Low-Dose Buprenorphine for Suicidal Ideation

In a placebo-controlled trial, very-low-dose, time-limited, sublingual buprenorphine was associated with decreased suicidal ideation in severely suicidal patients.

**Background:** For many years during the last 2 centuries, opioids were widely used to treat depression; however, because of their addictive potential and lethality in overdose, they were replaced by current antidepressants. Several lines of evidence point to a connection between separation distress, mental pain, depression, suicidal ideation, and endogenous opioids, leading to the hypothesis that opioids at very low doses might alleviate suicidal ideation. Buprenorphine is a partial mu-opioid agonist chosen for this study because of its low lethality. The very low doses used in the study were crucial for enabling independent home-based use for a short period.

**Methods:** Participants, aged 18–65 years (n=88; 63 women), were recruited from 4 centers in Israel over a 3.5-year period. All had clinically significant suicidal ideation, defined as a score of ≥11 on the Beck Scale for Suicide Ideation (BSSI) for ≥1 week. Those with a lifetime history of opioid abuse or a history of any substance or alcohol abuse within 2 years were excluded. Concurrent medication use was not an exclusion criteria, but antidepressant use had to have been stable for ≥28 days and no changes were allowed during the study period. Clinicians could modify other background pharmacotherapy as needed. Patients were randomly assigned in a 2:1 ratio to receive double-blind buprenorphine or placebo for 4 weeks. Buprenorphine was started at 0.1–0.2 mg/day and could be increased to a maximum of 0.8 mg/day. A week’s supply of medication was dispensed at a time; this amount was not considered to present an overdose risk. The primary study outcome was change from baseline on the BSSI.

**Results:** A total of 62 patients (71%) who received ≥1 dose of study medication and completed ≥1 post-baseline assessment were included in the analysis. Most patients were clinically unstable, and many were unable to cooperate with study staff, which resulted in a high dropout rate of 30% during the first week. Patients were severely suicidal; two-thirds had made ≥1 suicide attempt, nearly 30% of which were within the prior month. More than half met...
criteria for borderline personality disorder, and about 40% had major depressive disorder. The majority of patients were receiving additional therapy with an antidepressant (70%), a benzodiazepine or other hypnotic (49%), an antipsychotic (20%), and/or a mood stabilizer (18%). About one-fourth were currently hospitalized.

Patients in the buprenorphine group had a reduction of about 50% in mean BSSI score that was statistically significant, relative to placebo, by the end of week 2 (p=0.04) and remained so at 4 weeks (p=0.004). Concurrent treatment with antidepressants did not affect the relative likelihood of response, nor did the presence of borderline personality disorder. Patients who received buprenorphine also had better secondary outcomes, including reductions on the Suicide Probability Scale (p=0.03), Beck Depression Inventory (p=0.09), and an item of the Suicide Probability Scale thought to reflect mental pain (p=0.03).

The predominant adverse effects of buprenorphine were fatigue (49%), dizziness (40%), nausea (37%), and headache (32%). One patient in each treatment group attempted suicide during the study. No patient experienced withdrawal during the week after drug discontinuation.

Discussion: Despite the efficacy and favorable safety profile in this study, buprenorphine is potentially addictive and possibly lethal. The study authors caution that even at very low doses, the drug should be tested only in individuals who have been screened for the possibility of substance abuse.

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


From the University of Haifa, Israel; and other institutions. Funded by the Hope for Depression Research Foundation; and other sources. The authors did not include disclosure of potential conflicts of interest.

*See Reference Guide.

Zinc Augmentation in Schizophrenia

In a small, short-term, controlled trial, adding zinc sulfate to risperidone (Risperdal) resulted in significantly greater improvement in schizophrenia symptoms.

Background: Among its crucial roles in many essential brain functions, zinc is a neuromodulator of NMDA, GABAergic, and cholinergic neurotransmission, all of which are important in schizophrenia. Zinc deficiencies have been documented in patients with the disorder, but supplementation has not previously been investigated as a potential treatment.

