C lozapine and Anem ia

Anemia developed in one-fourth of a cohort of patients within 2 years of starting clozapine, indicating that patients receiving clozapine, particularly those with lower initial levels of hemoglobin, should be monitored for the development of this condition.\(^1\)

**Background:** Hematological abnormalities are not uncommon with clozapine, and patients taking the drug are required to undergo regular monitoring for agranulocytosis. Other hematological abnormalities, such as neutropenia and eosinophilia, have been reported, but little is known about the potential for clozapine to cause anemia. Iron-deficiency anemia is the most common form and its prevalence in patients with schizophrenia has been reported to be 2.5%.\(^2\)

**Method:** Study participants were enrolled in a clozapine registry in Toronto, Canada, between January 2009, when electronic medical records were introduced, and December 2010. To be included in the analysis, patients had to have hemoglobin measured at baseline and during 2 years of follow-up. Anemia was defined as a hemoglobin value of $< 120 \text{ g/L}$ in women and $< 130 \text{ g/L}$ in men. The analysis included 94 patients (mean age, 36 years; 72% men) without anemia at baseline.

**Results:** In the present sample, anemia developed during follow-up in 23 of the 94 patients (24.5%). Of the patients in whom anemia developed, 20 had either recurrent episodes or persistent anemia throughout the follow-up period. One patient also had neutropenia, and none had agranulocytosis. In a multivariate analysis, higher baseline hemoglobin levels were associated with lower risk of anemia during follow-up (hazard ratio,* $0.86; p=0.002$) and cigarette smoking was associated with increased risk (hazard ratio, 0.21; $p=0.02$); these associations were found only in men, not in women. Medical comorbidities had a modest association with anemia ($p=0.036$).

**Discussion:** The clinical consequences of anemia include lethargy and cognitive dysfunction, which can be mistaken for, or compound, the negative symptoms and cognitive deficits of schizophrenia. Clozapine may cause anemia via toxicity to hematopoietic precursors of myeloid and erythroid cells, but it is also possible that patients with refractory schizophrenia...
become anemic because of iron deficiency and poor diet. Regardless, it appears to be reasonable to monitor complete blood counts, rather than just the required white blood cell and neutrophil counts.

1Lee J, Bies R, Bhaloo A, Powell V, et al: Clozapine and anemia: a 2-year follow-up study. *Journal of Clinical Psychiatry* 2015; doi 10.4088/jcp.14m09143. From the Institute of Mental Health, Singapore; and other institutions. Funded by the Singapore Ministry of Health; and other sources. The authors declared no competing interests.


*See Reference Guide.

### Pharmacotherapy for Pathological Hoarding

Limited evidence suggests that pharmacotherapy with an SSRI or venlafaxine may be effective for patients with pathological hoarding.

**Background:** Research suggests that patients with OCD who engage in hoarding behavior are much less likely to experience response to treatment than those with OCD without hoarding. However, little research has focused on treatment of hoarding outside of OCD. The present meta-analysis was undertaken to synthesize the existing literature on pharmacological treatment of hoarding in patients with or without OCD.

**Methods:** The analysis included all studies published in any language that investigated treatment response in patients with pathological hoarding, with or without OCD. The 7 included studies were 1 randomized controlled trial, 3 open-label studies, and 3 case series, comprising a total population of 92 patients (65 with OCD and predominant hoarding, 27 with DSM-5 hoarding disorder). Response was defined as a >30% reduction in the Savings Inventory–Revised (SI-R) or a ≥25% reduction in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score.

**Results:** Response rates in the individual studies ranged from 37% to 76%. The SSRIs paroxetine and sertraline were effective in patients with OCD and hoarding behavior. The SNRI venlafaxine appeared to be effective in patients with DSM-5 hoarding disorder. Paroxetine produced a mean 6-point reduction in Y-BOCS score among 32 patients who received open-label treatment. Patients who received open-label sertraline (n=20) demonstrated a 47% reduction in Y-BOCS score. Those who received open-label extended-release venlafaxine showed a mean 32% reduction in SI-R score, as well as a mean 8-point reduction in Y-BOCS score. There was little or no support for augmentation of SSRIs with minocycline, naltrexone, or quetiapine. A small case series suggested that methylphenidate monotherapy was effective in patients with hoarding disorder, producing response in 2 of 4 patients, but its use was limited by adverse effects (i.e., insomnia, palpitations).

