A new second-generation antipsychotic, cariprazine, is in the late stages of development. Among available second-generation agents, its actions are most comparable to those of aripiprazole (soon to be available as a generic). According to a review of all available literature, cariprazine efficacy has been demonstrated in the dosage range of 1.5–9 mg/day. Further research is needed to determine whether cariprazine offers any advantages over aripiprazole.

Available antipsychotics each have differing pharmacodynamic properties that translate to small differences in efficacy and large differences in side-effect profiles. A number are available as generics, while the more expensive branded products tend to be those with fewer metabolic side effects. These “metabolically-friendlier” agents differ in dosing and administration recommendations as well as their effects on prolactin, ECG, and extrapyramidal symptoms/akathisia.

Cariprazine is a dopamine D3-preferring D3/D2 receptor partial agonist. The available phase 2 and 3 clinical data have been reported only as meeting presentations and a press release from the manufacturer. No study results have been published in peer-reviewed journals. Two short-term (6-week) phase 2 studies and 2 phase 3 studies of the same duration have been conducted in nearly 400 to >700 patients. All studies showed superiority of cariprazine to placebo in reducing Positive and Negative Syndrome Scale (PANSS) scores. Aripiprazole and risperidone were used as active controls in 2 studies, but the efficacy of these agents was not directly compared with cariprazine. Based on the results of these short-term studies, cariprazine appears to have a low liability for inducing metabolic side effects, prolactin increases, and ECG abnormalities. Among the more common adverse effects were insomnia; extrapyramidal disorder; sedation; akathisia; nausea; dizziness; vomiting; anxiety; and constipation. About one-third to nearly one-half of patients in these studies discontinued treatment prematurely, most often for worsening of schizophrenia.
Additional data are available from a 48-week open-label safety and tolerability extension study in a group of patients who had experienced response with acute treatment. Half of the 93 patients discontinued treatment early for various reasons, including 11% for adverse events and 3% for insufficient response. The most common adverse effects in the long-term study were akathisia in 14% of patients, insomnia in 14%, and weight gain in 12%.

Although the agents are similar, cariprazine has a different receptor binding profile than aripiprazole, but it remains to be seen whether this offers any advantages. Its receptor binding profile suggests the potential to improve cognition and negative symptoms, but this too remains to be investigated. The presence of a long-lasting active metabolite offers the opportunity to test longer dosing intervals, such as once a week. At present, logical candidates for cariprazine treatment are patients at metabolic or cardiovascular risk and those who must avoid weight gain. Patients who are sensitive to nausea, akathisia, and Parkinsonism will need monitoring.

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

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**Concomitant Fluvoxamine May Enhance Clozapine Efficacy**

A substantial portion of patients with refractory schizophrenia (40–70%) do not experience full response to clozapine, even when therapeutic blood levels are reached. Coadministration of fluvoxamine to manipulate clozapine metabolism is emerging as a promising augmentation strategy. Fluvoxamine inhibits the metabolism of clozapine and increases the ratio of clozapine to its major active metabolite, norclozapine. Concomitant treatment may enhance the efficacy of clozapine while minimizing side effects.

The therapeutic plasma level of clozapine is between 1050 and 1260 nmol/L. Norclozapine levels usually range between 65% and 90% of clozapine levels. Fluvoxamine inhibits the metabolism of both substances, but clozapine to a greater degree. Results of some studies suggest that the clozapine:norclozapine ratio can predict clinical response better than the level of either substance alone. A high ratio appears to be associated with clinical efficacy or fewer side effects.

The authors of this review propose that a clozapine:norclozapine ratio of ≥2 will offer clinical benefit and minimize adverse effects. Introducing fluvoxamine at the start of clozapine therapy may be the best way to achieve augmentation, rather than adding it when steady-state clozapine levels have already been reached. If both drugs are started simultaneously, therapeutic concentrations of clozapine are reached at lower oral doses than with monotherapy. Lower clozapine doses are associated with reduced costs as well as better tolerability.

Coadministration of these 2 drugs has been associated with significant side effects, including sudden onset of extrapyramidal symptoms; worsening of psychosis; ataxia; hypotension; acute dystonia; sialorrhea; and EKG changes. The authors caution that concomitant therapy should only be undertaken in facilities where therapeutic drug monitoring is available.

**Drug Trade Names:** clozapine—Clozaril; fluvoxamine—Luvox
Levomilnacipran Efficacy and Safety

A new SNRI in late-phase clinical development, levomilnacipran, is an active enantiomer of milnacipran (Savella; currently approved only for treatment of fibromyalgia in the U.S.). In a manufacturer-sponsored, placebo-controlled trial in patients with major depressive disorder, levomilnacipran showed dose-related efficacy and was generally safe and well tolerated.

