Fluvoxamine in Movement Disorders

Tardive dyskinesia and akathisia are well-known potential complications of long-term antipsychotic therapy for which there are no definitive treatments. Several recent case reports suggest fluvoxamine (Luvox) may improve symptoms of these medication-associated movement disorders.

A 43-year-old woman and a 41-year-old man both had a long history of antipsychotic treatment for schizophrenia, and both experienced tardive dyskinesia. The patients had 100 mg/day fluvoxamine added to their antipsychotic regimens in an attempt to control the dyskinesia. Within 4 weeks, both patients experienced substantial declines in Abnormal Involuntary Movement Scale scores: from 6 to 2 in the female patient and from 11 to 3 in the male.

A 36-year-old woman experienced tardive akathisia associated with antipsychotic treatment of schizophrenia. Her Barnes Akathisia Rating Scale score was 5, indicating severe symptoms. Within 3 weeks of adding 100 mg/day fluvoxamine, the akathisia resolved.

Although the mechanism is unclear, the authors speculate that the positive effects of fluvoxamine in these patients could be attributed to its sigma-1 receptor agonist activity. It is likely that chaperone activity of sigma-1 receptors by fluvoxamine may improve the motor side effects by the regulation for endoplasmic reticulum stress. They suggest that fluvoxamine could be a novel approach to movement-disorder treatment if these results are replicated in controlled trials.

Albayrak Y, Hashimoto K: Beneficial effects of sigma-1 agonist fluvoxamine for tardive dyskinesia and tardive akathisia in patients with schizophrenia: report of three cases. Psychiatry Investigation 2013;10 (December):417–420. From Namik Kemal University, Turkey; and Chiba University Center for Forensic Mental Health, Japan. The authors did not include disclosure of potential conflicts of interest.

Calcium Antagonist in Bipolar Depression

In a pilot study, the calcium channel blocker isradipine (DynaCirc) showed promising efficacy in patients with bipolar depression. The drug was identified as a candidate for treatment of bipolar disorder based on genome-wide association studies.
Methods: The 10 study participants (mean age, 42 years; 3 women) had diagnoses of bipolar I or II disorder and had received an adequate trial of ≥1 mood stabilizer—i.e., lithium, an anticonvulsant, or an atypical antipsychotic. Participants were required to have at least moderate depression and no more than mild manic symptoms. Those with cardiovascular disease or hypertension were excluded. Isradipine was added to ongoing medication and titrated to 5 mg b.i.d. over the 8-week study period.

Results: At baseline, all but 2 patients reported a current episode duration of >6 months and all but 1 reported having ≥10 prior episodes. Six patients discontinued isradipine before the study endpoint (all before week 6): 3 who felt they had not improved sufficiently, 1 who experienced possible hypomania, and 2 for reasons unrelated to treatment.

In an analysis based on all patients, isradipine was associated with a mean improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) of 2 points per week, from a baseline average of 30 points (p<0.001). Two patients experienced remission (MADRS score <10), and 2 others achieved response (≥50% improvement in MADRS score). Secondary outcomes, including a measure of cognitive function, also showed improvement on average. There were no serious adverse events and only modest, transient effects on heart rate and blood pressure.

Discussion: Genome-wide association studies have identified genetic loci associated with specific diseases, but these discoveries do not have clear implications. Sometimes these studies identify gene variants for which a current drug, which is FDA-approved for a different indication, can be ‘repurposed.’ Even then, it is not clear whether targeting the variant gene will make the disease better or worse. Bipolar disorder has been associated with a common variant of a genetic locus that codes for the L-type calcium channel. Isradipine targets this channel, crosses the blood-brain barrier more readily than other calcium channel blockers, is known not to exacerbate mania, and has an established safety record. Other calcium channel blockers have been investigated in bipolar disorder, but with inconsistent results, and rarely in bipolar depression. In spite of its limitations, which include small sample size, high dropout rate, and lack of placebo control, the present study presents preliminary evidence supporting the possible use of calcium antagonists in bipolar depression, but additional study is needed.

Ostacher M, Iosifescu D, Hay A, Blumenthal S, et al: Pilot investigation of isradipine in the treatment of bipolar depression motivated by genome-wide association. Bipolar Disorders 2014;16 (March):199–203. From Stanford University School of Medicine, Palo Alto, CA; and other institutions. Funded by the Stanley Center for Psychiatric Research at the Broad Institute, Cambridge, MA. Two study authors disclosed financial relationships with commercial sources. The remaining 4 authors declared no competing interests.

