Lisdexamfetamine for Binge Eating Disorder

In a manufacturer-sponsored, multicenter, placebo-controlled trial, lisdexamfetamine (Vyvanse) was associated with reduced binge eating behavior and weight loss in patients with moderate-to-severe binge eating disorder.¹

**Methods:** Study subjects (n=255; 82% women) were adults, aged 18–55 years (mean age, 39 years), who met DSM-IV-TR criteria for binge eating disorder and had no other eating disorder, ADHD, or other psychiatric illness. Patients were randomly assigned to receive placebo or fixed-dose lisdexamfetamine 30, 50, or 70 mg/day, with weekly stepped 20-mg titration for the 2 higher doses. The primary efficacy endpoint was change from baseline to week 11 in the number of binge eating days per week, determined by clinician interviews and confirmed by patients' binge eating diaries.

**Results:** The mean number of binge eating days per week at baseline was 4.5 in all groups. Lisdexamfetamine at the 2 higher doses, but not the lowest dose, was associated with a significantly greater reduction than placebo in the number of binge eating episodes (-4.1 vs. -3.3; p≤0.008) and a higher rate of response, defined as cessation of binge eating for 4 consecutive weeks (42–50% vs. 21%; p≤0.01). Results for several other secondary outcomes, including Clinical Global Impression–Improvement ratings, self-rated abnormal eating behavior, and obsessions and compulsions related to binge eating, all significantly favored lisdexamfetamine, particularly at the higher doses.

Body weight was assessed as a safety variable. Lisdexamfetamine was associated with weight loss, which averaged 9.5 pounds for the 3 dosages. The safety profile of lisdexamfetamine was consistent with the experience in adults with ADHD. One patient in the study died after taking an overdose of methamphetamine. This was believed to be unrelated to study medication, but it should be noted that lisdexamfetamine is a controlled substance and carries a black box warning about the potential for abuse and dependence.

**Discussion:** Pathologic overeating is believed to be related to dopaminergic and noradrenergic dysfunction. Lisdexamfetamine is a prodrug of dextroamphetamine, which inhibits
reuptake of dopamine and norepinephrine and elicits release of monoamine neurotransmitters. Antidepressants also affect these systems and reduce the frequency of binge eating behaviors, but they do not produce weight loss.

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

**Editor’s Note:** Under the FDA’s priority review program, which provides expedited review of agents intended to treat serious diseases or to provide a significant improvement over available therapies, lisdexamfetamine received approval for the treatment of binge eating disorder in January 2015. The agent is dispensed with a medication guide warning about risks including cardiac complications and psychotic symptoms.

1McElroy S, Hudson J, Mitchell J, Wilfley D, et al: Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry* 2015;72 (March):235–246. From Lindner Center of HOPE, Mason, OH; and other institutions. Funded by Shire Development, LLC. Eight study authors declared financial relationships with commercial sources, including Shire; the remaining 2 authors declared no conflicts of interest.

2FDA News Release: FDA expands uses of Vyvanse to treat binge-eating disorder. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

*See Reference Guide.

---

**Quetiapine for Generalized Anxiety Disorder**

In 2009, the Psychopharmacologic Drugs Advisory Committee of the FDA denied AstraZeneca’s application for a generalized anxiety disorder (GAD) monotherapy indication for quetiapine XR (*Seroquel*), not because the agent was ineffective, but because safety data were lacking. According to a literature review, quetiapine may play an important role in the treatment of GAD.

**Methods:** A literature search identified all published studies (n=9) of quetiapine for the primary management of GAD in adults. These included 3 studies of acute monotherapy, 1 of maintenance monotherapy, and 5 of acute adjunctive therapy. Most studies evaluated the sustained-release (XR) formulation, which appears to be identical in efficacy and tolerability to the immediate-release (IR) formulation.

**Results:** The 3 acute monotherapy trials were all placebo-controlled, and 2 also included an SSRI as an active comparator. The trials were large, with over 800 to nearly 1000 participants, and lasted 10 weeks—probably too little time to observe the full effects of quetiapine or SSRI treatment, and certainly not long enough to provide sufficient information on adverse effects. Quetiapine produced significant improvement in the Hamilton Anxiety Rating Scale (HAM-A), the common primary endpoint of the 3 trials. In some studies, improvement occurred as early as treatment day 4. The 150-mg/day dosage appears to offer the best response and remission rates, 62–71% and 37–43%, respectively. The 50-mg and 300-mg/day dosages were also significantly superior to placebo, but the highest dose did not offer superior efficacy to 150 mg.