Methods: Study subjects, aged 18–65 years (n=724; about two-thirds women) had major depressive disorder of ≥8 weeks' duration and a score of ≥30 on the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS). After a 1-week placebo run-in, patients received randomly assigned, double-blind, sustained-release levomilnacipran, at 40, 80, or 120 mg/day, or placebo for 8 weeks. The primary efficacy assessment was change from baseline on the MADRS. Functional impairment was measured with the Sheehan Disability Scale (SDS).

Results: A total of 713 patients received at least 1 dose of randomly assigned levomilnacipran or placebo. Rates of premature treatment discontinuation were significantly higher for levomilnacipran than placebo (27–35% vs. 22%; p<0.05). The most common adverse events leading to discontinuation were nausea, vomiting, and palpitations.

Baseline MADRS scores did not differ among the treatment groups (mean, 36). Significant improvements were observed in each levomilnacipran dosage group compared with placebo: mean decreases in MADRS scores at week 8 were 12 points with placebo, 15 points with the 40-mg levomilnacipran dose (p<0.05), 16 points with 80 mg levomilnacipran (p<0.01), and 17 points with 120 mg levomilnacipran (p<0.001). The 2 higher doses were significantly superior to placebo beginning at week 4. The MADRS response rate (≥50% improvement from baseline) was significantly higher for the 120-mg dose than placebo (42% vs. 29%; p=0.01), but it was not statistically superior for the lower doses. Remission rates ranged from 20% to 22% and did not differ for any active treatment group versus placebo. The higher levomilnacipran doses were superior to placebo for the SDS total score and the 3 subscales of work, social life, and family life.

The study raised no new concerns about the drug’s safety or tolerability. Levomilnacipran did not increase body weight, suicidal ideation, or the QTcF interval. It was associated with modest increases in liver enzyme levels, pulse rate, and blood pressure.

Discussion: Levomilnacipran has about 2-fold greater potency for norepinephrine than serotonin reuptake inhibition, giving it a 10-fold higher relative selectivity for norepinephrine than currently available SNRIs. The present study suggests that its positive effects are dose-related and that doses as high as 120 mg can be used with minimal effects on tolerability.

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

Asnis G, Bose A, Gommoll C, Chen C, et al: Efficacy and safety of levomilnacipran sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: a phase 3, randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry 2013;74 (March):242–248. From Albert Einstein College of Medicine, Bronx, NY; and Forest Research Institute, Jersey City, NJ. Funded by Forest Laboratories, Inc. All study authors disclosed financial relationships with commercial sources, including Forest Laboratories.

*See Reference Guide.

Clinical Features of Dopamine Agonist Withdrawal Syndrome

A retrospective study of patients treated at a movement disorders clinic has confirmed the occurrence of dopamine agonist withdrawal syndrome (DAWS).1 The syndrome resembles addictive drug withdrawal and appears to be associated with impulse control disorders.
**Background:** Dopamine agonist withdrawal syndrome was first described in a longitudinal study of patients with Parkinson’s disease. The syndrome is a severe stereotyped cluster of physical and psychological symptoms that correlate with dopamine agonist withdrawal in a dose-dependent manner. DAWS can cause significant distress or dysfunction, and it improves with dopamine agonist repletion but not with other Parkinson’s disease medications. Psychological symptoms include: anxiety; panic attacks; depression; agitation; irritability; and drug cravings. Physical symptoms resemble those of drug withdrawal and include: orthostatic hypotension, dizziness, nausea, and sweating.

**Methods:** In an attempt to establish the frequency and predictors of DAWS and to characterize outcomes of patients experiencing the syndrome, investigators reviewed the charts of 487 patients with Parkinson’s disease attending a movement disorders clinic. In the patients for whom dopamine agonist discontinuation was attempted, the diagnostic criteria for DAWS were retrospectively applied by a study neurologist using criteria developed from the first description of the syndrome. Patients with a clinical diagnosis of dementia were excluded from the analysis.

