Adjunctive Amantadine for OCD

Amantadine enhanced the efficacy of SSRI therapy for moderate-to-severe OCD in a placebo-controlled trial. Amantadine is an antiviral drug that also has neuroprotective effects and is sometimes prescribed off label to improve cognition in various disorders.

Background: Amantadine is an antagonist of the NMDA-type glutamate receptor. Glutamate is the major excitatory neurotransmitter of the CNS, and glutamatergic dysfunction has been implicated in OCD, several other psychiatric disorders, and neurodegenerative diseases. By blocking glutamate access to nerve cells, amantadine may have a neuroprotective effect against glutamate-induced excitotoxic damage.

Methods: Study participants were adults, aged 18–60 years, who met DSM-5 criteria for OCD and had a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of >21, indicating at least moderate severity. All patients received 100 mg/day fluvoxamine for 4 weeks, followed by 200 mg/day for the remainder of the 12-week study. Beginning with week 1, patients also received randomly assigned double-blind treatment with either 100 mg/day amantadine or placebo. The primary study outcome was change from baseline to week 12 in Y-BOCS total score. Secondary outcome measures were the Y-BOCS obsessive and compulsive subscales, and rates of partial response (Y-BOCS decrease of >25%), complete response (Y-BOCS decrease of >35%), and remission (Y-BOCS score <16).

Results: Of 106 patients (mean age, 35 years; mean duration of illness, 5 years) who were randomly assigned to treatment, 100 completed the study—51 in the amantadine group and 49 in the placebo group. The mean baseline Y-BOCS score was 30 in both treatment groups. Scores decreased with both treatments, but the change was significantly greater in those who received adjunctive amantadine. At week 12, mean scores were 17.6 in the amantadine group and 19.9 in the placebo group (p=0.03). Patients who received amantadine demonstrated a significantly larger reduction in the Y-BOCS obsession score than those who received placebo, with statistical significance beginning at the 4-week assessment (-4.1 vs -2.0; p=0.04) and lasting throughout the trial. Amantadine had no significant effect on compulsive symptoms. A total of 43 patients in the amantadine group, compared with 22 in the placebo group, met...
criteria for complete or partial response (84% vs 45%; p<0.001). Remission was achieved by 22 amantadine patients and 14 placebo patients (43% vs 29%; p=ns). Adverse effects, which included abdominal pain, appetite changes, headache, and constipation, were infrequent and did not differ between amantadine and placebo.

**Discussion:** Although the present findings are positive, before adjunctive amantadine is recommended for regular use in OCD, the results must be replicated in larger samples, in studies with longer durations of treatment, and in combination with other serotonin receptor inhibitors.

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

Naderi S, Faghih H, Aqamolaei A, Mortazavi S, et al: Amantadine as adjuvant therapy in the treatment of moderate to severe OCD: a double blind randomized trial with placebo control. Psychiatry and Clinical Neurosciences 2018; doi 10.1111/pcn.12803. From Tehran University of Medical Sciences, Iran; and other institutions. **Funded by the university.**

The authors declared no competing interests.

*See Reference Guide.

### Imipramine for Resistant Depression

In patients whose depression did not remit with venlafaxine, switching to imipramine was more effective than adding mirtazapine in a randomized open study. These results, although preliminary, suggest that switching to a tricyclic antidepressant may be a useful option in treatment-resistant depression.

**Methods:** Study subjects were adults, aged 18–70 years, receiving inpatient or outpatient treatment at a single mood-disorders clinic for unipolar depression of at least moderate severity (indicated by a baseline Hamilton Rating Scale for Depression [HAM-D] score ≥21). The first study phase consisted of 10 weeks of treatment with extended-release venlafaxine, titrated based on efficacy to a maximum of 300 mg/day. Patients whose depression did not remit with venlafaxine were then randomly assigned to an additional 10 weeks of treatment with either add-on mirtazapine, titrated to 30 mg/day, or to a switch to imipramine, titrated to achieve a combined imipramine/desipramine plasma level between 175 and 300 ng/mL. The primary efficacy outcome was remission, defined as a Hamilton Rating Scale for Depression (HAM-D) score of <8 on 2 consecutive visits or the last observation.

**Results:** Of 382 patients who received treatment with venlafaxine, 118 did not achieve remission, and of these, 112 (mean age, 48 years; 33% men) agreed to receive randomized second-stage treatment. At the start of randomized treatment, the mean HAM-D score was 28 in both groups. During randomized treatment, remission was achieved by 40 of 56 patients in the imipramine group, compared with 22 of 56 in the add-on mirtazapine group (71% vs 39%; p=0.001). The mean final HAM-D score was 6.4 in the imipramine group, compared with 14.1 in the venlafaxine–mirtazapine group (p<0.0001). A total of 5 patients in the imipramine group withdrew from imipramine treatment, 3 because of adverse events.

