formulations but have different pharmacological mechanisms. This study used a health-related quality-of-life scale to capture a broader range of treatment effects than the usual symptom-based rating scales. Changes in the intrapsychic foundations subscale of the QLS suggests that patients experienced improvement in such phenomena as sense of purpose, curiosity, empathy, and emotional interaction.

Naber D, Hansen K, Forray C, Baker R, et al: Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. Schizophrenia Research 2015; doi 10.1016/j.schres.2015.07.007. From the University Medical Center Hamburg-Eppendorf, Germany; and other institutions including Lundbeck and Otsuka. Funded by H. Lundbeck A/S and Otsuka Pharmaceutical Development and Commercialization, Inc. All study authors declared financial relationships with commercial sources, including Lundbeck and/or Otsuka.

**Drug Trade Names:** aripiprazole, long-acting injectable—Abilify Maintena; paliperidone, long-acting injectable—Invega Sustenna

*See Reference Guide.

**Effects of Long-Term Lithium**

Short-term lithium use is known to affect renal and endocrine function. Results of a retrospective analysis of laboratory data suggest long-term use is associated with a decline in renal function, especially in women under age 60 years and patients with consistently high lithium concentrations.

**Methods:** Routinely collected data from a single laboratory were analyzed in a study cohort that included all adults with ≥2 measurements of serum creatinine, thyrotropin, calcium, glycated hemoglobin, or lithium taken between October 1985 and March 2014. Persons exposed to lithium for whom ≥2 detectable serum lithium levels were found (n=2795) were compared with nearly 700,000 controls with no lithium exposure. Mean patient ages were 55 years in men and 50 years in women. Lithium levels had been monitored for a median of 3 years and a maximum of 28 years. Risk estimates for a decline in renal, thyroid, and parathyroid function were adjusted for age group, gender, and diabetes.

**Results:** Lithium use was associated with increased risk of decline in renal function to stage 3 chronic kidney disease (i.e., glomerular filtration rate <60 mL/min per 1.73 m²), hypothyroidism, and high total calcium concentrations. (See table.) Lithium exposure was not associated with hyperthyroidism or high serum calcium adjusted for serum albumin.
The effect of lithium on decline in renal function was greatest in women aged < 60 years, with smaller effects in older men and women and no effect in men aged < 60 years. The effects on hypothyroidism were significant in all age and gender subgroups, but greatest in younger women. The effect on calcium elevation was apparent in all groups except younger men. Patients with serum lithium concentrations higher than the population median of 0.6 mEq/L were at increased risk of decline in renal function, hyperthyroidism, and elevated serum calcium. Length of exposure to lithium was inversely associated with declines in renal function, which suggests the effect occurred early in treatment.

**Discussion:** Adverse effects are rare, in the case of significant renal impairment, or treatable, in the case of thyroid or parathyroid dysfunction. Stage-3 chronic kidney disease does not necessarily represent a clinically significant decline in renal function, but in a subset of these patients, it might progress to chronic renal failure, and a strengthened emphasis on monitoring is recommended, particularly for younger women.


*Lurasidone: Long-Term Weight Effects*

According to an analysis of pooled data from the manufacturer's long-term clinical trials, lurasidone is not associated with weight gain over 12 months of treatment. This finding is consistent with shorter-term observations that have led lurasidone to be classified among the few antipsychotics whose effects on weight are similar to placebo.

**Methods:** A post-hoc analysis was conducted of pooled data from 6 randomized trials of 20–160 mg/day lurasidone in patients with schizophrenia or schizoaffective disorder. Two of the trials had an active comparator, also flexibly dosed: quetiapine extended-release (200–800 mg/day) and risperidone (2–6 mg/day). Changes in weight, body mass index (BMI), and waist circumference were compared among adults aged 18–75 years who completed ≥12 months of study treatment with lurasidone (n=471) and those who completed the same duration of treatment with risperidone (n=89) or quetiapine (n=33).

**Results:** Between-group differences in weight change were evident as early as the first assessment at 3 months. Patients who received lurasidone had a mean weight loss of about 1 lb at 3 months, compared with mean weight increases in the risperidone (4.6 lbs; p<0.001) and quetiapine (3.5 lbs; p=ns) groups. At 12 months, weight remained relatively stable in the lurasidone and quetiapine patients, while those who received risperidone continued to gain weight. Lurasidone differed from risperidone, but not quetiapine, in changes in waist circumference and BMI (p<0.001 for both outcomes). Fewer patients taking lurasidone than...
risperidone gained >7% of their initial weight (16% vs. 26%), but the difference did not reach statistical significance. The percentage of patients who gained >7% of their initial weight with quetiapine (15%) was similar to lurasidone; however, twice as many patients receiving lurasidone lost >7% of their initial body weight (19% vs. 9%).

Asian patients, and particularly Asian women, were more likely than patients of other races to experience a >7% weight gain. Weight gain was also significantly greater in younger patients and in those with low baseline weight.

**Discussion:** The receptor activity profile of lurasidone, with low affinity for 5-HT2c and H1 receptors, suggests it may have a low propensity to induce weight gain, a finding supported by these results. Lurasidone may be a preferred option in patients at higher risk for weight gain, those with cardiovascular risk factors, or those who have experienced weight gain or metabolic disturbance with other antipsychotics.


**Drug Trade Names:** lurasidone—Latuda; quetiapine—Seroquel; risperidone—Risperdal

### Flibanserin for Hypoactive Sexual Desire Disorder

The FDA has approved the first treatment for acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women. HSDD is characterized by low sexual desire that causes marked distress. Flibanserin (*Addyi*) acts as a serotonin 1A receptor agonist and a serotonin 2A receptor antagonist. The mechanism by which it improves sexual desire and related distress is unclear. However, in clinical trials, women who received treatment with 100 mg flibanserin reported an increase in sexual desire, an increased number of satisfying sexual events, and reduced distress associated with HSDD.

Common adverse effects of flibanserin include dizziness; somnolence; nausea; fatigue; insomnia; and dry mouth. The agent is approved with a risk evaluation and mitigation strategy (REMS) program and will be available only from certified physicians and pharmacies. It will carry a Black Box Warning about the potential for severe hypotension and syncope in patients who drink alcohol or who use moderate-to-strong CYP3A4 inhibitors and in those with liver impairment. Bedtime dosing is recommended to reduce the risk for these serious adverse effects. Patients who do not experience improved sexual desire and reduced distress after 8 weeks of treatment should discontinue flibanserin.


### Adjunctive Brexpiprazole in Depression

According to results of 2 separate, manufacturer-sponsored, placebo-controlled trials conducted by the same investigators, adjunctive brexpiprazole dosages of 2 and 3 mg/day, but not 1 mg/day, were superior to placebo in patients with major depressive disorder who had previously experienced inadequate response with standard antidepressants.¹ ²

**Background:** Brexpiprazole is a newly approved serotonin-dopamine activity modulator with a different receptor affinity profile than aripiprazole, which reportedly confers a lower potential for adverse effects associated with dopamine blockade (e.g., extrapyramidal symptoms, hyperprolactinemia, and tardive dyskinesia).
Methods: The 2 identical (except for dosage), multinational trials were conducted in patients who had been experiencing depression for ≥8 weeks and who had an inadequate response, defined as a <50% decrease in self-rated depression, to an adequate trial of 1–3 antidepressants. After enrollment, all patients received treatment for 8 weeks with an antidepressant of their clinician’s choice, flexibly dosed, plus single-blind placebo. Those who continued to show an inadequate response were randomly assigned to continue with placebo or to receive fixed-dose brexpiprazole (1 or 3 mg/day in study 1 and 2 mg/day in study 2) for 6 weeks. The primary efficacy endpoint was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: The 2-mg dose of brexpiprazole had the most impressive results. In this trial (study 2), 826 patients began single-blind treatment with various SSRIs or venlafaxine. After 8 weeks, 379 patients (mean age, 44 years; 70% women) had a suboptimal response and were randomly assigned to adjunctive brexpiprazole or placebo. The mean Clinical Global Impression–Severity* (CGI-S) score at the start of double-blind treatment was 3.5, indicating patients were moderately ill and showed minimal improvement since study enrollment. The mean MADRS score at baseline was 27 in both groups. Adjunctive 2 mg brexpiprazole was superior to placebo for the primary endpoint at week 6 (see table), with statistical significance apparent from the first week of treatment onward. Brexpiprazole was also superior to placebo with regard to secondary measures of depression, overall illness severity, and disability. On the Sheehan Disability Scale, brexpiprazole produced greater numerical improvement than placebo in social life and family life subscales, although these did not reach statistical significance.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change from Baseline</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg/day Brexpiprazole</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>MADRS (primary)</td>
<td>-8.36</td>
<td>-5.15</td>
</tr>
<tr>
<td>CGI-S</td>
<td>-0.91</td>
<td>-0.57</td>
</tr>
<tr>
<td>MADRS Responders**</td>
<td>23.4%</td>
<td>15.7%</td>
</tr>
<tr>
<td>MADRS Remitters***</td>
<td>9.0%</td>
<td>14.9%</td>
</tr>
</tbody>
</table>

**≥50% reduction  ***≥50% reduction + final score of ≤10

In the other trial (study 1), >1500 patients were enrolled for 8 weeks of antidepressant monotherapy and 627 (mean age, 46 years; 68% women) were randomly assigned to adjunctive 1 mg or 3 mg/day brexpiprazole or placebo. Patients who received the 3-mg dose experienced a mean 8.29-point reduction in the MADRS score after 6 weeks, compared with a 6.33-point decline in the placebo group (p=0.007). The mean change in the group receiving the lower dose, 7.64 points, did not differ statistically from placebo. Changes in secondary endpoints favored the 2 brexpiprazole doses, with statistical significance for several (1 mg) or most (3 mg) of these endpoints.

The most frequent adverse events of 2 mg/day brexpiprazole were weight gain (8%) and akathisia (7%), which were generally mild to moderate. Compared with placebo, patients
receiving the 2-mg brexpiprazole dose gained an average of about 3.5 pounds during the 6 weeks (p<0.0001). Activation was uncommon, as were somnolence, fatigue, and sedation. Brexpiprazole did not appear to have clinically relevant effects on prolactin or metabolic function. The safety and tolerability of 1 mg and 3 mg brexpiprazole were similar to 2 mg.

**Discussion:** A change from baseline in the MADRS score of 2 points is believed to be clinically relevant. The mean placebo-adjusted change was >3 points with 2 mg brexpiprazole and 1.95 points with the 3-mg dose. Smaller changes may be meaningful in the present study population, given the long duration of the current depressive episode, which averaged nearly 18 months.

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


**Drug Trade Names:** aripiprazole—*Abilify*; brexpiprazole—*Rexulti*; venlafaxine—*Effexor*

*See Reference Guide.

**Medication Changes After Hospital Discharge**

According to the results of a retrospective study, <30% of patients continue prescribed psychotropic and somatic medications following discharge from a psychiatric hospital.

**Methods:** Prescription records were analyzed for 1324 patients who were discharged from a network of 4 psychiatric hospitals in the Netherlands between 2006 and 2009. Inpatient medication was provided by the hospital pharmacy, and data on outpatient medication was retrieved from a single large private insurer. Patients were included in the study if ≥3 months of post-discharge prescription data were available. The main study outcome was discontinuation of psychotropic or somatic medication that had been used in the 2 days before hospital discharge.

