Lisdexamfetamine for Residual Depressive Symptoms

In a manufacturer-sponsored pilot study, augmentation with lisdexamfetamine mesylate improved residual symptoms of depression in patients who had received 8 weeks of escitalopram treatment.

**Methods:** Study subjects were adults, aged 18–55 years, with nonpsychotic unipolar major depressive disorder who were either unmedicated or had not experienced full response to an antidepressant other than escitalopram. After a washout period, all patients received 20 mg/day escitalopram plus a placebo. After 8 weeks, patients with residual symptoms (Hamilton Rating Scale for Depression [HAM-D] score of ≥4) were randomly assigned to receive continued placebo or lisdexamfetamine for an additional 6 weeks. Lisdexamfetamine was initiated at 20 mg/day, and then increased to a maximum of 50 mg/day. The primary efficacy endpoint was change in Montgomery-Asberg Depression Rating Scale (MADRS) score from the start of augmentation to the end of study. Remission was defined as a total MADRS score of ≤10, and response as a ≥50% MADRS score reduction from the antidepressant-free baseline.

**Results:** Of 246 patients who enrolled, 239 received ≥1 dose of escitalopram; 173 received ≥1 dose of lisdexamfetamine or placebo, and 157 completed the full 14 weeks of treatment. The randomized group included 44 patients whose depression remitted with escitalopram and 129 with residual symptoms of depression. All patients who received lisdexamfetamine started on the 20-mg/day dosage. A total of 75% increased to the 30-mg/day dosage, and 42% increased to 50 mg/day.

In escitalopram nonremitters, lisdexamfetamine was associated with a numerically but not significantly larger decrease than placebo in mean MADRS score (7.1 vs. 4.9 points; p=0.09; effect size,* 0.3). Lisdexamfetamine was also numerically but not statistically superior to
A larger proportion of patients achieved response with lisdexamfetamine than with placebo (66% vs. 50%; p=0.08), but the difference was not significant. Remission rates in the 2 groups were 49% and 34% (p=ns), respectively. Patient-reported symptoms on the Quick Inventory of Depressive Symptomology–Self-Report showed a greater improvement with lisdexamfetamine than with placebo (p=0.02). The number needed to treat* (NNT) to produce 1 remission in escitalopram nonremitters was 7.

The escitalopram–lisdexamfetamine combination was well tolerated. No participant had emergent mania, suicidal ideation/behavior, or aggression.

**Discussion:** Lisdexamfetamine is currently FDA approved to treat ADHD in children and adults. Results of the present study are encouraging, and larger confirmatory clinical trials are underway. The effect size and NNT in the present study are on par with the figures for augmentation with atypical antipsychotics.

Trivedi M, Cutler A, Richards C, Lasser R, et al: A randomized controlled trial of the efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with residual symptoms of major depressive disorder after treatment with escitalopram. *Journal of Clinical Psychiatry* 2013;74 (August):802–809. From the University of Texas Southwestern Medical Center, Dallas; and other institutions including Shire Development LLC, Wayne, PA. **Funded by Shire Development LLC. All study authors disclosed financial relationships with commercial sources including Shire.**

**Drug Trade Names:** escitalopram—Lexapro; lisdexamfetamine dimesylate—Vyvanse

*See Reference Guide.

### Antipsychotics and Venous Thromboembolism Risk

Results of a case-control study indicate that antipsychotic treatment is associated with increased risk of venous thromboembolism (VTE) in Asian patients.

**Background:** Previous studies in white populations have also demonstrated an association, although not uniformly. Asians are believed to be at generally lower risk of VTE, but the association of risk with antipsychotic medications in Asian patients has received little investigation.

**Methods:** A nested case-control study was carried out using data from the Taiwanese National Health Insurance Research Database. Cases received a diagnosis of VTE between 2001 and 2010. Each case was matched for age and gender with up to 6 controls who had not experienced VTE at that time. Exposure to all available first- and second-generation antipsychotics was assessed in cases and controls. In addition, effects of antipsychotic exposure were analyzed according to the agents’ receptor binding affinity (high or low) for the serotonin 5HT2A, dopamine D2, and histamine H1 receptors.

**Results:** A total of 2162 patients experienced VTE and were matched with nearly 13,000 controls. The average age was 64 years, and about half were women. Current antipsychotic use was associated with an overall 52% increase in risk of VTE, compared with nonusers. Excess risk was mostly confined to new users—i.e., patients with a first antipsychotic prescription within 1 month of the event (adjusted odds ratio,* 3.26). Excess risk in continuous users was modest and not statistically significant. Risk was not increased for patients whose use of antipsychotics was >1 month in the past. All classes of antipsychotics were equally associated with increased risk, and risk did not differ according to drug potency, receptor binding affinity, or dosage.