**Results:** Of the 84 clinic patients in whom dopamine agonists were discontinued, 13 (16%) met criteria for DAWS. Development of impulse control disorders was the reason for dopamine agonist discontinuation in 42 of the 84 patients and in all 13 of those who had DAWS (p<0.0001). Each patient with DAWS had ≥4 of the 13 suggested clinical manifestations. The most frequent, occurring in >50% of patients, were depressed mood, fatigue, anxiety, and insomnia. Three patients had drug cravings, and 1 expressed suicidal thoughts. DAWS-related impairment was severe in 6 of the patients and mild to moderate in 7. The syndrome occurred after withdrawal of ropinirole in 7 patients, pramipexole in 5 patients, and pergolide in 1 patient. Risk for DAWS did not differ among the drugs. Three patients increased their levodopa dosage above that recommended in an attempt to relieve DAWS symptoms. Symptoms abated within 6 months in 8 of the patients, 3 patients required >1 year to recover, and 2 patients could not remain off of dopamine agonist treatment because of disabling DAWS symptoms.

**Discussion:** The frequency of DAWS among patients discontinuing dopamine agonists in this study—16%—was similar to the rate reported in the previous longitudinal study. In both studies, there was also a strong association with impulse control disorders and a virtual lack of any other clinical correlations. The symptoms were often very disruptive, many taking ≥1 year to resolve or requiring a return to dopamine agonist therapy, leading to a return of the impulse control problem.


**Drug Trade Names:** pergolide (not available in U.S.)—*Permax*; pramipexole—*Mirapex*; ropinirole—*Requip*  

### Agomelatine vs. SSRIs

The novel melatonergic/serotonergic antidepressant agomelatine was marginally more effective than SSRIs in a meta-analysis of head-to-head comparisons for long-term treatment.

**Methods:** A pooled analysis was conducted of the 24-week extension phases of 4 identically designed, acute-phase comparison studies of agomelatine with 3 different SSRIs (i.e., 1 each of fluoxetine and sertraline, and 2 of escitalopram). Participants had moderate-to-severe major depressive disorder, and 6 months of treatment was planned from the start of the acute trial.
The duration of acute-phase studies was 6–12 weeks. Dosages were 25–50 mg/day agomelatine, 20–40 mg/day fluoxetine, 50–100 mg/day sertraline, and 10–20 mg/day escitalopram. Efficacy was compared using the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impression-Improvement (CGI-I) scale in 627 patients taking agomelatine and 635 taking an SSRI.

**Results:** There were no significant differences between the agomelatine and SSRI groups on any baseline demographic or illness characteristic. Agomelatine was numerically, although not statistically, superior to the comparators in the individual trials. When the data were pooled, the difference reached statistical significance. The final average improvement in the HAM-D17 score differed by 1.08 points in favor of agomelatine (p=0.014). The difference in response (≥50% reduction in HAM-D) rates also favored agomelatine by 5% (p=0.03). Response rates in the individual studies ranged from 76% to 83% with agomelatine and from 63% to 81% with the comparators. Remission (HAM-D total score ≤6) rates were numerically but not statistically superior with agomelatine (47–66%) than with SSRIs (41–58%). Results were similar in separate analyses of a subset of patients with the most severe depression.

Seventy percent of patients completed 24 weeks of treatment with agomelatine, and 66% with an SSRI. Overall rates of adverse events were similar, but agomelatine was associated with fewer psychiatric adverse events (8% vs. 13%; p=0.001). Sexual side effects were somewhat less frequent with agomelatine than the SSRIs (1.3% vs. 2.9%; p=0.05). Agomelatine was associated with a higher frequency of transaminase increases: 1.8% of patients at the 25-mg dose and 2.6% of those receiving 50 mg, compared with 0.3% of patients treated with SSRIs.

**Discussion:** The magnitude of the superiority of agomelatine in the present analysis was comparable to other studies showing efficacy differences between some SSRIs. The clinical meaningfulness of these differences is uncertain, but the authors conclude that agomelatine is at least as effective as the SSRIs to which it was compared.

Demyttenaere K, Corruble E, Hale A, Quera-Salva M-A, et al: A pooled analysis of six month comparative efficacy and tolerability in four randomized clinical trials: agomelatine versus escitalopram, fluoxetine, and sertraline. CNS Spectrums 2013; doi 10.1017/S109285913000060. From the University Psychiatric Center KU Leuven, Belgium; and other institutions. Source of funding not stated. Several study authors disclosed financial relationships with commercial sources, including Servier, the manufacturer of Valdoxan.

**Drug Trade Names:** agomelatine (not available in U.S.)—Valdoxan; escitalopram—Lexapro; fluoxetine—Prozac; sertraline—Zoloft

### Duloxetine Safety in Pregnancy

The antidepressant duloxetine (*Cymbalta*) is listed by the FDA as Pregnancy Category C.* However, according to results of a manufacturer-sponsored postmarketing safety review, adverse pregnancy outcomes in women taking duloxetine are consistent with rates in the general population.

