Adjunctive Ziprasidone for Depression

In a randomized trial, adjunctive ziprasidone showed both antidepressant and anxiolytic efficacy in patients with persistent symptoms of unipolar major depression despite escitalopram treatment.\(^1\)

**Background:** Antipsychotics are common adjunctive treatments for residual symptoms in major depressive disorder. Ziprasidone has pharmacological features that differ from other antipsychotics approved for antidepressant augmentation (i.e., aripiprazole, olanzapine, quetiapine) and was shown in an open-label study to be an effective adjunct in treatment-resistant depression.\(^2\) The present study appears to be the first controlled trial to attempt to replicate those results.

**Methods:** This 2-phase study enrolled 458 patients, aged 18–65 years, with a primary diagnosis of unipolar major depressive disorder. In the lead-in phase, study patients received 8 weeks of open-label, flexible-dose escitalopram. Following this phase, the 139 patients (mean age, 44 years; 71% women) who continued to meet diagnostic criteria for major depression underwent 8 additional weeks of double-blind adjunctive treatment with either ziprasidone, flexibly dosed between 20 and 80 mg b.i.d., or placebo. The primary outcome measure was clinical response, defined as a \(\geq 50\%\) reduction in Hamilton Rating Scale for Depression (HAM-D) score. Two key secondary endpoints were selected to measure effects based on the pharmacological profile of ziprasidone: the Hamilton Anxiety Rating Scale (HAM-A) and the Visual Analog Scale for Pain.

**Results:** Adjunctive ziprasidone produced significantly higher rates of both clinician- and self-rated antidepressant response. Response rates for the clinician-rated HAM-D were 35% and 21% in the ziprasidone and placebo groups, respectively (\(p=0.04\)). Response rates for the self-rated Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) were 31% and 13%, respectively (\(p=0.03\)). HAM-D remission (i.e., final score of \(\leq 7\)) was achieved by 38% of the ziprasidone group, compared with 31% of the placebo group, a nonsignificant difference. However, the remission rate on the self-rated QIDS-SR (i.e., final score of \(\leq 5\)) was significantly higher in the ziprasidone group: 24% versus 10% (\(p=0.02\)).

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Overall, patients had mild anxiety symptoms (mean HAM-A score, 14) in addition to depression. Anxiety response (i.e., ≥50% reduction in HAM-A score) and remission (i.e., final score of ≤7) rates were also significantly higher with ziprasidone than with placebo: 35% versus 10% (p<0.001) and 45% versus 21% (p<0.01), respectively. The number needed to treat (NNT)* for a HAM-D response was 7, similar to other atypical antipsychotics approved for adjunctive treatment of depression, and the NNT for a HAM-A response was 4. Ziprasidone was not superior to placebo at reducing pain.

Ziprasidone was associated with significantly more somnolence/fatigue (34%), irritability (10%), anxiety/agitation (6%), and muscle twitching (11%) than placebo. Ten patients withdrew from the ziprasidone treatment arm (and none from the placebo group) because of adverse effects that included anxiety/agitation and akathisia, sedation, insomnia, and QTc prolongation. Ziprasidone was associated with an average QTc prolongation of 8.8 msec and a significantly greater mean weight gain of 8 lbs. compared with about 2 lbs. for placebo.

Discussion: Based on these results, ziprasidone appears to be a suitable option for adjunctive treatment of resistant depression. It may be particularly useful for patients with comorbid anxiety symptoms. The high rate of somnolence/fatigue in this study, 34%, was a surprising finding given the pharmacologic profile of ziprasidone but is similar to some other atypicals approved for this indication.

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

Antidepressants for Seasonal Depression

According to the results of a Cochrane Review, owing to a lack of randomized controlled trials of other agents, bupropion is the only evidence-based second-generation antidepressant suitable for prevention of seasonal affective disorder (SAD).

Methods: The investigators searched registries, databases, and other sources for published and unpublished comparative clinical trials of second-generation antidepressants for prevention of SAD in adults with a history of the disorder who were free of symptoms at study entry. Included studies were required to use random assignment and to compare an antidepressant with placebo or another antidepressant, light therapy, psychological therapy, melatonin, agomelatine, or lifestyle changes.

Results: The search identified only 3 randomized placebo-controlled trials of bupropion XL. No studies of alternate antidepressants or studies comparing an antidepressant with the other treatments of interest met inclusion criteria. Two additional studies (both evaluating citalopram) narrowly missed meeting these criteria because patients were already symptomatic at baseline. The 3 included studies, funded by the manufacturer of bupropion XL, included a total of 1100 patients with a history of SAD. The studies were judged to be at low risk for most sources of bias.