**Discussion:** Several hypotheses have been advanced to explain the association of antipsychotics with VTE, among them a decrease in physical activity leading to venous stasis and hyperprolactinemia leading to increased platelet aggregation. Although risk of VTE in Asian patients...
appears to be lower than in other populations, these patients should be carefully monitored for symptoms of VTE, including chest pain, dyspnea, or lower extremity edema, after starting antipsychotics. Preventive strategies, including adequate hydration and exercise, should be recommended.

Wu C-S, Lin C-C, Chang C-M, Wu K-Y, et al: Antipsychotic treatment and the occurrence of venous thromboembolism: a 10-year nationwide registry study. Journal of Clinical Psychiatry 2013;74 (September):918–924. From the Far Eastern Memorial Hospital, Taipei, Taiwan; and other institutions. Funded by the National Health Research Institutes, Taiwan; and other sources. One study author disclosed a financial relationship with a commercial source; the remaining 6 authors declared no potential conflicts of interest.

*See Reference Guide.

**Metformin for Weight Loss in Schizophrenia**

In a placebo-controlled study, metformin was modestly effective in reducing weight and ameliorating some metabolic risk factors in overweight patients with chronic schizophrenia.1 The results of this study, the largest to date, confirm previous findings that the effects of metformin are clinically significant but limited, according to an accompanying editorial.2

**Methods:** Study participants were overweight (body mass index [BMI] ≥27) outpatients with clinically stable schizophrenia. All patients received weekly diet and exercise counseling designed for persons with severe mental illness. In addition, the patients were randomly assigned to receive double-blind metformin or placebo for 16 weeks. Metformin was titrated to a maximum of 1000 mg b.i.d. The primary outcome measure was change in body weight.

**Results:** A total of 146 patients were enrolled and received study medication; 58 patients in each medication group completed the study. Average baseline BMI was 34.6, and more than half of patients were taking antipsychotic medications with high risk of weight gain.

Patients who received metformin lost a mean of 6.6 lbs over the 16 weeks of treatment, compared with 2.2 lbs in the placebo group (difference, 4.4 lbs; p=0.007). Thirteen patients who received metformin and 7 who received placebo lost >5% of their baseline weight. BMI was reduced by 1 point on average in the metformin group and by 0.3 points in the placebo group (p=0.006). Patients who received metformin experienced significantly larger reductions in triglycerides than the placebo group. Effects on total cholesterol, HDL and LDL cholesterol, fasting glucose, and insulin did not differ between treatments or fell short of statistical significance. Mean HbA1c levels fell by 0.06% with metformin and 0.011% with placebo (p=0.039).

Metformin was well tolerated and did not cause unexpected adverse effects. Subgroup analyses showed that metformin was significantly more effective in younger participants (aged <44 years), those with a baseline BMI <33 (the study median), men, and nonsmokers.

**Discussion:** Strategies that have been investigated for antipsychotic-induced weight gain include healthy lifestyle, switching to an antipsychotic with lower metabolic risk, and adding medications to lower weight or reverse lipid abnormalities. Each of these strategies has similar results: weight loss limited to about 6–7 lbs over 3–4 months. The present study is in general agreement with previous, smaller studies of metformin, but generalizability was enhanced by including overweight patients, as well as those who met criteria for obesity and those with different levels of chronicity of psychosis. Although weight loss with metformin was modest, there was some indication it might continue beyond 16 weeks.

Aside from being modest in comparison with weight gained on antipsychotic therapy, weight loss with metformin is highly heterogeneous in patients with psychosis. Enough data exist to recommend metformin as an evidence-based treatment for antipsychotic-induced weight gain,
but more research is needed on how to combine it with other strategies, including antipsychotic switching, topiramate, or the other recently approved weight loss drugs. Research is also necessary to identify the best candidates for metformin.

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

1Jarskog L, Hamer R, Catellier D, Stewart D, et al: Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder. American Journal of Psychiatry 2013;170 (September): 1032–1040. From the University of North Carolina at Chapel Hill; and other institutions. Funded by the NIMH. Five of the 9 study authors disclosed financial relationships with commercial sources; the remaining authors declared no conflicts of interest.

2Correll C, Sikich L, Reeves G, Riddle M: Metformin for antipsychotic-related weight gain and metabolic abnormalities: when, for whom, and for how long [editorial]? American Journal of Psychiatry 2013;170 (September):947–952. From North Shore-Long Island Jewish School of Medicine, Hempstead, NY; and other institutions. Funded by the NIMH; and other sources. All 4 authors disclosed financial relationships with commercial sources.