**Results:** Mean patient age was 45 years; 36% were discharged following treatment of a psychotic disorder, 29% depression or anxiety, and 20% substance use disorder. More than 80% of patients received ≥1 medication during the last 2 days of hospitalization. The most commonly used psychotropic medications were anxiolytics and sedatives (64%), followed by antipsychotics (49%), antidepressants (35%), and mood stabilizers (16%).

A total of 1029 patients received psychotropic medications during hospitalization; nearly half of these discontinued ≥1 medication after discharge. Anxiolytics and sedatives were the most commonly discontinued psychiatric medication (52%), followed by antipsychotics (25%), mood stabilizers (15%), and antidepressants (14%). Median duration of hospitalization was 63 days. Patients with shorter hospital stays (7–36 days) were less likely to discontinue medications (relative risk,* 0.88) than those in the highest tertile of hospital stay duration (≥97 days). One in 5 patients started a new psychotropic after discharge; for nearly half of these patients, the medication had been prescribed in the 3 months prior to admission but was not used during the hospital stay. About 5% of patients underwent a switch in psychotropic medication.
Discussion: It was not possible for the investigators to determine the reason for discontinuation or other medication changes. Nevertheless, these data emphasize hospital discharge as a time of discontinuity in health care. In addition to medically valid reasons, discontinuation may have been the result of patient noncompliance in filling prescriptions, lack of communication among health care providers, or insufficient communication between patients and providers.

Abdullah-Koolmees H, Gardarsdottir H, Yazir D, Stoker L, et al: Medication discontinuation in patients after discharge from a psychiatric hospital: a retrospective, follow-up study. *Annals of Pharmacotherapy* 2015; doi 10.1177/1060028015593763. From Utrecht University, the Netherlands; and other institutions. This study was conducted without funding. The authors declared no competing interests.

*See Reference Guide.

Reference Guide

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

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

**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.
Anemia developed in one-fourth of a cohort of patients within 2 years of starting clozapine, indicating that patients receiving clozapine, particularly those with lower initial levels of hemoglobin, should be monitored for the development of this condition.1

**Background:** Hematological abnormalities are not uncommon with clozapine, and patients taking the drug are required to undergo regular monitoring for agranulocytosis. Other hematological abnormalities, such as neutropenia and eosinophilia, have been reported, but little is known about the potential for clozapine to cause anemia. Iron-deficiency anemia is the most common form and its prevalence in patients with schizophrenia has been reported to be 2.5%.2

**Method:** Study participants were enrolled in a clozapine registry in Toronto, Canada, between January 2009, when electronic medical records were introduced, and December 2010. To be included in the analysis, patients had to have hemoglobin measured at baseline and during 2 years of follow-up. Anemia was defined as a hemoglobin value of <120 g/L in women and <130 g/L in men. The analysis included 94 patients (mean age, 36 years; 72% men) without anemia at baseline.

**Results:** In the present sample, anemia developed during follow-up in 23 of the 94 patients (24.5%). Of the patients in whom anemia developed, 20 had either recurrent episodes or persistent anemia throughout the follow-up period. One patient also had neutropenia, and none had agranulocytosis. In a multivariate analysis, higher baseline hemoglobin levels were associated with lower risk of anemia during follow-up (hazard ratio,* 0.86; p=0.002) and cigarette smoking was associated with increased risk (hazard ratio, 0.21; p=0.02); these associations were found only in men, not in women. Medical comorbidities had a modest association with anemia (p=0.036).

**Discussion:** The clinical consequences of anemia include lethargy and cognitive dysfunction, which can be mistaken for, or compound, the negative symptoms and cognitive deficits of schizophrenia. Clozapine may cause anemia via toxicity to hematopoietic precursors of myeloid and erythroid cells, but it is also possible that patients with refractory schizophrenia...
become anemic because of iron deficiency and poor diet. Regardless, it appears to be reason-
able to monitor complete blood counts, rather than just the required white blood cell and
neutrophil counts.

2015; doi 10.4088/jcp.14m09143. From the Institute of Mental Health, Singapore; and other institutions. **Funded by the
Singapore Ministry of Health; and other sources. The authors declared no competing interests.**

2Schoepf D, et al. Physical comorbidity and its relevance on mortality in schizophrenia: a naturalistic 12-year follow-up

*See Reference Guide.

### Pharmacotherapy for Pathological Hoarding

Limited evidence suggests that pharmacotherapy with an SSRI or venlafaxine may be effective
for patients with pathological hoarding.

**Background:** Research suggests that patients with OCD who engage in hoarding behavior are
much less likely to experience response to treatment than those with OCD without hoarding.
However, little research has focused on treatment of hoarding outside of OCD. The present
meta-analysis was undertaken to synthesize the existing literature on pharmacological treat-
ment of hoarding in patients with or without OCD.

**Methods:** The analysis included all studies published in any language that investigated treatment
response in patients with pathological hoarding, with or without OCD. The 7 included studies
were 1 randomized controlled trial, 3 open-label studies, and 3 case series, comprising a total
population of 92 patients (65 with OCD and predominant hoarding, 27 with DSM-5 hoarding
disorder). Response was defined as a >30% reduction in the Savings Inventory–Revised (SI-R) or
a ≥25% reduction in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score.

**Results:** Response rates in the individual studies ranged from 37% to 76%. The SSRIs paroxetine
and sertraline were effective in patients with OCD and hoarding behavior. The SNRI venlafaxine
appeared to be effective in patients with DSM-5 hoarding disorder. Paroxetine produced a mean
6-point reduction in Y-BOCS score among 32 patients who received open-label treatment.
Patients who received open-label sertraline (n=20) demonstrated a 47% reduction in Y-BOCS
score. Those who received open-label extended-release venlafaxine showed a mean 32% reduc-
tion in SI-R score, as well as a mean 8-point reduction in Y-BOCS score. There was little or no
support for augmentation of SSRIs with minocycline, naltrexone, or quetiapine. A small case
series suggested that methylphenidate monotherapy was effective in patients with hoarding
disorder, producing response in 2 of 4 patients, but its use was limited by adverse effects
(i.e., insomnia, palpitations).

**Discussion:** Despite the limitations of the studies in this meta-analysis (e.g., small samples,
short treatment durations) and in the meta-analysis itself (e.g., studies were few and of varying
designs, no drug was investigated in >1 study), the results support cautious optimism for phar-
macotherapy in hoarding disorder. Pathological hoarding is associated with poor attention,
which suggests a potential role for stimulants, and with poor insight, which may theoretically
respond to antipsychotics; additional research appears to be warranted.

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

*Psychiatry Research* 2015;229 (September 30):272–276. From the University of Sydney, Penrith, Australia. **Source of
funding not stated. The authors declared no conflicts of interest.**

**Drug Trade Names:**
- methylphenidate—Ritalin
- minocycline—Minocin
- naltrexone—ReVia
- paroxetine—Paxil
- quetiapine—Seroquel
- sertraline—Zoloft
- venlafaxine—Effexor.

*See Reference Guide.*
New Options for Schizophrenia & Bipolar Disorder

Aripiprazole lauroxil (Aristada) has received FDA approval for the treatment of schizophrenia in adults. The long-acting injectable should be administered every 4–6 weeks in to the patient’s arm or buttocks. Efficacy of aripiprazole lauroxil has been demonstrated in patients previously stabilized with oral aripiprazole. The most common adverse effect of aripiprazole lauroxil in clinical trials was akathisia.

Cariprazine (Vraylar) has also recently received FDA approval to treat schizophrenia and bipolar disorder in adults. Dopamine D2 receptor blockade is believed to be a necessary action of antipsychotics. Cariprazine is a partial agonist of both D2 and D3 receptors, which may theoretically augment its antipsychotic effects relative to other agents. The drug is pharmacologically similar to aripiprazole, which also functions as a D2 partial agonist. Extrapyramidal symptoms (EPS) were the most common adverse effects in trials of patients with schizophrenia. In addition to EPS, akathisia, dyspepsia, vomiting, somnolence, and restlessness were common in patients with bipolar disorder.

Like other atypical antipsychotics, both of the newly-approved agents will carry a boxed warning about risk of death with off-label use to control behavioral problems in elderly patients with dementia-related psychosis.

Asenapine Dosing

In a small, open-label study, a single bedtime dose of asenapine (Saphris) was better tolerated than the recommended twice-daily dosing, without a reduction in efficacy.

Background: The FDA approved dosing schedule for asenapine is 5 mg b.i.d. However, daytime sleepiness is problematic for many patients with this dosage. Because of its 24-hour half-life, it seems possible that asenapine could be administered once daily at bedtime to avoid the residual sleepiness.

Methods: Study subjects were 30 adults, aged 20–61 years (17 women), admitted with an acute exacerbation of schizophrenia or schizoaffective disorder. Patients received 14 days of randomly assigned sublingual asenapine at either the recommended 5-mg b.i.d. dosage or 10 mg administered at bedtime. Acceptability was assessed using a patient-rated Likert scale (1–7; 1=very acceptable and 7=completely unacceptable), as well as evaluation of discontinuation rates. Symptom improvement was measured using the Brief Psychiatric Rating Scale (BPRS).

Results: Patients who received the single bedtime dose reported significantly greater acceptability of asenapine with a mean score of 1.7 on the 7-point scale vs. 3.9 in the b.i.d. dosing group (p<0.05). Asenapine treatment was discontinued by 2 of 12 patients in the bedtime dosing group, compared with 8 of 18 patients in the b.i.d. dosing group (17% vs. 44%). Both discontinuations in the bedtime dosing group were due to inadequate efficacy, as were 4 in the b.i.d. dosing group. The remaining 4 patients who discontinued b.i.d. dosing did so because of intolerable adverse effects (3 for severe daytime drowsiness, 1 for akathisia).
Both asenapine dosing strategies improved symptoms. In an intent-to-treat analysis,* mean BPRS score reduction was significantly greater in the bedtime dosing group (p<0.05). However, efficacy did not differ in the completer analysis, suggesting that the higher completion rate in the bedtime dosing group was responsible for the better efficacy results in the intent-to-treat analysis.

**Discussion:** The results of this trial suggest that administering asenapine as a single 10-mg dose at bedtime may lead to fewer treatment discontinuations, thus improving outcomes. Because the present study was small and treatment was open label, studies with more rigorous methodology should be undertaken to replicate the results.

Sun X, Hamer R, McEvoy J: Asenapine once daily versus twice daily: impact on patient acceptance in a randomized, open-label, 14-day clinical trial [letter]. *Journal of Clinical Psychiatry* 2015;76 (July):992–993. From Duke University Medical Center, Durham, NC; and other institutions. **Funded by Merck Sharp & Dohme Corp. Two study authors declared financial relationships with commercial sources, including Merck. The remaining author reported no competing interests.**

*See Reference Guide.