**Discussion:** Despite the limitations of the studies in this meta-analysis (e.g., small samples, short treatment durations) and in the meta-analysis itself (e.g., studies were few and of varying designs, no drug was investigated in >1 study), the results support cautious optimism for pharmacotherapy in hoarding disorder. Pathological hoarding is associated with poor attention, which suggests a potential role for stimulants, and with poor insight, which may theoretically respond to antipsychotics; additional research appears to be warranted.

**Study Rating**—16 (89%): This study met most criteria for a systematic review/meta-analysis, but the source of funding was not stated.

Brakoulias V, Eslick G, Starcevic V: A meta-analysis of the response of pathological hoarding to pharmacotherapy. *Psychiatry Research* 2015;229 (September 30):272–276. From the University of Sydney, Penrith, Australia. Source of funding not stated. The authors declared no conflicts of interest.

*Drug Trade Names:* methylphenidate—Ritalin; minocycline—Minocin; naltrexone—ReVia; paroxetine—Paxil; quetiapine—Seroquel; sertraline—Zoloft; venlafaxine—Effexor.

*See Reference Guide.
### New Options for Schizophrenia & Bipolar Disorder

Aripiprazole lauroxil (*Aristada*) has received FDA approval for the treatment of schizophrenia in adults.\(^1\) The long-acting injectable should be administered every 4–6 weeks into the patient’s arm or buttocks. Efficacy of aripiprazole lauroxil has been demonstrated in patients previously stabilized with oral aripiprazole. The most common adverse effect of aripiprazole lauroxil in clinical trials was akathisia.

Cariprazine (*Vraylar*) has also recently received FDA approval to treat schizophrenia and bipolar disorder in adults.\(^2\) Dopamine D2 receptor blockade is believed to be a necessary action of antipsychotics. Cariprazine is a partial agonist of both D2 and D3 receptors, which may theoretically augment its antipsychotic effects relative to other agents. The drug is pharmacologically similar to aripiprazole, which also functions as a D2 partial agonist.\(^3\) Extrapyridlad symptoms (EPS) were the most common adverse effects in trials of patients with schizophrenia. In addition to EPS, akathisia, dyspepsia, vomiting, somnolence, and restlessness were common in patients with bipolar disorder.

Like other atypical antipsychotics, both of the newly-approved agents will carry a boxed warning about risk of death with off-label use to control behavioral problems in elderly patients with dementia-related psychosis.


*Drug Trade Names:* aripiprazole, oral—*Abilify*; aripiprazole lauroxil—*Aristada*; cariprazine—*Vraylar*

### Asenapine Dosing

In a small, open-label study, a single bedtime dose of asenapine (*Saphris*) was better tolerated than the recommended twice-daily dosing, without a reduction in efficacy.

**Background:** The FDA approved dosing schedule for asenapine is 5 mg b.i.d. However, daytime sleepiness is problematic for many patients with this dosage. Because of its 24-hour half-life, it seems possible that asenapine could be administered once daily at bedtime to avoid the residual sleepiness.

**Methods:** Study subjects were 30 adults, aged 20–61 years (17 women), admitted with an acute exacerbation of schizophrenia or schizoaffective disorder. Patients received 14 days of randomly assigned sublingual asenapine at either the recommended 5-mg b.i.d. dosage or 10 mg administered at bedtime. Acceptability was assessed using a patient-rated Likert scale (1–7; 1=very acceptable and 7=completely unacceptable), as well as evaluation of discontinuation rates. Symptom improvement was measured using the Brief Psychiatric Rating Scale (BPRS).

**Results:** Patients who received the single bedtime dose reported significantly greater acceptability of asenapine with a mean score of 1.7 on the 7-point scale vs. 3.9 in the b.i.d. dosing group (p<0.05). Asenapine treatment was discontinued by 2 of 12 patients in the bedtime dosing group, compared with 8 of 18 patients in the b.i.d. dosing group (17% vs. 44%). Both discontinuations in the bedtime dosing group were due to inadequate efficacy, as were 4 in the b.i.d. dosing group. The remaining 4 patients who discontinued b.i.d. dosing did so because of intolerable adverse effects (3 for severe daytime drowsiness, 1 for akathisia).
Both asenapine dosing strategies improved symptoms. In an intent-to-treat analysis,* mean BPRS score reduction was significantly greater in the bedtime dosing group (p<0.05). However, efficacy did not differ in the completer analysis, suggesting that the higher completion rate in the bedtime dosing group was responsible for the better efficacy results in the intent-to-treat analysis.