**Methods:** Data were analyzed from 2 sources: the manufacturer’s global pharmacovigilance database and the FDA’s Adverse Events Reporting System (AERS). The Lilly database consists of data from clinical trials, postmarketing studies, and spontaneous reports. This database identifies pregnancy outcomes as normal (i.e., birth of a normal newborn at 37–42 weeks’ gestation) or abnormal (i.e., spontaneous abortion; stillbirth; premature or post-term birth; congenital anomaly; birth complication; or ectopic pregnancy). The AERS database consists of voluntary reports from healthcare professionals and patients and mandatory reports of all exposures received by the manufacturer. In this database, abnormal pregnancy outcomes were defined as spontaneous or induced abortion, stillbirth, ectopic pregnancy, or congenital malformation. A data-mining method was used with the AERS database to
determine whether abnormal pregnancy outcomes with duloxetine differed from rates in pregnant women exposed to all other drugs or in those exposed to a group of other antidepressants representing multiple categories. Because the manufacturer’s and FDA databases are not mutually exclusive, the same event may have been reported to both and thus considered twice.

**Results:** The Lilly database contained 400 reports of duloxetine exposure with a known pregnancy outcome. Of 233 prospectively reported cases, 143 pregnancies (61%) were normal, 41 (18%) resulted in spontaneous abortion, and 25 (11%) were associated with a complication or condition; 19 deliveries (8%) were premature, and smaller numbers had other adverse outcomes. Adverse outcomes were more likely in women taking relevant concomitant medications (26% vs. 13%; *p*=0.02) and in those with a relevant medical history (30% vs. 17%; *p*=0.03). Analysis of the AERS database showed that adverse outcomes were no more likely with duloxetine than with other antidepressants or other drugs.

**Discussion:** The frequency of abnormal pregnancy outcomes prospectively reported in the Lilly database is generally consistent with historic control rates in the general population. More women who received duloxetine also used drugs that posed fetal risks, including benzodiazepines; NSAIDs; anticonvulsants; angiotensin converting enzyme (ACE) inhibitors; and other Class D drugs. While risks of antidepressant drug therapy in pregnancy do not appear to exceed the benefits of treatment, the authors suggest that the risk-benefit calculation may change if the drug is used for another approved indication or off label.

Hoog S, Cheng Y, Elpers J, Dowssett S: Duloxetine and pregnancy outcomes: safety surveillance findings. *International Journal of Medical Sciences* 2013;10:413–419. From Eli Lilly and Company, Indianapolis, IN. **Funded by Eli Lilly. The study authors are employed by Eli Lilly.**

*See Reference Guide.

### Memantine for Refractory OCD

Adjunctive memantine improved symptoms of severe obsessive-compulsive disorder in a small, randomized, 12-week trial.

**Background:** Memantine is an NMDA receptor antagonist that reduces glutamatergic excitotoxicity, believed to be a mechanism contributing to OCD symptoms. Promising results with memantine in OCD have been reported in a few case studies, an uncontrolled trial, and an 8-week placebo-controlled study.

**Methods:** Study subjects were 40 inpatients with OCD and a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥21. All participants began treatment with either clomipramine or an SSRI, followed 1 week later by randomized, double-blind 5–10 mg/day memantine or placebo.

**Results:** Participants had a mean age of 31 years, were 80% women, and had a mean duration of illness of 4 years. Outcomes were reported for the 29 patients who completed 12 weeks of treatment. A total of 9 patients withdrew from the study with no explanation during the first 2 weeks, and 2 others—one in each group—withdraw after reporting light-headedness and vertigo between weeks 2 and 8. Of those who completed the study, 14 received memantine and 15 placebo.

Y-BOCS scores decreased in both groups over time. Scores were similar in the 2 groups at 8 weeks (25 with memantine and 26 with placebo) but diverged in favor of memantine at the 12-week evaluation (final Y-BOCS scores, 20 with memantine vs. 24 with placebo; *p*=0.005). Full response (defined as a ≥35% reduction in Y-BOCS score) was achieved in 1 patient in the
memantine group by week 8. A total of 9 patients, all in the memantine group, achieved full
response by week 12. Clinical Global Impression (CGI) Severity scores favored memantine
by a >0.5-point margin at 12 weeks (p=0.04), but CGI Improvement scores did not differ signif-
ically between groups.

Discussion: Results of the present study suggest that SSRI or clomipramine monotherapy
leads to modest improvements that reach a plateau by 8 weeks of treatment and that adding
memantine may increase efficacy but only after ≥8 weeks.

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

trial, adjuvant memantine improved symptoms in inpatients suffering from refractory obsessive-compulsive disorders
(OCD). Psychopharmacology 2013; doi 10.1007/s00213-013-3067-z. From Hamadan University of Medical Sciences, Iran;
and other institutions. This study was conducted with no external funding. The authors declared no conflicts of
interest.