Patients were enrolled between September and November and provided treatment with 300 mg/day bupropion until the first week of spring. The primary outcome was time to onset of major depressive disorder, defined as meeting DSM-IV criteria or a threshold score on the
Structured Interview for the Hamilton Rating Scale for Depression-Seasonal Affective Disorder (SIGH-SAD) version. Bupropion was associated with a reduced risk of depression (15% vs. 27%; risk ratio,* 0.56). Numbers needed to treat* to prevent 1 episode of SAD depended on patients’ baseline risk and ranged from 5 in populations with a yearly recurrence rate of 50% to 8 in populations with a 30% recurrence rate.

Bupropion was associated with an overall similar adverse event rate to placebo but with significantly elevated rates of headache, insomnia, and nausea (risk ratios: 1.26, 1.46, and 1.63, respectively).

Discussion: The predictable pattern of SAD makes it particularly amenable to preventive treatment. Given the lack of comparative evidence, decisions regarding preventive treatment should be based on patient preferences and should consider the possibility that non-pharmacological treatments—such as light therapy, psychological therapies, and lifestyle interventions—may be effective and carry a lower side-effect burden.

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

Gartlehner G, Nussbaumer B, Gaynes B, Forneris C, et al: Second-generation antidepressants for preventing seasonal affective disorder in adults. Cochrane Database of Systematic Reviews 2015, Issue 11, Art. No. CD011268. From Cochrane Austria, Danube University Krems, Austria; and other institutions. This review was conducted without external funding. One study author disclosed financial relationships with commercial sources; the remaining 12 authors declared no competing interests.

Common Drug Trade Names: agomelatine (not available in U.S.)—Valdoxan; bupropion—Wellbutrin; citalopram—Celexa

*See Reference Guide.

Dasotraline Pharmacokinetics

In a manufacturer-sponsored, multicenter clinical trial of adults with a primary diagnosis of ADHD of moderate-or-greater severity, the investigational medication dasotraline was associated with significant improvement in ADHD symptoms.1 Scores on both the hyperactivity/impulsivity and the inattention subscales of the ADHD Rating Scale-IV (ADHD-RS-IV) were significantly improved, and 52% of patients who received 8 mg/day dasotraline met response criteria (≥30% reduction in ADHD-RS-IV total score). Pharmacokinetic data collected from this study, along with data from several other early-phase clinical studies of dasotraline, suggest that maintaining constant steady-state dopamine and norepinephrine reuptake inhibition with once-daily dosing is potentially effective in managing ADHD symptoms.2

Dopamine and norepinephrine are associated with the pathophysiology of ADHD, and drugs that maintain synaptic concentrations of the 2 neurotransmitters, such as methylphenidate (Ritalin), are useful in management of the disorder. Dasotraline is a potent inhibitor of dopamine and norepinephrine transporters and a weaker inhibitor of serotonin transporters. Once-daily administration is associated with stable plasma concentrations over 24 hours, a unique property among current ADHD medications.

According to data collected from multiple studies comprising 395 patients who received single or multiple oral administrations of 0.2–36 mg dasotraline, the drug reached peak plasma concentrations 10–12 hours post-dose and had dose-proportional peak concentrations. Elimination of the drug was slow, with a mean half-life of 47–77 hours. Steady-state plasma concentrations were reached after 10 days of dosing. Pharmacokinetics were influenced by body weight but not by age, gender, ethnicity, total bilirubin, or alanine aminotransferase. Dasotraline plasma concentrations were associated with decreases in the norepinephrine metabolite 3,4-dihydroxyphenylglycol plasma concentrations, indicating that norepinephrine
transporter inhibition was dose-dependent. Time to study dropout was similar for 4 mg dasotraline (the minimum effective dose) and placebo and significantly higher for the 8-mg dosage. Based on simulations, the average effect size* on ADHD symptoms was 0.25 standard deviations for 4 mg dasotraline after 4 weeks. The simulations predicted stronger effect sizes for trials lasting 8 weeks but only small additional increases in trials lasting 12 weeks, indicating an optimal trial duration of 8 weeks.


*See Reference Guide.

**Combined Treatment for Depression and Cognitive Impairment**

In an open-label pilot study, the combination of memantine and escitalopram in patients with depression and cognitive impairment improved cognition and may have delayed conversion to dementia.

