Memantine for Preclinical Lewy Body Dementia

A patient with preclinical Lewy body dementia experienced resolution of hallucinations and improved attention when treated with memantine (Namenda).

Lewy body dementia has core features of fluctuating cognitive function, frequent concrete visual hallucinations, and idiopathic parkinsonism. A supporting feature of the diagnosis is low uptake metaiodobenzylguanidine (MIBG) myocardial scintigraphy, which suggests an autonomic disorder. The NMDA receptor antagonist memantine has previously shown positive effects on visual hallucinations in Lewy body dementia. Frequent, complex visual hallucinations with insight but no dementia—termed Charles Bonnet syndrome (CBS)—is thought to be a preclinical stage of the disorder.

A 78-year-old woman, previously healthy and medication-free, began to experience daily visual hallucinations. She had insight and was aware that the visions were hallucinations. She had mild cognitive impairment (Mini-Mental State Examination [MMSE] score of 25), which did not fluctuate. She did not exhibit dementia or parkinsonism. She had normal findings on brain MRI and SPECT studies but low uptake on MIBG myocardial scintigraphy. Based on these findings, a diagnosis of CBS was made.

Memantine was started at 5 mg/day and gradually increased to 15 mg/day. The patient experienced complete resolution of the visual hallucinations within 1 week. Hallucinations recurred when the dosage was temporarily decreased to 10 mg/day. She reported no adverse effects of memantine and no further hallucinations after 4 months on the 15-mg/day dosage. Her MMSE score improved slightly, but memory test scores worsened, consistent with progression to dementia. No improvement was observed in MIBG myocardial scintigraphy, which suggests that memantine did not improve autonomic dysfunction.

Takaya M, Matusaka K, Yanagida M, Kimura R, et al: The effects of memantine on a patient having preclinical dementia with Lewy bodies. General Hospital Psychiatry 2012; doi 10.1016/j.genhosppsych.2012.06.017. From Osaka General Medical Center, Japan. The authors did not include disclosure of potential conflicts of interest.
Antipsychotic Drug Comparisons

Second-generation antipsychotics now account for three-fourths of all antipsychotic prescriptions. Because recent research has called into question their presumed superiority over first-generation agents, the Agency for Healthcare Research and Quality funded the first meta-analysis to include an assessment of the strength of the evidence.

Methods: Investigators identified all published and unpublished studies, conducted since 1950, comparing first- and second-generation antipsychotics in adults with schizophrenia or related psychosis. Of >9700 studies identified, 114 primary publications met criteria and were included in the meta-analysis. The studies were published between 1974 and 2012 and involved 22 drug comparisons. Most were randomized clinical trials, with a median 8 weeks of follow-up. Also included were 2 cohort studies with 3 and 22 years of follow-up.

Results: Of the controlled trials, one-third were judged to have a high risk of bias, while none were judged to have low risk. Two-thirds of the studies were funded by the pharmaceutical industry, and funding was not disclosed for 19% of the studies.

Few clinically important differences between drugs were observed. Haloperidol was superior to olanzapine for improving positive symptoms, but this result was dependent on the measurement scale used. The evidence for second-generation drugs’ superiority in treating negative symptoms was stronger, with clear evidence of superiority of olanzapine over haloperidol. The benefits of risperidone and aripiprazole, while statistically significant, were not considered clinically important. Analyses of response rates showed superiority of clozapine over chlorpromazine (3 studies), olanzapine over haloperidol (3 studies), and risperidone over haloperidol (6 studies).

Patient-oriented outcomes included measures of health-related quality of life, sexual function, employment, and economic independence. Results for functional outcomes showed no significant differences between first- and second-generation agents. Comparisons of adverse events generally favored second-generation agents over first-generation drugs. Olanzapine produced higher rates of metabolic syndrome than haloperidol, but the evidence was not high quality.

Discussion: The present analysis used a broad approach in an attempt to provide a useful perspective on the question. For most comparisons, there were no clinically important differences between first- and second-generation antipsychotics. However, in most cases the strength of evidence was low or insufficient and future research may lead to different conclusions.

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


Drug Trade Names: aripiprazole—Abilify; clozapine—Clozaril; haloperidol—Haldol; olanzapine—Zyprexa; risperidone—Risperdal

*See Reference Guide.

Genetic Influence on Antipsychotic Weight Gain

According to a study in patients taking newly-prescribed antipsychotics, genetic variants can be used to predict severe antipsychotic-induced weight gain. This observation has implications for preventing weight gain in patients requiring antipsychotic treatment and potentially for generalized obesity prevention.