Methods: Study subjects were inpatients, aged 18–65 years (n=30; 28 men), at a psychiatric hospital in Iran who were experiencing an acute episode of schizophrenia. Patients met DSM-IV-TR criteria for the disorder and had a score of ≥80 on the Positive and Negative Syndrome Scale (PANSS). Prior to study entry, patients received no oral antipsychotics for 1 week and no depot antipsychotics for ≥2 months. All patients received 6 mg/day risperidone. In addition, they were randomized to receive double-blind treatment with either 220 mg zinc sulfate t.i.d. (for a total daily dose of 150 mg elemental zinc) or placebo. Outcomes were assessed biweekly for 6 weeks using the PANSS, including the PANSS supplemental aggression risk subscale.

Results: Zinc supplementation was associated with significantly larger improvement than placebo in positive and negative symptoms, the PANSS total score, and aggression, but not general psychopathology. (See table, next page.) Change from baseline differed significantly between the 2 groups beginning at week 4 for most symptoms and at week 2 for positive symptoms. Adverse effects were not systematically investigated, but metallic taste appears to be the only effect that occurred more frequently with active treatment.
Adjunctive Raloxifene in Schizophrenia

Raloxifene (Evista), a selective estrogen receptor modulator (SERM), was an effective adjunctive treatment in postmenopausal women with schizophrenia in a placebo-controlled trial.¹ Its primary benefit was in reducing negative symptoms.

**Background:** Research indicates that estrogen levels are significantly lower in women with schizophrenia than in healthy women and that illness onset and relapses often coincide with the phases of the menstrual cycle when estrogen levels are low. A few studies have evaluated short-term therapeutic use of estrogen in women, but long-term use has the potential for negative effects on breast and uterine tissue. Raloxifene acts as an agonist of AMPA, NMDA, and serotonin receptors in some brain areas, has antiinflammatory activity, and can act as an agonist of dopamine D2 and D3 receptors. It was shown in a previous, small, 12-week trial to be an effective adjunct to antipsychotics in postmenopausal women.² The present study, conducted by the same researchers, was undertaken to replicate earlier results in a larger sample.

**Methods:** Subjects in this 24-week trial were 70 postmenopausal women (56 inpatients) with schizophrenia who were receiving stable antipsychotic medication and had prominent negative symptoms. Postmenopausal status was defined as age >50 years and ≥1 year of amenorrhea, or age 45–50 years with ≥1 year of amenorrhea and postmenopausal levels of follicular stimulating hormone (FSH). Women receiving hormone replacement therapy or with sex hormone abnormalities were not included. In addition to their current antipsychotic therapy, which remained unchanged for the duration of the study, patients were randomly assigned to receive double-blind adjunctive 60 mg/day raloxifene or placebo. Efficacy was assessed with the Positive and Negative Syndrome Scale (PANSS).

**Results:** Patients had a mean age of about 62 years and had schizophrenia onset in their mid-to-late 20s on average. The majority were taking second-generation antipsychotics or drug combinations. By chance, baseline PANSS symptom severity was greater in the women who received raloxifene—significantly so for the general psychopathology subscale (p=0.02).

In a last observation carried forward analysis,* compared with placebo, adjunctive raloxifene was associated with significant improvement in the PANSS total score and the negative and general psychopathology subscales (see table, next page), but not in positive symptoms. The
rate of negative symptom response (≥20% reduction in PANSS negative symptom score) was also significantly higher with raloxifene. A secondary analysis using the Scale for the Assessment of Negative Symptoms (SANS) found raloxifene was associated with significant improvement relative to placebo on the alogia subscale (p=0.048), but on none of the other 4 subscales or the total SANS score.

Raloxifene was not associated with extrapyramidal or other adverse effects, including those related to menopausal symptoms. There were no apparent adverse effects on breast or uterine tissue, vaginal bleeding, or thrombophlebitis.

**Discussion:** Results of this study suggest that adjunctive raloxifene may reduce general psychopathology and negative symptom burden in postmenopausal women with schizophrenia. Although positive symptoms were not affected, the authors speculate that the sample size may have been too small to detect small differences in these symptoms. Additional research appears to be warranted.

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

*See Reference Guide.

