Naltrexone Improved Self-Harm Behavior

A 32-year-old woman with recurrent major depressive disorder, borderline personality disorder, micro-psychotic episodes, and poor impulse control had multiple psychiatric hospitalizations because of dangerous cutting behavior. The self-injurious behavior had not been responsive to multiple pharmacological interventions or to dialectical behavioral therapy. Because it has been shown to reduce impulsive behavior and self-injury in patients with developmental delay, a trial of the opioid antagonist naltrexone (ReVia) was initiated. The patient was treated with 25 mg/day naltrexone, which was increased to 50 mg/day after 1 month, in addition to her regular medications.

At baseline, the patient engaged in cutting behavior 1–3 times per day and reported thinking about it constantly. Within 1 week of starting naltrexone, she reported a decreased urge to cut. After the dosage increase, cutting frequency was reduced to 1–2 times per week and she reported thinking about cutting substantially less often. After being treated for 5 months, she had only 1 episode of superficial cutting over the subsequent 6 months of treatment. Baseline liver function testing had shown mildly elevated enzyme levels and she experienced a relatively large increase in aspartate aminotransferase with treatment.

The authors suggest that treating self-injurious behavior may reduce or eliminate the need for atypical antipsychotics and mood stabilizers, but large-scale, randomized controlled trials of naltrexone in impulse-control disorders are needed.


Antiinflammatories May Attenuate SSRI Effects

According to a series of animal experiments, antiinflammatory medications may diminish the efficacy of SSRI antidepressants. An analysis of data from the Sequenced Treatment Alternatives

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Background: Several lines of evidence suggest that cytokines play a role in depression. Among them are the development of depression in some patients receiving medical treatments that affect cytokine levels and the observation that some cytokines regulate brain norepinephrine or serotonin systems. The protein p11, which regulates depressive states in animal models, is increased by SSRI, tricyclics, and ECT in association with decreases in depression-like behavior.

Rodent Models: In laboratory experiments, administering citalopram increased some cytokines in the frontal cortex of mice, but the increase was blocked by coadministration of ibuprofen. Coadministration of ibuprofen or aspirin blocked the increase of p11 attributed to citalopram or fluoxetine administration. However, NSAIDs did not affect the increase induced by the tricyclic antidepressant desipramine, suggesting that the effects of NSAIDs on p11 are specific to SSRIs. NSAIDs also blocked the behavioral response to antidepressants in mouse models of depression.

Human Populations: The possible interference of NSAIDs with SSRI treatment in humans was explored by analyzing data from the STAR*D trial of multi-stage antidepressant treatment. Stage 1 in STAR*D consisted of 12 weeks of open-label citalopram treatment. Data on clinical response and concomitant medications was available for 1546 patients. Rates of remission during this phase of the trial were 45% in patients taking NSAIDs and 55% in those not taking NSAIDs (p=0.0002). Results were similar in patients taking other analgesics: 37% achieved remission, compared with 54% of patients not taking analgesics (p=0.0002). Of patients who used both NSAIDs and other analgesics, 37% experienced a remission, compared with 53% of those using neither (p<.0001). No relationship was found with other concomitant agents such as vitamins.

Discussion: The STAR*D data did not distinguish fully between acute and chronic NSAID administration, and it is possible that patients’ underlying medical conditions may have contributed to treatment resistance. However, another analysis of STAR*D data showed no significant association between physical pain and antidepressant response. Despite some methodological weaknesses, the magnitude of effect in this clinical sample suggests that the NSAID effect is potentially important. The effects of NSAIDs and other analgesics on SSRI efficacy requires further investigation in a prospective randomized trial.


Drug Trade Names: citalopram—Celexa; desipramine—Norpramin, Pertofrane; fluoxetine—Prozac

Lithium May Protect Against Cognitive Decline

Long-term lithium treatment reduced the progression from mild cognitive impairment to Alzheimer’s disease in a small group of patients.