Safety of SSRI–Statin Comedication

Most SSRI antidepressants can be used safely in patients receiving statin therapy, with little if any risk of clinically meaningful pharmacokinetic interactions, according to a review. A few SSRI–statin combinations carry a theoretical risk, but precautions can be taken to minimize adverse effects.

Depression complicates the clinical course of diabetes and may result in increased cardiovascular and all-cause mortality. Therefore, depression should be vigorously treated in patients with coexisting diabetes. Drugs that increase appetite and weight, such as tricyclic antidepressants (TCAs) and mirtazapine, can worsen the course of diabetes. Cardiovascular outcomes can be adversely affected by TCAs and by most adrenergic antidepressants, such as venlafaxine. SSRIs avoid these risks and may be ideally suited to patients with diabetes. Most SSRIs (except possibly paroxetine) are not associated with weight gain, and they may reduce cardiovascular risks through multiple mechanisms.

SSRIs, however, are often associated with pharmacokinetic interactions. Increased blood levels of statins can result in hepatic enzyme elevation and dose-dependent myopathies; nevertheless,
even though some SSRIs and statins share metabolic pathways, the risk of pharmacokinetic
interaction between the 2 drug classes appears low. The major metabolism of statins is via 2
enzyme pathways: CYP3A4/5 (atorvastatin, lovastatin, simvastatin) and CYP2C9 (fluvasstatin).

The data suggest all SSRIs, even those that inhibit CYP3A4, can be safely administered with
atorvastatin, lovastatin, and simvastatin. Escitalopram, citalopram, and paroxetine are almost
certain to be safe with all statins, and rosuvastatin, pitavastatin, and pravastatin are almost
certain to be safe with all SSRIs. Although there is theoretical risk in combining fluvoxamine
with atorvastatin, lovastatin, or simvastatin (and possibly fluvastatin), the risk can be mini-
mized by prescribing lower statin doses and monitoring the patient. It is unlikely that CYP
gene polymorphisms will influence risk of SSRI-related drug interactions in patients taking
statins. A few patient groups require cautious prescribing, but these are easily identified:
patients with chronic liver disease or chronic debilitating disease, and others with impaired
CYP enzyme activity.

Andrade C: Selective serotonin reuptake inhibitor drug interactions in patients receiving statins. Journal of Clinical
Psychiatry 2014;75 (February):e95–e99. From the National Institute of Mental Health and Neurosciences, Bangalore,
India. Source of funding not stated. The author did not include disclosure of potential conflicts of interest.

Drug Trade Names: atorvastatin—Lipitor; citalopram—Celexa; escitalopram—Lexapro; fluvastatin—Lescol;
fluvoxamine—Luvox; lovastatin—Mevacor; mirtazapine—Remeron; paroxetine—Paxil; pitavastatin—Livalo;
pravastatin—Pravachol; rosuvastatin—Crestor; sertraline—Zoloft; simvastatin—Zocor; venlafaxine—Effexor

Intranasal Desmopressin for Negative Symptoms

Adjunctive intranasal desmopressin had promising effects on negative symptoms of schizo-
phrenia in a controlled trial in patients partially stabilized with risperidone. Although positive,
the effects of short-term, conservatively-dosed treatment require replication.

Background: Neurohypophyseal peptides, including oxytocin and arginine vasopressin (AVP),
are attracting interest as possible treatment targets in schizophrenia. AVP plays an important
role in memory, aggression, recognition, and social interaction. In patients with schizophrenia,
the AVP system has been shown to interact with deficits in dopaminergic and glutamatergic
neurotransmission. Desmopressin, or DDAVP, is a synthetic analog of AVP, currently indicated
for treatment of diabetes insipidus and nocturnal enuresis. Since only small amounts can cross
the blood-brain barrier, intranasal administration is believed to be more favorable in targeting
the CNS.

Methods: The study enrolled 44 inpatients (mean age, 34 years) with chronic schizophrenia
(mean duration, 9 years) who had a Positive and Negative Syndrome Scale (PANSS) total score
of ≥60 and symptoms that were partially stabilized with ≥4 weeks of risperidone at dosages of
5 or 6 mg/day. Participants were randomly assigned to 8 weeks of double-blind, adjunctive
desmopressin or placebo. Desmopressin was administered as a single 10-mcg nasal spray per
day for the first week, followed by 2 sprays daily for the rest of the study. Desmopressin was
initially administered by a nurse and then self-administered under supervision. Dosing was
conservative in the study to avoid potential fluid and electrolyte imbalances. Risperidone
dosages remained stable. Symptoms were assessed every 2 weeks. The primary study outcome
was the change from baseline in the PANSS negative symptom score.