---

### Brexpiprazole Efficacy in Acute Schizophrenia

In a multinational, phase III clinical trial, brexpiprazole (*Rexulti*) was effective and well tolerated in markedly ill patients experiencing an acute exacerbation of schizophrenia.¹

**Background:** Brexpiprazole is a newly approved second-generation antipsychotic for the treatment of schizophrenia in adults and as an add-on to antidepressants in adults with major depression.² The agent was designed with a serotonin and dopamine activity profile that would theoretically result in a low potential for some of the most concerning adverse effects of second-generation antipsychotics, including extrapyramidal symptoms and prolactin elevation.³

**Methods:** The study, conducted at 65 centers, enrolled adults experiencing an acute exacerbation of schizophrenia who would benefit from hospitalization or continued hospitalization. Following a 14-day screening phase, patients (n=636) were randomly assigned to 6 weeks of double-blind treatment with either placebo or brexpiprazole at a daily dose of 0.25 mg (presumed to be ineffective), 2 mg, or 4 mg. The primary outcome was change from baseline to week 6 in the Positive and Negative Syndrome Scale (PANSS) total score.

**Results:** Of 636 patients who received medication, 623 had ≥1 post-baseline assessment and were included in the efficacy analysis. Patients were markedly ill at study entry (mean PANSS score, 95), all had experienced previous acute exacerbations requiring treatment, and about 90% were currently receiving antipsychotic medication. About 64% of participants completed the study. Discontinuation rates were 59% with placebo and ranged from 62 to 68% with active treatment. As expected, the 0.25-mg dose of brexpiprazole was not effective. For the primary endpoint, the average effect of the 2 higher doses of brexpiprazole was superior to placebo (p<0.0001), permitting comparison of individual dosage groups. (See table.) The difference in mean PANSS total scores between brexpiprazole and placebo reached statistical significance at 1 week for the 2-mg dose and 2 weeks for the 4-mg dose and remained significant throughout the study. Of 5 PANSS subscales, 4 were significantly improved with brexpiprazole: positive symptoms, negative symptoms, disorganized thought, and uncontrolled hostility/excitement. Treatment effects were also statistically superior to placebo for the Clinical Global Impression–Severity (CGI-S) score,* a key secondary endpoint.
Changes from baseline to week 6 in patients receiving brexpiprazole or placebo

### PANSS total score (primary endpoint)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline PANSS total score</th>
<th>Final PANSS total score</th>
<th>Significance vs. placebo</th>
<th>Effect size*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=178)</td>
<td>96</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg Brexpiprazole (n=180)</td>
<td>96</td>
<td>75</td>
<td>p&lt;0.0001</td>
<td>0.41</td>
</tr>
<tr>
<td>4 mg Brexpiprazole (n=178)</td>
<td>95</td>
<td>75</td>
<td>p=0.0006</td>
<td>0.36</td>
</tr>
</tbody>
</table>

### CGI–Severity (key secondary endpoint)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline CGI-S score</th>
<th>Final CGI-S score</th>
<th>Significance vs. placebo</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=181)</td>
<td>4.8</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg Brexpiprazole (n=181)</td>
<td>4.9</td>
<td>3.7</td>
<td>p=0.006</td>
<td>0.29</td>
</tr>
<tr>
<td>4 mg Brexpiprazole (n=178)</td>
<td>4.8</td>
<td>3.6</td>
<td>p=0.002</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Overall, adverse events occurred less frequently with brexpiprazole than with placebo; however, most of the events were related to the underlying illness, rather than treatment. Akathisia occurred more frequently with 2 mg and 4 mg brexpiprazole than placebo (4.4%, 7.2%, and 2.2%, respectively), but was usually mild to moderate in severity and did not limit treatment. Increases in body weight of ≥7% occurred in about 9% of patients taking brexpiprazole and 4% of the placebo group. There were no clinically significant differences between brexpiprazole and placebo in lipid and glucose levels, prolactin levels, extrapyramidal symptom ratings, or suicidal ideation or behavior.

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


2 FDA News Release: FDA approves new drug to treat schizophrenia and as an add on to an antidepressant to treat major depressive disorder. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements. See Psychiatry Drug Alerts 2015;29 (July):49.


*See Reference Guide.

### IV Clomipramine for Resistant OCD

In an open-label trial, intravenous clomipramine produced rapid response in patients with severe obsessive-compulsive disorder refractory to other treatments.

**Background:** SSRIs are currently considered first-line treatment for OCD. Second-line treatment consists of switching to a different SSRI or venlafaxine, or SSRI augmentation with antipsychotic medication or cognitive behavioral therapy. There is little guidance on what to do if these approaches fail. Alternatives include different augmentation agents (e.g., oral clomipramine, buspirone, pindolol, riluzole), different monotherapies (e.g., tramadol, ondansetron, an MAOI), or brain stimulation. Monotherapy with IV clomipramine has shown promise in several small uncontrolled studies.

**Methods:** Study participants were 30 outpatients, recruited from a university clinic, who were required to have OCD of ≥3 years' duration, with functional impairment and severe symptoms.
All had experienced nonresponse to ≥2 trials of anti-obsessional medication, each given for at least 8–12 weeks with ≥6 weeks at the maximum tolerated dose. Comorbid mood, anxiety, or personality disorders were not grounds for exclusion. All patients were hospitalized to receive the IV clomipramine, which was titrated from 50 mg/day to a maximum of 225 mg/day over 5–7 days. Low-dose benzodiazepines were the only permitted concurrent medications during hospitalization. After IV treatment, patients were switched to oral clomipramine and discharged. Response was defined as a ≥25% improvement in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score.

Results: Patients had a mean age of 32 years, one-third were women, and OCD symptoms had been present for an average of 16 years. Previously unsuccessful treatments included combinations of ≥1 SSRI and a TCA in 26 patients. Two patients each had received only trials of TCA or SSRI monotherapies. At study entry, the majority of patients (73%) were receiving either oral clomipramine or imipramine monotherapy. Comorbidities included depression in 4 patients, an anxiety disorder in 1, and personality disorders in 8. All patients completed the inpatient phase of the study; 2 were lost to follow-up during outpatient treatment.

During IV treatment, patients experienced a statistically significant average 31% decrease in the Y-BOCS total score, from a mean of 26 (severe) to 18 (moderate). Improvement was maintained throughout the 24 weeks of follow-up, with the average score dropping to 16 at study end. A total of 23 patients (77%) met response criteria at discharge, and 18 (60%) continued to meet the criteria at 24 weeks. Compared with men, women had significantly greater improvement in compulsions, but the genders did not differ in changes in obsessions. There were no adverse effects of IV clomipramine treatment except transient palpitations in 1 patient.

Discussion: It has been hypothesized that IV clomipramine has greater bioavailability than the oral drug because it bypasses hepatic first-pass metabolism and avoids conversion to a metabolite with lesser serotonergic effects. In the present study, reduction of symptoms was rapid, and patients who experienced good response continued to improve with oral clomipramine.

Karameh W, Khani M: Intravenous clomipramine for treatment-resistant obsessive-compulsive disorder. International Journal of Neuropsychopharmacology 2015; doi 10.1093/ijnp/pyv084. From SEHA Corporate, Abu Dhabi, UAE; and American University of Beirut Medical Center, Lebanon. Source of funding not stated. The authors declared no competing interests.

Drug Trade Names: buspirone—Buspar; clomipramine—Anafranil; imipramine—Tofranil; ondansetron—Zofran; pindolol—Visken; riluzole—Rilutek; tramadol—Ultram; venlafaxine—Effexor

Antidepressants and Ischemic Stroke Mortality

The most common neuropsychiatric complication after stroke is post-stroke depression. In a population-based study, early antidepressant treatment during hospitalization for an ischemic stroke was associated with a large decrease in mortality in the subsequent month.

Methods: Registry data was collected for nearly 6000 Danish adults (mean age, 70 years; 44% women) who were admitted during a 7-year period for a first ischemic stroke. Antidepressants were prescribed for post-stroke depression or for pathological crying, another relatively common neurologic complication of stroke. The present analysis was based on 955 patients newly prescribed an antidepressant for these indications and an equal number of propensity-matched* controls who had no antidepressant treatment. The primary study endpoint was mortality within 30 days.

Results: Antidepressants were started a median of 5 days after admission (range, 2–11 days). During the 30-day follow-up, 30 deaths occurred in the patients who received antidepressants and 318 in the non-treated group (adjusted odds ratio,* 0.28). The effects of antidepressant treatment did not differ according to patient age or gender. Antidepressants were beneficial

Antidepressants and Ischemic Stroke Mortality

The most common neuropsychiatric complication after stroke is post-stroke depression. In a population-based study, early antidepressant treatment during hospitalization for an ischemic stroke was associated with a large decrease in mortality in the subsequent month.

Methods: Registry data was collected for nearly 6000 Danish adults (mean age, 70 years; 44% women) who were admitted during a 7-year period for a first ischemic stroke. Antidepressants were prescribed for post-stroke depression or for pathological crying, another relatively common neurologic complication of stroke. The present analysis was based on 955 patients newly prescribed an antidepressant for these indications and an equal number of propensity-matched* controls who had no antidepressant treatment. The primary study endpoint was mortality within 30 days.

Results: Antidepressants were started a median of 5 days after admission (range, 2–11 days). During the 30-day follow-up, 30 deaths occurred in the patients who received antidepressants and 318 in the non-treated group (adjusted odds ratio,* 0.28). The effects of antidepressant treatment did not differ according to patient age or gender. Antidepressants were beneficial
at all levels of stroke severity but had larger effects with greater stroke severity. For example, in patients with very severe stroke, the odds ratio for death was 0.08.

**Discussion:** These results suggest early antidepressant use is a safe approach to poststroke depression, and there may be no need to wait for the full 14 days of depressive symptom duration before initiating treatment. It should be noted that information on specific antidepressants was not available for the study. However, SSRIs are the recommended first-line treatment and likely account for the majority of antidepressant prescriptions. Possible underlying mechanisms for the benefit of antidepressants include antiinflammatory effects, restoration of capillary blood flow, antiplatelet effects of SSRIs, and earlier recovery from depression promoting participation in rehabilitation and faster mobilization. Randomized trials are now in progress to replicate these results.

Mortensen J, Johnsen S, Larsson H, Andersen G: Early antidepressant treatment and all-cause 30-day mortality in patients with ischemic stroke. *Cerebrovascular Diseases* 2015; doi 10.1159/000435819. From Aarhus University Hospital, Denmark. Funded by the Tryg Foundation; and other institutions. The authors declared no conflicts of interest.

**Dextromethorphan–Quinidine for Agitation in Alzheimer’s**

In a preliminary, manufacturer-sponsored trial, the combination of dextromethorphan and quinidine (*Nuedexta*) reduced agitation in patients with Alzheimer’s disease.1

**Background:** Safe, effective treatments are lacking for agitation in patients with Alzheimer’s disease. Dextromethorphan–quinidine is currently approved for treatment of pseudobulbar affect, and research has shown the agent reduces agitation in patients with the disorder.

**Methods:** The study was conducted at 42 U.S. treatment sites, including outpatient Alzheimer’s disease clinics as well as assisted living and nursing facilities. Study participants (n=220; 126 women) were aged ≥50 years, met diagnostic criteria for probable Alzheimer’s disease, and had clinically significant agitation, which was defined as poorly organized and purposeless psychomotor activity characterized by verbal or physical aggression or nonaggressive physical behaviors such as pacing or restlessness. Patients receiving Alzheimer’s medication (e.g., memantine or a cholinesterase inhibitor) were not excluded provided the dosage had been stable for ≥2 months. Participants were randomly assigned to 5 weeks of either placebo or dextromethorphan–quinidine. After 5 weeks, non-responding patients in the placebo group were re-randomized to receive active medication or placebo for another 5 weeks. Those who had received active treatment during the first 5 weeks continued with no change. Dextromethorphan–quinidine was titrated to a maximum dosage of 30/10 mg b.i.d. The primary efficacy outcome was change from baseline in the Agitation/Aggression domain of the Neuropsychiatric Inventory (NPI), which measures the frequency and severity of behaviors and is scored from 0 (no symptoms) to 12 (daily symptoms, with marked severity).

