Fluoxetine plus Lovastatin for Depression

Experimental evidence suggests the antiinflammatory mechanisms of statins may confer antidepressant effects, but results of epidemiologic studies have been contradictory. In what appears to be the first randomized controlled trial, lovastatin, given as an adjunct to fluoxetine, was superior to placebo in a group of patients with depression.

Methods: Study subjects were 68 patients (mean age, 32 years; about one-third male) with major depressive disorder according to DSM-IV criteria and a Hamilton Rating Scale for Depression (HAM-D) score of >17. Patients with a personal or family history of bipolar disorder were excluded. All participants received fluoxetine at a maximum dosage of 40 mg/day plus randomly assigned, double-blind 30 mg/day lovastatin or placebo. Patients were evaluated using the HAM-D at baseline and at 2 and 6 weeks.

Results: A total of 61 patients completed the study; no patient discontinued the trial due to adverse effects. The outcome analysis was based on all patients who received ≥2 weeks of medication and attended ≥1 follow-up evaluation.

HAM-D scores improved significantly during treatment in both groups: from 29 to 16 with lovastatin, and from 28 to 20 with placebo. At week 6, HAM-D reduction was significantly greater with adjunctive lovastatin than with placebo (13 vs. 8 points; p<0.001).

There were no serious adverse events. Rates of most mild-to-moderate adverse events (e.g., nausea; vomiting; itching; abdominal pain; insomnia) were similar in the 2 treatment groups, but decreased appetite was significantly more common with lovastatin (1 vs. 8 patients; p<0.01).

Discussion: Results of previous research suggest depression and stressful life events are associated with increased levels of inflammatory cytokines. Statins are commonly prescribed to lower lipids but also inhibit inflammation. They may also inhibit the activity of an enzyme called...
IDO (indoleamine (2,3)-dioxygenase), an inflammatory product that degrades the serotonin precursor tryptophan. Although positive, results of this short-term, relatively small trial require replication.

**Study Rating***—15 (88%): This study met most criteria for a randomized controlled trial; however, the source of funding was not stated.

Ghanizadeh A, Hedayati A:Augmentation of fluoxetine with lovastatin for treating major depressive disorder, a randomized double-blind placebo-controlled clinical trial. *Depression and Anxiety* 2013; doi 10.1002/da.22195. From Shiraz University of Medical Sciences; and Fasa University of Medical Sciences, Iran. **Source of funding not stated.** The authors did not include disclosure of potential conflicts of interest.

**Drug Trade Names:** fluoxetine—Prozac; lovastatin—Mevacor

*See Reference Guide.

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**Antidepressant Class and Self-Harm Risk**

A large claims-based study found no difference in the incidence of deliberate self-harm between patients given a new prescription for SSRI or SNRI antidepressants. The results suggest physicians need not weigh differential suicide risk when deciding which class of drugs to prescribe.

**Background:** Previously, 2 FDA meta-analyses found elevated rates of suicidal behavior associated with antidepressant use in patients aged ≤24 years, but not in patients aged 25–64 years. It is possible that SNRIs, which generally have a shorter half-life, are associated with greater risk due to discontinuation effects, anxiety, sleep difficulty, or other mechanisms. Because suicidal behavior is a rare outcome, the FDA studies lacked the statistical power to investigate the possibility that risks differ by antidepressant class.

**Methods:** The present cohort study included patients, aged 10–64 years, who received a first antidepressant prescription for depression between 1998 and 2010. Data were obtained from >98 health plans covering >61 million patients. For each patient, the defined exposure period began the day after initiation of the first antidepressant and extended for 1 year or until they switched or added a second antidepressant. The outcome of interest was a medical claim for injury due to deliberate self-harm. Each patient given a prescription for an SNRI was propensity-score matched* with up to 2 patients given SSRIs. Bupropion was excluded from the analysis because of its frequent use for smoking cessation.

**Results:** Two age groups were analyzed separately: nearly 103,000 patients aged 10–24 years and nearly 340,000 aged 25–64 years. In the younger patient group, 76% were given a prescription for an SSRI, 6% took an SNRI, and the rest used another antidepressant. Among the older patients, 68% started an SSRI and 11% started an SNRI. In both age groups, rates of self-harm were nearly identical in users of the 2 drug classes. In the younger group, self-harm occurred in 66 patients receiving an SSRI and in 39 patients receiving an SNRI (15.3 vs. 17.6 per 1000 person-years). In those aged 25–64 years, self-harm occurred in 81 and 49 patients (2.5 and 2.8 per 1000 person-years), respectively. In both age groups, nearly 40% of all self-harm events occurred during the first 30 days of treatment; the majority of events (70%) occurred within 90 days of the new prescription.

