Histamine Antagonism in Resistant Schizophrenia

Adjunctive use of the histamine H2 receptor antagonist famotidine reduced symptom severity in a randomized trial of patients with severe, resistant schizophrenia.

**Background:** Histamine functions as a neurotransmitter in the brain. Of the 4 receptor subtypes, H2 receptors are present at high density in the thalamus, which is believed to be important in schizophrenia because of its essential role in sensory gating and attention. There is strong evidence from animal studies of a relationship between histamine and schizophrenia and more modest clinical evidence from case reports and uncontrolled studies. Famotidine was investigated in the present study because of its high selectivity for the H2 receptor.

**Methods:** Study subjects (n=30) were recruited from psychiatric hospitals and assisted living centers. All had schizophrenia, with a duration of ≥5 years and a high level of symptoms despite adequate trials of multiple antipsychotic medications. Subjects received a wide range of antipsychotic medications; 11 were taking clozapine. Those already receiving an H2 antagonist or with serious, unstable medical conditions were excluded. After a 1-week placebo run-in, patients received randomly assigned adjunctive treatment with either 100 mg famotidine b.i.d or placebo for 4 weeks. The primary outcome measure was the Scale for the Assessment of Negative Symptoms (SANS). Secondary measures were the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) scales.

**Results:** At study end, patients in the famotidine group had a mean 5-point reduction in the SANS total score, from a baseline of 57. Those in the placebo group showed no change in SANS total score. However, the between-group difference was not statistically significant. Famotidine was also associated with a 9-point reduction in mean PANSS total score, from a baseline of 80, while the placebo group showed a <1 point improvement (p=0.04). Analysis of the PANSS subscales indicated the strongest improvement occurred in general psychopathology relative to...
positive and negative symptoms. CGI scores showed a similar statistically significant pattern. A single patient in the famotidine group worsened on all outcome measures during the trial. When this outlier was excluded from the analysis, improvement effect sizes* were 0.48 for SANS, 0.55 for PANSS, and 1.15 for CGI. Famotidine was well tolerated; no serious adverse effects were reported, and no patient discontinued treatment. Two patients in the active treatment group experienced nausea and gastric discomfort.

**Discussion:** The near 10% reduction in schizophrenia symptoms observed in famotidine-treated patients in this study suggests that the agent may be an effective add-on to antipsychotics in those with severe, treatment-resistant symptoms. The authors suggest that because clinical improvement with famotidine was continual, treatment for >4 weeks might have produced larger between-group differences. However, because very high doses of famotidine are required to penetrate the blood-brain barrier and achieve high receptor occupancy in the brain, long-term treatment with this agent may not be ideal. Nevertheless, this research suggests the histamine system may be a promising target for schizophrenia drug development.

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

Meskanen K, Ekelund H, Laitinen J, Neuvonen P, et al: A randomized clinical trial of histamine 2 receptor antagonism in treatment-resistant schizophrenia. *Journal of Clinical Psychopharmacology* 2013;33 (August):472–478. From the University of Helsinki, Finland; and other institutions. **Funded by the Medical Society of Finland, Helsinki University Central Hospital; and the Lilly Foundation.** Two study authors disclosed financial relationships with commercial sources; the remaining authors declared no conflicts of interest.

*Drug Trade Names:* clozapine—*Clozaril*; famotidine—*Pepcid*

*See Reference Guide.*

**Lisdexamfetamine Reduces Negative Symptoms**

In a manufacturer-sponsored pilot study, lisdexamfetamine dimesylate (*Vyanse*) reduced negative symptoms of schizophrenia in a group of patients whose positive symptoms were well controlled with antipsychotic medications.

**Methods:** The study enrolled 92 clinically stable outpatients receiving maintenance monotherapy with second-generation antipsychotics. Participants were required to have minimal positive symptoms but predominant negative symptoms, with scores indicating at least moderate severity on ≥2 global symptom domains on the Scale for the Assessment of Negative Symptoms (SANS). The study excluded patients at increased risk of adverse events due to positive symptoms of delusions, hallucinations, or suspiciousness/persecution. Those with depression and bradykinesia were also excluded to avoid mistaking improvement in these symptoms for improvement of negative symptoms. Patients were required to have a close informant outside the clinic who could monitor their safety. After 3 weeks of screening and observation, all patients received open-label, flexible-dose lisdexamfetamine for 10 weeks: 7 weeks of dose optimization, followed by 3 weeks of maintenance. Participants with stable reductions in SANS scores during these 3 weeks were randomly assigned to 4 additional weeks of blinded treatment with either lisdexamfetamine or placebo-controlled withdrawal. The primary efficacy outcome measure was the 18-item SANS, which excluded attention ratings and global items.