**Discussion:** There have been few studies of imipramine or other heterocyclic antidepressants in resistant depression, and these few have varied in methods and results. Given the lack of strong evidence supporting other alternatives, the authors recommend considering tricyclics, particularly imipramine, as the preferred first step in moderate-to-severe, treatment-resistant depression.

Navarro V, Bouhafa I, Obach A, et al: Switching to imipramine versus add-on mirtazapine in venlafaxine-resistant major depression. *Journal of Clinical Psychopharmacology* 2019;39 (January/February):63–66. From the Hospital Clinic of Barcelona, Spain; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

*Common Drug Trade Names:* desipramine—Norpramin; imipramine—Tofranil; mirtazapine—Remeron; venlafaxine—Effexor
Psychotropic/Antiretroviral Interactions: Antipsychotics

The prevalence of HIV in those with severe mental illness, including schizophrenia and acute psychosis, is much higher than in the general population. As a result, concomitant use of antipsychotics and antiretroviral therapies (ART) is likely to occur.

Many antiretrovirals are metabolized by the hepatic cytochrome P450 (CYP450) system. (See the printable ART cytochrome P450 properties table at www.alertpubs.com/sdaonlinecontent for details.) While there is limited data regarding interactions between ART and antipsychotics (particularly first-generation antipsychotics), many of these agents are also metabolized via the CYP450 system, and the potential for interactions exists. (See table A.)

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Potential Interactions</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Increased levels when given concomitantly with CYP 3A4 or 2D6 inhibitors.</td>
<td>Dosage adjustments are required for both the oral and depot long-acting intramuscular formulations with concomitant administration of strong CYP 3A4 and/or 2D6 inhibitors, specifically ritonavir and cobicistat. Unboosted protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) affecting CYP 3A4 (e.g., efavirenz) also pose a theoretical concern.</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Clozapine and zidovudine have been associated with clinically significant agranulocytosis and bone marrow suppression; limited data support compounding myelosuppressive effects with concomitant use.</td>
<td>Patients should be carefully monitored when the combination of clozapine and zidovudine is necessary.</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>CYP 3A4 inhibitors can alter lurasidone metabolism.</td>
<td>Coadministration of strong CYP 3A4 inhibitors (e.g., ritonavir, cobicistat) is contraindicated, and the lurasidone dose should be reduced when coadministered with moderate CYP 3A4 inhibitors (e.g., atazanavir).</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Coadministration of agents with CYP 1A2 and uridine diphosphate glucuronosyltransferase activity, specifically ritonavir, can cause subtherapeutic olanzapine levels and/or shorten olanzapine half-life.</td>
<td>Olanzapine dose adjustment may be necessary when given concomitantly with ritonavir-containing ART regimens.</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>CYP 3A4 and 2D6 inhibitors (e.g., ritonavir) can increase quetiapine half-life and precipitate excessive weight gain and hyperglycemia as well as produce marked sedation and mental confusion.</td>
<td>Dosage adjustments may be required.</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Concomitant administration of indinavir or ritonavir with risperidone can alter risperidone metabolism and precipitate EPS or NMS. Cases of angioedema have also been reported.</td>
<td>Starting risperidone at the lowest possible dose is recommended, followed by titration to clinical efficacy while monitoring for toxicity.</td>
</tr>
</tbody>
</table>
As a class, antipsychotic medications have a risk of prolonging the QT interval, as do several antiretrovirals including the PIs lopinavir–ritonavir, saquinavir, and nelfinavir and the NNRTIs rilpivirine and efavirenz. While there is little-to-no clinical data available detailing the degree of QT prolongation with most agents, caution and monitoring of high-risk patients are warranted.

Another important consideration when coprescribing antipsychotics and ART is the potential for psychiatric symptom exacerbation. The NNRTIs, in particular efavirenz, have been associated with neuropsychiatric adverse effects, including psychosis, nightmares/vivid dreams, fatigue, and insomnia. There have also been reports of new-onset psychosis with several drugs in the NNRTI class.