In the study of maintenance monotherapy, 432 patients receiving open-label quetiapine were randomly assigned to either continue their established dose or switch to placebo. All 3 doses of quetiapine were associated with prolonged time to an "anxiety event," defined as a recurrence of significant anxiety symptoms or use of off-study anxiety medications. Anxiety events occurred in 10% of patients receiving quetiapine and 39% of the placebo group, and median times to recurrence of anxiety were 107 and 69 days, respectively. The trial was terminated prematurely as a result of meeting a predetermined number of anxiety events, and the long-term safety could not be investigated.

In the augmentation trials, quetiapine was added to traditional anxiolytic, SSRI, or SNRI therapy. The trials varied in background therapy, duration (8–18 weeks), design (2 were open-label and uncontrolled), GAD severity, comorbidity, and reported outcomes. Because of this
heterogeneity, it is difficult to draw conclusions about the efficacy of adjunctive quetiapine in GAD. The 3 controlled trials did not report any advantage of quetiapine over placebo in response or remission rates. Remission occurred in 48% and 72% of patients in the 2 open-label studies.

Adverse effects of quetiapine were those already reported in the product labeling. There is little information on adverse effects specific to patients with GAD, and further observation is required because patients’ tolerance of antipsychotic medications may vary based on psychiatric diagnosis.

Kreys T-J, Phan S: A literature review of quetiapine for generalized anxiety disorder. *Pharmacotherapy* 2015;35 (February): 175–188. From California Northstate University, Elk Grove; and the University of Georgia, Albany. This review was conducted without funding. The authors declared no conflicts of interest.

### Vortioxetine and Cognitive Deficits

In a manufacturer-sponsored controlled trial, vortioxetine was associated with statistically significant but modest improvement in cognitive function in patients with major depression.

**Background:** Mood disorders are often accompanied by impairments in cognitive function. The present study was conducted to explore the effect of vortioxetine on specific cognitive domains, following earlier reports suggesting positive effects on cognitive function.

**Methods:** Study subjects were 602 adults, aged 18–65 years, from 80 centers in the U.S. and Europe. Participants were experiencing a current depressive episode in the context of recurrent major depressive disorder and reported cognitive problems such as difficulty concentrating, slow thinking, and difficulty learning or remembering new things. Patients were randomly assigned to 8 weeks of treatment with either vortioxetine, placebo, or duloxetine, the latter as an active control for antidepressant effects. Vortioxetine was administered at 10 or 20 mg/day at the clinician’s discretion. The primary efficacy measure was the Digital Symbol Substitution Test (DSST), which measures multiple cognitive domains: executive function, processing speed, attention, spatial perception, and visual scanning. A major secondary endpoint was the Perceived Deficits Questionnaire (PDQ), a patient-reported measure of cognitive function.

**Results:** About 85% of each treatment group completed the 8-week study. The group receiving vortioxetine showed a larger improvement than the placebo group on the DSST (p=0.019), with an effect size* of 0.25. Duloxetine and vortioxetine had similar effects on the DSST; however, duloxetine was numerically but not statistically superior to placebo. A path analysis* showed that 76% of the effect of vortioxetine on the DSST was direct, rather than secondary to relief of depression.

Both vortioxetine and duloxetine were associated with improvement in the PDQ domains of attention/concentration and planning/organization (p≤0.001 for both drugs). Patients taking the 2 active medications had overall improvement in depression on the Clinical Global Impression scale and the Montgomery-Asberg Depression Rating Scale. Vortioxetine was associated with improvement on the Trail-Making Tests of processing speed and executive function, but not on several of the study’s other secondary cognitive measures. Patients who received vortioxetine showed a statistically significant improvement on the University of San Diego Performance-Based Skills Assessment (p<0.001), while the duloxetine group did not.

**Discussion:** Cognitive performance has not been measured in a consistent manner in studies of antidepressant treatment. The present study used a measure that was believed to capture the main aspects affected by depression: verbal learning, verbal memory, attention, executive function, and working memory.
Although duloxetine was also associated with improvement in some cognitive measures, significant improvements occurred in fewer areas than with vortioxetine, and path analysis showed these changes were the result of duloxetine’s antidepressant effects. Conclusions about the relative efficacy of the drugs for depression-related cognitive dysfunction cannot be drawn from this study.

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


**Drug Trade Names**: duloxetine—Cymbalta; vortioxetine—Brintellix

*See Reference Guide.

### Antidepressants and Cognitive Decline

In a large, nationally representative sample of older adults followed for 6 years, antidepressant use did not modify the well-established association between depression and cognitive decline.