**Discussion:** The authors note that this study evaluates only whether the risk of self-harm differs between the 2 most commonly prescribed antidepressant classes. The study does not examine whether prescribing an antidepressant for patients with depression is advisable.

Miller M, Pate V, Swanson S, Azreal D, et al: Antidepressant class, age, and the risk of deliberate self-harm: a propensity score matched cohort study of SSRI and SNRI users in the USA. *CNS Drugs* 2013; doi 10.1007/s40263-013-0120-8. From Harvard School of Public Health, Boston, MA; and the University of North Carolina at Chapel Hill. **Funded by the NIMH; and other sources.** The authors declared no conflicts of interest.

*See Reference Guide.
Three new second-generation antipsychotic agents have been introduced since 2009, another is near approval, and several others are in the pipeline. These agents have a lower propensity to induce weight gain and metabolic abnormalities relative to older second-generation drugs.

The 3 recently approved agents—asenapine, iloperidone, and lurasidone—have roughly similar efficacy, with numbers needed to treat* (NNTs) to achieve a ≥20%–≥30% reduction in Positive and Negative Syndrome Scale (PANSS) score ranging from 4 to about 8, depending in part on the dose evaluated and on the target symptom. Lurasidone—as adjunctive or monotherapy—has a similar NNT for bipolar depression, and asenapine is effective in bipolar mania and mixed states. All 3 have a relatively benign metabolic adverse effect profile. Lurasidone appears to be best in class for avoiding weight gain and is also neutral with regard to lipids, prolactin, and the QT interval. The others have modest electrocardiography (ECG) effects that are probably not relevant in routine patient care. The main distinctions among the 3 drugs that may influence treatment selection are logistic. Lurasidone is dosed once daily but must be taken with a meal. The others are labeled for twice-daily dosing. Iloperidone must be titrated over several days to avoid the risk of inducing orthostatic hypotension, which limits its use for rapid control of psychotic symptoms. Asenapine is absorbed in the mouth and will not work if swallowed or taken with food or fluids.

Cariprazine (FDA approval pending) is a partial dopamine D2 antagonist, a mechanism it shares with aripiprazole. It has little efficacy data available for schizophrenia, but NNTs of 5 and 7 were reported in trials in bipolar mania/mixed episodes. It appears to have a benign metabolic profile and is not associated with QT prolongation.

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<th>Characteristics of Antipsychotics Either Newly Approved or with Approval Pending</th>
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<td><strong>Illoperidone</strong></td>
</tr>
<tr>
<td><strong>Approved Indications</strong></td>
</tr>
<tr>
<td><strong>Target Dose</strong></td>
</tr>
<tr>
<td><strong>Dose Frequency</strong></td>
</tr>
<tr>
<td><strong>Titration Required</strong></td>
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<td><strong>Dose Administration</strong></td>
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<tr>
<td><strong>Receptor Activity</strong></td>
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Other investigational agents include the partial dopamine D₂ antagonist brexpiprazole, also similar to aripiprazole, and zicronapine, an antagonist of dopamine D₁ and D₂ and serotonin 5-HT₂A receptors. Too little information is available to assess the clinical utility of brexpiprazole or zicronapine. Two other investigational drugs with novel mechanisms have had promising effects as adjunctive treatments in clinical trials. Bitopertin, a glycine transporter type 1 inhibitor, differs from all other antipsychotics, which target dopamine D₂ receptors. Adjunctive bitopertin was effective in negative symptoms at a low dose (NNT, 5), but not a higher dose. It is also under investigation for residual symptoms, acute exacerbation of schizophrenia, and cognitive dysfunction. EVP-6124 is a selective alpha-7 nicotinic acetylcholine receptor agonist that is expected to improve attention and memory. Preliminary evidence suggests adjunctive EVP-6124 may improve global cognitive function and negative symptoms.

Citrome L: A review of the pharmacology, efficacy and tolerability of recently approved and upcoming oral antipsychotics: an evidence-based medicine approach. CNS Drugs 2013; doi 10.1007/s40263-013-0105-7. From New York Medical College, Valhalla. This review was conducted without external funding. The author disclosed financial relationships with commercial sources including the manufacturers of all drugs discussed.

Drug Trade Names: asenapine—Saphris; iloperidone—Fanapt; lurasidone—Latuda
*See Reference Guide.

