Modafinil Augmentation in Depression

Adjunctive modafinil is safe and effective in the treatment of unipolar and bipolar depression, according to the results of a meta-analysis.\(^1\) If used early in treatment, the authors suggest, modafinil may improve antidepressant compliance by preventing fatigue and sleepiness caused by antidepressant drugs.

**Background:** The non-amphetamine modafinil and its R-enantiomer, armodafinil, are both FDA-approved for treatment of fatigue related to sleep disorders. Previous research evaluated the effects of modafinil on depression with mixed results, and a 2008 meta-analysis, based on only 2 controlled trials, did not support its use.\(^2\) Since then, several additional randomized controlled trials have been completed and are included in the present analysis.

**Methods:** All randomized, placebo-controlled trials of adjunctive modafinil or armodafinil in unipolar or bipolar depression were identified by literature search. The meta-analysis included 4 trials with a total of 568 patients with major depressive disorder and 2 studies of bipolar depression—1 of modafinil in 85 patients and 1 of armodafinil in 257 patients. Study durations ranged from 6 to 8 weeks. Modafinil was added to an SSRI in the unipolar depression studies and to mood stabilizer therapy—including lithium, olanzapine, and valproic acid—in the bipolar depression studies. In 2 of the 3 studies for each indication, augmentation was initiated after $\geq 2$ weeks of adequate background therapy. Percentage improvement in Hamilton Rating Scale for Depression (HAM-D) score was the primary efficacy outcome in unipolar depression and in the Inventory of Depressive Symptomatology (IDS) in bipolar depression.

**Results:** Modafinil was associated with a significant reduction in depressive symptoms in both unipolar and bipolar depression. The investigators excluded 1 outlier study of unipolar depression, which had a small sample size and unusually positive results. In the remaining studies, modafinil was associated with an effect size* of 0.18 ($p=0.04$) in unipolar depression and 0.30 ($p=0.006$) in bipolar depression. Patients with more severe depression showed...
greater improvement with modafinil augmentation. The magnitude of symptom reduction was similar in unipolar and bipolar depression.

Remission was defined as a HAM-D score of \( \leq 7 \) in studies of unipolar depression and as an IDS score of \( \leq 11 \) in bipolar depression. Rates of remission were significantly higher with modafinil than with placebo (odds ratio, *1.61). The number needed to treat* with modafinil for 1 additional remission was 10. However, the difference in response rates between modafinil and placebo did not reach statistical significance (odds ratio, 1.62; \( p=0.07 \)).

Modafinil was associated with a significant improvement in depression scores as early as the first week of treatment. In the few studies in which this information was available, modafinil was associated with significant improvements in sleepiness and fatigue in the early weeks of treatment. Adverse effects of modafinil did not differ statistically from placebo.

**Discussion:** Because augmentation therapy was initiated after varying durations of background therapy (i.e., 0–8 weeks), this analysis does not resolve the question of whether modafinil should be prescribed from the start of antidepressant treatment or added later. Although modafinil was well tolerated, the authors point out infrequent but concerning adverse effects: 2 incidents of suicidal ideation in patients who received modafinil at the start of antidepressant therapy, and, in 1 study, a 2% incidence of hypomania, compared with 1% for placebo.

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

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**Lisdexamfetamine for Executive Dysfunction in Depression**

In a manufacturer-sponsored controlled trial, adjunctive lisdexamfetamine dimesylate (*Vyvanse*) improved executive dysfunction in adults with remitted or partially remitted depression.

**Background:** Some patients receiving treatment for depression experience considerable executive dysfunction despite improvement in their mood symptoms. Previous research has suggested that stimulants may improve executive function, probably via modulation of cortical dopaminergic and noradrenergic systems.

**Methods:** Study participants were patients, aged 18–55 years, with a \( \geq 2 \) year history of recurrent, nonpsychotic major depression who had been receiving stable SSRI monotherapy for >8 weeks. Executive function was measured with the Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A). To be eligible, participants were required to have a BRIEF-A Self-Report Global Executive Composite (GEC) T score of \( \geq 60 \) (i.e., 1 standard deviation above the population norm). Double-blind, adjunctive lisdexamfetamine or placebo was added to ongoing SSRI therapy, and doses were optimized individually to a maximum of 70 mg/day. After 9 weeks of randomized treatment, all patients received placebo for 2 weeks to observe the effects of lisdexamfetamine withdrawal. The primary efficacy outcome measure was the BRIEF-A Self-Report GEC T score. This 75-item scale assesses aspects of executive function in daily life over the past month. The test has 2 subscales that measure behavioral regulation and metacognition.
**Results:** A total of 143 patients were enrolled and received randomized treatment, and 119 completed the trial. Equal numbers discontinued lisdexamfetamine and placebo. At baseline, mean self-report BRIEF-A scores were 74 and 77 in the placebo and lisdexamfetamine groups, respectively.