**Results:** Of 92 patients enrolled, 69 completed the 10-week open-label phase and 56 completed the randomized withdrawal phase. The median lisdexamfetamine dosage at the end of the dose-optimization phase was 50 mg/day. In the 69 patients who received ≥1 lisdexamfetamine dose, SANS scores decreased significantly from 60 at baseline to 47 at week 10 (p<0.001). Improvement was evident beginning in the first week and continued throughout treatment. Response criteria (≥20% decrease in SANS total score) were met by 53% of study patients.
Scores remained stable during the randomized withdrawal phase, with no difference in average scores or response rates between the 2 groups.

Exacerbation of schizophrenia, a concern with stimulants, occurred in 1 patient during open-label treatment and in 2 others (1 in each group) during the randomized withdrawal phase. One patient had exacerbation of hallucinations, and 1 experienced depression during the open-label phase. Other adverse events were consistent with the known effects of lisdexamfetamine. There were no significant amphetamine withdrawal symptoms.

**Discussion:** Hyperactivity of dopamine D2 receptors is believed to underlie positive symptoms of schizophrenia, while negative symptoms and cognitive impairment may be related to deficits in transmission at D1 receptors. After initial enthusiasm for amphetamines, which activate D1 receptors, as a treatment for negative symptoms, use was discontinued because of their potential psychotogenic effects. The present study suggests that if further research replicates their efficacy, amphetamines may be used safely as adjunctive therapy in carefully selected and managed patients with predominantly negative symptoms.

Lasser R, Dirks B, Nasrallah H, Kirsch C, et al: Adjunctive lisdexamfetamine dimesylate therapy in adult outpatients with predominant negative symptoms of schizophrenia: open-label and randomized-withdrawal phases. *Neuropsychopharmacology* 2013; doi 10.1038/npp.2013.111. From Shire Development, LLC, Wayne, PA; and other institutions. Funded by Shire. The authors all disclosed relationships with commercial sources, including Shire.

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**Aripiprazole-Related Hypertension**

Hypertension developed in 2 patients who had been switched to aripiprazole from other antipsychotics. These cases, added to a small number of similar reports in the literature, suggest aripiprazole should be used cautiously in patients with a history of high blood pressure (BP) or cardiovascular disease.

A 69-year-old woman with a 35-year history of schizophrenia had a 2-year history of hypertension, which was controlled with salt reduction and temporary use of amiodipine. Her psychosis had been treated successively over the years with risperidone, perospirone, quetiapine, and olanzapine, but each had to be withdrawn because of various noncardiac adverse effects. With 6 mg/day aripiprazole, the patient experienced dizziness and headache and her BP increased to 200/110 mmHg. Her BP dropped to 130/80 mmHg immediately after aripiprazole was switched to risperidone.

The second patient, a 63-year-old man, had a 9-year history of bipolar disorder and a 1-year history of hypertension that was controlled with temporary use of nifedipine and salt restriction. Because of persisting depressive episodes, he was switched from olanzapine to aripiprazole. After a dosage escalation to 24 mg/day, his BP was elevated to 180/90 mmHg. The BP elevation did not respond to antihypertensive drugs but resolved with discontinuation of aripiprazole.

Although hypotension is a more common side effect of atypical antipsychotic drugs, hypertension has been reported with aripiprazole in 4 previous published cases, including 1 adolescent. The effect has been associated with a history of hypertension or cardiovascular disease. Several possible mechanisms have been proposed, among them agonistic effects on 5-HT2A receptors in smooth muscle, α-1A adrenergic activity, and suppression of nitric oxide production in the brain.

Yasui-Furukori N, Fujii A: Worsened hypertension control induced by aripiprazole. *Neuropsychiatric Disease and Treatment* 2013;9:505–507. From Hirosaki University, Japan. The authors declared no competing interests.

**Drug Trade Names:** amiodipine—Norvasc, and others; aripiprazole—Abilify; nifedipine—Adalat, Procardia; olanzapine—Zyprexa; perospirone—Lullan; quetiapine—Seroquel; risperidone—Risperdal
Suicidal ideation, worsening of anxiety, and dysphoria developed the day after ketamine infusion in 2 patients with refractory obsessive-compulsive disorder (OCD) and a history of depression.1 This observation underscores the need for close follow-up of patients treated with ketamine, ideally in a structured inpatient unit with adequate support.