Dermatologic Side Effects of Psychotropic Drugs

Adverse cutaneous reactions occur with all of the major classes of psychotropic drugs. Although the incidence is low, psychotropic drug use is common, and the reactions can limit medication adherence, increase morbidity, and have the potential to be life-threatening.

Adverse cutaneous reactions are of 2 types. Type A reactions are attributable to the pharmacologic or toxic effects of the drug, are dose-dependent, and can occur in any patient. Type B reactions are immunologically mediated; they are idiosyncratic and may be limited to patients with a metabolic or genetic predisposition. Most cutaneous reactions to psychotropic drugs are type B.

Cutaneous drug reactions are most likely to occur during the winter months, in women, African-Americans, the elderly, and substance abusers, and after a high initial loading dose of the drug. Diagnosis of these reactions depends on knowledge of the agents that are likely to cause a certain type of reaction and the timing of events. In some cases, self-inflicted lesions must be ruled out.

Cutaneous drug reactions to mood stabilizers are rare but can be among the most serious. Risk is highest with lamotrigine and carbamazepine. The most common type of reaction is an exanthematous macular and papular eruption, but these drugs can also cause Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These necrolysis spectrum eruptions are differentiated based on extent of involvement of body surface area: <10% is designated SJS, 10–30% is considered SJS/TEN, and >30% is TEN. Mortality from these reactions ranges from 5% to 30%, depending on the extent of involvement, and death is usually caused by infection.

Cutaneous reactions occur in approximately 0.05% of patients taking antidepressants. Tricyclics have the highest reported rate at 0.07%, and risks seem to be lower with SNRIs than other antidepressants. The most common reactions are exanthematous eruptions and urticaria with or without angioedema. Hyperhidrosis can be caused by SSRIs or SNRIs.

The most common skin reactions to neuroleptics are photosensitivity and hyperpigmentation. Various rashes have been reported at low frequency for several of the second-generation antipsychotics. Benzodiazepines and barbiturates can cause exanthematous skin eruptions, which can progress to TEN.
Treatment of cutaneous reactions nearly always consists of discontinuing the causal drug. With lithium and carbamazepine, a dose reduction can lead to resolution of the rash. Other treatments are symptomatic: antihistamines and topical or systemic steroids.

**Web Extra**—Visit [www.alertpubs.com](http://www.alertpubs.com) for a printable table of common psychotropics and their reported cutaneous reactions.

Mitkov M, Trowbridge R, Lockshin B, Caplan J: Dermatologic side effects of psychotropic medications. *Psychosomatics* 2013; doi 10.1016/j.psym.2013.07.003. From Creighton University School of Medicine, Phoenix, AZ; and other institutions. **Source of funding not stated. The authors did not disclose potential conflicts of interest.**

**Drug Trade Names:** carbamazepine—Carbatrol, Equetro, and others; lamotrigine—Lamictal, and others

### Adjunctive Quetiapine Ineffective in GAD

In a study in patients with generalized anxiety disorder, adjunctive extended-release quetiapine (*Seroquel XR*) was not superior to placebo.

**Background:** Although GAD is not an approved indication for quetiapine, the drug has been shown in several studies to be effective monotherapy for the disorder. The present study is the first large-scale, randomized, controlled trial to evaluate quetiapine as an adjunct to antidepressant therapy in patients with GAD who previously experienced inadequate response to an SSRI or SNRI.

**Methods:** Study subjects, aged 18–65 years (n=402), had continuing symptoms of GAD, with Hamilton Anxiety Rating Scale (HAM-A) scores of ≥20, despite ≥8 weeks of therapy with an adequate dose of an SSRI or SNRI. Following a 1-week placebo lead-in, participants had randomly assigned adjunctive quetiapine or placebo added to ongoing medication. Quetiapine was started at 50 mg/day and increased to 150 mg/day on day 3, with a further increase to 300 mg/day if significant symptoms persisted. The primary efficacy outcome measure was change from randomization in the HAM-A total score.

**Results:** Of the 402 patients enrolled, about 80% completed the study. In a last-observation-carried-forward analysis,* HAM-A scores decreased by about 10 points after 8 weeks, from a baseline mean of 25, in each treatment group. Final scores did not differ significantly between the groups. Treatment response (≥50% decrease in HAM-A score) was achieved by 41% of the quetiapine group and 36% of the placebo group. The number needed to treat* to achieve 1 response to quetiapine treatment was 21. There were modest differences in secondary outcomes that did not show a consistent pattern. The adverse effects of quetiapine were similar to those previously reported and included dry mouth, somnolence, sedation, headache, and dizziness.