Both antipsychotics and ART have been associated with metabolic effects, and subsequent cardiovascular risk. Concomitant use of the drugs can have compounding effects on metabolic changes. In addition, antipsychotics with a high affinity for muscarinic receptors (e.g., clozapine, olanzapine) are known to produce anticholinergic effects, such as dry mouth, constipation, and sedation. Agents with strong alpha 2 receptor affinity (e.g., risperidone) can cause hypotension. Aripiprazole has been linked to concerns about a theoretical increase in suicidality in patients with schizophrenia. Concomitant administration of ART regimens that inhibit the metabolism of these antipsychotics could exacerbate these adverse effects.

Potential interactions with other second-generation antipsychotics (i.e., asenapine, brexpiprazole, cariprazine, iloperidone, paliperidone, pimavanserin, ziprasidone) were not detailed in the report. However, the possibilities can be inferred based on each individual agent’s CYP profile.² (See table B.)

**Editor's Note.** This is the third report in a 5-part series on psychotropic/antiretroviral interactions. We previously covered interactions with antidepressants and stimulants. (See Psychotropic/Antiretroviral Interactions: Antidepressants in the November 2018 issue and Psychotropic/Antiretroviral Interactions: Stimulants in the December 2018 issue.) Interactions involving mood stabilizers and medications for opioid and alcohol use disorders will be addressed in the next 2 issues.

1Goodlet K, Zmarlicka M, Peckham A: Drug-drug interactions and clinical considerations with co-administration of antiretrovirals and psychotropic drugs. CNS Spectrums 2018; doi 10.1017/S109285291800113X. From Midwestern University College of Pharmacy, Glendale, AZ; and other institutions. Source of funding not stated. Two of 3 study authors disclosed potentially relevant relationships; the remaining author declared no competing interests.


**Common Drug Trade Names:** aripiprazole—Abilify; asenapine—Saphris; atazanavir—Reyataz; brexpiprazole—Rexulti; cariprazine—Vraylar; clozapine—Clozaril; cobicistat—Tybost; efavirenz—Sustiva; iloperidone—Fanapt; indinavir—Crixivan; lopinavir–ritonavir—Kaletra; lurasidone—Latuda; nelfinavir—Viracept; olanzapine—Zyprexa; paliperidone—Invega; pimavanserin—Nuplazid; quetiapine—Seroquel; rilpivirine—Edurant; risperidone—Risperdal; ritonavir–Norvir; saquinavir—Invirase; zidovudine—Retrovir; ziprasidone—Geodon

<table>
<thead>
<tr>
<th>Agent</th>
<th>Metabolic Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asenapine</td>
<td>CYP1A2 oxidation and UGT1A4 glucuronidation</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Primarily CYP3A4 and CYP2D6</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Carbonyl reduction, hydroxylation (CYP2D6), and O-demethylation (CYP3A4)</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>CYP2D6 and 3A4</td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>Primarily via CYP3A4 and CYP3A5</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Extensively hepatic, primarily via glutathione and aldehyde oxidase, and to a lesser degree via CYP3A4 and CYP1A2 (minor)</td>
</tr>
</tbody>
</table>
Benzodiazepines in Veterans with PTSD

Results of a retrospective cohort study of veterans with posttraumatic stress disorder suggest that benzodiazepines increase risk for completed suicide, suicide attempts, and suicidal ideation, as well as increase health care utilization.

**Background:** According to U.S. Department of Veterans Affairs (VA) guidelines, benzodiazepines are not recommended for treatment of PTSD. However, clinicians still prescribe these agents when first- and second-line medications do not adequately treat symptoms.

**Methods:** The study, conducted using a VA database of electronic health records, included veterans who received a diagnosis of PTSD between 2001 and 2014 and received treatment within the VA system for ≥6 months. The exposed group consisted of patients with a new prescription for a benzodiazepine within 1 year following a PTSD diagnosis. Each exposed patient was propensity score matched* on the basis of demographics, comorbidities, and other therapies with 2 controls, also with PTSD but not given a benzodiazepine prescription. The primary outcomes of interest were suicide death and measures of health care utilization.

**Results:** The study cohort consisted of nearly 81,000 benzodiazepine users and 162,000 non-users. Benzodiazepine use was associated with higher overall mortality than non-use (hazard ratio [HR], 1.86). Nearly 4% of benzodiazepine users and 3% of non-users committed suicide (HR, 2.74). Benzodiazepines were also associated with increased rates of suicidal behavior (HR, 1.56), suicidal thoughts (HR, 1.52), and suicide attempts (HR, 1.85). In addition, these drugs were associated with increased rates of most types of health care utilization over 6 years of follow-up, with incidence rate ratios* of 1.27 for hospitalization, 1.16 for emergency department visits, 1.19 for general outpatient visits, and 1.37 for outpatient mental health visits. There was no significant difference in the rate of outpatient substance abuse visits.