The patients were among 10 participants in an open-label trial of ketamine for refractory OCD.2 One, a 64-year-old woman with a history of OCD, posttraumatic stress disorder (PTSD), and major depressive disorder, had not experienced response to previous trials of multiple SSRIs, antipsychotics, and glutamate-modulating agents. Her current medications were fluvoxamine, riluzole, N-acetylcysteine, and alprazolam. Before ketamine treatment, she reported subthreshold depressive symptoms and no suicidality. Within an hour after infusion of ketamine, the patient experienced marked decreases in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and Hamilton Rating Scale for Depression (HAM-D) scores. However, over the next few days, she remained pessimistic about her symptoms, slept poorly, and reported suicidal thoughts without suicidal plans or intentions. Her obsessive-compulsive and depressive symptoms soon returned to baseline levels; and she was discharged 1 month after ketamine infusion.

Transient suicidal ideation also developed in a 25-year-old woman with OCD, which had been nonresponsive to multiple SSRIs and antipsychotics. She had a history of trichotillomania, depression, PTSD, and personality disorder not otherwise specified, and reported subthreshold depressive symptoms upon admission. Her current medications were clomipramine and escitalopram. This patient had rapid and marked improvement of OCD and depressive symptoms within a few hours of ketamine infusion. However, she complained of fragmented sleep the night after infusion and, on the following day, reported depressed mood, suicidal thinking, and worsening anxiety and trichotillomania. Her OCD symptoms returned to baseline after about a week.

In both women, adverse effects of ketamine peaked at about 24 hours post-infusion and then subsided. It is possible that the patients’ worsening mood and anxiety was related to reactivation of past symptoms, to an interaction of comorbid personality vulnerabilities and disorders such as PTSD, and/or to a rapid return of OCD symptoms. Ketamine may also have interacted with concomitant medications. Although ketamine has a very short half-life, its metabolites may persist for at least 24 hours. Clinicians should be aware that delayed negative consequences of ketamine infusion can occur and follow patients carefully in the post-infusion period.


Drug Trade Names: alprazolam—Xanax; clomipramine—Anafranil; escitalopram—Lexapro; fluvoxamine—Luvox; riluzole—Rilutek

Antidepressants and Lithium-Induced Hypernatremia

Results of a retrospective study of elderly outpatients suggest that concomitant antidepressant use protects against lithium-induced hypernatremia.

Methods: Charts from 3 geriatric psychiatry clinics were reviewed to identify outpatients, aged ≥65 years, who took lithium for at least 2 months between 1995 and 2010. The records of 55 patients who met study criteria were reviewed to identify hypernatremia, defined as
having at least 1 serum sodium level of ≥147 mEq/L, following the initiation of lithium. Sodium and lithium levels were routinely checked at the clinics approximately every 3 months. The analysis excluded hypernatremia with alternative causes or associated with medical conditions known to cause diabetes insipidus.

**Results:** A total of 35 (64%) patients took antidepressants during lithium use. The 2 groups were similar with regard to age; gender; primary psychiatric illness; use of other psychotropic medications; and medical comorbidities.

Hypernatremia occurred during lithium use in 3 antidepressant users and in 8 patients taking lithium alone (9% vs. 40%; odds ratio,* 0.14; p=0.011). A protective effect was observed for both SSRI and non-SSRI antidepressants. Dose and duration of lithium use did not appear to alter the association.

**Discussion:** Lithium can induce nephrogenic diabetes insipidus, which may be associated with clinically important hypernatremia resulting in somnolence and confusion and sometimes requiring hospitalization in elderly patients. Antidepressants are known to cause hyponatremia, particularly in the elderly. The primary mechanism is believed to be the syndrome of inappropriate antidiuretic hormone secretion (SIADH), which is an infrequent side effect of most of the antidepressants used by patients in the study. It is possible that antidepressant-induced sub-syndromal SIADH may lower the risk of lithium-induced hypernatremia. Hypernatremia can be life-threatening, as can overly aggressive correction of the condition, particularly in the elderly. It remains to be shown whether antidepressants can be used in the prevention of lithium-associated hypernatremia.