Drug Trade Names: metformin—Glucophage; topiramate—Topamax

*Lamotrigine Augmentation in OCD

A 24-year-old woman, who had a diagnosis of obsessive-compulsive disorder since age 12 years, presented with obsessions of an aggressive, religious, and sexual nature. Medication trials over the years had included clomipramine; fluoxetine; fluvoxamine; paroxetine; lithium; bupropion; buspirone; clonazepam; and lorazepam. On presentation, she was receiving cognitive behavioral therapy in addition to 40 mg/day paroxetine, 400 mg/day lithium, and 1 mg/day clonazepam, but her Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score was 29. The paroxetine dosage was increased to 60 mg/day, and lithium was replaced with 25 mg/day lamotrigine, titrated over 4 weeks to 100 mg/day. At the 5-week evaluation, the patient showed marked improvement and her Y-BOCS score was 14. At 6 months, the improvement was sustained, and the patient reported feeling that lamotrigine had helped her more than any other treatment. At 18-month follow-up, she continued to have only mild OCD symptoms and limited functional impairment.

A 46-year-old woman had a 22-year history of treatment-resistant OCD. On presentation, her regimen included 225 mg/day clomipramine, 200 mg/day fluvoxamine, and 2 mg/day alprazolam and her Y-BOCS score was 30. She was experiencing intrusive and repetitive thoughts, along with checking compulsions and motor tics. Fluvoxamine was discontinued, and 2 weeks later she was started on 25 mg/day lamotrigine, which was titrated to 100 mg/day. Five weeks after lamotrigine initiation, she reported some improvement and the lamotrigine was increased to 200 mg/day. After 5 weeks at that dosage, her tics completely resolved and her Y-BOCS score was reduced to 21. After an additional 9 weeks, her Y-BOCS score was further decreased to 16 and tics continued to be absent. No adverse effects were reported.

SSRIs are accepted as first-line pharmacotherapy for OCD. Although the recommendations for resistant disease are not as well established, they generally include augmentation with clomipramine or an antipsychotic. Recently, augmentation with glutamatergic agents has also been recommended. Lamotrigine, which has these properties, has been effective in small studies of obsessive symptoms in schizophrenia and bipolar disorder. Limited evidence, including these 2 case reports, suggests it may be an effective augmentation strategy in SSRI-resistant OCD.

Arrojo-Romero M, Alonso M, de Leon J: Lamotrigine augmentation of serotonin reuptake inhibitors in severe and long-term treatment-resistant obsessive-compulsive disorder. Case Reports in Psychiatry 2013; doi 10.1155/2013/612459. From Complejo Hospitalario Universitario, Santiago de Compostela, Spain; and other institutions.

Drug Trade Names: alprazolam—Xanax; bupropion—Wellbutrin; buspirone—BuSpar; clomipramine—Anafranil; clonazepam—Klonopin; fluoxetine—Prozac; fluvoxamine—Luvox; lamotrigine—Lamictal; lorazepam—Ativan; paroxetine—Paxil
Antidepressants in Bipolar Disorder

Evidence-based recommendations for the use of antidepressants in bipolar disorder cannot be made given the state of current data, according to a report from the International Society for Bipolar Disorders (ISBD) Task Force on Antidepressant Use in Bipolar Disorders. However, based on a systematic review of the evidence base, the expert task force did make some recommendations.

The panel recommends that non-antidepressant medications—including lithium, lamotrigine, olanzapine, quetiapine, and lurasidone—be used as monotherapy in bipolar depression before an antidepressant is considered.

Although it is not clear whether antidepressants cause the emergence of mania or whether mood stabilizers protect against them, the experts recommended antidepressants in bipolar I disorder only with concomitant mood-stabilizer therapy. Antidepressants appear to be relatively well tolerated in type II bipolar disorder, but there is no evidence they are effective in treating acute depression in this group.

Adjunctive antidepressants should be avoided in patients with current manic symptoms and agitation or rapid cycling, mixed features, current mood instability, or a history of antidepressant-associated mania or hypomania. The use of prophylactic antidepressants combined with mood stabilizers, although common, has received little study. There is some evidence supporting the short-term efficacy of combined olanzapine–fluoxetine in acute treatment of bipolar depression, while the evidence base indicates a lack of efficacy for paroxetine and bupropion both as monotherapy and as adjuncts to mood stabilizing medications. A single review found that tricyclics, tetracyclics, and venlafaxine are associated with higher risk of mania than SSRIs. Otherwise, there is little evidence to guide the selection of an antidepressant.