**Discussion:** The authors note an unexpectedly large placebo response in the study, which may have played a role in the failure of quetiapine to separate statistically from placebo. In addition, the treatment-resistant nature of patients’ illness may have negatively affected quetiapine efficacy. Further studies appear to be warranted to determine if quetiapine has a true lack of effect as adjunctive therapy for GAD.

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

Khan A, Atkinson S, Mezhebovsky I, She F, et al: Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in patients with generalized anxiety disorder and a history of inadequate treatment response: a randomized, double-blind study. *Annals of Clinical Psychiatry* 2013;25 (November):E7–E22. From the Northwest Clinical Research Center, Bellevue, WA; and other institutions including AstraZeneca Pharmaceuticals, Wilmington, DE. **Funded by AstraZeneca. Five of the 6 study authors disclosed financial relationships with commercial sources; the remaining author declared no conflicts of interest.**

*See Reference Guide.
**Adjunctive Quetiapine in Depression**

Additional analysis of previously published data suggests that adjunctive quetiapine (*Seroquel*) is effective whether used with SSRI or SNRI antidepressants.

**Methods:** Investigators pooled data from 2 previously published, large, multicenter, multinational placebo-controlled trials of similar design. Participants in both trials had major depression and were experiencing inadequate response to ≥6 weeks of treatment with an SSRI or SNRI. Patients received 6 weeks of randomly assigned quetiapine at 150 or 300 mg/day, or placebo, added to ongoing SSRI or SNRI therapy. The primary efficacy measure was the Montgomery-Asberg Depression Rating Scale (MADRS), with response defined as a ≥50% reduction in the total score and remission as a score of ≤8 at 6 weeks.

**Results:** A total of 919 patients were randomized and started treatment. Background medication was an SSRI in nearly 70% of patients and an SNRI in about 30%. At week 6, there was a robust placebo response in both antidepressant subgroups but superior results with adjunctive quetiapine. In the SSRI group, MADRS scores decreased by 13 points with placebo and by 15 points for each dose of quetiapine (p<0.05; effect size,* 0.23 for both doses). MADRS response rates were 49% with placebo and 59% with 300 mg/day quetiapine (p<0.05). The lower quetiapine dose did not differ statistically from placebo. Remission occurred in 27% of the placebo group and 38% of each quetiapine group (p<0.05).

Results were similar in patients taking SNRIs. The average MADRS score decreased by 11 points with placebo and nearly 15 points with the 2 quetiapine doses (p<0.01 for both doses; effect sizes, 0.41 and 0.44, respectively). MADRS response occurred in 42% of the placebo group and in 60% of the 300-mg quetiapine group (p<0.05). The lower quetiapine dose did not differ statistically from placebo. Remission rates were 16% with placebo and 31–32% for the 2 quetiapine doses (p<0.05 for both).

Additional secondary endpoints were included in this analysis, beyond those in the initial publications. In both antidepressant groups, adjunctive quetiapine was superior to placebo with regard to scores on the Hamilton Rating Scale for Depression, the Clinical Global Impression–Severity scale, and the Pittsburgh Sleep Quality Index. MADRS scores with quetiapine augmentation began to diverge from placebo as early as 1 week.

*Bauer M, Demyttenaere K, El-Khalili N, Thase M, et al: Pooled analysis of adjunct extended-release quetiapine fumarate in patients with major depressive disorder according to ongoing SSRI or SNRI treatment. *International Clinical Psychopharmacology* 2013; doi 10.1097/YIC.000000000000011. From the University Hospital Carl Gustav Carus, Dresden, Germany; and other institutions. **Funded by AstraZeneca Pharmaceuticals. All study authors disclosed financial relationships with commercial sources, including AstraZeneca.***

**Gabapentin for Alcohol Dependence**

In a 12-week placebo-controlled trial, gabapentin (*Neurontin*) showed dose-related efficacy in patients with alcohol dependence.

**Background:** Nearly 8.5 million Americans suffer from alcohol dependence; however, <10% of these patients receive an FDA-approved medication for the disorder. Although indicated for neuropathic pain and epilepsy, gabapentin has been shown to reduce alcohol craving, sleep disturbance, and mood in patients attempting to abstain from alcohol. Limitations in study designs and other methodological issues prevented definitive conclusions from these studies. The present study was designed to address those limitations.