**Methods**: The Health and Retirement Study is an ongoing study of U.S residents, aged >50 years at enrollment in 1992. Alternate-year interviews of participants include assessments of depression and cognitive function. Prescription drug data were also available beginning in 2005. The sample for the present analysis (n=3714) consisted mostly of people who were aged ≥65 years in 2007, community-dwelling, and able to participate in cognitive-function tests. Cognitive function was tested on 4 occasions between 2004 and 2010, using a 27-point scale based on a battery of memory and computational tests. Cognitive function was classified as normal, impaired function, or dementia based on these scores. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) Scale.

**Results**: At baseline, 12% of the study participants were taking an antidepressant. Depressive symptoms were associated with reduced baseline cognitive function, but there was no difference in cognitive function at baseline between those taking or not taking antidepressants. During the 6-year follow-up, both users and nonusers of antidepressants experienced a decline in cognitive function, which did not differ between the groups. In an analysis that was adjusted for sociodemographic variables, functional impairment, comorbidity, depressive symptom burden, and the anticholinergic activity of the antidepressant, rates of cognitive decline still did not differ between users and nonusers of antidepressants. (See table.)

<table>
<thead>
<tr>
<th>Patient Group</th>
<th># Patients</th>
<th>Baseline Cognitive Function Score</th>
<th>6-Year Cognitive Function Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Depression (CES-D ≤3), no antidepressant treatment</td>
<td>2832</td>
<td>15.3</td>
<td>14.5</td>
</tr>
<tr>
<td>Low Depression (CES-D ≤3), receiving antidepressant treatment</td>
<td>324</td>
<td>15.1</td>
<td>14.4</td>
</tr>
<tr>
<td>High Depression (CES-D &gt;3), no antidepressant treatment</td>
<td>437</td>
<td>13.1</td>
<td>12.6</td>
</tr>
<tr>
<td>High Depression (CES-D &gt;3), receiving antidepressant treatment</td>
<td>121</td>
<td>14.2</td>
<td>12.8</td>
</tr>
</tbody>
</table>

**Discussion**: Because antidepressant use does not appear to protect against cognitive decline in older patients with depression, adding nonpharmacological approaches that may be associated with cognition (e.g., social engagement, physical activity) should be considered for these patients.

Saczynski J, Rosen A, McCammon R, Zivin K, et al: Antidepressant use and cognitive decline: the Health and Retirement Study. *American Journal of Medicine* 2015; doi 10.1016/j.amjmed.2015.01.007. From the University of Massachusetts Medical School, Worcester; and other institutions. Funded by the National Institute on Aging; and other sources. The authors declared no conflicts of interest.
SSRI plus Stimulant in Geriatric Depression

In elderly patients with chronic depression, the combination of citalopram and methylphenidate resulted in a more robust antidepressant response than either agent alone.

Methods: This randomized trial was carried out in 143 older adults (average age, 70 years; 78 women) with a current episode of unipolar major depression and no or minimal cognitive impairment. Patients were seen in the clinic, weekly for 4 weeks of methylphenidate titration, and then every 2 weeks until the 16-week endpoint. Methylphenidate was dosed flexibly at 5–40 mg/day, depending on response and tolerability, with response defined as a Clinical Global Impression–Improvement (CGI-I)* rating of 1 or 2. Citalopram was dosed flexibly in the same manner, in the 20- to 60-mg/day range. Patients in the 2 monotherapy groups received a placebo for the alternate drug. The primary outcome measure was change from baseline on the Hamilton Rating Scale for Depression (HAM-D). Remission was defined as a HAM-D score of ≤6. The rate of HAM-D reduction by the fourth week of treatment (based on the methylphenidate titration schedule) was also evaluated. Neuropsychological tests of cognitive function were carried out at baseline and study end.

Results: Patients had a history of 3–4 depressive episodes on average, with a mean duration of nearly 4 years for the present episode. About 40% met criteria for treatment resistance, with failure of ≥2 adequate trials of antidepressants from different classes. By 16 weeks, combination therapy was associated with a significantly larger average reduction in HAM-D score than citalopram alone (p=0.02) or methylphenidate alone (p=0.005). During the first 4 weeks of treatment, combination therapy was associated with greater improvement than citalopram monotherapy (p=0.03), but not methylphenidate alone. Efficacy did not differ significantly between the monotherapy groups. After week 4, improvement was significantly more rapid with combination therapy than with methylphenidate (p=0.04); improvement was not more rapid with combination therapy than with citalopram. By week 16, remission occurred in 62% of the combination therapy group, compared with 42% of patients who received citalopram alone (p=ns), and 29% of the methylphenidate group (p=0.003).