Methods: Investigators conducted a genome-wide association study in a cohort of 139 patients, aged ≤19 years, with no prior exposure to antipsychotics. Patients were treated with aripiprazole,
olanzapine, quetiapine, or risperidone according to clinical indication. The statistical analysis was based on weight gain at 12 weeks. Patients taking olanzapine were excluded from the analysis because the frequency of extreme weight gain was significantly higher with this drug than with the other 3. Results of the analysis were then validated in 3 additional cohorts: 73 adults with no previous exposure to atypical antipsychotics who were given a prescription for clozapine after unsuccessful trials of conventional agents; 40 adults hospitalized for treatment with an atypical antipsychotic, not necessarily for the first time; and 92 patients with first-episode schizophrenia receiving an atypical antipsychotic by random assignment. Treatment adherence was monitored in all studies, and nonadherent patients were excluded from the analysis.

**Results:** In the initial pediatric cohort, 20 single-nucleotide polymorphisms were identified at a single locus, each of which exceeded the p<0.00001 threshold for statistically significant association with antipsychotic-induced weight gain. The locus, on chromosome 18, is located near the MC4R (melanocortin 4 receptor) gene, previously implicated in obesity. The identified locus also overlaps a region previously identified in general-population studies of obesity, body mass index (BMI), and type 2 diabetes. For each of the polymorphisms, the effect was recessive: homozygosity of the less common variant was associated with greater weight gain, while heterozygosity or homozygosity of the dominant variant was associated with smaller weight gain. Results did not differ among the 3 drugs or according to patient gender, race, or baseline BMI.

These results were replicated in the 3 additional cohorts. In the initial cohort, homozygosity of the minor alleles was also associated with antipsychotic-induced increases in triglycerides, leptin, insulin resistance, and total fat mass, as well as borderline-significant changes in total cholesterol and HDL cholesterol.

**Discussion:** According to the investigators' previous work, extreme weight gain (>20% of baseline weight) occurs in about one-fourth of patients taking aripiprazole, quetiapine, or risperidone and in the majority of patients taking olanzapine. The present research may lead to identification of patients who should be steered toward drugs with less liability for weight gain, particularly individuals without psychosis. MC4R antagonists are now in development and may eventually be co-administered with antipsychotics in patients with a high-risk genotype.

Malhotra A, Correll C, Chowdhury N, Muller D, et al: Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic-induced weight gain. *Archives of General Psychiatry* 2012; 69 (September): 904–912. From the Feinstein Institute for Medical Research, Manhasset, NY; and other institutions. **Funded by the NIH; and the Brain and Behavior Research Foundation. Nine of the 15 study authors disclosed relationships with commercial sources.**

**Drug Trade Names:** aripiprazole—Abilify; clozapine—Clozaril; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal

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**Adjunctive Nefazodone in Bipolar Depression**

Adding nefazodone to existing mood-stabilizer treatment significantly improved depressive symptoms in a small group of patients with bipolar depression.

**Background:** Nefazodone use has been associated with rare cases of severe liver injury, and Bristol Myers Squibb discontinued its branded formulation (Serzone) in 2003. Although generic formulations exist, the inability to predict this potentially fatal adverse effect has limited the drug’s use. However, because nefazodone selectively blocks postsynaptic 5-HT2A, the authors hypothesized that when used in addition to a mood stabilizer, it would improve depressive symptoms without inducing mania. They noted that, “[nefazodone] nonetheless serves as a model for the possible value of antidepressants with postsynaptic 5-HT2A blockade.”
Methods: Study subjects were 13 adults, aged ≥18 years (7 females), with nonpsychotic bipolar depression who were receiving a mood stabilizer that had been held at a stable dose for ≥1 month. Participants were required to have a Hamilton Rating Scale for Depression (HAM-D) score of >15 and a Young Mania Rating Scale (YMRS) score of <12. Those with a history of rapid cycling in the past year were excluded. Baseline medications included divalproex (n=6); lithium (n=3); carbamazepine (n=2); clozapine (n=1); lamotrigine (n=2); olanzapine (n=2); and topiramate (n=1). Open-label nefazodone was added to patients’ current regimen at 100 mg/day, and then increased weekly in 100-mg increments to a target of 300–600 mg/day. Dosage changes were not permitted for other medications. The primary outcome was change in HAM-D score. Response was defined as a ≥50% reduction in score, and remission as a score of ≤7.