**Discussion:** The results of this trial suggest that administering asenapine as a single 10-mg dose at bedtime may lead to fewer treatment discontinuations, thus improving outcomes. Because the present study was small and treatment was open label, studies with more rigorous methodology should be undertaken to replicate the results.

Sun X, Hamer R, McEvoy J: Asenapine once daily versus twice daily: impact on patient acceptance in a randomized, open-label, 14-day clinical trial [letter]. *Journal of Clinical Psychiatry* 2015;76 (July):992–993. From Duke University Medical Center, Durham, NC; and other institutions. **Funded by Merck Sharp & Dohme Corp. Two study authors declared financial relationships with commercial sources, including Merck. The remaining author reported no competing interests.**

*See Reference Guide.

### Brexpiprazole Efficacy in Acute Schizophrenia

In a multinational, phase III clinical trial, brexpiprazole (*Rexulti*) was effective and well tolerated in markedly ill patients experiencing an acute exacerbation of schizophrenia.1

**Background:** Brexpiprazole is a newly approved second-generation antipsychotic for the treatment of schizophrenia in adults and as an add-on to antidepressants in adults with major depression.2 The agent was designed with a serotonin and dopamine activity profile that would theoretically result in a low potential for some of the most concerning adverse effects of second-generation antipsychotics, including extrapyramidal symptoms and prolactin elevation.3

**Methods:** The study, conducted at 65 centers, enrolled adults experiencing an acute exacerbation of schizophrenia who would benefit from hospitalization or continued hospitalization. Following a 14-day screening phase, patients (n=636) were randomly assigned to 6 weeks of double-blind treatment with either placebo or brexpiprazole at a daily dose of 0.25 mg (presumed to be ineffective), 2 mg, or 4 mg. The primary outcome was change from baseline to week 6 in the Positive and Negative Syndrome Scale (PANSS) total score.

**Results:** Of 636 patients who received medication, 623 had ≥1 post-baseline assessment and were included in the efficacy analysis. Patients were markedly ill at study entry (mean PANSS score, 95), all had experienced previous acute exacerbations requiring treatment, and about 90% were currently receiving antipsychotic medication. About 64% of participants completed the study. Discontinuation rates were 59% with placebo and ranged from 62 to 68% with active treatment.

As expected, the 0.25-mg dose of brexpiprazole was not effective. For the primary endpoint, the average effect of the 2 higher doses of brexpiprazole was superior to placebo (p<0.0001), permitting comparison of individual dosage groups. (See table.) The difference in mean PANSS total scores between brexpiprazole and placebo reached statistical significance at 1 week for the 2-mg dose and 2 weeks for the 4-mg dose and remained significant throughout the study. Of 5 PANSS subscales, 4 were significantly improved with brexpiprazole: positive symptoms, negative symptoms, disorganized thought, and uncontrolled hostility/excitement. The PANSS anxiety/depression subscale was not affected by brexpiprazole treatment, but the study population was not selected for marked levels of anxiety or depression. Treatment effects were also statistically superior to placebo for the Clinical Global Impression–Severity (CGI-S) score,* a key secondary endpoint.
Overall, adverse events occurred less frequently with brexpiprazole than with placebo; however, most of the events were related to the underlying illness, rather than treatment. Akathisia occurred more frequently with 2 mg and 4 mg brexpiprazole than placebo (4.4%, 7.2%, and 2.2%, respectively), but was usually mild to moderate in severity and did not limit treatment. Increases in body weight of ≥7% occurred in about 9% of patients taking brexpiprazole and 4% of the placebo group. There were no clinically significant differences between brexpiprazole and placebo in lipid and glucose levels, prolactin levels, extrapyramidal symptom ratings, or suicidal ideation or behavior.

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


2. FDA News Release: FDA approves new drug to treat schizophrenia and as an add on to an antidepressant to treat major depressive disorder. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements. See Psychiatry Drug Alerts 2015;29 (July):49.


*See Reference Guide.

**IV Clomipramine for Resistant OCD**

In an open-label trial, intravenous clomipramine produced rapid response in patients with severe obsessive-compulsive disorder refractory to other treatments.

**Background:** SSRIs are currently considered first-line treatment for OCD. Second-line treatment consists of switching to a different SSRI or venlafaxine, or SSRI augmentation with antipsychotic medication or cognitive behavioral therapy. There is little guidance on what to do if these approaches fail. Alternatives include different augmentation agents (e.g., oral clomipramine, buspirone, pindolol, riluzole), different monotherapies (e.g., tramadol, ondansetron, an MAOI), or brain stimulation. Monotherapy with IV clomipramine has shown promise in several small uncontrolled studies.