### Asenapine/Ciprofloxacin Interaction

A 44-year-old woman with bipolar I disorder was admitted for worsening depression. She had been receiving 5 mg/day asenapine for 1.5 months prior to admission. Additional medications, all of which were continued on admission, included 20 mg/day baclofen, 60 mg/day dextansoprazole, 20 mg/day fluoxetine, 1 mg/day lorazepam, and 2250 mg/day divalproex. A urinary tract infection detected on admission precipitated additional treatment with 500 mg ciprofloxacin b.i.d. Within 33 hours of starting ciprofloxacin, the patient was unable to close her jaw, which was consistent with an acute dystonic reaction. Treatment with 50 mg intramuscular diphenhydramine resolved the dystonia, and the antibiotic was switched to 100 mg nitrofurantoin b.i.d. with no further complications. The patient had previously experienced a severe dystonic reaction to haloperidol.

A potential interaction between asenapine and ciprofloxacin has not been previously reported. However, ciprofloxacin is a potent inhibitor of CYP1A2, the pathway via which asenapine is primarily metabolized, and interactions between it and other second-generation antipsychotics that are metabolized through this pathway have been reported. Other possible contributing
factors to the reaction include the effects of inflammation/infection on CYP1A2, as well as potential inhibition of asenapine glucuronidation by divalproex. These may have exacerbated the patient’s symptoms, but the dystonia was more likely related to ciprofloxacin as it was not noted until after the drug was initiated. According to the Drug Interaction Probability Scale,* the likelihood of a drug/drug interaction in this case is considered probable.


Common Drug Trade Names: asenapine—Saphris; ciprofloxacin—Cipro; dexlansoprazole—Dexilant; divalproex—Depakene, Depakote; haloperidol—Haldol; fluoxetine—Prozac; lorazepam—Ativan; nitrofurantoin—Macrobid, Macroantin

*See Reference Guide.

Flibanserin for Hypoactive Sexual Desire in Women

The only FDA-approved treatment for hypoactive sexual desire disorder (HSDD), flibanserin can be considered for use in selected premenopausal women, according to a review. However, use should be limited to patients who are premenopausal; not pregnant; in stable, healthy relationships; willing to abstain from alcohol; and who do not take medications that may cause interactions.

Flibanserin was approved by the FDA in August 2015 for treatment of HSDD. The disorder is recognized by the American College of Obstetrics and Gynecology but has been dropped from the DSM-5, where its symptoms were instead included in the criterion for female sexual interest/arousal disorder. Other treatments for diminished sexual desire in women include off-label bupropion, transdermal testosterone (in postmenopausal patients), and various psychological treatments. Other medications and supplements, including sildenafil, have been shown to be ineffective.

Flibanserin addresses the proposed pathophysiology of HSDD, a relative deficiency in noradrenergic and dopaminergic activity and a relative excess in serotonergic activity in the prefrontal cortex. Flibanserin has a terminal half-life of about 11 hours and requires administration for 3 days to achieve steady-state levels. Because it may cause CNS depression leading to hypotension and dizziness, bedtime administration is required. Its availability is limited to a REMS (Risk Evaluation and Mitigation Strategy) program because of the risk of hypotension/syncope, which is increased with concomitant alcohol use. Patients should discontinue flibanserin after 8 weeks if they do not experience any benefit.

A total of 4 industry-sponsored phase III clinical trials of flibanserin have been conducted, along with an extension study, and a phase II pharmacokinetic trial. Three of the placebo-controlled trials were 24 weeks in duration, 1 was 48 weeks, and the extension trial lasted 1 year. Study participants experienced a strong placebo response but a marginal, statistically significant increase in the average number of satisfying sexual events per month with flibanserin. A variety of secondary outcome measures also showed improvement, although inconsistently across trials. Flibanserin was generally well tolerated, with dizziness, somnolence, nausea, fatigue, and insomnia the most common adverse events. Some women became pregnant while participating in the trials, and several spontaneous abortions or other pregnancy complications occurred, but investigators did not attribute them to study medication.