Results: All participants completed ≥2 weeks of treatment; 9 of 13 (69%) completed the 8-week protocol. The mean HAM-D score decreased from 26.1 at baseline to 18.5 with nefazodone treatment (p=0.02; effect size,* 0.44). A total of 8 patients (62%) met response criteria, and by study end, 4 patients (31%) met remission criteria. Overall, YMRS scores remained low (<5) and did not change during nefazodone treatment. Treatment-emergent mania developed in 1 patient receiving 600 mg/day nefazodone. Adverse effects included sedation (n=5); diarrhea (n=3); nausea (n=2); GI upset (n=2); and insomnia, headache, dizziness, and decreased libido (n=1 each). Hepatic function was not systematically evaluated during the study, but no patient demonstrated clinical signs of dysfunction.

Discussion: These results suggest that adjunctive nefazodone has moderate antidepressant efficacy with modest risk of mood destabilization in patients with bipolar depression. However, because of the small sample and the open-label design, the results must be considered preliminary. The author acknowledges that in light of the potential for liver toxicity, these positive results are not likely to increase nefazodone use.

Goldberg J: A preliminary open trial of nefazodone added to mood stabilizers for bipolar depression. Journal of Affective Disorders 2012; doi 10.1016/j.jad.2012.04.037. From Mount Sinai School of Medicine; New York, NY; and Silver Hill Hospital, New Canaan, CT. Funded by Bristol Myers Squibb; and other sources. The author disclosed financial relationships with several commercial sources.

Drug Trade Names: carbamazepine—Epitol, Tegretol; clozapine—Clozaril; divalproex—Depakene, Depakote; lamotrigine—Lamictal; mirtazapine—Remeron; olanzapine—Zyprexa; topiramate—Topamax; trazodone—Desyrel

*See Reference Guide.

Agomelatine Rapidly Improves Anhedonia

In a preliminary clinical trial, agomelatine (not available in the U.S.) was superior to extended-release venlafaxine at improving anhedonia in patients with major depressive disorder, beginning after the first week of treatment.

Methods: An 8-week, randomized, open-label trial was carried out in 60 patients with DSM-IV major depressive disorder. Following a 7-day antidepressant washout, patients were randomly assigned to 8 weeks of treatment with either 25–50 mg/day agomelatine or 75–150 mg/day venlafaxine. The primary outcome was improvement on the Snaith-Hamilton Pleasure Scale (SHAPS) for anhedonia.

Results: Patients in both treatment groups experienced significant reductions from baseline in mean SHAPS scores, as well as improvement on the secondary depression and anxiety measures. In the agomelatine group, the reduction in SHAPS anhedonia score was statistically significant beginning at the 1-week assessment. SHAPS scores differed between the 2 treatment groups at all assessments: week 1 (p<0.05), week 2 (p<0.01), and week 8 (p<0.01). Patients in the agomelatine group also had significant improvement in Clinical Global Impressions scores
at week 8 (p<0.05), while those in the venlafaxine group did not. Depression and anxiety symptom scores did not differ between the 2 groups at any time point. Adverse events affected fewer patients taking agomelatine (n=1) than venlafaxine (n=11). Five patients stopped taking venlafaxine because of GI effects. One patient who received agomelatine developed confusion severe enough to withdraw from treatment.

**Discussion:** Anhedonia is a core feature of depression and a frequent residual symptom after treatment. Agomelatine has melatonergic as well as serotonergic activity. Hypothetically, melatonergic effects leading to circadian rhythm resynchronization could help regulate hedonic capacity.

**Editor’s Note:** Agomelatine is available for the treatment of depression in many European countries. It was expected to be presented for FDA approval in the U.S. by 2012. However, late in 2011 Novartis discontinued development of the drug, presumably because of unimpressive efficacy results and the potential for liver toxicity.

**Study Rating**—15 (88%): This study met most criteria for a randomized trial, but treatment was open-label and study raters were not blinded to treatment assignment.

**Drug Trade Names:** agomelatine (not available in the U.S.)—Valdoxan; venlafaxine—Effexor

**Agomelatine for GAD Relapse Prevention**

In a manufacturer-sponsored controlled trial, the dual-mechanism antidepressant agomelatine, recently introduced in Europe, was superior to placebo in preventing relapse in patients with generalized anxiety disorder.