**Discussion:** While benzodiazepines can provide short-term symptomatic relief in PTSD, they are not effective in treating the core symptoms of the disorder, and they are associated with worse overall symptom severity, anxiety, aggression, substance abuse, and social function. They can cause or worsen depression and dissatisfaction with life. Potential explanations for these poor long-term outcomes include discontinuation syndromes, disruptive stress responses, avoidance of cognitive and emotional processing of trauma, and worsening of underlying PTSD pathophysiology.

Deka R, Bryan C, LaFleur J, Oderda G, et al: Benzodiazepines, health care utilization, and suicidal behavior in veterans with posttraumatic stress disorder. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m12038. From the VA San Diego Health Care System, La Jolla, CA; and other institutions. **Funded by the VA; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Adjunctive Brexpiprazole for Function in Depression

A pooled analysis of manufacturer-sponsored randomized controlled trials suggests that adjunctive brexpiprazole improves functioning in patients with major depressive disorder not fully responsive to antidepressants.¹ The effect size, while small, indicates a clinically meaningful benefit.

**Background:** According to a previously published meta-analysis, while adjunctive atypical antipsychotics may reduce depressive symptoms, they generally do not have beneficial effects on functioning, and tolerability is a concern.² Another systematic review of the atypical antipsychotics approved for adjunctive treatment of depression found only aripiprazole and brexpiprazole improve functioning, both to a similar extent.³ The present analysis was undertaken to clarify the effects of brexpiprazole on patient function.
**Methods:** The post-hoc analysis was based on data from short-term phase 2 or 3 studies whose primary efficacy outcome was improvement in depressive symptoms. Function, measured using the Sheehan Disability Scale (SDS), was the key secondary outcome in the trials. In a total of 6 trials of similar design, patients received antidepressant therapy for 8–10 weeks. Those who demonstrated a <50% reduction in depressive symptoms were randomly assigned to receive adjunctive brexpiprazole or placebo for 6 weeks. Depending on the study, the brexpiprazole dosage was either fixed or flexible in the range of 0.15–3 mg/day. The SDS measures function on 3 items: social life, family life, and work/studies.

**Results:** Of 2066 patients (mean age, 44 years; 69% women) who entered the randomized phase of a study, >90% of these patients completed randomized treatment. Mean baseline SDS scores were about 5.7 (maximum score, 10) indicating moderate functional impairment.

Patients in the brexpiprazole group showed a greater improvement in mean total SDS than the placebo group with final scores of 4.53 and 4.98 in the groups, respectively (effect size,* 0.22; p<0.001). Patients who received brexpiprazole also showed larger improvements than those who received placebo in social life (effect size, 0.23; p<0.001) and family life (effect size, 0.23; p<0.001). There were no significant improvements in the work/studies domain, but >6 weeks is typically required to demonstrate improvement in this domain.

**Discussion:** While no minimum clinically important difference (i.e., the smallest difference in score that patients perceive as beneficial) has been established for the SDS, final scores after the 1.2-point decrease with brexpiprazole treatment approached the suggested SDS threshold for functional response (score ≤4).


*Common Drug Trade Names:* aripiprazole—*Abilify*; brexpiprazole—*Rexulti*

*See Reference Guide.

---

**Antidepressants and Hip Fracture in the Elderly**

In a matched cohort of patients aged ≥65 years, rates of hip fracture were higher among those who received antidepressant therapy than in those who did not. However, risk was greatest before the start of antidepressant therapy and decreased gradually over 1 year of treatment.1 This finding suggests that these patients have an elevated risk of hip fracture regardless of antidepressant use.

**Background:** The association between antidepressants and injury-causing falls is well known, but evidence supporting a causal association of antidepressant use and hip fracture is weak. Individuals with serious medical disorders and concomitant depression may have an increased risk of fracture before they start antidepressant therapy. The increase in fracture risk could parallel an increase in the risk of developing depression, possibly reflecting general susceptibility during times of other adversity. In order to clarify the causality of the association, the present study included a nonexposure control period for each patient.

**Methods:** The investigators analyzed Swedish national health insurance data to assemble a cohort of all persons aged ≥65 years who had received a new prescription for an antidepressant between 2005 and 2011. Each patient was matched with a control, of the same age and gender,
who did not receive an antidepressant during the study period. Rates of hip fracture were compared between the groups for a 2-year period beginning 1 year prior to the antidepressant prescription.