Background: While lithium use is believed to inhibit glycogen synthase kinase 3 beta activity, which is central in the pathophysiology of Alzheimer’s disease, clinical trials have failed to show significant cognitive benefits in patients with Alzheimer’s disease. To determine the protective effects of low-dose lithium in patients at risk of but without clinically manifest Alzheimer’s disease, a randomized controlled trial was conducted in patients with amnestic mild cognitive impairment.

Methods: The single-center, placebo-controlled trial evaluated 45 patients, aged >60 years, with amnestic mild cognitive impairment and no known psychiatric disorders. Participants were
randomized to 1 year of treatment with either lithium (n=23) or placebo (n=22). Lithium dosages were titrated to target serum levels of 0.25–0.5 mEq/l, with a maximum dosage of 600 mg b.i.d. Primary outcomes included changes in cognition and general functioning, as well as changes in cerebrospinal fluid markers for Alzheimer’s disease (e.g., tau, amyloid-beta peptide). Safety, tolerability, and advancement to Alzheimer’s disease were secondary outcomes.

**Results:** After 12 months, 11 patients (24%) had advanced to Alzheimer’s disease. While this was numerically more frequent in the placebo group than in the lithium group (7 vs 4 patients), the difference was not statistically significant. Patients in the lithium group had significant reductions in concentration of phosphorylated tau, compared with placebo-treated patients who experienced a slight increase (p=0.02). Compared with those whose cognitive impairment did not advance, the cerebrospinal fluid of patients (from both groups) who advanced to Alzheimer’s disease contained higher concentrations of total tau and phosphorylated tau and lower concentrations of amyloid-beta peptide. All patients experienced slight but statistically significant worsening of global function. However, patients in the placebo group, but not the lithium group, experienced statistically significant decline on measures of cognitive function.

Tolerability was generally good, with 4 patients (2 from each group) withdrawing before study end. There was no significant difference in the occurrence of adverse effects between the lithium and placebo groups, and most were mild and transient.

**Discussion:** Given the positive findings of this trial, the authors suggest that lithium’s protective effect may be dependent upon stage of cognitive deterioration. This knowledge, if confirmed by future studies, may prove helpful in determining when to initiate treatment.

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


*See Reference Guide.

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**Antidepressant Combinations vs Monotherapy for Depression**

In a randomized trial, treatment with combined antidepressant regimens was not more effective than monotherapy in chronic or recurrent unipolar major depression.

**Methods:** Participants were 665 patients, aged 18–75 years, recruited from both primary care and psychiatric practices, with either recurrent or chronic major depression and a Hamilton Rating Scale for Depression (HAM-D) score of ≥16. Participants were moderately to severely ill at baseline, with a mean HAM-D score of 24 and a mean Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) score of 16. Depression was recurrent in 78%, and 75% had anxious features. Participants were randomly assigned to 1 of 3 treatment groups: escitalopram plus placebo; escitalopram plus bupropion; or venlafaxine plus mirtazapine. Maximum allowable dosages were 20 mg/day for escitalopram, 200 mg b.i.d for bupropion, 300 mg/day for venlafaxine, and 45 mg/day for mirtazapine. Participants were blind to one of the medications in their combination, while investigators were not blinded to any treatment. Patients were assessed at the end of a 12-week acute treatment phase and again after 7 months. The primary study outcome was remission, defined as QIDS-SR scores of ≤6 and ≤8 on the last 2 consecutive weeks of the acute treatment phase, respectively. Patients were permitted to receive continuation treatment if they had at least partial response during acute treatment.
Results: A total of 480 patients (72%) completed 12 weeks of treatment. There were no differences in attrition between the study groups. The final mean escitalopram dosage in the monotherapy group was 16 mg/day, compared with 12 mg/day when combined with bupropion (p<0.0001). The final mean dosages for venlafaxine and mirtazapine were 178 mg/day and 18 mg/day, respectively.

The 3 treatments did not differ in efficacy. By the end of acute treatment, remission rates ranged from 38% to 39%. After 7 months, rates ranged from 42% to 47%. Although specific adverse effects were not detailed, the venlafaxine–mirtazapine combination was associated with the strongest adverse effect burden. Escitalopram plus bupropion was associated with somewhat more side effects than escitalopram alone. Chronic depression and melancholic features have been suggested to lower remission rates. However, the results did not differ when the data were reanalyzed separately for these patient groups.