**Results:** The efficacy analysis included 218 patients, of whom 88% completed the study. Nearly 90% of participants were outpatients. Baseline Clinical Global Impression–Severity (CGI-S)* ratings for agitation were moderate in 66%, marked in 30%, and severe or extreme in 4%.

The mean baseline NPI Agitation/Aggression score of 7 was reduced to 3.8 in the active treatment group at the 5-week evaluation (p<0.001 for change from baseline), compared with 5.3 in the placebo group (p<0.001 for between-group comparison). In stage 2, mean NPI Agitation/Aggression scores decreased from 5.8 to 3.8 in the dextromethorphan–quinidine group and from 6.7 to 5.8 in the placebo group (p=0.02 for between-group comparison). Stratification by baseline mini-mental state exam scores, CGI-S scores for agitation, and background treatment with cholinesterase inhibitors or other psychotropic medications did not alter the findings. Secondary outcome measures, including caregiver distress, generally favored the active treatment.
Discussion: An accompanying editorial called the results of this study encouraging but modest and difficult to interpret. However, given the limited existing treatment options, it called for further development of dextromethorphan–quinidine as an off-label treatment for agitation. The editorial also noted that the treatment was well tolerated, with no increases in sedation or QTc prolongation, falls, or diarrhea, no detrimental effects on cognition or activities of daily living, and no increase in mortality. This safety profile contrasts favorably with atypical anti-psychotics, the usual pharmacologic treatment for agitation in dementia. However, the study may have been too small and short in duration to observe the less common of these effects.

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

1Cummings J, Lyketsos C, Peskind E, Porsteinsson A, et al: Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. JAMA 2015;314 (September 22/29):1242–1254. From the Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV; and other institutions. Funded by Avanir Pharmaceuticals Inc. Twelve of the study authors declared financial relationships with commercial sources, including Avanir; the remaining author declared no competing interests.


Drug Trade Names: memantine—Namenda; dextromethorphan–quinidine—Nuedexta

*See Reference Guide.

Reference Guide

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

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.

Intent-to-Treat Analysis (ITT): An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone who begins treatment is included regardless of treatment completion. ITT analyses are done to avoid the effects of crossover, drop-out, and other factors that could alter the results or inflate the magnitude of effects.

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 statistical 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.

Contributing Editors: Kate Casano, MSHyg; Bennett Silver, MD
Consulting Editor: Steven J. Schleifer, MD, Rutgers–New Jersey Medical School
Executive Editor: Trish Elliott  Associate Editor: Tara Hausmann  Assistant Editor: Kasey Madara
Founding Editor: Michael J. Powers

Off-Label Drug Use Statement: Some drugs discussed for specific indications in Psychiatry Drug Alerts articles may not be approved for labeling and advertising for those indications by the United States Food and Drug Administration.
Aripiprazole Augmentation for Late-Life Depression

In a randomized, placebo-controlled, multi-center trial, adjunctive aripiprazole was moderately effective at inducing remission in older patients with refractory depression. Although aripiprazole generally had a favorable risk–benefit ratio in older patients, safety concerns include akathisia and parkinsonism.

Methods: The study enrolled participants aged ≥60 years with at least moderate depression, indicated by a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥15. All patients received treatment with venlafaxine monotherapy for at least 12 weeks and up to 24 weeks if needed to clarify remission status. Remission was defined as a MADRS score of ≤10 at both of the 2 final study visits of each phase. Those who did not achieve remission with venlafaxine for ≥4 weeks at the highest tolerated dosage of 150–300 mg/day were randomly assigned to augmentation with either aripiprazole or placebo. Aripiprazole was titrated to a target dosage of 10 mg/day, which could be increased to 15 mg/day if necessary. The primary study outcome was remission, ascertained after 12 weeks of randomized treatment. Patients continued to receive double-blind treatment for an additional 12 weeks to determine stability of remission.

Results: Of 468 patients who received venlafaxine, 181 (39%) received ≥12 weeks of treatment without meeting remission criteria and were then randomly assigned to an augmentation group. After 12 weeks of randomized treatment, remission occurred in 40 of 91 patients who received aripiprazole augmentation and 26 of 90 in the venlafaxine-plus-placebo group (44% vs. 29%; p=0.03). The number needed to treat* to achieve remission was 6.6, similar to that found with augmentation treatments in younger adults. Patients who received aripiprazole had a significantly larger decrease in MADRS score than the placebo group by week 2.

The most frequent adverse effects reported with aripiprazole relative to placebo were increased dream activity, weight gain (averaging 4.3 lb.), and tremor. Akathisia occurred in more patients taking aripiprazole than placebo (26% vs. 12%), but most cases were mild. Akathisia persisted through the final study visit in 5 patients in the aripiprazole group and 2 in the placebo group.
Akathisia was associated with a temporary increase in suicidal ideation in 3 patients in the aripiprazole group. Parkinsonism developed in 17% of the aripiprazole group and 2% of the placebo group. Rates of emergent suicidal ideation were similar in the 2 treatment groups (21% and 29% in the aripiprazole and placebo groups, respectively). Aripiprazole was not associated with dyskinesia, an increase in total body fat, or adverse changes in plasma lipids, glucose, or insulin. Responses to aripiprazole were maintained during the 12-week continuation phase.

**Discussion:** This appears to be one of the first well-powered trials of second-line antidepressant treatments in patients with resistant late-life depression, and the results suggest aripiprazole may be a useful option for these patients.

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

Lenze E, Mulsant B, Blumberger D, Karp J, et al: Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. *Lancet* 2015; doi:10.1016/S0140-6736(15)00308-6. From Washington University School of Medicine, St Louis, MO; and other institutions. *Funded by the NIMH; and other sources.* Nine study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.

*See Reference Guide.*

### Atomoxetine Dosing in Adult ADHD

According to results of a manufacturer-sponsored, retrospective study, a substantial proportion of adults with ADHD who take atomoxetine (*Strattera*) are given suboptimal doses.

**Background:** Clinical trial results indicate that treatment with an adequate dose of atomoxetine and for sufficient time is important for symptom improvement in adults. According to the dosing recommendations, treatment should be initiated at 40 mg/day for ≥3 days, followed by escalation to the target daily dosage of 80 mg/day. The dosage can be increased to 100 mg/day if the response is not adequate after 2–4 weeks.

**Methods:** Prescription data were collected from a medical and pharmacy claims database, which includes >45 million employees and their dependents covered by a variety of health plans throughout the U.S. For adults aged ≥18 years, data were analyzed for the most recent episode of atomoxetine prescription as monotherapy from 2006 through 2011. Data were excluded for the first 30 treatment days to allow for the upward titration period. Adult patients (n=12,412) with a diagnosis of ADHD, who were continuously enrolled in their health plan for ≥18 months and who received atomoxetine monotherapy were classified into 4 dosage cohorts based on the daily average for all prescriptions: suboptimal (<80 mg), recommended (80–100 mg), above-recommended (>100 mg), and fluctuating (those whose dose could not be classified in another category). Persistence was defined as the time continuously on atomoxetine before a 30-day gap in prescription coverage.

**Results:** Dosing was determined to be suboptimal in 37% of patients, in the recommended range in 27%, above recommended in 2%, and fluctuating in 35% (see table). More than 90% of patients discontinued atomoxetine within 1 year of initial prescription. Treatment persistence was about 130 days, the same in suboptimal- and recommended-dosing cohorts. Suboptimal dosing was more likely to occur in women (p<0.001) and less likely in patients who had received previous ADHD medication (p<0.001).

<table>
<thead>
<tr>
<th>Mean Atomoxetine Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong> (n=12,412)</td>
</tr>
<tr>
<td>68.5 mg/day</td>
</tr>
</tbody>
</table>
Discussion: The estimate of underdosing in this study may be conservative since many of the patients who received fluctuating doses were likely being underdosed. The authors suggest underdosing may be more common in women because they have less disruptive symptoms and better coping strategies than men. Patients with previous exposure to other ADHD medications may be treated more aggressively with atomoxetine because of a history of treatment resistance.


Genetic Marker for Schizophrenia Drug Response

In a cohort of adults with schizophrenia, genetic markers in the human leukocyte antigen (HLA) region were associated with response to antipsychotic drug therapy. This observation supports the growing recognition that the disorder may be mediated by immunologic and/or inflammatory mechanisms and also supports the possibility of personalized schizophrenia treatment.

Methods: Study participants were 89 patients (66 men), newly hospitalized for schizophrenia in 1 of 2 French hospitals. Patients were medication-free for ≥4 weeks before enrollment and were started on either olanzapine or risperidone on admission. For inclusion, patients were required to have a baseline Positive and Negative Syndrome Scale (PANSS) score of >70 and a Brief Psychiatric Rating Scale (BPRS) score of >45. Clinical response was assessed after 6 weeks of treatment using both the PANSS and the BPRS. Genetic data were analyzed using an array of >14,000 single-nucleotide polymorphisms (SNPs) selected for their implications in drug transport, metabolism, or targets; brain receptors; or diverse immune-inflammatory pathways. HLA class I and class II gene alleles were also determined and included in a separate analysis. The association between genotypes and drug response was the primary outcome.

Results: A single SNP was found to have a significant negative association with change from baseline in PANSS general score. This SNP, rs3129996, is located on chromosome 6, not far from the HLA locus. The SNP also exhibited weaker associations with change from baseline in the PANSS total score, positive symptom score, and BPRS score. This allele was present in 8.6% of the patient sample and was associated with poorer response to antipsychotic drug therapy, with similar effects in patients taking olanzapine or risperidone. A total of 7 other SNPs were also associated with change from baseline in the PANSS general score at significant or near-significant levels. Two HLA polymorphisms associated with improved response to antipsychotic drugs were also identified. These variants were present in 36% of patients.

Discussion: The vast majority of genetic studies of antipsychotic drug response have been focused on loci implicated in monoamine rather than immunologic/inflammatory pathways. Some genome-wide association studies have confirmed a role for the HLA region on chromosome 6, a key regulator of the immune response, in increasing the risk of schizophrenia. Some antipsychotic drugs have been observed to alleviate abnormal immune or inflammatory markers in subsets of patients. The single SNP identified in this study is associated with reduced expression of ABCF1, a gene previously associated with both schizophrenia risk and autoimmune disorders and inflammation. The identified HLA allele association has also been previously linked with antipsychotic treatment response in a smaller patient population.

Le Clerc S, Taing L, Fond G, Meary A, et al: A double amino-acid change in the HLA-A peptide-binding groove is associated with response to psychotropic treatment in patients with schizophrenia. Translational Psychiatry 2015; doi 10.1038/tp.2015.97. From the Conservatoire National des Arts et Metiers, Paris, France; and other institutions. Funded by the Foundation Fondamental; and other sources. The authors declared no conflicts of interest.

