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.


*See Reference Guide.

**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 a ≥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>Treatment</th>
<th>NNT*</th>
<th>Clinically Relevant Harm</th>
<th>NNH**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine–Fluoxetine</td>
<td>4</td>
<td>≥7% weight gain</td>
<td>6</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6</td>
<td>Sedation/somnolence</td>
<td>5</td>
</tr>
<tr>
<td>Olanzapine monotherapy (U.S. trial)</td>
<td>12</td>
<td>≥7% weight gain</td>
<td>6</td>
</tr>
<tr>
<td>Olanzapine monotherapy (international trial)</td>
<td>11</td>
<td>≥7% weight gain</td>
<td>5</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>12</td>
<td>Sedation/somnolence</td>
<td>37</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>29</td>
<td>Mood switch</td>
<td>200</td>
</tr>
<tr>
<td>Lurasidone monotherapy</td>
<td>5</td>
<td>Akathisia</td>
<td>15</td>
</tr>
<tr>
<td>Adjunctive lurasidone</td>
<td>7</td>
<td>Nausea</td>
<td>16</td>
</tr>
<tr>
<td>Adjunctive armodafinil</td>
<td>9</td>
<td>Anxiety</td>
<td>29</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. Armomadin 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: armomadin—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 comparable to those calculated for other atypical antipsychotics in a meta-analysis of acute mania treatments. 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.


*See Reference Guide.

**Changes to Pregnancy and Lactation Labeling**

The FDA has updated its standards for how information about medication use during pregnancy 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.

FDA issues final rule on changes to pregnancy and lactation labeling information for prescription drug and biological products. FDA News Release: Available at http://www.fda.gov/newsevents/newsroom/pressannouncements.

**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.