Drug Trade Names: clomipramine—Anafranil; memantine—Namenda

*See Reference Guide.

Antipsychotic Safety Labeling Changes

The product labels for the antipsychotics asenapine, clozapine, and ziprasidone were recently
updated with new information on adverse reactions and/or warnings.

Postmarketing reports indicate that application site reactions are possible with sublingual
asenapine use. Reactions, which occur primarily in the sublingual area and often lead to
discontinuation, include ulcers, blisters, peeling/sloughing, and inflammation.

Safety labeling changes for clozapine include warnings about postmarketing hepatobiliary and
urogenital adverse reactions. These include hepatotoxicity; hepatic steatosis; hepatic necrosis;
hepatic fibrosis; hepatic cirrhosis; liver injury; liver failure; and renal failure.

Ziprasidone is known to elevate prolactin levels, but the clinical significance of the elevation is
unclear for most patients. The updated labels for ziprasidone capsules, oral suspension, and
injection include a new warning that long-standing hyperprolactinemia, when associated with
hypogonadism, can lead to decreased bone density.

Safety labeling changes approved by FDA Center for Drug Evaluation and Research (CDER). March 2013; available at

Drug Trade Names: asenapine—Saphris; clozapine—Clozaril; ziprasidone—Geodon

Depot Antipsychotics: Post-Injection Syndrome

Post-injection delirium/sedation syndrome (PDSS) is a rare, potentially serious complication
after injection of olanzapine, according to a review of published clinical trials. PDSS has not
been documented with other depot antipsychotics, but more research is needed to rule out any
association. Risk of PDSS can be reduced with attention to injection technique and patient
observation.

PDSS, sometimes called simply post-injection syndrome, is a specific adverse event profile
related to excessive sedation or delirium closely following injection of a long-acting antipsy-
chotic drug. For this review, all literature on long-acting antipsychotics and PDSS published
since 2005 was identified. The analysis includes 8 studies of olanzapine, 15 studies of
risperidone, and 14 studies of paliperidone. All were drug registration trials; there were no
comparative studies.

In the olanzapine trials, which included about 45,000 injections in >2000 patients, there
were 30 reported cases of PDSS occurring in 29 patients. PDSS occurred in 1.4% of all
patients (a rate of <7 per 10,000 injections). In these trials, olanzapine was injected at doses of 45–405 mg at 2-, 3-, or 4-week intervals; the dose was limited to ≤300 mg with 2-week intervals. Most injections were given using a 19-gauge needle, alternating sides of the buttocks between visits. The recommended post-dose observation period was increased from 10–20 minutes in the early studies to 45 minutes and then to 3 hours after PDSS was first observed. Eighty percent of the reported cases occurred within the first hour post-injection. Symptoms were consistent with olanzapine overdose, and all patients recovered within 1.5–72 hours.

No cases of PDSS were observed in the risperidone or paliperidone trials. Post-injection sedation or somnolence did occur in 3% of the patients who received paliperidone and in 2% of patients who received risperidone, but these events did not meet all criteria for PDSS.

In the olanzapine studies, PDSS was attributed to a possible inadvertent intravascular injection of the drug. Long-acting olanzapine is a salt-based formulation that is more highly soluble in blood than muscle tissue, resulting in release of a large amount of drug following accidental injection into a blood vessel or capillary-rich tissue. Z-track injection can reduce the risk of inadvertent leakage, but this technique can be painful. Z-track injection is not required for risperidone. Additional steps to reduce risk include use of local anesthetic for pain, use of the correct dosing interval, alternating the injection site, and adequate post-injection observation.

Novakovic V, Adel T, Peselow E, Lindenmayer J-P: Long-acting injectable antipsychotics and the development of postinjection delirium/sedation syndrome (PDSS). *Clinical Neuropharmacology* 2013:2 (March/April):59–62. From Mount Sinai School of Medicine, New York, NY; and other institutions. *This study was conducted with no external funding. The authors declared no conflicts of interest.*

*Drug Trade Names: olanzapine—Zyprexa; paliperidone—Invega; risperidone—Risperdal*

### Reference Guide

**Pregnancy Category C:** If animal studies have shown adverse fetal effects, or if there are no adequate and well-controlled studies in humans and the benefits of the drug in pregnant women may outweigh the potential risks, the agent is classified as Category C. According to the FDA, these drugs should be used during pregnancy only when clearly needed if the potential benefit justifies the potential risk to the fetus.

**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.