Common Drug Trade Names: olanzapine—Zyprexa; risperidone—Risperdal
# Genetics and Antidepressant Response

In a randomized trial, a genetic marker predicted differential response and adverse effect liability among 3 antidepressants.\(^1\) This research represents an encouraging step forward, but it is unlikely that clinically useful antidepressant outcome prediction will ever be based on genetic markers alone, according to an accompanying editorial.\(^2\)

**Methods:** The ABCB1 gene encodes P-glycoprotein, a transporter protein that influences brain levels of several commonly used antidepressants. Ten different ABCB1-related single-nucleotide polymorphisms (SNPs) were assessed in patients with major depressive disorder. Patients, aged 18–65 years, with DSM-IV nonpsychotic unipolar major depression and a Hamilton Rating Scale for Depression (HAM-D) score of ≥16 were randomly assigned to 8 weeks of treatment with escitalopram, sertraline, or extended-release venlafaxine. The primary study outcomes were remission, defined as a score of ≤5 on the Quick Inventory of Depressive Symptomatology (Self Report), and overall scores on the Frequency, Intensity, and Burden of Side Effect Rating scale.

**Results:** Genotypes were assessed in 888 patients, of whom 683 (mean age, 39 years; 57% women) completed ≥2 weeks of treatment and comprised the intent-to-treat population; 576 completed the full 8 study weeks. In the intent-to-treat population, 1 of the 10 evaluated markers was associated with antidepressant response. Participants with the common variant of this allele, rs10245483, had a greater overall likelihood of remission (adjusted odds ratio, * 3.5; p<0.001) than those carrying the minor allele. Participants who were homozygous for the more common variant of this allele experienced significantly better response with escitalopram (p=0.032) and sertraline (p=0.02) than patients homozygous for the less common allele, who had better response with venlafaxine (p=0.018). There was no effect of heterozygosity on clinical response. In a population with a similar gene frequency, the number needed to screen would be 10 to yield 1 additional response by correctly identifying a patient homozygous for either allele and prescribing an antidepressant accordingly.

The same SNP was the only allele associated with adverse effects. Patients carrying the major allele experienced significantly fewer adverse effects with escitalopram (p=0.037), and homozygotes for the minor allele experienced significantly fewer adverse effects with venlafaxine (p=0.017).

**Editorial:** This encouraging study is one of very few replications of a previous result in antidepressant pharmacogenomics. However, the effect sizes were too small to be useful in clinical decision making. Many more genetic markers will be required to predict antidepressant response more precisely, requiring larger studies with sample sizes in the tens of thousands. Meanwhile, the limited heritability of antidepressant response (i.e., how much of the variation can be explained by genetic differences) limits the accuracy of prediction using genetic markers alone. It is more likely that progress will come from an approach similar to that used in breast cancer treatment, in which genetic profile data is combined with clinical variables, family history, and other biomarkers.

---


**Common Drug Trade Names:** escitalopram—*Lexapro*; sertraline—*Zoloft*; venlafaxine, extended release—*Effexor XR*

*See Reference Guide.*
Timing of Sertraline for PMDD

Results of a multisite, placebo-controlled trial suggest that initiating sertraline (*Zoloft*) treatment at symptom-onset can improve some components of premenstrual dysphoric disorder.

**Background:** Evidence supports the use of SSRIs, either as daily treatment or during the luteal phase, to manage symptoms of PMDD. However, symptoms are typically present for only 4–7 days per month. Previous small studies have suggested that treatment for only 1 week or only at symptom onset may be effective. The present randomized trial was undertaken to evaluate efficacy of symptom-onset dosing of sertraline in women with PMDD.

**Methods:** Study participants were 252 women, aged 18–48 years, who met diagnostic criteria for PMDD during a ≥2-month pretrial assessment period. Women were randomly assigned to 6 months of double-blind treatment with either sertraline or placebo and instructed to take study medication beginning on the day they first noticed onset of premenstrual symptoms and to stop within a few days of menstrual flow, when their symptoms typically abated. Sertraline was started at 50 mg/day and could be increased to 100 mg/day with nonresponse. Women whose symptoms did not respond to treatment after 2 months were offered rescue treatment with daily sertraline. The primary outcome measure was the Premenstrual Tension Scale (PMTS), a 10-item measure of mood, physical, and functional symptoms of PMDD. Symptoms were rated 5–7 days after onset of menses during 6 menstrual cycles of treatment.

**Results:** A total of 188 study subjects completed the trial, including 3 women in the sertraline group and 9 in the placebo group who received rescue treatment. Women began taking their study medication after about 2 symptomatic days each month and took it for an average of about 7 days per cycle. Change from baseline in mean PMTS score did not differ significantly between the groups receiving sertraline or placebo. However, significant differences favoring sertraline were found on the Inventory of Depressive Symptomatology, clinician-rated version (IDS-C; p=0.02). Rates of response (Clinical Global Impression–Improvement [ CGI-I] rating of ≤2) and remission (CGI-I score of 1) also favored the sertraline group, although with statistical significance only for response. (See table.) On the Daily Record of Severity of Problems, which measures 11 symptoms of PMDD, sertraline was associated with significantly greater improvement in the anger/irritability subscale (p<0.01), but not the depressive symptoms or physical symptoms subscales. There was no evidence of withdrawal symptoms after cessation of treatment each month.

**Discussion:** The present study suggests irritability symptoms may be most responsive to symptom-onset sertraline, in line with the hypothesis that anger and irritability are the hallmark of the disorder. Although the primary efficacy measure did not show a significant advantage of sertraline over placebo, the authors suggest the finding may be related to the large placebo response, which was likely driven by expectations of improvement arising from repeated counseling.

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

| Rates of response and remission with sertraline or placebo |
|---|---|---|
| **Response** | Sertraline 67% | Placebo 52% | p=0.02 |
| **Remission** | 42% | 32% | p=0.10 (ns) |

Yonkers K, Kornstein S, Gueorguieva R, Merry B, et al: Symptom-onset dosing of sertraline for the treatment of premenstrual dysphoric disorder: a randomized clinical trial. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2015.1472. From Yale University School of Medicine, New Haven, CT, and other institutions. **Funded by the NIMH.** One study author disclosed financial relationships with pharmaceutical-industry sources. The remaining 5 authors declared no competing interests.

*See Reference Guide.
Lurasidone for Bipolar Depression

Available data, although very limited, suggests lurasidone has promising efficacy for treating bipolar depression. Its safety and tolerability may make it preferable among the agents approved to treat this condition.

There is substantial literature on the pharmacology of lurasidone, which was FDA approved for the treatment of bipolar depression in 2013. However, evidence of its efficacy in the disorder is scarce because of the short time since its approval for this indication. Additional information about safety and tolerability is available from many clinical trials in patients with schizophrenia.

According to a current theory, norepinephrine reuptake and 5-HT\textsubscript{1A} agonism are core deficits in bipolar depression, unlike unipolar depression. Lurasidone is pharmacologically appropriate to treat these abnormalities. Among the available atypical antipsychotics, with which it shares numerous pharmacologic actions, lurasidone has the highest affinity for the 5-HT\textsubscript{7} receptor, which may underlie its antidepressant properties. This activity, combined with alpha\textsubscript{2C}-adrenergic and 5-HT\textsubscript{1A} agonism, may confer cognitive benefits such as improved learning and memory.

Low activity at various other receptors may reduce liability for adverse effects associated with other atypical antipsychotics, such as weight gain, negative cognitive symptoms, and cardiovascular side effects. Despite being a high-affinity D\textsubscript{2} receptor antagonist, lurasidone is associated with lower risk than other antipsychotics of inducing CNS depressive effects, extrapyramidal symptoms, and anticholinergic effects.

The evidence for efficacy of lurasidone in bipolar depression includes only 2 clinical trials, both of which had some important methodological limitations. In one study, lurasidone monotherapy in 2 dosage ranges, 20–60 mg/day and 80–120 mg/day, given for 6 weeks, was superior to placebo in reducing patients’ average Montgomery-Asberg Depression Rating Scale (MADRS) scores. Superiority was observed in both dosage groups after 1–2 weeks of treatment. Lurasidone was also associated with larger improvement on the Clinical Global Impression–Bipolar (CGI-BP) scale and higher rates of response and remission than placebo. The second study was a placebo-controlled trial of flexible-dose lurasidone as an adjunct to lithium or valproate. After 6 weeks, significantly greater decreases in the MADRS and CGI-BP were observed with lurasidone than placebo. Another research group compared the number needed to treat* (NNT) for lurasidone and the other approved treatments for bipolar depression—i.e., quetiapine and the olanzapine–fluoxetine combination. For clinical response (≥50% reduction in MADRS score), the NNT was 5 for the 2 doses of lurasidone as monotherapy and 7 for adjunctive lurasidone, estimates which are comparable to the other available treatments.

According to the schizophrenia literature, lurasidone may cause less weight gain, hyperlipidemia, and/or hyperglycemia than other recently approved atypical antipsychotics. In schizophrenia trials, the most common adverse effects were nausea, somnolence, akathisia, sedation, and parkinsonism. These were usually mild or moderate, and rates of treatment discontinuation were low. Lurasidone was associated with increases in prolactin, but to a lesser degree than similar drugs. In the 2 bipolar-disorder trials, adverse effects were similar to those observed in the schizophrenia literature.


Common Drug Trade Names: lurasidone—Latuda; olanzapine–fluoxetine—Symbyax; quetiapine—Seroquel; valproate—Depacon, Depakote

*See Reference Guide.
Antipsychotic Comparison in First-Episode Schizophrenia

Aripiprazole may be the preferred alternative to risperidone in most patients with first-episode schizophrenia, according to results of a comparison study.

**Background:** Optimal treatment of first-episode of schizophrenia may improve long-term outcomes. At present, risperidone is the most widely used antipsychotic for first-episode patients, but there is little data comparing treatments in these patients, and risperidone is associated with large weight gains. The present study was undertaken to determine if aripiprazole, which produces fewer metabolic effects, would provide efficacy similar to risperidone in first-episode patients.

**Methods:** The randomized trial was conducted at 10 urban or suburban treatment centers. Participants were aged 15–40 years, had a diagnosis of any schizophrenia spectrum disorder, and had ≤2 weeks of lifetime exposure to antipsychotic medication. Ratings of moderate or worse were required on ≥1 of the Brief Psychiatric Rating Scale (BPRS) items of conceptual disorganization, grandiosity, hallucinatory behavior, or unusual thought content. Patients with diabetes or metabolic syndrome were excluded. Participants received randomized, double-blind risperidone at a dosage of 1–6 mg/day, or 5–35 mg/day aripiprazole, starting at the lowest dose and increased in increments of 1 mg for risperidone and 5 mg for aripiprazole. All patients also received a psychoeducational packet that covered healthy body weight and recommendations for eating and exercise. The primary outcome was response, defined as a rating of mild or better on all 4 BPRS items and 2 consecutive Clinical Global Impression–Improvement (CGI-I) ratings of much or very much improved.

**Results:** The study included 198 participants (71% men) with a mean age of 22 years, from diverse ethnic backgrounds, and usually of low-to-middle socioeconomic status. Participants had psychotic symptoms for an average of >2 years before starting antipsychotics. About one-fourth of the study patients were antipsychotic-medication-naive at randomization. Patients in both groups received study treatment for a similar amount of time (mean, about 8 weeks), with average dosages in the middle of the range for each drug.