After 9 weeks, average BRIEF-A scores decreased to 55 in the patients who received lisdexamfetamine and to 61 in the placebo group (mean between-group difference of 8 points; p=0.0009; effect size,* 0.6). Changes in informant-report BRIEF-A scores also favored lisdexamfetamine, but treatment was not related to results of performance-based neurocognitive testing, another secondary efficacy outcome. Residual depressive symptoms were also improved in both groups, but to a greater degree with active treatment. Mean Montgomery-Asberg Depression Rating Scale scores decreased from a baseline of about 12 in each group, to 7.6 with lisdexamfetamine and 8.9 with placebo (p=0.05). Clinical Global Impression ratings indicated patients were borderline-to-moderately ill at baseline; following treatment, 61% were much or very much improved with lisdexamfetamine and 39% with placebo.

Adverse events were similar with lisdexamfetamine and placebo. One patient discontinued lisdexamfetamine after losing consciousness; this was the only serious adverse event believed to be drug-related. Three additional patients discontinued lisdexamfetamine: 1 each because of rash, worsening of depression, and suicidal ideation. There were no drug effects on weight or blood pressure and no apparent rebound or withdrawal effects.

**Discussion:** Considering the limited attention given to patients’ experience in drug trials, it may be clinically relevant that improvement was evident on both informer and self-report scales.

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


*See Reference Guide.

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**Statins and Poststroke Depression**

An association between cholesterol levels, lipid-lowering treatments, and depression has been suggested, but previous research results have been mixed. In a cohort of patients involved in a study of mental health in stroke survivors, statin therapy was associated with a reduced incidence of poststroke depression.

**Methods:** The study cohort consisted of 423 consecutive patients with MRI-confirmed acute ischemic stroke, treated at a university hospital in South Korea between 2006 and 2010. Statin therapy was prescribed according to the American Heart Association/American Stroke Association guidelines. Patients were evaluated for depression after stroke and 1 year later by raters blinded to statin-use status who applied DSM-IV criteria for major or minor depression. Depression severity was assessed using the self-report Hospital Anxiety and Depression Scale and the Hamilton Rating Scale for Depression.

**Results:** Major or minor depression was present in 108 patients (26%) at baseline; 36 of these patients (9% of the total) met criteria for major depression. A total of 251 patients (59%) took statins at baseline; 8 of these patients were already receiving statin therapy when they had their stroke and 243 had new prescriptions. Statin users had higher baseline LDL cholesterol and triglyceride levels than nonusers but were similar in other respects. At 1-year follow-up, 172 of the available 288 patients were receiving statin therapy; 11 of these patients had not been taking a statin at baseline.
Statin use was not associated with depression at baseline. However, at 1-year follow-up, statin therapy was associated with lower rates of major depression (odds ratio, 0.38; p=0.04) and of any depression (odds ratio, 0.42; p=0.008). Relative risk estimates were narrowed only slightly after the analysis was adjusted for multiple factors including depression history; age; education; social support; and continued statin use at follow-up. According to the symptom severity measurements, patients who used statins at baseline had significant improvement (or less deterioration) in their mood over the 1 year poststroke, while nonusers had deteriorating severity scores.

**Discussion:** Possible underlying mechanisms for the protective effect of statins include lowering of high cholesterol levels, which were shown to be a risk factor for depression in community samples, and vasoprotective or antiinflammatory effects. The preventive effect observed in this population is larger than effects previously reported in patients with ischemic heart disease, which suggests statins may modify the effects of stroke-induced brain pathology. In the present study, statins were prescribed primarily to treat hypercholesterolemia. Their effects in normocholesterolemic stroke patients require investigation.

**Study Rating*—14 (100%):** This study met all criteria for an observational study.


*See Reference Guide.