Results: At 8 weeks, mean PANSS negative symptom scores decreased from about 17 at base-
line to 11 in the desmopressin group and to 13.6 in the placebo group (mean difference, 2.09
points; p=0.001; effect size,* 1.11). Negative symptom scores in the 2 groups diverged statistically
beginning with the 4-week evaluation. Positive symptom scores did not differ between the
treatment groups, but desmopressin was associated with significantly greater improvements
than placebo in PANSS general psychopathology and total scores, with effect sizes of about 0.9
at week 8. Ratings of depressive and extrapyramidal symptoms did not differ between the 2 treatments. Desmopressin was not associated with laboratory abnormalities, and adverse effects (e.g., increased appetite, cough, itching, drowsiness) were mild and transient.

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

Hosseini S, Farokhnia M, Rezaei F, Gouglol A, et al: Intranasal desmopressin as an adjunct to risperidone for negative symptoms of schizophrenia: a randomized, double-blind, placebo-controlled, clinical trial. *European Neuropsychopharmacology* 2014; doi 10.1016/j.euroneuro.2014.02.001. From Tehran University of Medical Sciences, Iran; and other institutions. Funded by Tehran University of Medical Sciences. The authors declared no competing interests.

**Drug Trade Names**: desmopressin, intranasal—Minirin; risperidone—Risperdal

*See Reference Guide.

### Clozapine Augmentation with Ziprasidone

In a placebo-controlled trial, adjunctive ziprasidone improved negative and cognitive symptoms in patients with refractory schizophrenia.

**Methods**: Participants in this 16-week study were 40 patients (age range, 21–51 years; 27 women) with persistent positive or negative symptoms of schizophrenia despite an adequate trial of clozapine. Patients had been receiving clozapine monotherapy at the maximum tolerated dose for ≥1 year. They received randomly assigned 80 mg/day ziprasidone or placebo, added to their regular, stable clozapine. Response was evaluated with the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), the Calgary Depression Scale for Schizophrenia (CDSS), and a battery of neurocognitive tests.

**Results**: A total of 33 patients completed the study. In the ziprasidone group, 2 patients withdrew because of perceived lack of efficacy and 2 because of treatment-emergent side effects, akathisia and sedation. In the placebo group, 1 patient withdrew for perceived lack of efficacy and 2 were withdrawn for noncompliance. All 40 patients were included in the last observation carried forward analysis.*

Compared with placebo, ziprasidone was associated with significantly greater improvement in negative symptoms (p=0.006) and general psychopathology (p=0.009). Effect sizes* for these 2 domains were large. Positive symptoms were not improved with ziprasidone. The BPRS total score also showed improvement with ziprasidone, although it did not reach statistical significance. Among the neurocognitive tests, ziprasidone was associated with greater improvement in verbal fluency and in attentional resistance to distraction.

<table>
<thead>
<tr>
<th>Clinical Changes from Baseline to 16 Weeks</th>
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<tr>
<td>Ziprasidone (n=20)</td>
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</tr>
<tr>
<td><strong>Baseline</strong></td>
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<td>PANSS Positive</td>
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<td>PANSS General Psychopathology</td>
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<td>PANSS Total</td>
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Adjuunctive ziprasidone was generally well tolerated. However, patients who received the study drug had a significant prolongation of the QTc interval from baseline (mean change, 4.91 ms).

**Discussion**: The activity profile of ziprasidone suggests a decreased risk of extrapyramidal effects and weight gain and the potential for both antidepressant and anxiolytic activity. In
addition, ziprasidone is metabolized in the liver via a non-cytochrome P450 pathway, making it an attractive option for augmentation of other antipsychotics. Results of the present study suggest it may be a useful adjunct for patients with resistant schizophrenia with predominantly negative symptoms.

Muscatoello M, Pandolfo G, Mico U, Castronuovo E, et al: Augmentation of clozapine with ziprasidone in refractory schizophrenia: a double-blind, placebo-controlled study. *Journal of Clinical Psychopharmacology* 2014;34 (February): 129–133. From the University of Messina, Italy. *This study was conducted with no external funding. One study author disclosed financial relationships with commercial sources; the remaining authors declared no conflicts of interest.*

**Drug Trade Names:** clozapine—*Clozaril;* ziprasidone—*Geodon*

*See Reference Guide.*

**Citalopram for Agitation in Alzheimer’s Disease**

In a randomized trial, citalopram (*Celexa*) was associated with clinically significant improvement in agitation in patients with Alzheimer’s disease. However, the study leaves unanswered questions about the safety and optimal use of citalopram in this patient population, according to an accompanying editorial.