Response rates at 12 weeks were 63% for aripiprazole and 57% for risperidone, a non-significant difference. BPRS scores improved markedly over time in both groups (p<0.0001), with no difference in overall positive or negative symptom improvement. Avolition-apathy improved with aripiprazole and worsened with risperidone; the between-group difference was modest but statistically significant (p=0.03). The groups did not differ with regard to changes in BPRS and CGI–Severity scores, both of which improved significantly (p<0.0001).

<table>
<thead>
<tr>
<th>Significant Metabolic Differences Between Aripiprazole and Risperidone</th>
<th>Aripiprazole (n=102)</th>
<th>Risperidone (n=96)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cholesterol</strong></td>
<td>Baseline</td>
<td>158 mg/dL</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>163 mg/dL</td>
<td>Endpoint</td>
</tr>
<tr>
<td><strong>LDL Cholesterol</strong></td>
<td>Baseline</td>
<td>86 mg/dL</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>92 mg/dL</td>
<td>Endpoint</td>
</tr>
<tr>
<td><strong>Fasting Glucose</strong></td>
<td>Baseline</td>
<td>85 mg/dL</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>84 mg/dL</td>
<td>Endpoint</td>
</tr>
<tr>
<td><strong>Prolactin (Women)</strong></td>
<td>Baseline</td>
<td>62 ng/mL</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>10 ng/mL</td>
<td>Endpoint</td>
</tr>
<tr>
<td><strong>Prolactin (Men)</strong></td>
<td>Baseline</td>
<td>29 ng/mL</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>7 ng/mL</td>
<td>Endpoint</td>
</tr>
</tbody>
</table>

Although efficacy was similar, differences emerged in the adverse-effect profiles of the 2 drugs. Aripiprazole was associated with significantly worse akathisia at weeks 1, 4, and 6 (p=0.03). Other, non-akathisia extrapyramidal effects did not differ. Both drugs were associated with similar changes in body weight; patients gained an average of 11–13 lbs. Aripiprazole was associated with more favorable levels of
total cholesterol, LDL cholesterol, and fasting glucose, but not HDL cholesterol, triglycerides, or fasting insulin. Prolactin levels were significantly lower at each assessment with aripiprazole than with risperidone.

Discussion: The present study suggests that low-dose risperidone may be preferred in patients with the potential for akathisia, but aripiprazole is preferred for most others. The results reinforce the need to follow guideline recommendations for laboratory testing, since it appears that metabolic differences can appear without weight differences.

Robinson D, Gallego J, Manju J, Petrides G, et al: A randomized comparison of aripiprazole and risperidone for the acute treatment of first-episode schizophrenia and related disorders: 3-month outcomes. Schizophrenia Bulletin 2015; doi 10.1093/SCHBUL/SBV125. From the Feinstein Institute for Medical Research, Manhasset, NY; and other institutions. Funded by the NIH and other sources. Nine study authors disclosed relationships with commercial sources; the remaining 9 authors declared no conflicts of interest.

Common Drug Trade Names: aripiprazole — Abilify; risperidone — Risperdal

Reference Guide

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.

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.
Cariprazine for Manic Symptoms

According to a secondary analysis of pooled data from the manufacturer's clinical trials, cariprazine (Vraylar) was associated with improvement across the spectrum of manic symptoms in patients with bipolar I disorder. This atypical antipsychotic was recently FDA approved for treatment of schizophrenia and manic or mixed episodes of bipolar disorder.

**Methods:** Data were pooled from 3 phase II or III clinical trials of similar design, conducted in adult inpatients with bipolar I disorder and experiencing acute manic or mixed episodes. Patients were hospitalized for at least the first 2 weeks of treatment and received 3–12 mg/day cariprazine or placebo for 3 weeks. Participants were required to have a Young Mania Rating Scale (YMRS) total score of ≥20 and a score of ≥4 (moderate severity) on ≥2 of the 4 core YMRS items of irritability, speech, content, and disruptive-aggressive behavior. First-episode patients were excluded from all 3 studies. The current analysis evaluated treatment effects on the 4 core YMRS items, each of the 11 YMRS items, and categorical shifts to mild/no symptoms from higher levels of symptom severity.

**Results:** A total of 1065 patients received either cariprazine or placebo in the 3 studies. Patients had a mean age of 39 years, the majority (60%) were men, the mean duration of bipolar disorder was 13 years, and patients were highly symptomatic at baseline. More than 90% had at least moderate severity ratings on the YMRS items of elevated mood, increased motor activity-energy, sleep, language-thought disorder, and speech.

Cariprazine was associated with significant improvement on all of the 11 YMRS items (p<0.001 vs. placebo for each item). Treatment effect sizes* ranged from 0.31 for increased motor activity to 0.49 for disruptive-aggressive behavior and 0.55 for irritability. Patients who received cariprazine had a higher likelihood than the placebo group of achieving mild or absent symptom ratings for all of the 4 core items (odds ratio,* 2.0; p<0.0001). Shifts from the highest severity ratings (marked/worse symptoms) to the lowest (mild/no symptoms) occurred in significantly more cariprazine-treated than placebo-treated patients for 9 of the 11 YMRS items and 3 of the 4 core items. (The fourth item, disruptive-aggressive behavior, was highly severe at

---

*Psychiatry Drug Alerts (ISSN 0894-4873) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psych@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. Postmaster: Send address changes to Psychiatry Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405. © 2015 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription $99 a year in the U.S.; $107.50 Canada; $117.50 elsewhere; $151 institutional. Back issues and single copies are available for $10.00 each, prepaid. Subscribers may enroll in the 12-month CME program for $77.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.
baseline in too few subjects to evaluate.) The proportion of patients who shifted from the worst to the mildest symptom category on the 4 core YMRS items was 51% for cariprazine versus 29% for placebo. More cariprazine-treated patients also were in the lowest severity category for all 11 YMRS items: 23% versus 14% for placebo.

**Discussion:** The improvement profile found in this study indicates that cariprazine produces robust gains across the spectrum of manic symptoms, with the strongest effects on irritability, which is often the predominant presenting feature of an acute manic episode. Deconstructing an acute manic episode into individual symptoms may be useful in the management of sub-syndromal or residual symptoms between episodes.

Vieta E, Durgam S, Lu K, Ruth A, et al: Effect of cariprazine across the symptoms of mania in bipolar I disorder: analyses of pooled data from phase II/III trials. *European Neuropsychopharmacology* 2015; doi 10.1016/j.euroneuro.2015.08.020. From the University of Barcelona, Spain; and other institutions. **Funded by Forest Laboratories; and Gedeon Richter. All study authors declared potential conflicts of interest with commercial sources, including Forest Laboratories and Gedeon Richter.**

*Lisdexamfetamine in Binge Eating Disorder*

In 2 manufacturer-sponsored, randomized, phase-III trials, lisdexamfetamine dimesylate significantly reduced the number of weekly binge-eating episodes in adults with moderate-to-severe binge eating disorder.

**Methods:** Each study recruited patients, aged 18–55 years (average age, 37–39 years), from about 50 sites, mostly in the U.S. The majority of participants were female (86%), caucasian (75%), and overweight or obese (91%). Diagnosis of moderate-to-severe binge eating disorder was based on dual criteria: ≥3 binge eating days per week for 2 consecutive weeks and a Clinical Global Impression–Severity (CGI–S) score of ≥4. Following a 2–4 week screening period, participants were randomly assigned to 12 weeks of double-blind treatment with lisdexamfetamine (n=373), titrated to 50 or 70 mg/day, or placebo (n=372). The primary efficacy endpoint was change from baseline in binge-eating days per week during weeks 11 and 12.

**Results:** In both studies, lisdexamfetamine was associated with a greater reduction in weekly binge eating than placebo. The number of binge-eating episodes per week was reduced by a mean of 3.9 episodes with lisdexamfetamine versus 2.3–2.5 with placebo from baseline averages of nearly 5 (p<0.001; effect sizes,* 0.83 and 0.97 in studies 1 and 2, respectively). Secondary endpoints also favored lisdexamfetamine. In the combined study populations, the number of patients who achieved cessation of binge eating for ≥4 weeks was 139 with lisdexamfetamine, compared with 49 with placebo (38% vs. 14%; p<0.001; odds ratios,* 3.8–4.1). The odds ratio for improvement in CGI–Improvement ratings at study end were 5.1 and 8.3 with lisdexamfetamine in studies 1 and 2, respectively. Compared with placebo, lisdexamfetamine also produced significantly greater weight loss, averaging about 6% vs. <1% (p<0.001; effect sizes, 1.6 and 1.2 in the studies, respectively). Obsessions and compulsions related to binge eating were also reduced to a significantly greater degree with lisdexamfetamine (p<0.001; effect sizes >1 in both studies).

Safety and tolerability of lisdexamfetamine were consistent with the known profile. Dry mouth, headache, and insomnia were each reported by >10% of patients who received the drug. Syncope resulted in treatment discontinuation in 2 lisdexamfetamine-group patients.

**Discussion:** Antidepressants have shown efficacy in reducing binge-eating episodes and related psychopathology but have had only modest effects on weight. Topiramate and sibutramine have been effective in all 3 areas, but sibutramine is no longer available and topiramate use is limited by adverse effects. Results with orlistat have been mixed. Lisdexamfetamine is currently
the only medication FDA approved to treat binge eating disorder in adults. Results of these studies suggest it has both significant and clinically relevant effects on binge eating episodes, related psychopathology, and weight; and it is well tolerated.

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

McElroy S, Hudson J, Ferreira-Cornwell M, Radewonuk J, et al: Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder; results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology* 2015; doi 10.1038/npp.2015.275. From Lindner Center of HOPE, Mason, OH; and other institutions. **Funded by Shire Development, LLC, Wayne, PA. All study authors disclosed financial relationships with commercial sources, including Shire.**

*Common Drug Trade Names: lisdexamfetamine—Vyvanse; orlistat—Xenical; sibutramine (no longer marketed in the U.S.)—Meridia; topiramate—Topamax*

*See Reference Guide.

**Investigational Antipsychotic: Efficacy and Tolerability**

In a multisite, randomized, phase II controlled trial, ITI-007, an investigational antipsychotic with a novel pharmacologic profile, reduced symptoms of schizophrenia in patients experiencing an acute exacerbation. The results also provide preliminary evidence of a benign adverse-effect profile and broader spectrum of activity relative to existing antipsychotics.

**Background:** ITI-007 is a novel molecular entity that combines dose-related modulation of D2 and 5-HT1A receptors and phosphorylation of intracellular signaling proteins. It lacks activity at many receptors that are associated with the adverse effects of other antipsychotics.

**Methods:** Study participants were 335 patients (average age, 40 years; 82% men) previously responsive to antipsychotic therapy, who were suffering an acute exacerbation. All were hospitalized for the duration of the study and, following withdrawal of prior antipsychotics, received treatment for 28 days. Patients were randomly assigned to either 60 mg/day or 120 mg/day ITI-007, corresponding to 50% and 70% of estimated striatal dopamine receptor occupancy; to risperidone (*Risperdal*) as an active control; or to placebo. The primary efficacy measure was change from baseline to day 28 on the Positive and Negative Syndrome Scale (PANSS) total score.