**Methods:** Study participants were 30 outpatients, recruited from a university clinic, who were required to have OCD of ≥3 years’ duration, with functional impairment and severe symptoms.
All had experienced nonresponse to ≥2 trials of anti-obsessional medication, each given for at least 8–12 weeks with ≥6 weeks at the maximum tolerated dose. Comorbid mood, anxiety, or personality disorders were not grounds for exclusion. All patients were hospitalized to receive the IV clomipramine, which was titrated from 50 mg/day to a maximum of 225 mg/day over 5–7 days. Low-dose benzodiazepines were the only permitted concurrent medications during hospitalization. After IV treatment, patients were switched to oral clomipramine and discharged. Response was defined as a ≥25% improvement in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score.

**Results:** Patients had a mean age of 32 years, one-third were women, and OCD symptoms had been present for an average of 16 years. Previously unsuccessful treatments included combinations of ≥1 SSRI and a TCA in 26 patients. Two patients each had received only trials of TCA or SSRI monotherapies. At study entry, the majority of patients (73%) were receiving either oral clomipramine or imipramine monotherapy. Comorbidities included depression in 4 patients, an anxiety disorder in 1, and personality disorders in 8. All patients completed the inpatient phase of the study; 2 were lost to follow-up during outpatient treatment.

During IV treatment, patients experienced a statistically significant average 31% decrease in the Y-BOCS total score, from a mean of 26 (severe) to 18 (moderate). Improvement was maintained throughout the 24 weeks of follow-up, with the average score dropping to 16 at study end. A total of 23 patients (77%) met response criteria at discharge, and 18 (60%) continued to meet the criteria at 24 weeks. Compared with men, women had significantly greater improvement in compulsions, but the genders did not differ in changes in obsessions. There were no adverse effects of IV clomipramine treatment except transient palpitations in 1 patient.

**Discussion:** It has been hypothesized that IV clomipramine has greater bioavailability than the oral drug because it bypasses hepatic first-pass metabolism and avoids conversion to a metabolite with lesser serotonergic effects. In the present study, reduction of symptoms was rapid, and patients who experienced good response continued to improve with oral clomipramine.

**Karameh W, Khani M:** Intravenous clomipramine for treatment-resistant obsessive-compulsive disorder. *International Journal of Neuropsychopharmacology* 2015; doi 10.1093/ijnp/pyv084. From SEHA Corporate, Abu Dhabi, UAE; and American University of Beirut Medical Center, Lebanon. **Source of funding not stated.** The authors declared no competing interests.

**Drug Trade Names:** buspirone—Buspar; clomipramine—Anafranil; imipramine—Tofranil; ondansetron—Zofran; pindolol—Visken; riluzole—Rilutek; tramadol—Ultram; venlafaxine—Effexor

## Antidepressants and Ischemic Stroke Mortality

The most common neuropsychiatric complication after stroke is post-stroke depression. In a population-based study, early antidepressant treatment during hospitalization for an ischemic stroke was associated with a large decrease in mortality in the subsequent month.

**Methods:** Registry data was collected for nearly 6000 Danish adults (mean age, 70 years; 44% women) who were admitted during a 7-year period for a first ischemic stroke. Antidepressants were prescribed for post-stroke depression or for pathological crying, another relatively common neurologic complication of stroke. The present analysis was based on 955 patients newly prescribed an antidepressant for these indications and an equal number of propensity-matched* controls who had no antidepressant treatment. The primary study endpoint was mortality within 30 days.

**Results:** Antidepressants were started a median of 5 days after admission (range, 2–11 days). During the 30-day follow-up, 30 deaths occurred in the patients who received antidepressants and 318 in the non-treated group (adjusted odds ratio,* 0.28). The effects of antidepressant treatment did not differ according to patient age or gender. Antidepressants were beneficial.
at all levels of stroke severity but had larger effects with greater stroke severity. For example, in patients with very severe stroke, the odds ratio for death was 0.08.

**Discussion:** These results suggest early antidepressant use is a safe approach to poststroke depression, and there may be no need to wait for the full 14 days of depressive symptom duration before initiating treatment. It should be noted that information on specific antidepressants was not available for the study. However, SSRIs are the recommended first-line treatment and likely account for the majority of antidepressant prescriptions. Possible underlying mechanisms for the benefit of antidepressants include antiinflammatory effects, restoration of capillary blood flow, antiplatelet effects of SSRIs, and earlier recovery from depression promoting participation in rehabilitation and faster mobilization. Randomized trials are now in progress to replicate these results.