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


Drug Trade Names: bupropion—Wellbutrin; lamotrigine—Lamictal; lurasidone—Latuda; olanzapine—Zyprexa; olanzapine–fluoxetine—Symbyax; paroxetine—Paxil; quetiapine—Seroquel venlafaxine—Effexor

*See Reference Guide.

Antipsychotic Continuity and Mortality

High-continuity use of antipsychotic medications was associated with reduced mortality in a cohort study of patients with schizophrenia.

Background: The 2009 Patient Outcomes Research Team (PORT) guidelines, created by the Agency for Healthcare Research and Quality, recommend continual antipsychotic use to maintain symptom relief and reduce relapse risk in patients with schizophrenia. PORT guidelines for use of first-generation drugs also recommend concomitant use of antiparkinsonian medications, as well as avoidance of high antipsychotic doses. The present study evaluated the effects on mortality of adherence to PORT guidelines on antipsychotic continuity, use of concomitant antiparkinsonian medication, and antipsychotic dose appropriateness.

Methods: The study cohort (n=2132) consisted of Medicaid recipients from Maryland. Participants were all enrolled in Medicaid for ≥2 years before the start of follow-up in 1994 and received antipsychotic medication at any time during the study period, from 1994 to 2004. To measure antipsychotic continuity, medication possession ratios (MPRs) were calculated as
the ratio of the total number of days each patient took an antipsychotic, divided by the number of days they were eligible for the medication. Chlorpromazine dosing equivalents were determined for first-generation antipsychotics, but not for second-generation drugs, most of which do not have known upper effective dosing limits.

**Results:** The majority of patients (n=2027) were given a prescription for a first-generation antipsychotic. Among this group, 84% received concomitant antiparkinsonian medication. A total of 337 cohort members (16%) died during follow-up. The most common causes of death were cardiovascular disease (28%), cancer (17%), infectious disease (10%), respiratory disease (9%), and undetermined harm (8%; may have included suicide). High average continuity was associated with decreased risk of death from suicide or harm: 0.5% of patients with >90% average continuity died from this cause, compared with 3% of those who used <10% of their eligible medication. In contrast, 4.3% of patients with >90% average continuity vs. 4.1% of those with <10% continuity died due to cardiovascular disease.

Annual antipsychotic continuity was highly variable; in any given year, 47% of patients took >90% of their medication and 25% took <10%. After controlling for medical comorbidities and mental health visits, high antipsychotic continuity was associated with reduced all-cause mortality (hazard ratio,* 0.75 for >90% vs. <10% continuity). In the subgroup of patients who took first-generation antipsychotics, the highest doses were associated with higher mortality (hazard ratio, 1.88 for those taking ≥1500 mg chlorpromazine equivalents, compared with those taking <300 mg) and use of antiparkinsonian medication was associated with reduced mortality (hazard ratio, 0.72). A larger number of mental health visits across the study period was protective against death, even when continuity and other medication-related factors were considered.

**Discussion:** These findings suggest that adherence to the PORT recommendations for schizophrenia medication is associated with reduced mortality. Use of outcomes monitoring systems and innovative service delivery programs should be implemented to improve adherence to these guidelines.

Cullen B, McGinty E, Zhang Y, dosReis S, et al: Guideline-concordant antipsychotic use and mortality in schizophrenia. *Schizophrenia Bulletin* 2013;39 (September):1159–1168. From Johns Hopkins School of Medicine, Baltimore, MD; and other institutions. **Funded by the NIMH. The authors declared no conflicts of interest.**

*See Reference Guide.

**Levomilnacipran: Efficacy and Safety**

According to a review of the pivotal placebo-controlled registration trials, the recently introduced antidepressant levomilnacipran (*Fetzima*) has efficacy and safety that are similar to other recently introduced antidepressants. An important advantage may be its lack of association with clinically relevant weight gain.

**Background:** Levomilnacipran received FDA approval in July 2013 for the treatment of major depressive disorder. It is an SNRI with 10-fold greater selectivity for norepinephrine, relative to serotonin reuptake inhibition, than other available antidepressants in this class.

**Methods:** A literature search identified 5 double-blind, placebo-controlled, short-term trials and 1 relapse-prevention study of levomilnacipran, all conducted by the manufacturer. Data from the studies was pooled, and the number needed to treat* (NNT) and number needed to harm* (NNH) were calculated for levomilnacipran relative to placebo.