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### Levothyroxine in Bipolar Depression

In a controlled trial of patients with resistant bipolar depression, adjunctive treatment with levothyroxine (*Synthroid*) at supraphysiologic doses was superior to placebo in women but not in men.

**Methods:** Study participants were 62 outpatients with a DSM-IV diagnosis of either bipolar I or II disorder who were currently depressed. All patients had a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥14 despite adequate mood stabilizer and/or antidepressant treatment for ≥6 weeks. Patients with other axis I disorders, substance dependence, endocrine disorders, or serious cardiovascular disease were excluded. After a 1-week placebo run-in, adjunctive levothyroxine or placebo was added to stable ongoing medication. Levothyroxine was started at 100 mcg/day and increased to 300 mcg/day at week 3. The primary outcome measure was change from baseline in HAM-D score at the 6-week endpoint.

**Results:** Of the 62 study participants, 35 had bipolar I disorder and 27 had bipolar II disorder; 32 were women. At baseline, 21 patients (34%) were receiving monotherapy with a mood stabilizing drug. The remaining 41 patients (66%) were receiving a combination of 1 or 2 mood stabilizers and 1 or 2 antidepressants; 15 of these patients also received an antipsychotic. Overall, there was not a significant difference in efficacy between levothyroxine and placebo. At 6 weeks, the mean decrease in HAM-D score was 7.8 points in patients who received levothyroxine and 5.1 points in the placebo group (p=ns). However, when results were analyzed separately by gender, levothyroxine was associated with significantly greater HAM-D improvements in women (42% reduction, vs 17% with placebo; p=0.018), but not men. Rates of response (≥50 decrease in HAM-D score) and remission (HAM-D score ≤7) favored levothyroxine numerically in both genders and overall, but differences were not statistically significant.

Six patients in the placebo group and 1 in the levothyroxine group withdrew from the study for nonresponse. Three stopped taking levothyroxine because of adverse effects (mild thyro-
toxicosis, exanthema, and a switch into mania), which required no special care. There were no treatment-related changes in body weight, blood pressure, or ECG.

Discussion: Most textbooks, reviews, and treatment guidelines recommend adjunctive thyroid hormone for resistant mood disorders. In previous studies, supraphysiologic doses (300–600 mcg/day) were more effective than replacement doses in rapid cycling and refractory bipolar depression. The gender difference in depression response to thyroid hormone has been observed previously. The lack of overall statistical significance in the present study may be partly attributable to a low threshold for enrollment (the mean HAM-D at study entry was 21) and a high placebo response rate (about 25% in both men and women).

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


*Cognitive Enhancers for Mild Cognitive Impairment

According to results of a meta-analysis, cognitive enhancers, including cholinesterase inhibitors and memantine, are not effective in patients with mild cognitive impairment. The results also indicated that these drugs are associated with adverse GI effects, headache, and possibly increased cardiovascular risk.

Background: Cognitive enhancers are often used to treat dementia, and their use has been suggested as a means to delay the progression of mild cognitive impairment to dementia. The present analysis was undertaken to evaluate the safety and efficacy of these agents in patients with mild cognitive impairment.

Methods: Studies comparing cognitive enhancers with each other, placebo, or supportive care were identified by comprehensive literature search. For inclusion in the meta-analysis, studies were required to include participants with a diagnosis of mild cognitive impairment based on cutoff scores using validated instruments.

Results: The search identified 10 reports describing 8 randomized placebo-controlled trials, published between 1999 and 2007. There were 4 studies of donepezil, 2 of galantamine, and 1 each of memantine and rivastigmine. Outcome measures were the Mini-Mental State Examination (MMSE), the Alzheimer’s Disease Assessment Scale Cognitive Behavior subscale (ADAS-cog), the Alzheimer’s Disease Cooperative Study–Activities of Daily Living Inventory, and the Neuropsychiatric Inventory. Three studies also examined mortality, and 6 reported on harms of the treatments.