CGI-I scores of 1 or 2 were noted in 84% of the combined therapy group, 57% of the citalopram group, and 39% of the methylphenidate group (p=0.001 for the combined group vs. each monotherapy). Cognitive outcomes of treatment were variable, with greater improvement in some areas of cognitive function observed in the 2 groups receiving citalopram. The treatment groups did not differ in any measure of tolerability or adverse effects.

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

Lavretsky H, Reinlieb M, St. Cyr N, Siddarth P, et al: Citalopram, methylphenidate, or their combination in geriatric depression: a randomized, double-blind, placebo-controlled trial. American Journal of Psychiatry 2015; doi 10.1176/appi.ajp.2014.14070889. From the University of California, Los Angeles. Funded by the NIH. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no conflicts of interest.

Drug Trade Names: citalopram—Celexa; methylphenidate—Ritalin

*See Reference Guide.

Long-Term Renal Safety of Lithium

Results of a longitudinal study in a large, unselected population suggest lithium therapy may be associated with kidney damage that could later lead to end-stage renal disease (ESRD).¹

Methods: Data were analyzed from 630 patients (average age at treatment initiation, 46 years) treated at a single Swedish regional hospital. The study subjects began lithium treatment between 1981 and 2010 and received treatment for ≥10 years cumulatively. If a patient had a 365-day period without any positive lithium measurements, treatment was considered...
discontinuous and that time period was subtracted from the cumulative treatment total. Serum creatinine levels closest in time to the first and last lithium measurements were considered as initial and final creatinine levels. Those with initially abnormal levels were excluded. The age- and gender-adjusted glomerular filtration rate (GFR) was estimated, and used to classify patients according to the stages of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative. (See table.)

**Results:** Patients showed a continuous yearly increase in average serum creatinine beginning with the first year of treatment. After ≥10 years on lithium, 45% of patients had a ≥30% increase in serum creatinine level. One-third of patients had an abnormally low estimated GFR after ≥10 years on lithium, and almost 5% had Stage 4 or 5 chronic kidney disease (CKD; 27 and 2 patients, respectively).

**Discussion:** Previous research by these investigators found risk for ESRD in lithium treated patients to be greater than in the general population (relative risk, 7.8). However, it is not clear whether there is a safe level of renal function for continuation of lithium treatment. More than half of patients in the present study had virtually unchanged creatinine levels throughout treatment, despite similar lithium treatment duration and initial creatinine concentrations. This suggests that other factors such as concomitant illnesses and individual vulnerability, which could not be evaluated in the present study, may influence risk.

![CKD by Stage After 10 Years of Lithium Treatment](image)

**Brexpiprazole in Acute Schizophrenia**

The investigational second-generation antipsychotic brexpiprazole, designed to minimize adverse effects, was effective in a multi-dose phase III trial in patients hospitalized with an acute exacerbation of schizophrenia.

**Background:** Brexpiprazole was designed with a serotonin and dopamine activity profile that would theoretically result in a low potential for some of the most concerning side effects of second-generation antipsychotics, including prolactin elevation and extrapyramidal symptoms.

**Methods:** This trial was conducted at 64 centers in 8 countries, with a little more than one-third of patients from U.S. centers. Study participants had a diagnosis of schizophrenia and were suffering an acute exacerbation of psychotic symptoms with marked deterioration of function, warranting inpatient admission or continued hospitalization. After a washout of concomitant antipsychotic drugs, patients were randomly allocated to receive double-blind 1, 2, or 4 mg/day brexpiprazole or placebo for 6 weeks. Change from baseline in the Positive and Negative Syndrome Scale (PANSS) was the primary efficacy outcome. Change from baseline in the Clinical Global Impression–Severity (CGI-S)* scale score was the key secondary endpoint.
**Results:** A total of 674 patients (251 women) received randomized treatment, and 68% completed the study. The rate of study completion was similar in all treatment groups. Patients were markedly ill at study entry, with a mean CGI-S score of nearly 5 and a mean PANSS total score of 95.

The 4-mg brexpiprazole dose was associated with a significantly greater improvement in PANSS total score than placebo; at week 6, scores were 75 and 81.5, respectively (p<0.0022). Average reductions in PANSS scores with the 4-mg dose were a clinically meaningful 20–30%. The lower doses were associated with numerically larger improvements than placebo, but this difference was not statistically significant. Patients who received the 4-mg dose also had a significantly greater reduction in CGI-S scores relative to placebo (1.2 points vs. 0.81 points; p=0.0015). Multiple secondary endpoints also supported the efficacy of 4 mg brexpiprazole; again, the lower doses were numerically but not statistically superior to placebo.