**Results:** The cohort consisted of >204,000 exposed individuals and an equal number of controls (mean age at index date, 80 years; 63% women). The incidence of hip fracture was more than double among patients who received antidepressants both before (5642 vs 2189) and after (7137 vs 2625) initiation of therapy. Excess risk was evident during the most remote period, 6 months to 1 year before the antidepressant prescription (odds ratio [OR],* 1.65); increased steadily before reaching a peak 16–30 days before the prescription (OR, 5.47); and fell gradually until 1 year after the index date (OR, 2.93). Risk was increased in both men and women, but with a higher peaks in men (e.g., OR during the 16- to 30-day window, 9.38 vs 4.82 in women). Similar patterns of association were seen in patients aged ≤84 years and in those aged ≥85 years. In separate analyses of the 3 most commonly prescribed antidepressants—citalopram, mirtazapine, and amitriptyline—associations with hip fracture were significant for all or most of the risk periods and did not differ between the agents.

**Discussion:** Although the present findings do not preclude the possibility that antidepressants increase the risk of falling, they do raise questions about the findings of previous observational studies. If the study had examined only associations starting at the index date and going forward, the conclusion that the association between antidepressant use and hip fracture might be causal would be reasonable. However, the finding that risk was greatest during the non-exposure control period suggests the presence of other causal factors. Regardless of whether the association with hip fracture is causal, the authors urge caution when prescribing antidepressants for older patients as there is the potential for other serious adverse effects including QT prolongation, hyponatremia, and gastrointestinal bleeding.

**Editorial.** It is important to note that onset of depressive symptoms is common after hip fracture and can persist for up to a year after the fracture event. In addition, antidepressants are prescribed at a high rate following hip fractures, sometimes for inappropriate indications like insomnia, pain, or poor motivation in rehabilitation therapy. For most older patients, the toll of untreated depression probably outweighs risks associated with antidepressant use. If an antidepressant is warranted, clinicians should take an individualized, preventive approach to prescribing, with avoidance of sedating or anticholinergic agents and a careful dose-escalation schedule.

---


2Iaboni A, Maust D: A status update on the association between antidepressants and fractures: breaking up [editorial]? JAMA Psychiatry 2019; doi 10.1001/jamapsychiatry.2018.3632. From the University Health Network, Toronto, Canada; and other institutions. One author disclosed a potentially relevant financial relationship.

**Common Drug Trade Names:** amitriptyline—Elavil; citalopram—Celexa; mirtazapine—Remeron

*See Reference Guide.*

---

**Clozapine REMS Update**

The Risk Evaluation and Mitigation Strategy (REMS) Program for clozapine—designed to ensure patients have continued access to the drug as well as information on appropriate management of potential adverse effects, including severe neutropenia—is undergoing important changes. These modifications, summarized below, will take effect on February 28, 2019.

- Both prescribers and pharmacies must be certified in the REMS program or they will no longer be permitted to prescribe/dispense clozapine. However, patients can no longer be enrolled in the REMS program by their pharmacist; all enrollments must be completed by the...
prescriber or their designee. If you prescribe clozapine in an outpatient setting but are not yet certified, you can complete the process at www.clozapinerems.com. Once a prescriber is certified, his/her prescriber designees must also enroll online.

- Clinicians who prescribe clozapine for an inpatient who is already enrolled in the program do not need to be certified in the REMS program. However, newly-treated patients must be registered in the REMS Program prior to receiving their first dose.

- In accordance with the clozapine prescribing information, patients’ absolute neutrophil count (ANC) must be monitored regularly. Values must then be submitted directly to the clozapine REMS database. While monitoring is required, outdated ANC levels will not prevent a pharmacy from dispensing clozapine. However, if the most recent ANC on file for a patient indicates moderate or severe neutropenia, the pharmacy will not be authorized to dispense the medication unless the prescriber documents that the benefits of clozapine treatment outweigh the risks associated with neutropenia by submitting a treatment rationale to the REMS program. These can be filed online at www.clozapinerems.com or by calling the Clozapine REMS Program Contact Center at 844-267-8678. If a patient does not have an ANC on file in the REMS database, the pharmacy will not be authorized to dispense clozapine.


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.

**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 1 group has half the risk of the other group.

**Incidence Rate Ratio:** The number of new cases of a condition in a defined (specified) group or population expressed as a ratio. For example, if there are 1000 people and a condition develops in 14 of them, the incidence rate is 14 per 1000 or 1.4%.

**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.

**Propensity Score Matching:** A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias, making it possible to obtain average treatment effects.

**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.