Donepezil treatment showed a small advantage over placebo after a mean of 36 weeks in studies that used the MMSE as an outcome. However, the difference was not judged to be clinically relevant. Studies of other drugs and other outcome measures found few differences between active treatment and placebo. Results of the ADAS-cog favored cognitive enhancers through 84 weeks of follow-up, but with longer follow-up, there was no difference between active treatment and placebo, suggesting the agents do not slow progression to dementia. There was no favorable effect of galantamine on activities of daily living or of donepezil on behavior. Mortality did not differ between patients who did or did not receive a cognitive enhancer. There were increased rates of nausea, diarrhea, vomiting, and headaches with the 4 cognitive enhancers, compared with placebo, but no increase in serious adverse events. In 1 study, patients who received galantamine had a higher rate of bradycardia but a lower incidence of falls than the placebo group.
**Discussion:** Cognitive enhancers are indicated to treat dementia, but patients and their families are increasingly requesting their use in mild cognitive impairment. Although this analysis is based on a small number of relatively low quality studies, the results do not support the use of cognitive enhancers in patients with mild cognitive impairment.

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

Tricco A, Soobiah C, Berliner S, Ho J, et al: Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review and meta-analysis. *Canadian Medical Association Journal* 2013;185 (November 5): 1393–1401. From the University of Toronto; and the University of Calgary, Canada. Funded by the Drug Safety and Effectiveness Network/Canadian Institutes of Health Research. Six study authors disclosed potential conflicts of interest; the remaining 3 declared no conflicts of interest.

**Drug Trade Names**: donepezil—Aricept; galantamine—Razadyne; memantine—Namenda; rivastigmine—Exelon

*See Reference Guide.

### Atypical Antipsychotics: Mechanisms of Metabolic Effects

Weight gain and metabolic effects with second-generation antipsychotics have important health- and treatment-related consequences. However, studies of the mechanisms of weight gain in patients taking these drugs are inconclusive, according to a literature review.

Results of studies in healthy volunteers, although not consistent, suggest that a few weeks' exposure to atypical antipsychotics can lead to increased calorie intake without a change in dietary composition. In patients with mental illness, longer exposure to second-generation antipsychotics may lead to a shift in intake from carbohydrates to saturated fats and proteins and increased hunger and appetite disinhibition. In an analysis of 4 olanzapine trials, increased appetite was not consistently correlated with weight gain, but weight change in the first 2–4 weeks of treatment was predictive of overall gain. In other studies, clozapine and olanzapine were associated with food craving and binge eating in substantial proportions of patients.

Studies of atypical antipsychotics' effects on resting energy expenditure, which accounts for 68–80% of total energy expenditure, are inconclusive, and results differ according to study design. It is not known whether any of the observed changes are the result of drug treatment. Physical activity is generally low in patients with schizophrenia, but it is not clear whether this is a consequence of medication or of the disease. There are few large, prospective, well-designed studies in medication-naive patients, which would be needed to separate the different mechanisms involved in antipsychotic-related weight gain and the direction of causality.

It is clear that weight gain and metabolic side effects have increased since the introduction of second-generation antipsychotics. The main prognostic factors are young age; being treatment-naive; low body mass index before treatment; drug type and dose; and polypharmacy. Regardless of the mechanism of these effects, lifestyle recommendations (e.g., reduced caloric intake, appropriate food selection, and increased physical activity) should accompany second-generation antipsychotic prescriptions.


**Drug Trade Names**: clozapine—Clozaril; olanzapine—Zyprexa

### Weight and Metabolic Effects of Asenapine

In patients with schizophrenia or bipolar disorder, asenapine is associated with more weight gain than placebo but less than olanzapine, according to an FDA-requested review of asenapine clinical trials. Its effects on lipids and fasting glucose were also intermediate between placebo and olanzapine.
Methods: The review included 17 double-blind trials: 13 using olanzapine as a comparator and 4 that were strictly placebo-controlled. In 4 trials, both olanzapine and placebo controls were used. For this analysis, study data were aggregated into 2 pools, separately comparing asenapine with each alternative. The placebo-controlled trials included >1700 patients who received randomized treatment, and the olanzapine-controlled trials included >3400. Durations ranged from brief, 1- to 2-week pharmacology studies, to acute-treatment trials lasting several weeks, to extension studies of ≥1 year. Participants received treatment for a mean of about 25 days (range, 1–6 weeks) in the placebo-controlled trials and for >200 days (range, 3–100 weeks) in the olanzapine trials. Asenapine was generally administered at dosages of 5 or 10 mg b.i.d. and olanzapine at 5–20 mg/day.

Results: In the placebo trials, patients gained an average of 2.6 lbs by study endpoint with asenapine and 0.3 lbs with placebo (p<0.0001). No weight gain was evident in 53% of placebo-treated patients and in 38% of those who received asenapine. Patients who received placebo experienced substantial improvements in lipids and fasting glucose, which the authors attribute to discontinuation of their previous antipsychotics.

