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 measureable 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

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**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.

Ball S, Atkinson S, Sparks J, Bangs M, et al: Long-term, open-label, safety study of edivoxetine 12 to 18 mg once daily as an adjunctive treatment for patients with major depressive disorder who are partial responders to selective serotonin reuptake inhibitor treatment. *Journal of Clinical Psychopharmacology* 2015;35 (June):1–7. From Eli Lilly and Company, Indianapolis, IN; and other institutions. **Funded by Eli Lilly and Company. All study authors disclosed financial relationships with commercial sources, including Eli Lilly.**

### 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.

Pijnenborg G, Timmerman M, Derks E, Fleischhacker W, et al: Differential effects of antipsychotic drugs on insight in first episode schizophrenia: data from the European First-Episode Schizophrenia Trial (EUFEST). European Neuropsychopharmacology 2015; doi 10.1016/j.euroneuro.2015.12.012. From GGZ-Drenthe, Assen, the Netherlands; and other institutions. Funded by Pfizer, AstraZeneca, and Sanofi-Aventis. Three study authors disclosed financial relationships with commercial sources; the remaining 3 authors declared no conflicts of interest.

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.


**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. Effect sizes* for cariprazine were impressive, according to an editorial, but the value it may add to existing treatments is uncertain.

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>Efficacy Outcomes</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.

1Calabrese 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.

2Tohen 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.