**Methods:** Study participants, aged 50–90 years, were recruited from clinics for late-life depression or memory disorders. All patients had a DSM-IV diagnosis of unipolar major depression or dysthymia of at least moderate severity. They were also required to have cognitive impairment, based on subjective complaints, Clinical Global Impression–Severity (CGI-S) scores of "mild" or greater for cognition, mini-mental state exam (MMSE) scores of ≥24, and either errors on the MMSE 5-minute recall task or abnormal performance on a neuropsychological test. Following a taper of previous antidepressants, escitalopram was started at 10 mg/day and increased to 20 mg/day if tolerated. After 2 weeks, memantine was added and also titrated to a maximum of 20 mg/day. Antidepressant response was measured using the 24-item Hamilton Rating Scale for Depression (HAM-D), with remission defined as a final score of <8. The Selective Reminding Test with Immediate Recall (SRT-IR) was the primary outcome measure for cognitive performance.

**Results:** Of 35 patients who began treatment, 28 completed 12 weeks and 26 completed 48 weeks. Mean age at study entry was 65 years, and 63% of patients were women; 29 patients had major depressive disorder, and 6 had dysthymia. Average age at depression onset was 45 years, and the average duration of the current episode was 32 months. Either because of adverse effects or lack of efficacy, 4 patients received bupropion augmentation during the study period and 14 were switched from escitalopram to another antidepressant (i.e., desvenlafaxine, duloxetine, or venlafaxine).

At study end, HAM-D scores were significantly improved from a baseline mean of 20 to a final score of 5 (p<0.001). Depression remitted in 56% of patients. CGI–Improvement scores were significant for both depression and cognition (p<0.001 for both). A single patient had conversion to an Alzheimer’s disease diagnosis during the study. Patients showed improvement in SRT-IR scores during the study from a mean of 39 at baseline to 47 at endpoint (p=0.01). The mean MMSE score was 28 at baseline and did not change. Patients showed improvement on tests of category fluency for letters and the Boston Naming test, but not on other neuropsychiatric tests. The drug combination was well tolerated, with no major adverse effects.

**Discussion:** In other pilot studies, treatment of depression and mild cognitive impairment with antidepressants and acetylcholinesterase inhibitors was associated with cognitive
improvement of a similar magnitude to that observed in the present study. The conversion rate to Alzheimer’s disease was at the lower end of the range reported in naturalistic studies of patients with depression and cognitive impairment. Because memantine and escitalopram act on different neurotransmitter systems, they may have additive or synergistic effects on cognition, an attractive possibility that merits further investigation.


**Common Drug Trade Names:** bupropion—Wellbutrin; desvenlafaxine—Pristiq; duloxetine—Cymbalta; escitalopram—Lexapro; memantine—Namenda; venlafaxine—Effexor

**Adjunctive Fluvoxamine with Clozapine**

Preliminary evidence suggests fluvoxamine may be a useful adjunct to clozapine, particularly for patients with negative or depressive symptoms and those who cannot achieve sufficient plasma clozapine levels.

About half of patients with refractory schizophrenia experience response with clozapine. Adjunctive fluvoxamine may increase clozapine efficacy by increasing plasma drug levels, prolonging the half-life, and altering the ratio of the parent compound to its primary metabolite. Clozapine is mainly metabolized by the cytochrome P450 enzyme CYP1A2. The half-life is short enough to cause breakthrough symptoms in some patients with once-daily dosing. N-desmethyloclozapine (NDMC) is the major active metabolite, and the ratio of clozapine to NDMC may be more predictive of response than clozapine levels. Fluvoxamine potentially inhibits CYP1A2, resulting in higher clozapine plasma levels, a marked prolongation of the half-life by as much as 370%, and correspondingly lower levels of NDMC. A potent serotonin 5-HT2c antagonist, NDMC contributes to the clozapine side effects of weight gain, seizures, and possibly bone-marrow suppression.

A systematic literature review identified 21 case reports and 3 case series (a total of 29 patients) of adjunctive fluvoxamine with clozapine published through October 2015. Initial average dosages were 500 mg/day for clozapine and 130 mg/day for adjunctive fluvoxamine. The most frequent indication (in 33% of patients) for adjunctive fluvoxamine was obsessive-compulsive symptoms. In these patients, the mean clozapine-to-NDMC ratio nearly doubled, from 1.63 to 3.08. The studies reported significant clinical improvement with augmentation in 18 patients (75%), adverse effects in 14 (58%), and dose adjustments in 21 (88%).