Discussion: Prior reports suggested that prescribing combination therapy from the outset might improve rates of remission in major depression. However, remission rates in this study are comparable to those expected in patients receiving monotherapy.

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

St. John’s Wort and SAM-e for Depression

According to results of a systematic review, St. John’s wort and s-adenosyl methionine (SAM-e) are at least modestly effective in the short-term treatment of mild-to-moderate depression.

Background: Alternative therapies are widely used in depression and have been the subject of numerous reviews and meta-analyses. Given the current suicidality warnings on conventional antidepressants, it is likely that use of alternative agents will increase. The 2 most widely used "natural" antidepressants are St. John’s wort and SAM-e. St. John’s wort is a medicinal herb that has regulatory approval as an antidepressant in some European countries. SAM-e is a naturally occurring substance whose levels in serum and cerebrospinal fluid have been shown to correlate with emotional state.

Methods: A literature review was undertaken to identify all randomized, placebo-controlled studies of St. John’s wort or SAM-e in patients with major depressive disorder. The efficacy review included 17 St. John’s wort studies and 14 SAM-e studies, all conducted in adults. All of the SAM-e studies had important methodological limitations, including heterogeneous patient groups, small sample sizes, and use of "completer" data sets. A separate safety review with less stringent inclusion criteria examined 32 clinical trials of St. John’s wort and 17 of SAM-e in depression and other conditions.

Results: In 10 of the 17 studies, St. John’s wort was superior to placebo, with a mean effect size* of 0.64. St. John’s wort was effective in studies of patients with mild-to-moderate depression but not in the studies of more severely depressed patients. A single study with long-term follow-up found St. John’s wort to be mildly, but not significantly more effective than placebo at preventing relapse. Five of 9 SAM-e studies reported efficacy in mild-to-moderate depression, with a mean effect size of 1.0. Results were also positive in 4 of 5 studies of patients with
more severe depression, with a mean effect size of 0.87. Most St. John’s wort studies had minimal information on adverse events, and only 9 had full adverse event reporting. There were no reports of St. John’s wort-related suicidal behavior or ideation, but there were a few instances of worsening depression. Adverse-event reporting was also poor in the SAM-e studies. Although SAM-e was not associated with emergent suicidality, studies reported mania or hypomania, psychomotor excitation, and anxiety.

**Discussion:** St. John’s wort is believed to be a broad-spectrum reuptake inhibitor, affecting up to 5 neurotransmitters. SAM-e is believed to affect some of the same neurotransmitters. It is likely that at higher doses, the adverse effects of these agents might resemble those of conventional antidepressants. Although the clinical trials found no risk of suicidality, they were short-term, not designed to examine this effect, and likely to be biased by patients’ expectations of safety.

The results of this review indicate that appropriate dosing is not well established for either agent, there is no evidence for their long-term efficacy, and mechanisms of action are not fully understood. Although the information on St. John’s wort appears to be more reliable than that for SAM-e, based on the available evidence, the study author concluded that “neither product can be recommended in place of conventional antidepressants for patients with moderate-to-severe depression, in patients less than age 18 years, or for long-term monotherapy treatment of depression of any severity level, without physician supervision.” In addition, he recommends applying the conventional antidepressant black box warning to all patients treated with a "natural" antidepressant.

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

Carpenter D: St. John’s wort and s-adenosyl methionine as "natural" alternatives to conventional antidepressants in the era of the suicidality boxed warning: what is the evidence for clinically relevant benefit? *Alternative Medicine Review* 2011;16:17–39. From Helicon Therapeutics, Inc., San Diego. This review was conducted with no external funding. The author disclosed financial relationships with Helicon Therapeutics and GlaxoSmithKline.

*See Reference Guide.

### Vilazodone in MDD

In a manufacturer-sponsored study, the recently approved antidepressant vilazodone was modestly superior to placebo in patients with major depression. The agent had relatively low liability for sexual side effects and did not induce weight gain.