**Methods:** Participants were enrolled if they had a diagnosis of probable Alzheimer’s disease and had clinically significant agitation for which a physician determined medication was appropriate. All patients and their caregivers received a standardized psychosocial intervention consisting of educational materials, counseling, and 24-hour availability of crisis management. Patients were randomly assigned to receive citalopram titrated to a target of 30 mg/day or placebo for 9 weeks. Partway through the study, the protocol was amended to accommodate an FDA advisory regarding dose-related QT prolongation with citalopram; patients with QTc prolongation were excluded, and electrocardiogram monitoring was instituted. The primary efficacy measures were the agitation subscale of the Neurobehavioral Rating Scale (NBRS-A), which measures agitation, hostility/uncooperativeness, and disinhibition; and the modified Alzheimer Disease Cooperative Study–Clinical Global Impression of Change (mADCS-CGIC) scale (modified to assess global change in agitation).

**Results:** A total of 186 patients were randomized, >90% completed 9 weeks of follow-up, and about 80% remained on treatment throughout. Patients had an average age of 78 years, about half were men, and 89% were community-dwelling. Most were taking cholinesterase inhibitors or memantine for Alzheimer’s disease.

Citalopram was associated with significant improvement in agitation compared with placebo. Mean scores on the NBRS-A decreased from 7.6 points at baseline to 4.1 with citalopram and to 5.4 with placebo (p=0.01). Modified ADCS-CGIC scores indicated that 40% of citalopram patients showed moderate or marked improvement, compared with 26% of the placebo group (odds ratio* for improvement, 2.13). Caregiver distress, a secondary outcome, was also significantly reduced with citalopram (p=0.02).

Adverse events were relatively modest and consistent with known SSRI-associated effects. However, ECG monitoring, available for 48 patients, showed a mean 18-ms increase in QTc interval with citalopram relative to placebo. One patient in the citalopram group had QTc intervals above the 90th percentile, and one patient in the placebo group met criteria for QTc prolongation. Citalopram was also associated with cognitive worsening (average Mini-Mental State Examination decrease of about 1 point) and with a higher incidence of falls.

**Discussion:** The positive effects of 30 mg/day citalopram in Alzheimer’s-related agitation appear to be clinically relevant. However, the cognitive worsening and QTc prolongation raise concerns about this dose. A dose reduction to 20 mg was an option in this study, but too few patients (about 15%) received this dose to evaluate its efficacy.


**Editorial.** There is currently no FDA-approved treatment for agitation in Alzheimer’s disease, and atypical antipsychotics, the main alternative, are also associated with safety concerns. The modest decline in cognitive function in this study is within the range of measurement error and may not be a major concern, perhaps outweighed by the drug’s positive effects on caregiver distress.

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

1Porsteinsson A, Drye L, Pollock B, Devanand D, et al: Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA* 2014;311 (February 19):682–691. From the University of Rochester School of Medicine and Dentistry, NY; and other institutions. Funded by the National Institute on Aging; and the NIMH. Several study authors disclosed financial relationships with commercial sources.

2Small G: Treating dementia and agitation [editorial]. *JAMA* 2014;311 (February 19):677–678. From the University of California, Los Angeles. The author disclosed financial relationships with multiple commercial sources.

*See Reference Guide.

### Pimavanserin for Psychosis in Parkinson's Disease

In a phase III clinical trial, pimavanserin, the first in a new class of drugs, was effective in patients with Parkinson’s disease psychosis. The drug was well tolerated and without worsening of parkinsonism.

**Background:** More than half of all patients with Parkinson’s disease will experience psychosis at some point, and psychotic symptoms affect up to 75% of patients with Parkinson’s disease dementia. Current treatment guidelines recommend consideration of comorbidities and reduction of dopaminergic therapy. Atypical antipsychotics are commonly used when these measures fail, but there are serious safety concerns associated with use of these agents, particularly in elderly patients with dementia. Pimavanserin, an investigational selective 5-HT2A inverse agonist with no effect on other neurotransmitter systems, is believed to have antipsychotic efficacy without producing the adverse effects associated with currently available drugs.

**Methods:** Subjects in this manufacturer-sponsored multicenter trial were 199 patients, aged ≥40 years, with a ≥1-year history of Parkinson's disease plus psychotic symptoms that had been present ≥1 month, occurred at least once per week, and were severe enough to warrant treatment with antipsychotics. Patients were also required to have a Mini-Mental State Examination (MMSE) score of ≥21 and no delirium. During the lead-in period, all study subjects received 2 weeks of nonpharmacologic psychosocial therapy. Those who continued to meet criteria for at least moderate hallucinations or delusions were randomly assigned to 6 weeks of double-blind treatment with either 40 mg/day pimavanserin or placebo. The primary study outcome measure was the Parkinson's disease-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD).