**Methylphenidate for Apathy in Alzheimer's**

In a placebo-controlled trial, methylphenidate improved some measures of apathy in patients with Alzheimer's disease.¹

**Background:** Evidence suggests that apathy in Alzheimer’s disease is related to a decrease in dopaminergic neurotransmission, a deficit that could be improved by methylphenidate. Results of a previous crossover trial indicated that the drug had robust effects against apathy.²

**Methods:** The 6-week trial was carried out in 60 patients (mean age, 76 years) who met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) diagnostic criteria for possible or probable Alzheimer’s disease. Participants had clinically significant apathy, according to scores on the Neuropsychiatric Inventory (NPI), with apathy episode frequency rated as "often" or greater and severity rated as "moderate" or "marked". Mini-Mental State Examination (MMSE) scores of ≥10 were also required for study entry. Patients were randomly assigned to receive double-blind treatment with either 20 mg/day methylphenidate or placebo in twice-daily doses. The 18-item Apathy Evaluation Scale (AES), a validated measure of apathy in Alzheimer’s disease, was the primary outcome measure.

**Results:** Patients had received a diagnosis of dementia a mean of 3 years before enrollment. While only 8 patients had a history of depression, 22 were taking SSRIs at baseline. Forty-three were taking acetylcholinesterase inhibitors, and 37 were taking memantine. Of the 60 randomized patients, 57 completed 6 weeks of follow-up and 50 were taking study medication throughout the period.

*See Reference Guide.*
In an intent-to-treat analysis, methylphenidate was associated with a numerically lower (i.e., better) mean score than placebo on the AES (49 vs. 52) at 6 weeks, but the difference was not statistically significant. On the other primary outcome measure, the Clinical Global Impression Change score, 6 patients (21%) who received methylphenidate and 1 patient (3%) who received placebo were rated as having marked or moderate improvement in apathy (odds ratio,* 3.7; p=0.02). Differences in the change in NPI apathy scores also favored methylphenidate (3 vs. 5; p=0.02). Patients who received methylphenidate showed a 1-point increase in MMSE score after 6 weeks, compared with a very slight decline in the placebo group.

Clinically significant hallucinations occurred in 2 methylphenidate patients. Methylphenidate was also associated with somewhat more weight loss and anxiety than placebo. Four patients stopped taking methylphenidate because of side effects, which included anxiety, hypertension, nausea, and nervousness.

Discussion: The sample size calculation for this study was based on the previous crossover trial; therefore, the present study may have lacked power to show a statistically significant effect on the AES score. A larger, more definitive trial to replicate these results appears to be warranted.

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

In a naturalistic study of older patients with anxiety and/or depression, slow titration of paroxetine (Paxil) was associated with greater medium-term improvement and fewer treatment discontinuations compared with starting on the full dose.

Background: Treatment guidelines commonly recommend gradual titration of antidepressants in older patients to avoid early worsening of anxiety, but the effectiveness of this practice has not been studied specifically.

Methods: The 47 study participants met DSM-IV criteria for unipolar depression or anxiety disorder and had scores of ≥13 on the Hamilton Rating Scale for Depression (HAM-D) or the Hamilton Anxiety Rating Scale (HAM-A). Thirty patients had a diagnosis of major depressive disorder alone, and 11 had major depression with a comorbid anxiety disorder. The remaining 6 patients had anxiety disorders without meeting diagnostic criteria for depression. The trial was open-label, and treatment assignment was naturalistic, not randomized. Paroxetine was started at the full dosage of 10 mg/day in 22 patients. In 25, daily paroxetine was started via an oral drop solution at 2.5 mg/day for 2 days, and then titrated upward by 2.5 mg on alternate days, reaching the full 10-mg dose on day 7. Primary study outcomes were the percent reductions on the 21-item HAM-D, the HAM-D subscales, and the HAM-A, administered weekly through the 8th week of treatment.

Results: At baseline, patients in the gradual-titration group had significantly higher scores on the psychic anxiety subscale of the HAM-D (3.1 vs. 2.2; p=0.03). During the first 3 days of

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Drug Trade Names: memantine—Namenda; methylphenidate—Ritalin, and others

*See Reference Guide.
treatment, patients who received full-dose paroxetine had significant worsening of psychic anxiety (HAM-D score, 2.4; 11% increase) compared with improvement (HAM-D score, 2.8; 11% decrease) in the slow-titration group (p=0.03). Statistically significant differences in psychic anxiety between the groups was also observed at weeks 2 and 5 (p<0.05) and weeks 6 through 8 (p<0.01).

Baseline HAM-D total scores were 17.7 and 16.8 in the slow titration and full-dose groups, respectively. At week 2, the mean HAM-D total scores were reduced by 38% and 17% to scores of 11 and 14 in the slow-titration and full-dose groups, respectively (p=0.02). At week 8, HAM-D decreases were significantly greater in the slow titration group (p=0.01); final scores were 5 and 9, respectively.

Average HAM-A total scores also differed between the groups throughout most of the study. At week 8, HAM-A scores were decreased from a baseline mean of 18 in both groups to 4 in the slow-titration group and 9 in the full-dose group (p=0.006).