**Results:** A total of 81% of patients completed study treatment. Only 5 patients (2 in the ITI-007 groups) discontinued treatment because of an adverse effect. The efficacy analysis was conducted in 311 patients for whom ≥1 post-baseline assessment was available. The 60-mg dose of ITI-007 was associated with a significant reduction in the PANSS total score of 13.2 points (p=0.017 vs. placebo; effect size,* 0.4). The 120-mg dose was not significantly more effective than placebo. Risperidone was also superior to placebo, indicating that the study was a valid test of treatment efficacy. Rates of response, defined as a ≥30% improvement in PANSS total score, were 40% for both 60 mg ITI-007 and risperidone and 23% with placebo.

About one-third of patients had prominent negative symptoms at baseline. In this group, 60 mg ITI-007 reduced the PANSS negative symptom subscale score (effect size, 0.34), although the difference from placebo was not statistically significant. In the 13% of patients with comorbid depression, 60 mg ITI-007 also significantly reduced the Calgary Depression Scale for Schizophrenia (CDSS) score (p=0.044; effect size, 1). Effects of treatment on the prosocial factor, derived from the PANSS to encompass symptoms related to social function, were also statistically significant (p<0.001 vs. placebo; effect size, 0.59). Risperidone was also superior to placebo for this outcome (p=0.01; effect size, 0.42).

The incidence of any treatment-emergent adverse effects with 60 mg ITI-007 did not differ from placebo. Neither dose of the investigational drug was associated with an increase in extrapyramidal symptoms. Both doses of ITI-007 were associated with somewhat less weight gain than...
risperidone (median gains with ITI-007, 2 lbs. vs. 6 lbs. with risperidone). Patients taking ITI-007 had smaller increases in prolactin, fasting glucose, total cholesterol, and triglycerides than the risperidone group.

**Discussion:** The apparent efficacy against a broad spectrum of schizophrenia symptoms was suggested by the positive effects on symptom subgroups, but requires confirmation in future studies.

Lieberman J, Davis R, Correll C, Goff D, et al: ITI-007 for the treatment of schizophrenia: a 4-week randomized, double-blind, controlled trial. *Biological Psychiatry* 2015; doi 10.1016/biopsych.2015.08.026. From the Columbia University College of Physicians and Surgeons, NY; and other institutions including Intra-Cellular Therapies, Inc., NY. Funded by Intra-Cellular Therapies Inc. All 8 study authors declared relationships with commercial sources, including 6 with Intra-Cellular Therapies Inc.

*See Reference Guide.

### Transmucosal Ketamine for Resistant Depression

In a retrospective chart review, transmucosal ketamine, administered by mouth and absorbed through the oral mucosa, was effective in patients with refractory depression attending a day hospital program.

**Background:** Ketamine, in sub-anesthetic doses, has been shown to produce rapid and robust improvement in depression. However, cardiovascular and dissociative adverse effects are concerning and the need for IV administration limits its use. Alternative routes of administration are under investigation. Intramuscular and intranasal administration may be problematic, and oral administration results in low bioavailability. Transmucosal administration, as described in this study, leads to greater bioavailability than oral administration—30% versus 17%.

**Methods:** Charts were retrospectively reviewed for patients who received off-label, transmucosal ketamine for resistant major depression, defined as failure to respond to ≥2 trials of antidepressant monotherapy of ≥6 weeks’ duration or ≥4 trials that included other methods, such as drug combinations and ECT. Ketamine was administered in small amounts (about 1 mL) and held in the mouth rather than being swallowed. Patients received ketamine in addition to their usual care, which included ongoing drug treatment and group psychotherapy. Ketamine, 0.5–1.0 mg/kg, was given by placing the solution on the tongue and instructing the patient to hold it in the mouth as long as possible. Administration was repeated every 2 weeks, or more often if indicated. For the present analysis, patients were identified as responders based on the clinician's notes in their chart and/or whether a controlled substance database showed >1 filled ketamine prescription.

**Results:** Over a 2.5-year period, 17 patients (mean age, 48 years; 88% women) received ketamine while other medications were generally held stable. Concomitant medications included SNRIs in 10 patients; SSRIs in 6; stimulants, benzodiazepines, and folate replacement each in about half; and antipsychotics in 6. Three patients had a history of substance abuse.

A total of 13 patients (76%) were classified as responders to transmucosal ketamine—11 on the basis of clinical notes and 2 based on repeatedly filled ketamine prescriptions. The onset of improvement was noted within 24 hours of administration, and patients who did not experience response within 24 hours typically received no benefit from ketamine. Of the 11 responders for whom information was available, 7 went on to a maintenance dosing regimen of every 2 weeks, 3 every 10 days, and 1 every week. Clinical notes for 2 patients indicated that they continued to benefit from ketamine ≥6 months after the first treatment; long-term efficacy information was not available for the remaining patients. There were no
apparent drug interactions with ketamine, and 2 patients experienced mild adverse events: transient light headache and slight dizziness.

**Discussion:** The present study was exploratory, conducted in a patient population with multiple comorbidities, including chronic pain, ADHD, anxiety, and a history of substance abuse, who were usually taking multiple other medications. It is reassuring that there were no serious adverse effects, drug interactions, or recurrence of substance misuse. Transmucosal ketamine merits a more systematic investigation as antidepressant treatment.

Nguyen L, Marshalek P, Weaver C, Cramer K, et al: Off-label use of transmucosal ketamine as a rapid-acting antidepressant: a retrospective chart review. *Neuropsychiatric Disease and Treatment* 2015;11:2667–2673. From West Virginia University, Morgantown; and other institutions. Source of funding not stated. Three study authors disclosed relevant financial relationships; the remaining 3 authors declared no competing interests.

### Antibiotics, Depression, and Anxiety

In an epidemiologic study, antibiotic exposure, especially if recurrent, was associated with increased risk for depression and anxiety but not psychosis.

**Background:** Changes in the composition of the gut microbiota have been linked with behavioral changes in animals. Studies in humans tend to support the link, but they have been mostly limited to the effects of probiotic administration on anxiety and depression.

**Methods:** Data were analyzed from The Health Improvement Network (THIN), a U.K. general practice database of >10 million patients. Case patients were those aged 15–65 years who received a new diagnosis of depression, anxiety, or psychosis in 1995–2013. Each case was matched with up to 4 controls by age, gender, practice site, duration of follow-up, and calendar time. The primary exposure was antibiotic treatment >1 year prior to the date of diagnosis, to avoid any potential bias from antibiotic prescription for early symptoms of mental illness. Exposures were assessed for the 7 most common antibiotic classes: penicillins; cephalosporins; macrolides; quinolones; sulfonamides; tetracyclines; and imidazole. As a control exposure, antifungal and antiviral use was also assessed.

**Results:** The study population included >200,000 patients with depression, about 14,500 with anxiety, and about 2700 with psychosis. Penicillin was the most commonly prescribed antibiotic, used by about one-third of cases and controls. The mean patient age was 37 years, and nearly 60% were women.

Risk of depression was increased with a single course of each of the 7 antibiotic classes. For penicillin, the adjusted odds ratio* was 1.23. Increases were of a similar magnitude for single courses of the other antibiotics with odds ratios ranging from 1.21 to 1.26. Treatment with multiple courses was associated with increased incidence of depression for all antibiotic classes, with a 50% increase in patients receiving >5 courses of penicillin (odds ratio, 1.56). Risk was not attenuated after adjustment for the number of past infectious events. Depression risk was also mildly increased in patients who received a single course of an antifungal or antiviral (odds ratios, 1.17 and 1.12, respectively), but there was no increase in risk with repeated exposures. The increased risk for depression was maintained in an analysis limited to antibiotic prescriptions 5–10 years in the past.

Risk of anxiety was significantly associated with the use of penicillins and sulfonamides. Odds ratios ranged from 1.17 to 1.35 for a single course of treatment and increased to 1.33–1.46 in patients exposed to 2–5 courses of treatment. There was no increase in psychosis with any of the antibiotics, antifungals, or antivirals.

**Discussion:** Although the study design did not allow for an assessment of causality, risk was not increased with repeated antiviral or antifungal courses. In addition, past number of infectious events did not further increase depression risk with antibiotics, while the number of
specific antibiotic courses did, possibly suggesting that the risk is not due to infection alone. The apparent increased risk for depression and anxiety with antibiotics provides another reason to reduce unnecessary antibiotic treatment.

Lurie I, Yang Y-X, Haynes K, Mamtani R, et al: Antibiotic exposure and the risk for depression, anxiety, or psychosis: a nested case-control study. *Journal of Clinical Psychiatry* 2015; doi 10.4088/JCP.15m09961. From Tel-Aviv University, Israel; and other institutions. Funded by the NIH. The study authors declared no financial relationships with pharmaceutical-industry sources.

*See Reference Guide.

### Optimal Duration of Adjunctive Antipsychotics for Mania

In a randomized discontinuation trial, adjunctive antipsychotics were effective in preventing relapse following recovery from mania. However, no additional benefits were apparent after 6 months and the adverse event burden was increased.

**Methods:** Study participants were adults with bipolar I disorder, who received treatment for an acute manic episode within the previous 12 weeks with lithium or valproate and adjunctive olanzapine or risperidone. Patients had experienced the remission for between 2 and 6 weeks before randomization, which was stratified by drug combination. Patients were randomly assigned to have their antipsychotic discontinued immediately, to have it withdrawn after 24 weeks, or to have it withdrawn after 52 weeks. Mood stabilizers were maintained at a stable dose. The primary outcome was the time to any mood episode: depression, mania, hospitalization for treatment of mood symptoms, or a suicide attempt.

**Results:** Planned enrollment was 540 patients, but due to slow response and expiration of funding, recruitment was terminated with 159 patients. A total of 21% of patients discontinued the study early for reasons other than relapse. In the group that discontinued immediately, 39 relapse events occurred (75%) and 29 occurred in each of the groups that continued antipsychotic treatment (54% and 55% in the 24- and 52-week groups, respectively).

Results for individual secondary outcomes—time to manic episodes, depressive episodes, and discontinuation for any reason—also favored continued treatment for 24 or 52 weeks. Although mania is a defining feature of bipolar disorder, depressive relapses outweighed mania/hypomania by a ratio of 3:1. However, adjunctive antipsychotics were more effective in preventing manic relapses. Consistent with other research, risperidone was only effective in preventing mania and olanzapine was more effective in preventing depression than mania.

<table>
<thead>
<tr>
<th>Risk of a primary outcome event according to time of discontinuation of adjunctive antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio*</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>24 weeks vs. immediate</td>
</tr>
<tr>
<td>52 weeks vs. immediate</td>
</tr>
<tr>
<td>52 weeks vs. 24 weeks</td>
</tr>
</tbody>
</table>

The occurrence of adverse effects was generally similar in all groups. However, patients in the 52-week group gained significantly more weight: 7 lbs., compared with negligible changes in the other 2 groups. Average weight gain in the 52-week group was 12 lbs. with olanzapine and 3 lbs. with risperidone. Average changes in other metabolic parameters did not differ among groups.