In the olanzapine trials, patients gained a mean of 2 lbs with asenapine vs. 6.8 lbs with olanzapine (p<0.0001). Thirty percent of patients taking olanzapine and 44% of those taking asenapine did not gain weight. Results of these comparisons were similar in separate analysis of patients with schizophrenia and bipolar disorder. Effects of the drugs on body mass index were similar to weight. Asenapine was associated with some metabolic changes, but to a lesser degree than olanzapine: mean fasting glucose increased by 2.0 vs. 3.3 mg/dL, LDL cholesterol decreased by 0.3 mg/dL vs. a 3.1-mg/dL increase with olanzapine (p<0.01), and triglycerides decreased by 0.9 mg/dL vs. a 24.3-mg/dL increase with olanzapine (p<0.0001).

Discussion: Asenapine had a more favorable metabolic profile than olanzapine in studies lasting ≥1 year. The reason for this difference is unknown, but the authors propose antagonism of serotonin receptors in the thalamus and hypothalamus, which may regulate appetite and energy expenditure.

Kemp D, Zhao J, Cazorla P, Landbloom R, et al: Weight change and metabolic effects of asenapine in patients with schizophrenia and bipolar disorder. Journal of Clinical Psychiatry 2013; doi 10.4088/jcp.12m08271. From the Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, OH; and other institutions. Funded by Merck & Co., Inc. All study authors disclosed financial relationships with commercial sources; 6 of the 7 were with Merck, the manufacturer of asenapine.

Drug Trade Names: asenapine—Saphris; olanzapine—Zyprexa

Biological Agent for Depression

Rellidep, a biological extract of chicken embryos, had antidepressant effects in an uncontrolled pilot study. The mechanism of action is believed to be antagonism of the neurokinin-2 (NK-2) receptor and, secondarily, glutamate receptor antagonism. The agent had no apparent adverse effects.

Methods: The open-label, fixed-dose study was conducted in 20 patients, aged 18–65 years (mean age, 45 years; 61% female), who met DSM-IV-TR criteria for single-episode or recurrent major depressive disorder and had a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥18. Antidepressant medication and natural health products for depression were not permitted, and patients could not receive psychotherapy during the trial. All participants received 500 mg Rellidep b.i.d. for 8 weeks as monotherapy.

Results: In an intent-to-treat analysis,* the mean HAM-D score decreased from about 25 at baseline to 12 at study end (p<0.001). Patients also demonstrated statistically significant improvement in secondary outcomes: responder analysis (15 of 20 patients, based on the HAM-D total
score); Clinical Global Impression–Severity and –Improvement; Montgomery-Asberg Depression Rating Scale; Beck Depression Inventory; Hamilton Anxiety Rating Scale; and Medical Outcomes Study Short Form-36, a measure of functional capacity. However, they did not demonstrate improvement in sexual function. Of patients who experienced response, nearly all did so by treatment week 4. There were no medication-related adverse events or laboratory changes attributable to Rellidep.

**Discussion:** Interest is growing in the many biological pathways that may contribute to depression, beyond the serotonergic and noradrenergic systems. Other hormones, such as cortisol and thyroid hormone, may contribute, as may inflammatory processes. Although this is the first study of Rellidep in depression, similar biological tissue extracts have shown promise in relieving depression and sexual dysfunction.

Sadavoy J, Bain J: An open-label, pilot study evaluating the safety and antidepressant effects of Rellidep in major depressive disorder. *Journal of Clinical Psychopharmacology* 2013; doi 10.1097/JCP.0000000000000068. From the University of Toronto, Canada; and United Paragon Associates. **Funded by United Paragon Associates. The authors disclosed financial relationships with commercial sources including United Paragon Associates, the developer of Rellidep.**

*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.

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

**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 the treatment.

**Observational Study Rating:** The study rating is a measure of how well the study, as reported in the journal, conforms to well-documented quality standards. Our rating system evaluates the report of the study and not necessarily the study itself. The rating for observational study reports includes 9 domains: study question; population; comparability of subjects; exposure or intervention; outcome measurement; statistical analysis; results; discussion; and funding/sponsorship. The domains listed in italics are considered key domains and are worth 2 points each on the rating scale. The remaining domains are each worth 1 point. The maximum attainable score for observational study quality is 14.

**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 program 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.