**Methods:** Study participants were treatment-seeking volunteers who responded to print or internet advertisements and met DSM-IV criteria for alcohol dependence. After meeting a
3-day abstinence requirement, they were randomly assigned to 12 weeks of double-blind treatment with 900 mg/day gabapentin, 1800 mg/day gabapentin, or placebo. In addition, each participant received 20 minutes of manual-guided counseling every week and was encouraged to use self-help groups or other psychosocial treatments. The primary efficacy outcomes were complete abstinence and abstinence from heavy drinking. A heavy drinking day was defined as ≥4 drinks for women and ≥5 drinks for men.

**Results:** A total of 150 participants with generally moderate-to-severe alcohol dependence were enrolled, treated, and included in the intention-to-treat analysis. Of these, 65 patients did not complete the trial for various reasons, including adverse events (n=9) and treatment failure (n=7). The rates of study withdrawal, overall and for specific reasons, did not differ among the 3 treatment groups.

Gabapentin had a significant dose-related effect on rates of complete abstinence (p=0.04) and heavy drinking (p=0.02). Rates of sustained abstinence were 4% for placebo, 11% for 900 mg gabapentin, and 17% for 1800 mg gabapentin. Rates of no heavy drinking were 22.5%, 30%, and 45%, respectively. For the 1800-mg dose, the number needed to treat* for 1 additional response vs. placebo was 8 for abstinence and 5 for no heavy drinking. Treatment effects were sustained in 65 participants who attended a 24-week follow-up visit. Secondary outcomes, including various self-reported measures of alcohol consumption, γ-glutamyltransferase levels (a biomarker), craving, mood, and sleep, also showed a significant dose-related effect of gabapentin. The drug was well tolerated, and adverse events did not differ from placebo. There was no evidence of drug diversion or substitution. A minority of patients (<10%) attended individual counseling and/or Alcoholics Anonymous meetings during the study; these did not differ in the treatment groups and were not associated with differences in outcome.

**Discussion:** Gabapentin is believed to normalize the stress-induced GABA (γ-aminobutyric acid) activation in the amygdala that is associated with alcohol dependence. In addition, the drug is not appreciably metabolized by the liver, which could be an important factor for patients with alcohol-related liver disease. The present study, designed to assess the highest and lowest approved doses of gabapentin, supports its efficacy and safety in the treatment of alcohol dependence.

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


*See Reference Guide.

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**Agomelatine in Clinical Practice**

In an open-label post-marketing practice-based study, agomelatine (not available in the U.S.) monotherapy improved depressive symptoms, sleep, and daily functioning in a group of patients with major depression.

**Methods:** Study participants (n=111; mean age, 46 years) were outpatients at 13 hospital-affiliated psychiatry clinics in Slovakia. All patients had moderate-to-severe major depressive disorder; those with chronic (>2 years) or treatment-resistant depression were excluded. Agomelatine was started at 25 mg/day and could be increased to 50 mg/day after 2 weeks if the Montgomery-Asberg Depression Rating Scale (MADRS) total score remained elevated. The primary outcome measure was the MADRS.

**Results:** A total of 94 study patients completed the 8 weeks of treatment. Nine patients withdrew because of lack of efficacy, 2 because of side effects (i.e. GI symptoms, nightmares), and
the rest for various reasons unrelated to treatment. By week 8, the average MADRS score decreased from 29 to 11.5 points, 75% of patients had achieved response, and 47% had achieved remission. The Sheehan Disability Scale showed significant improvement in all 3 dimensions of function—work, social, and family—beginning after week 1. Patients’ self-rated sleep also showed significant improvement beginning at week 1. Adverse effects were mild to moderate, and the most frequent were headache and tension (n=6) and anxiety (n=4).

Pecenak J, Novotny V: Agomelatine as monotherapy for major depression: an outpatient, open-label study. *Neuropsychiatric Disease and Treatment* 2013;9:1595–1604. From Comenius University and University Hospital, Bratislava, Slovakia. Funded by Servier, Slovakia. One author reported relationships with commercial sources, including Servier; the second author declared no conflicts of interest.

### 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.

#### Last Observation Carried Forward (LOCF)

A method of data analysis in which missing data for individual patients is replaced by the last observed value of that variable.

#### 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.

#### Propensity-Score Matching

Selection bias can be problematic when using observational data, making causal relationships difficult to establish. Propensity score matching is a correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

#### 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](http://www.alertpubs.com).

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**STATEMENT OF OWNERSHIP, MANAGEMENT, AND CIRCULATION**