In addition, 7 prospective cohort studies and 2 open-label randomized trials (a total of 212 patients, a majority with schizophrenia) were also identified. Clozapine was most often given as a flexible dosage of >100 mg/day, and fluvoxamine as a fixed dosage of ≤100 mg/day. Clozapine steady state was achieved after 2 weeks of adjunctive fluvoxamine in most studies. The indication for augmentation was negative symptoms in 4 cohort studies; the other 3 were pharmacokinetic studies. The 2 controlled trials assessed the metabolic side effects of clozapine as affected by fluvoxamine. These clinical studies found significant improvement in various measures of overall symptoms and functioning. Adjunctive fluvoxamine appeared to have little effect on positive symptoms, mixed effects on negative symptoms, and possible effects on depression and obsessive-compulsive symptoms. However, the clinical effects of augmentation were difficult to quantify because the studies did not report outcomes in a consistent manner and did not attempt to correlate symptoms with clozapine blood levels.

In 1 study, adjunctive fluvoxamine prevented weight gain, and increases in body mass index and glucose, compared with clozapine monotherapy. The other controlled study showed no
metabolic benefit of added fluvoxamine, but mean granulocyte counts were higher with clozapine monotherapy than with adjunctive fluvoxamine, despite a lack of association of fluvoxamine with lower NDMC plasma levels. No studies investigated seizure risk with augmentation or reported seizures as an adverse event. The pharmacokinetic studies showed that adjunctive fluvoxamine increased clozapine and NDMC in a dose-dependent manner.

Although the evidence is too preliminary to warrant recommending adjunctive fluvoxamine for general clinical use, it might be considered in certain situations. Additional research is warranted. The authors caution that if adjunctive fluvoxamine is used, it should be titrated slowly and regular therapeutic monitoring should be conducted. Special precaution should be taken with patients who have experienced dose-related adverse effects with clozapine monotherapy.

Polciwiiartek C, Nielsen J: The clinical potentials of adjunctive fluvoxamine to clozapine treatment: a systematic review. Psychopharmacology 2015; doi 10.1007/s00213-015-4161-1. From Aalborg University Hospital and Aalborg University, Denmark. This review was conducted without funding. One study author disclosed financial relationships with commercial sources; the second author declared no competing interests.

Common Drug Trade Names: clozapine—Clozaril; fluvoxamine—Luvox

Levomilnacipran and Depression-Related Fatigue

According to an exploratory post-hoc analysis of pooled clinical trial data, levomilnacipran (Fetzima) reduces depression-related symptoms of fatigue.¹

**Background:** In the large-scale STAR*D study, nearly 61% of patients with depression continued to have residual fatigue after 14 weeks of treatment.² These patients experienced significantly worse functional outcomes and had a reduced likelihood of depression remission. However, little research has addressed residual fatigue. The SNRI levomilnacipran was considered a candidate treatment for depression-related fatigue because of its stronger noradrenergic activity. Reduced noradrenergic activity may underlie reduced motivation and energy, loss of interest, and decreased pleasure.

**Methods:** A secondary analysis of pooled data from 5 manufacturer-sponsored, placebo-controlled studies was undertaken to evaluate the effects of levomilnacipran treatment on fatigue. Patients, aged 18–80 years, received treatment for 8–10 weeks with 40–120 mg/day extended-release levomilnacipran in fixed-dose or flexible-dose designs. The primary depression endpoint in each study was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. The present analysis assessed the effect of levomilnacipran on 4 different measures of fatigue: the MADRS item 7 (lassitude: difficulty or slowness in initiating and/or performing daily activities; scored from 0 to 6) and 3 items on the 17-item Hamilton Rating Scale for Depression (HAMD) measuring work and activities, retardation (slowing of thought and speech or decreased motor activity), and general somatic symptoms.

**Results:** Of the studies’ pooled population of 2598 patients, 74% had high levels of fatigue at study entry, as defined by a MADRS item-7 score of ≥4 (with 4 defined as difficulties in starting simple routine activities that are then carried out with effort). Compared with placebo, levomilnacipran was associated with a small but statistically significant average decrease in the item 7 score (0.3 points; effect size,³ 0.18). Effects were also statistically significant for the 3 HAM-D items, with effect sizes ranging from 0.09 for retardation to 0.21 for work/activities. For all fatigue symptoms, patients who received levomilnacipran were more likely than those in the placebo groups to achieve remission of fatigue symptoms (odds ratio,³ 1.3 for MADRS item 7; p<0.001 vs. placebo; and similar results from the HAM-D items).