Additional concerns regarding flibanserin include the use of industry-supported questionnaires in the trials, the possibility of unpublished negative trials, and the perception of external
pressure on the FDA to approve the drug. There is also concern about possible off-label use, particularly in postmenopausal women, who may be more likely to take interacting medications and to experience dangerous falls as a result of dizziness.


Common Drug Trade Names: bupropion—Wellbutrin; flibanserin—Addyi; sildenafil—Viagra

**Quetiapine plus Lamotrigine for Bipolar Depression**

In a randomized trial, augmenting quetiapine with lamotrigine resulted in greater improvement in bipolar depression than treatment with quetiapine alone.¹ This approach takes advantage of the differing time scales and mechanisms of action of the 2 drugs, with quetiapine providing relief of acute symptoms while allowing slower-acting lamotrigine to gain traction.²

**Background:** A number of agents are FDA approved as monotherapy for bipolar depression, including both quetiapine and lamotrigine. However, most guidelines recommend avoiding monotherapy when possible, especially in bipolar I disorder.

**Methods:** Study participants, recruited from multiple sites in the U.K., were 266 patients aged ≥16 years with type I or II bipolar disorder who, in their clinician’s judgement, required new treatment for a depressive episode. All patients were started on quetiapine monotherapy for 1 or 2 weeks, with an eventual minimum dosage of 150 mg/day and a target dosage of 300 mg/day. Patients who tolerated and adhered to the quetiapine run-in (n=202) received double-blind, randomly assigned add-on treatment with either lamotrigine, increased gradually to 200 mg/day, or placebo. In addition, patients not already taking folic acid were randomized to either 500 µg/day folic acid or placebo. Treatment was continued for 52 weeks. The primary outcome was depressive symptoms, rated with the 16-item Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR16) at 12, 22, and 52 weeks.

**Results:** In the full sample including patients receiving both active and placebo folic acid, adjunctive lamotrigine was associated with numerically lower QIDS-SR16 scores than placebo beginning at week 12 and lasting throughout the study. (See table.) The between-group difference was statistically significant only at 52 weeks (p=0.017). Rates of depression remission, defined as a QIDS-SR16 score of ≤5, were significantly higher with lamotrigine than placebo at week 12 (31% vs. 16%; p=0.026) and week 52 (36% vs. 13%; p=0.012). Lamotrigine was associated with a modest increase in manic symptoms during the first 12 weeks, but not afterward.

| Improvement in Bipolar Depression—Adjunctive Lamotrigine vs. Placebo |
|------------------|----------------|----------------|----------------|----------------|
| QIDS-SR 16 Score | Baseline | 12 Weeks | 22 Weeks | 52 Weeks |
| Lamotrigine      |          |          |          |          |
| (n=101)          | 15.3     | 10.9     | 9.6      | 9.2      |
| (n=83)           |          |          |          |          |
| (n=61)           |          |          |          |          |
| Placebo          | 15.0     | 12.5     | 11.6     | 12.0     |
| (n=101)          |          |          |          |          |
| (n=81)           |          |          |          |          |
| (n=63)           |          |          |          |          |
| (n=47)           |          |          |          |          |

Patients randomly assigned to folic acid did not have an antidepressant response that differed from placebo. Among patients who received lamotrigine, those who also received folic acid had no change from baseline to week 12 in the QIDS-SR16; instead, the response was confined to those who received lamotrigine with a folic-acid placebo, for whom scores were an average of 4 points lower (p=0.004).
Discussion: In previous short-term clinical trials, lamotrigine has shown only weak antidepressant effects probably because it requires a 6-week titration period. The present study suggests that the rapid onset of action of quetiapine might make this slow titration less of a problem.


Malhi G: CEQUEL the sequel: bipolar disorder combination therapy [editorial]. Lancet Psychiatry 2016;3 (January):2–3. From the University of Sydney and Royal North Shore Hospital, Australia. The author declared financial relationships with commercial sources.