**Results:** Of the 5 short-term clinical trials, 4 were considered positive in supporting the efficacy of levomilnacipran. The studies spanned 8–10 weeks and included dosages of 40–120 mg/day. Response was defined as a ≥50% decrease in Montgomery-Asberg Depression Rating Scale
(MADRS) score, and remission as a final MADRS score of ≤10. The pooled NNT for treatment response was 10. For remission, the NNT was 16. Omitting the single study with negative results from the analysis resulted in a small improvement in the NNTs. In the 24-week relapse-prevention trial, relapse rates were 20% for placebo and 14% for levomilnacipran, resulting in a nonsignificant NNT.

The NNH for various adverse events ranged from 10 to 100. The most frequent adverse event, nausea, occurred in 17% of patients who received levomilnacipran and had an NNH of 10. Ejaculation disorder and erectile dysfunction had NNHs of 23 and 20, respectively. The incidence of suicidal ideation and behavior and other serious adverse events was similar with levomilnacipran and placebo. Levomilnacipran was associated with no weight gain in any of the studies.

Discussion: Levomilnacipran appears to be another viable option in the treatment of depression, and its favorable weight gain profile may be an important benefit. However, all available evidence comes from trials supported by its manufacturer, and only 1 long-term study exists. Additional long-term studies, as well as ones with active comparators, are necessary to clarify the place of levomilnacipran in the treatment of depression.

Varenicline in Patients with Treated Depression

In a manufacturer-sponsored, placebo-controlled trial in patients with stably treated current or recent major depression, varenicline (Chantix) was effective for smoking cessation and was well tolerated.

Background: Patients with depression are prone to experience more severe nicotine withdrawal symptoms when quitting smoking, potentially making the mitigating effects of varenicline on withdrawal particularly important in this group. However, concern about neuropsychiatric adverse effects has been reported with varenicline treatment, and patients with psychiatric disorders were excluded from the phase III clinical trials.

Methods: The multicenter trial was conducted in 525 smokers, aged 18–75 years, with current or recent unipolar major depressive disorder. Patients were either receiving a stable dose of antidepressant medication or had a successfully treated major depressive episode within the past 2 years. Participants were randomly assigned to 12 weeks of 1 mg varenicline b.i.d. or placebo, and were followed for an additional 40 weeks. All patients received the same manual-guided smoking-cessation counseling. The primary efficacy endpoint was the carbon monoxide-confirmed continuous abstinence rate for the last 4 weeks of treatment. Adverse neuropsychiatric events were actively solicited throughout follow-up using the Neuropsychiatric Adverse Event Interview, designed by the study sponsor, which asks questions about agitation; mania; hostility; paranoia; hallucinations; delusions; and derealization or depersonalization. Patients were also assessed with the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), and various measures of suicidality.

Results: At baseline, about three-fourths of patients were taking antidepressant medication, usually an SSRI or SNRI. Their depression was in remission or at most mildly symptomatic. On average, patients had smoked cigarettes for 27 years and were smoking 22 cigarettes a day. Of the 525 patients, 100 discontinued treatment before week 12 (41 varenicline, 59 placebo).
By week 12, 36% of the varenicline group and 16% of the placebo group had quit smoking (odds ratio,* 3.35; p<0.001). A total of 354 patients (68% of the varenicline group and 67% of the placebo group) were followed through week 52. Participants who took varenicline were about 2.5 times more likely than the placebo group to remain abstinent through weeks 24 and 52. Scores for depression and anxiety showed small but continuing improvement in both groups.

The most common adverse events leading to treatment discontinuation were depression or depressed mood, occurring in about 2% of each group. Two varenicline patients had serious psychiatric adverse events—psychotic disorder, depression, and suicidal ideation—as did 4 placebo patients. Suicidal ideation was present at baseline in about 7% of both groups and remained at this level through follow-up.

**Discussion:** Results of this study suggest varenicline is both safe and effective in patients with treated depression. However, vigilance is recommended when treating patients with more complex psychiatric disease.

Anthenelli R, et al: Effects of varenicline on smoking cessation in adults with stably treated current or past major depression. *Annals of Internal Medicine* 2013;159 (September 17):390–400. From the VA San Diego Healthcare System, CA; and other institutions including Pfizer, Cambridge, MA, and New York, NY. Funded by Pfizer. All study authors disclosed financial relationships with commercial sources, including Pfizer.

*See Reference Guide.

### Reference Guide

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

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

**Number Needed to Harm (NNH):** A measure of how many patients need to be exposed to a risk factor to cause harm in 1 patient that would not otherwise have been harmed. Lower NNH indicates more attributable risk.

**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 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio >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.