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

Yatham L, Beaulieu S, Schaffer A, Kauer-Sant’Anna M, et al: Optimal duration of risperidone or olanzapine adjunctive therapy to mood stabilizer following remission of a manic episode: a CANMAT randomized double-blind trial. *Molecular Psychiatry* 2015; doi 10.1038/mp.2015.158. From the University of British Columbia, Vancouver, Canada; and other institutions. Funded by the Canadian Institutes of Health Research. Eleven of the 22 authors declared financial relationships with commercial sources. The remaining authors declared no competing interests.

*Common Drug Trade Names: olanzapine—Zyprexa; risperidone—Risperdal; valproate—Depakote*

*See Reference Guide.*
Antipsychotics and Hip Fracture

According to results of a population-based study, antipsychotic medications are associated with a 34% increase in risk of hip fracture over 10 years. Risk appears to be greatest with first-generation agents.¹

Methods: Patient data for the study was extracted from the National Health Insurance Research Database in Taiwan. Case patients were those aged ≥20 years with a diagnosis of a schizophrenia spectrum disorder who had experienced a hip fracture in 2002–2011. Each case patient was age- and gender-matched with up to 5 controls, also with schizophrenia. The investigators examined the effects of any antipsychotic utilization in the 6 months before hip fracture; current (within the past month) or past use (within 2 months); new or continuous use; first- versus second-generation antipsychotic use; and 15 different antipsychotics grouped by binding profile for 4 different neurotransmitter receptors.

Results: The analysis was based on 605 patients with a hip fracture (mean age, 59 years; 45% women) and >2800 controls (mean age, 57 years; 44% women). Use of antipsychotics, particularly first-generation agents, was associated with hip fracture risk. (See table.) Fracture risk was significantly increased in current, new, and continuous users of antipsychotics (p<0.05 for all), but not in past users. Risk was dose-related for first-generation agents only. Among individual agents, hip fracture risk was significantly increased with current use of sulpiride, haloperidol, and thioridazine.

Greater risk was associated with drugs with low binding affinity for 5-HT₂A, H₁, and α-1 adrenergic receptors and with both low and high dopamine D₂ receptor binding affinity.

Discussion: Short-term antipsychotic adverse effects (e.g., sedation, hypotension) can lead to falls and, potentially, hip fracture. In addition, antipsychotics’ prolactin-elevating effects and serotonergic-related effects on bone formation could also lead to osteoporosis and increased fracture risk with long-term use. However, past use was not associated with increased risk in this study, suggesting the association is not solely due to osteoporosis; rather a combination of short- and long-term effects may underlie the increased risk.² The lower risk with second-generation agents, despite their prolactin-elevating effects, may be related to the greater propensity for first-generation agents to cause postural instability and other extrapyramidal effects. Patients already at risk of fracture might be steered away from prolactin-elevating drugs and first-generation agents. Regardless of the causal explanation, hip-fracture risk should be treated as an avoidable side effect.


Common Drug Trade Names: haloperidol—Haldol; sulpiride (not available in the U.S.)—Dolmatil; thioridazine—Mellaril

*See Reference Guide.
**Chewable Methylphenidate ER**

The FDA has granted approval for the first chewable formulation of extended-release methylphenidate (QuilliChew ER). In a clinical trial of children aged 6–12 years with ADHD, QuilliChew improved both attention and behavior beginning 45 minutes after ingestion and lasting through an 8-hour laboratory classroom challenge. The new formulation, for use in patients aged ≥6 years, will be available in 20-, 30-, and 40-mg tablets that can be taken with or without food and is expected to be in pharmacies in the first quarter of 2016. The recommended starting dosage is 20 mg/day; dosages >60 mg/day are not recommended. As with other stimulants, patients should be evaluated for cardiac disease before starting treatment with QuilliChew, and use is contraindicated with concurrent or recent MAOI use. QuilliChew contains phenylalanine, which can be harmful to patients with phenylketonuria. Adverse effects appear to be similar to other methylphenidate formulations.


**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.

**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.

---

**DO YOU STILL NEED CME CREDIT?**

**ENROLL NOW FOR PROGRAMS CORRESPONDING TO YOUR 2015 NEWSLETTERS**

Visit www.alertpubs.com/continuing-education.html and choose either:

- **Interactive Online CME**
  Scored instantly. Earn credits as you go. Start now and complete at your own pace.

- **Traditional Print Format**
  Print copy is delivered by mail; you receive credit for the full program when you return the answer sheet for grading.

M.J. Powers & Co. Publishers is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

---

**Contributing Editors:** Kate Casano, MSHyg; Bennett Silver, MD

Consulting Editor: Steven J. Schleifer, MD, Rutgers–New Jersey Medical School

Executive Editor: Trish Elliott  Associate Editor: Tara Hausmann  Assistant Editor: Kasey Madara

Founding Editor: Michael J. Powers

**Off-Label Drug Use Statement:** Some drugs discussed for specific indications in Psychiatry Drug Alerts articles may not be approved for labeling and advertising for those indications by the United States Food and Drug Administration.
A

ADHD, 1, 10, 17, 41, 82, 96
agomelatine, 29
Alzheimer’s disease. See also dementia, 38, 53, 57, 79
amisulpride, 36
amitriptyline, 34
anemia, 73
anencephaly, 63
antibiotics, 89, 93
antidepressant switching, 52
antidepressants. See also individual drugs, 1, 2, 5, 12, 15, 20, 23, 26, 29, 34, 35, 47, 52, 55, 58, 61, 69, 71, 78, 81, 84, 86, 90, 92
anti-inflammatory drugs, 2, 58
anxiety, 14, 18, 61, 62, 71, 93
aripiprazole, 13, 33, 43, 52, 54, 65, 66, 69, 75, 81, 87
armodafinil, 5
asenapine, 34, 75
atomoxetine, 10, 48, 82
atrial septal defects, 63
atypical antipsychotics. See individual drugs.

B

behavioral disturbances of dementia, 42
binge eating disorder, 17, 90
bioequivalence, 33
biomarkers, 1, 84
bipolar depression, 1, 9, 26, 54, 86
bipolar disorder, 9, 11, 26, 33, 75, 86, 89, 94
birth defects, 63
breastfeeding, 7, 12
brexpiprazole, 22, 49, 65, 69, 77
bupropion, 29, 43, 55
bupropion, 29, 43, 55
C

C-reactive protein, 1
cannabinoid, 3
carbamazepine, 11, 54
cariprazine, 6, 39, 75, 89
celecoxib, 2, 50
cerebrolysin, 38
chlorpromazine, 12
citalopram, 12, 21, 63
clozapine, 12, 65, 73
cognitive function, 19, 20, 21, 38, 44, 57
congenital malformations, 10, 11, 63
cortical gray matter, 31
cytokine inhibitors, 2

dasotraline, 1, 41
dementia. See also Alzheimer’s disease, 42
depression, 2, 5, 6, 9, 11, 14, 15, 19, 20, 21, 26, 28, 29, 43, 47, 49, 51, 52, 61, 69, 76, 78, 81, 92, 93
dextromethorphan–quinidine, 79
donepezil, 53
dopamine and norepinephrine reuptake inhibitors, 1, 41
dose reduction, antipsychotic, 59
doxepin, 34, 48
drug interactions, 58, 67
duloxetine, 12, 13, 19
E
escitalopram, 1, 12, 63, 84
esmirtazapine, 60
edivoxetine, 35
encenicline, 57
end-stage renal disease, 21

F
flibanserin, 69
fluoxetine, 5, 12, 34, 54, 63, 86
fluphenazine, 12
fluvoxamine, 12, 50
fracture, 23, 95

G
generalized anxiety disorder, 14, 18, 61, 62
generic drugs, 33
genetic markers, 83, 84
geriatric depression, 21, 81
gestational diabetes, 11, 45
GLYX-13, 28

H
haloperidol, 12, 34, 36, 37, 42, 95
hoarding, 74
hospital discharge, 71
hypoactive sexual desire disorder, 69

I
immune dysregulation, 50
inflammatory processes, 50
insight, 36, 74
insomnia, 47, 49, 60, 74
intracranial hemorrhage, 58
ischemic stroke, 78
ITI-007, 91

K
ketamine, 27, 28, 47, 92

L
lamotrigine, 5, 7, 11, 43, 54
lisdexamfetamine, 17, 90
lithium, 9, 11, 21, 37, 43, 54, 67, 86, 94
long-acting injectable antipsychotics, 30, 65, 66, 75
loxapine, 34
lurasidone, 5, 12, 26, 54, 68, 86

M
mania, 6, 7, 9, 11, 26, 37, 39, 54, 89, 94
memantine, 7, 53, 79
methylphenidate, 10, 21, 43, 74, 89, 96
midazolam, 27
minocycline, 2, 74
mirtazapine, 60
mixed bipolar depression, 26

N
nabilone, 3
neonatal adaptation syndrome, 11, 45
neuropeptide, 38
neutropenia, 65
nicotinic receptor agonist, 57
nitrous oxide, 15
nonsteroidal antiinflammatory drugs, 2, 58
nontraditional dosage forms, 34
nortriptyline, 1

O
obsessive-compulsive disorder, 13, 50, 77
olanzapine, 13, 25, 33, 36, 42, 43, 54, 59, 94
olanzapine–fluoxetine, 5, 54,

P
paliperidone, 4, 12, 30, 66
paroxetine, 12, 54, 63, 74
pathological crying, 78
perphenazine, 12
persistent pulmonary hypertension, 46
personalized prescribing, 47
pimozide, 12
pioglitazone, 9
post-stroke depression, 78
postpartum psychosis, 37, 38
pregabalin, 14, 61, 62
pregnancy, 7, 10, 11, 12, 45, 46, 47, 63
premenstrual dysphoric disorder, 85
preterm birth, 10, 45
PTSD, 3

Q
quetiapine, 5, 12, 18, 36, 42, 43, 49, 54, 68
QuilliChew ER, 96

R
raloxifene, 44
recurrent major depression, 19, 51
relapse prevention, 4, 30
renal function, 21, 67
resistant depression, 27, 28, 29, 43,
49, 52, 72, 81, 92
risk evaluation and mitigation strategy,
34, 65, 69
risperidone, 12, 25, 42, 43, 59, 68,
83, 87, 91, 94

S
schizoaffective disorder, 4, 36, 44, 57,
59, 62, 68, 75
schizophrenia, 22, 30, 31, 33, 34, 36, 44, 49,
57, 59, 62, 65, 66, 68, 73, 75, 76, 83, 87, 89,
91, 95
selective estrogen receptor modulator, 44
selegiline, 34
sertraline, 12, 62, 63, 74, 84, 85
SNRIs. See also individual drugs, 12, 13,
23, 36, 52, 62, 92
spontaneous abortion, 10
SSRIs See also individual drugs, 2, 12, 14,
23, 35, 46, 52, 62, 63, 64, 69, 74, 77, 79,
85, 92
substance use disorder, 71
sudden cardiac death, 25
suicidal ideation, 27, 35, 47

T
teratogens, 11, 12, 63
thioridazine, 13, 95
thiothixene, 12
ticagrelor, 57
transmucosal ketamine, 92
trazodone, 34, 47
 treatment algorithm, 37
 trifluoperazine, 12

V
valproate, 7, 11, 54, 86, 94
venlafaxine, 12, 30, 70, 74, 77, 81, 84
ventricular arrhythmia, 25
vortioxetine, 19, 48, 51, 57

W
weight gain, 5, 11, 54, 60, 86, 87

Z
ziprasidone, 13, 36, 54