**Methods:** Participants in this multicenter clinical trial were adults with a primary clinical diagnosis of GAD. All had a minimum score of 22 on the 14-item Hamilton Rating Scale for Anxiety (HAM-A) and depression symptoms of no more than minimal severity. All patients received 16 weeks of 25 mg/day open-label agomelatine, which could be increased to 50 mg/day in patients with insufficient improvement. After 16 weeks, patients who met criteria for clinical response (HAM-A score of ≤10 and a ≤4-point change since week 12) were randomly assigned to maintenance therapy with either agomelatine or placebo. Patients who improved but did not meet these criteria were not randomized but continued on agomelatine. After another 26 weeks, all agomelatine-treated patients were randomly assigned to continued active medication or placebo for another week so that the short-term effects of discontinuation could be observed. The primary efficacy endpoint was relapse, defined by clinical judgement or a HAM-A total score of ≥15, during the randomized study phase.

**Results:** At study entry, the median duration of illness was 8 years and the average baseline HAM-A score was 28, indicating severe illness. A total of 477 patients began open-label treatment, 329 (69%) completed this phase, and 227 patients (48%) received randomized maintenance treatment. A total of 100 patients improved by week 16 but did not meet criteria for randomization; they were continued on open-label agomelatine. For those 100 patients, mean HAM-A scores decreased from 15 at week 16 to 8 at week 42.

In the randomized patients, relapse rates were lower with agomelatine than placebo (20% vs 31%, respectively; p=0.046). Agomelatine was superior to placebo in preventing relapse in a subset of the most severely ill patients, 135 persons with baseline HAM-A scores of ≥25 and Clinical Global Impression–Severity scores of ≥5 (21% vs 43% relapsed; p=0.006).
Agomelatine was well tolerated and did not appear to cause discontinuation symptoms. The most common agomelatine-related symptoms that exceeded rates in the placebo group were headache, nausea, gastroenteritis, and dizziness.

**Discussion:** Agomelatine is an antidepressant with both serotonergic and melatonergic activity that has also shown antianxiety effects in patients with depression. Several other antidepressants from multiple classes have been found to be effective in relapse prevention in GAD. The present data suggest agomelatine may have comparable efficacy to these agents.

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

Stein D, Abokas A, Albarran C, Olivier V, et al: Agomelatine prevents relapse in generalized anxiety disorder: a 6-month randomized, double-blind, placebo-controlled discontinuation study. *Journal of Clinical Psychiatry* 2012;73 (July):1002–1008. From Groote Schuur Hospital, Cape Town, South Africa; and other institutions. **Funded by Servier, Suresnes, France.** All study authors disclosed relationships with commercial sources, including Servier.

*See Reference Guide.

### Vortioxetine in Generalized Anxiety Disorder

In a randomized clinical trial, the investigational antidepressant vortioxetine (LU AA21004) was superior to placebo in treating generalized anxiety disorder (GAD).

**Background:** Vortioxetine is a multimodal antidepressant believed to work via both serotonin reuptake inhibition and mixed agonistic and antagonistic activity at different serotonin receptor sites. It is associated with increased levels of serotonin, norepinephrine, dopamine, acetylcholine, and histamine in the ventral hippocampus and median prefrontal cortex. A 10-mg/day dosage was shown to be effective in depression.

**Methods:** Subjects (n=300) in this phase III, multicenter study, conducted mostly in Eastern European countries and South Africa, were adults with a primary diagnosis of GAD, of at least moderate severity (Hamilton Rating Scale for Anxiety [HAM-A] scores ≥20), and with few or no depressive symptoms. Patients received randomly assigned double-blind 5 mg/day vortioxetine or placebo for 8 weeks. The primary efficacy measure was change from baseline in HAM-A score.

**Results:** About 40% of patients had received previous treatment for GAD. Almost all had received medication, and about half had been treated with an SSRI. The average baseline HAM-A score was 27.

At 8 weeks, HAM-A scores were decreased by a mean of 14 points with vortioxetine, compared with 11 points with placebo (p<0.001; effect size,* 0.55). Secondary efficacy outcomes also showed vortioxetine to be superior to placebo. Rates of response, defined as a ≥50% decrease from baseline in HAM-A total score, were 62% with vortioxetine and 40% with placebo (odds ratio,* 2.4; p<0.001; number needed to treat,* 5). Remission, defined as a HAM-A total score of ≤7, occurred in 30% of the vortioxetine group and in 18% of the placebo group (odds ratio, 2.0; p<0.021; number needed to treat, 9).

Subgroup analyses showed no differences in vortioxetine response between men and women. However, it was less effective in patients over age 55 years than in younger patients and in patients with a history of pharmacotherapy for anxiety. Treatment was more effective in patients with more severe GAD.