Mortensen J, Johnsen S, Larsson H, Andersen G: Early antidepressant treatment and all-cause 30-day mortality in patients with ischemic stroke. *Cerebrovascular Diseases* 2015; doi 10.1159/000435819. From Aarhus University Hospital, Denmark. *Funded by the Tryg Foundation; and other institutions. The authors declared no conflicts of interest.*

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**Dextromethorphan–Quinidine for Agitation in Alzheimer’s**

In a preliminary, manufacturer-sponsored trial, the combination of dextromethorphan and quinidine (Nuedexta) reduced agitation in patients with Alzheimer’s disease.1

**Background:** Safe, effective treatments are lacking for agitation in patients with Alzheimer’s disease. Dextromethorphan–quinidine is currently approved for treatment of pseudobulbar affect, and research has shown the agent reduces agitation in patients with the disorder.

**Methods:** The study was conducted at 42 U.S. treatment sites, including outpatient Alzheimer’s disease clinics as well as assisted living and nursing facilities. Study participants (n=220; 126 women) were aged ≥50 years, met diagnostic criteria for probable Alzheimer’s disease, and had clinically significant agitation, which was defined as poorly organized and purposeless psychomotor activity characterized by verbal or physical aggression or nonaggressive physical behaviors such as pacing or restlessness. Patients receiving Alzheimer’s medication (e.g., memantine or a cholinesterase inhibitor) were not excluded provided the dosage had been stable for ≥2 months. Participants were randomly assigned to 5 weeks of either placebo or dextromethorphan–quinidine. After 5 weeks, non-responding patients in the placebo group were re-randomized to receive active medication or placebo for another 5 weeks. Those who had received active treatment during the first 5 weeks continued with no change. Dextromethorphan–quinidine was titrated to a maximum dosage of 30/10 mg b.i.d. The primary efficacy outcome was change from baseline in the Agitation/Aggression domain of the Neuropsychiatric Inventory (NPI), which measures the frequency and severity of behaviors and is scored from 0 (no symptoms) to 12 (daily symptoms, with marked severity).

**Results:** The efficacy analysis included 218 patients, of whom 88% completed the study. Nearly 90% of participants were outpatients. Baseline Clinical Global Impression–Severity (CGI-S)* ratings for agitation were moderate in 66%, marked in 30%, and severe or extreme in 4%.

The mean baseline NPI Agitation/Aggression score of 7 was reduced to 3.8 in the active treatment group at the 5-week evaluation (p<0.001 for change from baseline), compared with 5.3 in the placebo group (p<0.001 for between-group comparison). In stage 2, mean NPI Agitation/Aggression scores decreased from 5.8 to 3.8 in the dextromethorphan–quinidine group and from 6.7 to 5.8 in the placebo group (p=0.02 for between-group comparison). Stratification by baseline mini-mental state exam scores, CGI-S scores for agitation, and background treatment with cholinesterase inhibitors or other psychotropic medications did not alter the findings. Secondary outcome measures, including caregiver distress, generally favored the active treatment.
Discussion: An accompanying editorial called the results of this study encouraging but modest and difficult to interpret. However, given the limited existing treatment options, it called for further development of dextromethorphan–quinidine as an off-label treatment for agitation. The editorial also noted that the treatment was well tolerated, with no increases in sedation or QTc prolongation, falls, or diarrhea, no detrimental effects on cognition or activities of daily living, and no increase in mortality. This safety profile contrasts favorably with atypical anti-psychotics, the usual pharmacologic treatment for agitation in dementia. However, the study may have been too small and short in duration to observe the less common of these effects.

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

1Cummings J, Lyketsos C, Peskind E, Porsteinsson A, et al: Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. JAMA 2015;314 (September 22/29):1242–1254. From the Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV; and other institutions. Funded by Avanir Pharmaceuticals Inc. Twelve of the study authors declared financial relationships with commercial sources, including Avanir; the remaining author declared no competing interests.


Drug Trade Names: memantine—Namenda; dextromethorphan–quinidine—Nuedexta

*See Reference Guide.

Reference Guide

Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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.

Intent-to-Treat Analysis (ITT): An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone who begins treatment is included regardless of treatment completion. ITT analyses are done to avoid the effects of crossover, drop-out, and other factors that could alter the results or inflate the magnitude of effects.

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 statistical 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.