Common Drug Trade Names: lamotrigine—Lamictal; quetiapine—Seroquel

Experimental Neurogenic Antidepressant

In an early-phase clinical study, NSI-189, an experimental compound that promotes hippocampal neurogenesis, was safe and efficacious in a small group of patients with depression.¹

Background: Currently available antidepressants generally share monoaminergic activity as their mechanism of action. NSI-189, a benzylpiperazine-aminopyridine, stimulates neurogenesis of human hippocampus-derived neural stem cells and has shown behavioral efficacy in animal models of depression. The present study was undertaken to identify the maximum safe dose of NSI-189 that could be administered for ≥28 days in patients with major depression and to explore its effects on depressive symptoms, electroencephalogram (EEG) measures, and hippocampal volumetric changes.

Methods: Study participants were 24 patients, aged 18–60 years (12 women), who were experiencing a current episode of recurrent major depressive disorder. At study entry, patients were either medication free with a history of antidepressant therapy or underwent a washout of current antidepressant therapy. Eligible patients with a Montgomery-Asberg Depression Rating Scale (MADRS) score of 15–30 were randomly assigned to double-blind treatment with 1 of 3 NSI-189 dosage groups—40 mg/day, 40 mg b.i.d., or 40 mg t.i.d.—or placebo. Each group consisted of 6 patients receiving active treatment and 2 receiving placebo, and all patients received study medication as inpatients for the 28 study days. Treatment was discontinued at discharge (day 28). Depression was evaluated on days 14 and 28 and at regular intervals through an additional 8 weeks of follow-up.

Results: NSI-189 was well tolerated throughout the dosage range. Adverse events were generally similar to placebo, and none were serious. NSI-189 had a half-life of about 19 hours, and steady state levels were reached after 4 days. Drug exposure was nearly dose-proportional.

In a pooled analysis, the 3 NSI-189 dosages were associated with greater improvement in depression than placebo as measured using the clinician-rated MADRS (effect size,* 0.95) and Clinical Global Impression–Improvement scale (effect size, 0.57), and the patient-rated Symptoms of Depression Questionnaire (effect size, 0.9) and Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (effect size, 0.94). Improvements were maintained throughout the 12-week follow-up, for the most part. Of the 18 patients who received active treatment, 12 were considered responders on day 28, with a ≥50% decrease in MADRS score; 4 were considered partial responders, with post-treatment MADRS scores indicating mild depression; and 2 were nonresponders, with MADRS scores remaining within the original moderate depression range.

Structural MRI scans, used to measure volumes of the hippocampus where NSI-189 is believed to induce neurogenesis, showed a modest, nonsignificant increase in left hippocampal volume in treated patients, but no change on the right side. EEG data did not raise any safety concerns.
**Discussion:** Results of this study suggest a potentially new target or mechanism for antidepressant drug development. Although results are preliminary and require replication, NSI-189 appears to be a promising treatment for major depression with effects that may be more durable than existing antidepressant agents.

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

Fava M, Johe K, Ereshefsky L, Gertsik L, et al: A phase 1B, randomized, double blind, placebo controlled, multiple-dose escalation study of NSI-189 phosphate, a neurogenic compound, in depressed patients. *Molecular Psychiatry* 2015; doi 10.1038/mp.2015.178. From Massachusetts General Hospital, Boston; and other institutions including Neuralstem Inc., Germantown, MD. **Funded by Neuralstem. All study authors disclosed financial relationships with commercial sources including Neuralstem.**

*See Reference Guide.

### Orally Disintegrating Mixed Amphetamine Salts

*Adzenys XR* (extended-release mixed amphetamine salts) has received FDA approval as the first orally disintegrating extended-release product for the treatment of ADHD in children aged ≥6 years and adults. The agent was determined to be bioequivalent to *Adderall XR*, and will be available in the same 6 dosage strengths. *Adzenys XR* contains amphetamine in a mixture of immediate-release and polymer-coated delayed-release resin particles; it is not a generic version of *Adderall XR*. Product launch is expected after March 2016.


### Reference Guide

**Drug Interaction Probability Scale (DIPS):** A tool similar to the Naranjo Probability Scale designed to evaluate the causation of an adverse event thought to be produced by the interaction between 2 drugs. Based on a score generated by answering 10 questions, the probability is assigned as doubtful, possible, probable, or highly probable. The DIPS is available online at http://www.pmidcalc.org.

**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.

**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 are posted at www.alertpubs.com.

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