The primary adverse effects attributable to vortioxetine were nausea (11% of patients vs 3% of placebo patients), headache (7% vs 6%), and dizziness (5% vs 3%); <1% of patients experienced sexual side effects. A total of 9 patients stopped taking vortioxetine because of adverse effects. There were no serious adverse events with the active medication.
**Discussion:** This is 1 of 2 clinical trials of vortioxetine in GAD. The other trial, conducted in the U.S., did not find vortioxetine superior to placebo, despite an identical study design. Possible reasons for the difference will be discussed in the U.S. study publication, which is in preparation and will be covered in an upcoming issue of *Psychiatry Drug Alerts*.

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

Bidzan L, Mahableshwarkar A, Jacobsen P, Yan M, et al: Vortioxetine (LU AA21004) in generalized anxiety disorder: results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. *European Neuropsychopharmacology* 2012; doi 10.1016/j.euroneuro.2012.07.012. From the Medical University of Gdansk, Poland; and other institutions. *Funded by Takeda Pharmaceutical Company.* Three of the 5 study authors disclosed relationships with commercial sources, including Takeda; the remaining 2 authors did not disclose potential conflicts of interest.

*See Reference Guide.*

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**Treatment Selection and Depression Outcomes**

According to results of a systematic review, antidepressants and psychotherapy for major depression are not superior to alternative therapies or to active intervention control treatments. Combination treatment may provide a slight advantage. These results suggest that the type of treatment offered may be less important than engaging patients with depression in an active treatment program of any kind.

**Methods:** All pivotal, placebo-controlled, antidepressant drug-registration trials submitted to the FDA since 1987 (n=62; 13,802 patients; leading to registration of 11 drugs) were reviewed. In addition, exhaustive searches for treatments of traditionally accepted psychotherapies (cognitive, behavioral, and related treatments) and accepted alternative therapies (acupuncture and exercise) were also conducted. All trials included adult outpatients, aged 18–65 years, receiving acute treatment for a major depressive disorder including dysthymia and postpartum depression. Patients with treatment-resistant disease were excluded. Depressive symptoms were measured using the Hamilton Rating Scale for Depression (HAM-D), the Beck Depression Inventory (BDI), or the Montgomery-Asberg Depression Rating Scale (MADRS). Control treatments were designated as either active (e.g., sham acupuncture, therapies not specific to depression) or inactive (placebo, waiting list, or treatment-as-usual).

**Results:** The analysis showed that antidepressant drugs were significantly superior to placebo (p<0.001) and that the combination of drugs plus psychotherapy was superior to other active treatments. However, there were no differences among any of the single-modality active treatments. In trials with blinded raters, combination therapy was associated with a 53% symptom reduction, compared with rates of 46–47% for antidepressants, psychotherapy, or alternative treatments and 42% for active controls. Average symptom reductions were 38% for placebo and 36% for treatment-as-usual, which were both superior to a waiting-list control. (See table.) All active treatments differed significantly from placebo except for alternative therapy, perhaps because of less statistical power owing to a smaller number of trials. Studies with unblinded raters tended to find larger effects than those with double-blinding.

<table>
<thead>
<tr>
<th>Percentage Symptom Reduction</th>
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<tbody>
<tr>
<td>Combination Therapy</td>
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<td>Antidepressants</td>
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<td>Psychotherapy</td>
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<td>Alternative Therapies</td>
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<td>Treatment-As-Usual</td>
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<td>Waiting-List Control</td>
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**Discussion:** A number of recent articles have emphasized the inability of many antidepressant trials to demonstrate statistical superiority of the drug to placebo. Psychotherapies have also come under scrutiny for showing equivalent efficacy to active control treatments. The present analysis supports the hypothesis that differences among depression treatments and
most types of controls are small, and even smaller if the analysis is limited to studies with stringent blinding. It is likely that most treatments, including active control conditions and even placebo treatment, share common therapeutic factors such as evaluation, expectation for improvement, and participation in a therapeutic ritual with an expert healer.

**Study Rating**—16 (89%): This study met most criteria for a systematic review but individual study quality was not assessed.

Khan A, Faucett J, Lichtenberg P, Kirsch I, et al: A systematic review of comparative efficacy of treatments and controls for depression. *PLoS One* 7(7): e41778; doi 10.1371/journal.pone.0041778. Published online July 30, 2012. From Northwest Clinical Research Center, Bellevue, WA; and other institutions. *This study was conducted without funding. The authors declared no conflicts of interest.*

*See Reference Guide.

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

**Number Needed to Treat (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 is the treatment.

**Odds Ratio:** A comparison of the probability of an event in two 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.