**Results:** A total of 185 patients received at least 1 dose of randomly assigned medication and completed at least 1 post-baseline assessment. A total of 89 subjects in the pimavanserin group and 87 in the placebo group completed the 6 weeks of treatment.

At study end, pimavanserin was associated with a 37% improvement on the SAPS-PD, compared with a 14% improvement with placebo (p=0.0006). The effect size* for change in the SAPS-PD was 0.50. The proportion of patients experiencing a ≥20% reduction in the SAPS-PD was 63% with pimavanserin and 47% with placebo (p=0.02). Pimavanserin was also associated with significantly greater improvements in Clinical Global Impression ratings and with significantly less caregiver burden. The effects of pimavanserin were independent of patient age, gender, and baseline MMSE score.
Pimavanserin was associated with worsening of psychosis in 6 patients. There was no other evidence of adverse effects, including sedation, deterioration in motor function, or laboratory abnormalities. Pimavanserin was associated with a mean QTcB interval prolongation of 7.3 ms.

**Discussion:** Results of this study suggest that pimavanserin may be a viable treatment option for patients with Parkinson’s disease psychosis, for which the only previously available option was the use of unlicensed atypical antipsychotics with questionable efficacy and safety. Additional research is needed to confirm efficacy in Parkinson’s psychosis and to evaluate pimavanserin efficacy in psychosis associated with Alzheimer’s disease and other dementias.

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


*See Reference Guide.

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### Drugs to Counteract Antipsychotic-Induced Weight Gain

The literature supports metformin as the first choice to counteract antipsychotic-induced weight gain and metabolic abnormalities, according to a systematic review and meta-analysis. Evidence also supports the use of topiramate, reboxetine, sibutramine, and add-on aripiprazole, although the evidence supporting these agents is more limited.

**Methods:** The review was based on research published before November 2013 and on unpublished studies identified from clinical trial registries. Studies were included if they were randomized, placebo-controlled trials of concomitant medications to counteract metabolic consequences of antipsychotics in predominantly schizophrenic patient populations. The primary outcome of the meta-analysis was change in weight gain at study endpoint.

**Results:** The systematic review was based on 50 clinical trials, and the meta-analysis on 40 that had sufficient data. The trials included a total of more than 2500 patients and were an average of 12 weeks in duration (range, 4–24 weeks). Twenty-three studies were industry-funded directly or via investigator-initiated grants, 8 had an unclear source of funding, and the rest were not funded by industry. The vast majority of studies were restricted to patients taking clozapine or olanzapine.

The 40 studies included in the meta-analysis reported the effects of 19 different interventions on body weight. Combined data from 10 studies showed a significant effect of metformin, with a mean weight gain of 7 lbs less than placebo. However, the results of metformin studies were heterogeneous, with 7 positive and 3 negative findings.

Three studies found that add-on aripiprazole resulted in a mean of 4.5 lb lower weight gain than placebo, but this result was heavily influenced by a single large study. Pooled data also showed positive effects for sibutramine (3 studies), topiramate, and reboxetine (2 studies each). The positive effects of treatment on body weight extended to all patient subgroups and were especially large in first-episode patients.

A few studies presented data on clinically relevant weight gain, usually defined as a ≥7% change in body weight. Metformin and aripiprazole were superior to placebo in inducing clinically relevant weight loss, with numbers needed to treat (NNT)* of 3 and 9, respectively. Metformin, reboxetine, and the reboxetine–betahistine combination were effective in preventing ≥7% weight gain, with NNTs of 10, 7, and 4 respectively.
Metformin also consistently reduced fasting glucose and insulin levels and reduced insulin resistance. Metformin and aripiprazole were associated with significant decreases in HbA1c relative to placebo. Metformin, aripiprazole, and sibutramine had mixed but positive effects on lipid levels.

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

Mizuno Y, Suzuki T, Nakagawa A, Yoshida K, et al: Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. *Schizophrenia Bulletin* 2014; doi 10.1093/schbul/sbu030. From Keio University School of Medicine, Tokyo, Japan; and other institutions. This analysis was conducted without funding. All study authors disclosed financial relationships with commercial sources.

*Drug Trade Names: aripiprazole—A bilify; clozapine—Clozaril; metformin—Glucophage; olanzapine—Zyprexa; reboxetine (not available in the U.S.)—Vestra; sibutramine (no longer available in the U.S.)—Meridia; topiramate—Topamax*

*See 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.

**Last Observation Carried Forward (LOCF):** 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 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 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.

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