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 cyclooxegenase-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.


**Funded by Tehran University of Medical Sciences.** The authors declared no conflicts of interest.

*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.¹² 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.

1. Jacobsen 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.**


3. Dunlop 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.**

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**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.

<p>| Aripiprazole Augmentation vs. Antidepressant Switching: Efficacy Outcomes at 6 Weeks |
|-----------------------------------------------|-----------------------------------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Aripiprazole augmentation (n=50)</th>
<th>Antidepressant switch (n=46)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS, mean change from baseline</td>
<td>-16.3</td>
<td>-7.6</td>
</tr>
<tr>
<td>Response (≥50% decrease in MADRS score)</td>
<td>60%</td>
<td>33%</td>
</tr>
<tr>
<td>Remission (MADRS score, ≤10)</td>
<td>54%</td>
<td>19%</td>
</tr>
<tr>
<td>Clinical Global Improvement* score of 1 or 2</td>
<td>70%</td>
<td>41%</td>
</tr>
</tbody>
</table>

**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-capsule, fixed-dose combination of donepezil and memantine is bioequivalent to coadministered commercially available versions of the 2 drugs. 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.

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 ratings. 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.

Vázquez 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 Aretaeus 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.
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.