A total of 3 patients in the slow-titration group discontinued paroxetine prematurely, 2 because of adverse effects (i.e., nausea, blurred vision). Nine patients in the rapid titration group withdrew, 6 because of side effects (i.e., abdominal pain; constipation; diarrhea; sexual dysfunction; sedation; paradoxical anxiety).

Gibino S, Mori E, De Ronchi D, Serretti A: Potential benefits of slow titration of paroxetine treatment in an elderly population: eight-week results from a naturalistic setting. *Journal of Clinical Psychopharmacology* 2013;33 (August):565–569. From the University of Bologna, Italy. Source of funding not stated. One study author disclosed financial relationships with commercial sources; the remaining authors declared no conflicts of interest.

### Long-Term Effects of Reducing Antipsychotic Exposure

In patients experiencing remission after first-episode psychosis, early antipsychotic dose reduction or discontinuation was associated with better long-term functional recovery compared with maintenance therapy, despite a higher rate of relapse during the first few years.\(^1\) This research reinforces the importance of reducing the overall antipsychotic load and focusing on treatment goals beyond relapse prevention, according to an editorial.\(^2\)

**Methods:** This analysis of long-term outcomes from an earlier study included patients with first-episode psychosis, who had been experiencing remission for ≥6 months. These patients were randomly assigned to discontinuation or dose reduction (DR) or to maintenance therapy, and then followed for 2 years after the start of first remission. For the present analysis, patients in the initial trial were re-interviewed 5 years later, 7 years after the start of remission. Of 128 patients participating in the original trial, 103 were included in the 7-year follow-up. Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS), and social functioning with the Groningen Social Disabilities Schedule (GSDS). The study used 7 of the functional domains of the GSDS: self-care; housekeeping; family relationships; partner relationships; relationships with peers; community integration; and vocational functioning. Functional remission was defined as no or minimal disability in all 7 domains.

**Results:** At 7 years, about two-thirds of patients in both groups were experiencing symptomatic remission. Functional remission was significantly more frequent in the DR group: 46% vs. 20% (p=0.01). Symptomatic remission without functional remission was present in 29% of the DR group and 49% of the maintenance therapy group.

Overall, 67 patients (65%) had ≥1 relapse of psychosis during the 7 years, with a similar proportion in the 2 groups. Patients who discontinued or reduced their medication had a higher relapse rate at first, but after 3 years, the frequency of relapse in the 2 groups converged.
A total of 34 patients had stopped taking antipsychotics or reduced their haloperidol-equivalent dosage to <1 mg by year 7. Twenty-two of these patients were in the DR group, and 12 in the maintenance therapy group. Of these 34 patients, 29 (85%) were experiencing symptomatic remission and 19 (56%) were experiencing functional remission; 18 (53%) patients were experiencing both symptomatic and functional remission and were considered recovered. These patients had about half the number of relapses as patients who stayed on full-dose medication (0.71 vs. 1.51; p=0.005).

**Discussion:** A lower antipsychotic load may have contributed to the better functional outcomes in the DR group. For all its positive effects, dopamine blockade may compromise mental functions such as alertness, curiosity, drive, and activity levels, as well as aspects of executive function. Dose reduction and discontinuation may relieve dopamine blockade that has become redundant when patients achieve symptomatic remission, improving functional capacity in the long term.

**Editorial:** To a large degree, relapse prevention has become the driver of treatment and research rather than an intermediate goal. The present study should put relapse prevention in perspective; although undesirable, relapse may be a price worth paying for better long-term functional recovery. In clinical practice, excessive doses of antipsychotics are often used to manage distress and behavioral symptoms, rather than psychosocial treatments or benzodiazepines. Combining dose reduction strategies with specialized early psychosis care is likely to increase the number of patients with functional recovery.

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1 Wunderink L, Nieboer R, Wiersma D, Sytema S, et al: Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry* 2013; doi 100.1001/jamapsychiatry.2013.19. From Friesland Mental Health Services, Leeuwarden; and the University of Groningen, The Netherlands. **Funded by Janssen-Cilag Netherlands; and Friesland Mental Health Services. The authors declared no conflicts of interests.**

2 McGorry P, Alvarez-Jimenez M, Killackey E: Antipsychotic medication during the critical period following remission from first-episode psychosis: less is more [editorial]. *JAMA Psychiatry* 2013; doi 10.1001/jamapsychiatry.2013.264. From the University of Melbourne, Parkville, Australia. **The authors declared no conflicts of interests.**

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**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.

**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.

**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.