No treatment-emergent adverse events met the criteria for common adverse events, defined as an incidence ≥5% and at least twice the rate of placebo. Most serious adverse events were related to the underlying course of schizophrenia (e.g., aggression, psychosis); for these the incidence was lower with brexpiprazole than with placebo (≤2.5% vs. 5.4%). Brexpiprazole was associated with moderate weight gain, which averaged >3 lbs. after 6 weeks of treatment with the 4-mg dose.

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


*See Reference Guide.

---

**Antidepressant Fracture Risks Compared**

SNRI and SSRI antidepressants are associated with a similar risk of fracture, according to results of a cohort study of patients aged ≥50 years.

**Background:** Fracture risks associated with SSRIs and older antidepressant classes are well documented, but less is known about SNRIs. Antidepressants are known to increase fractures in older patients by causing dizziness and falls upon initiation. Drugs that affect serotonin downregulate osteoblast activity, decreasing bone mineral density; norepinephrine-inhibiting drugs can increase bone resorption thus reducing bone density. This study was conducted to determine whether initiating an SNRI would result in a lower fracture risk than starting an SSRI.

**Methods:** Combined data from commercial managed care plans throughout the U.S. were gathered using the PharMetrics Claims Database and then used to retrospectively identify a cohort of patients, aged ≥50 years, who filled a new prescription for an SSRI or an SNRI between 1998 and 2010. Patients who had received any other antidepressant in the previous 12 months were excluded. The outcome of interest was fracture of the hip, humerus, radius, or ulna in the 360 days after starting therapy. Patients were removed from follow-up when they switched antidepressants, even within the same class, or when they added a second antidepressant. The analysis was weighted for the propensity of patients to be given a prescription for an SNRI rather than an SSRI.

**Results:** The analysis included >335,000 patients given a prescription for an SSRI and 61,000 given an SNRI. In the primary analysis, rates of fracture per 1000 patient-years within the first 360 days of treatment did not differ between the 2 drug classes: 7.5 for SNRIs and 6.7 for SSRIs (hazard ratio,* 1.03 for SNRIs vs. SSRIs). Rates did not differ between drug classes in analyses with different follow-up times, ranging from the initial month to the first 5 years following treatment.
initiation. Fracture rates associated with the 2 drug classes were the same in patients without a depression diagnosis. However, in those with depression, SNRIs were associated with a slightly, nonsignificantly elevated risk (hazard ratio, 1.31).

**Discussion:** Although the underlying mechanism for fracture risk differs between the SSRIs and SNRIs, results of this research suggest that actual risks are similar in both classes. The suggestion that depression status may modify the effect of SNRIs on fracture requires further investigation.

Lanteigne A, Sheu Y-H, Sturmer T, Pate V, et al: Serotonin-norepinephrine reuptake inhibitor and selective serotonin reuptake inhibitor use and risk of fractures: a new-user cohort study among US adults aged 50 years and older. CNS Drugs 2015; doi 10.1007/s40263-015-0231-5. From Harvard School of Public Health, Boston, MA; and other institutions. Funded by the NIMH. One study author declared potentially relevant financial relationships; the remaining 6 authors declared no conflicts of interest.

*See Reference Guide.

**Reference Guide**

**Clinical Global Impression–Improvement (CGI-I) Scale:** A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

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

**Path Analysis:** A method employed to determine whether or not a multivariate set of nonexperimental data fits well with a particular (a priori) causal model.

**Relative Risk:** The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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.

**ARE YOU GETTING ALL THE INFORMATION YOU NEED?**

As a regular subscriber, you already know the importance of keeping up with the latest research findings in psychopharmacology. But there’s more to psychiatry than psychopharmacology. Psychiatry Alerts NOS can provide you with updates on nonpharmacological treatments in psychiatry as well as the newest information on diagnostic and assessment tools.

Here’s a sample of titles from recent Psychiatry Alerts NOS issues.

- Avatar Therapy for Hallucinations
- Culturally Sensitive Depression Care
- ECT Augmentation for Resistant Schizophrenia
- Exposure Therapy for Prolonged Grief Disorder
- Amino Acid Profiling in Major Depression

Contact us at 973-898-1200 or psych@alertpubs.com to request a sample copy of Psychiatry Alerts NOS.