Patients with high and low initial fatigue experienced similar improvement in MADRS total score. Levomilnacipran had similar effect sizes on most fatigue measures in men and women,
in patients older or younger than 60 years, and in pre- and postmenopausal women. Patients with obesity (BMI of ≥30) showed little-or-no treatment-related effects on fatigue symptoms.

**Discussion:** These results suggest that treatment with levomilnacipran may be effective in reducing fatigue in patients with depression, regardless of patient age or gender. However, because of the study design, no conclusions can be drawn about the relative efficacy of levomilnacipran and other antidepressants.

1Freeman M, Fava M, Gommoll C, Chen C, et al: Effects of levomilnacipran ER on fatigue symptoms associated with major depressive disorder. *International Clinical Psychopharmacology* 2015; doi 10.1097/YIC.0000000000000104. From Harvard Medical School, Boston, MA; Forest Research Institute, Jersey City, NJ; and other institutions. **Funded by Forest Laboratories. All 6 study authors disclosed financial relationships with commercial sources.**


*See Reference Guide.

**Cholinesterase Inhibitor Adverse Events**

According to a large, international pharmacovigilance study, neuropsychiatric problems are the most frequent type of cholinesterase inhibitor-related adverse drug reaction (ADR). The global pattern of reported adverse events differs from the package labeling, which lists gastrointestinal (GI) problems as the most frequent ADR.

**Methods:** The World Health Organization’s ADR database, VigiBase, contains >8 million case reports from >100 countries. Suspected ADRs are spontaneously reported by health professionals, patients, and drug manufacturers. Data for the present analysis were extracted from all reports to VigiBase in 1998–2013 that involved the 3 cholinesterase inhibitors available for treatment of dementia: donepezil, rivastigmine, and galantamine.

**Results:** Nearly 44,000 cholinesterase inhibitor-related ADRs were the subject of about 19,000 reports (each consisting of a single patient with, possibly, multiple events). Nearly 90% of reports were from Europe, the U.S., and Canada. The mean patient age was 77 years, and 40% of the events occurred in men. Donepezil and rivastigmine each accounted for about 41% of reports, and galantamine for 17%.

Contrary to the adverse event data from clinical trials that showed GI effects to be most common, nearly one-third of all reported ADRs in this study were neuropsychiatric events. Among the more frequent were disturbances in consciousness; syncope and related symptoms; neurological signs and symptoms; confusion and disorientation; hallucinations; anxiety symptoms; and behavioral and social disturbance. GI events accounted for 15% of all reports, general events (e.g., fever and administration site reactions) accounted for 12%, and cardiovascular disorders for 12%.

Information on severity of ADRs was available in VigiBase only after 2005. About 70% of the reported ADRs between 2006 and 2013 were serious, resulting in death, hospitalization, disability, or other important negative outcomes; 2% of the ADRs were fatal. Neuropsychiatric disturbances accounted for 34% of serious ADRs, general disorders 14%, and cardiovascular disorders 12%. Expected cholinergic adverse effects were frequently reported as serious, including nausea and vomiting, confusion, and diarrhea. More than 900 reports (5.5% of the total) described serious events related to excitatory reactions of the central nervous system, such as seizures, anxiety, aggression, and insomnia. About 2% of the serious incidents were linked with medication error or maladministration.

**Discussion:** The global occurrence of cholinesterase inhibitor-related adverse events is consistent with the global market for these agents, which are mainly used in affluent countries. The high proportion of reports related to donepezil and rivastigmine is consistent with these agents'
position as market leaders. Cholinesterase inhibitors may not be the cause of some proportion of reported neuropsychiatric and cardiovascular adverse events, given the high background incidence in this patient population. However, there is a pharmacological rationale for some types of neuropsychiatric events: increased acetylcholine levels in the brain, possibly leading to an increase in neuronal excitation. In clinical practice, the possibility that a neuropsychiatric disturbance is cholinesterase inhibitor-related should be considered before treating the disturbance with specific drugs.

Kroger E, Moulis M, Wilchesky M, Berkers, M, et al: Adverse drug reactions reported with cholinesterase inhibitors: an analysis of 16 years of individual case safety reports from VigiBase. *Annals of Pharmacotherapy* 2015;49 (November): 1197–1206. From the Centre Hospitalier Universitaire de Quebec, Canada; and other institutions. Funded by the Canadian Institutes for Health Research; and other sources. The authors declared no competing interests.

**Common Drug Trade Names**: donepezil—Aricept; galantamine—Razadyne; rivastigmine—Exelon

**Reference Guide**

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

**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.

**Risk Ratio**: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

**Study Rating**: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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