**Background:** Vilazodone is a novel dual-action antidepressant that is a selective and highly potent serotonin A1 receptor partial agonist and serotonin reuptake inhibitor. Its potency for serotonin reuptake inhibition is 30 times that of fluoxetine, and it enhances serotonin levels to a greater degree than conventional SSRIs. However, in other clinical trials vilazodone has not been consistently superior to placebo or to other antidepressants.

**Methods:** An 8-week randomized, placebo-controlled trial was conducted in 463 patients with major depressive disorder, either first-episode (28%) or recurrent (72%). Those with treatment-resistant depression or substance abuse were excluded. Vilazodone was started at 10 mg/day and titrated to 40 mg/day. The primary study outcome was change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) score.

**Results:** In an intent-to-treat analysis, average MADRS scores decreased by 13 points with vilazodone and by 11 points with placebo (p=0.009). While the difference between groups became statistically significant at week 4, the overall effect size of 0.23 was small. Response rates (250% decrease in MADRS score) were 44% with vilazodone and 30% with placebo (p=0.002). Remission rates were also higher with vilazodone (27% vs 20%), but the difference
was not statistically significant, a finding which the authors attributed to insufficient exposure to the recommended dose and insufficient length of observation.

The predominant adverse effects of vilazodone were diarrhea and nausea, and these were usually mild to moderate and transient. There were no instances of treatment-emergent suicidal ideation or behavior, and no laboratory or electrocardiographic abnormalities were found. About 20% of each group discontinued treatment. In the vilazodone group, adverse events led to discontinuation in 12 patients (5%), including 4 who had GI events. Vilazodone was weight-neutral, with a mean weight gain of <1 lb at week 8. The incidence of sexual dysfunction, which affects 30–40% of antidepressant-treated patients, was relatively low (4.7%) in vilazodone-treated patients.

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


*Drug Trade Names:* fluoxetine—Prozac; vilazodone—Viibryd

Mirtazapine for SSRI-Induced Sexual Dysfunction

According to results of a retrospective study, low-dose mirtazapine augmentation may improve SSRI-associated sexual dysfunction.

**Background:** Sexual dysfunction affects up to 30% of SSRI-treated patients. While there are numerous methods to manage SSRI-induced sexual dysfunction, few studies have evaluated the potential benefits of mirtazapine. This retrospective observational study represents one of the first evaluations of mirtazapine augmentation for various sexual dysfunctions in both male and female patients.

**Methods:** Outpatients with major depressive disorder (n=20; 11 male; mean age, 28 years) suffering from sexual dysfunction associated with antidepressant monotherapy (escitalopram, n=5; sertraline, n=4; clomipramine, n=3; fluvoxamine, n=3; paroxetine, n=3; citalopram, n=2) received augmentation with 15–45 mg/day mirtazapine. All patients had received treatment for ≥6 weeks prior to augmentation, and most (n=15; 75%) received ≤30 mg/day mirtazapine. The most common dysfunctions included decreased libido, erectile dysfunction, and delay of orgasm or ejaculation. Patients with organic or pre-existing sexual dysfunctions were excluded, as were those aged >45 years and those receiving other psychotropic drugs. Outcomes were measured at weeks 4 and 8 using the Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impression-Improvement (CGI-I) scale, and the Arizona Sexual Experience Scale (ASEX).

**Results:** Mean HAM-D scores decreased from 17 at baseline to 11 at 4 weeks (p<0.05), and to 9 at 8 weeks (p<0.01). Mean ASEX scores also showed significant decreases from 23 at baseline to 17 and 12 at weeks 4 and 8, respectively. By study end, 13 patients (68%) had CGI-I ratings of "much improved" or "very much improved." There were no differences in age, gender, or baseline HAM-D scores between responders and nonresponders. There was also no correlation between HAM-D and ASEX changes, suggesting the improvement in sexual function was not dependent on the improvement in depression.

Adjunctive treatment with mirtazapine was well tolerated overall, with one patient discontinuing treatment due to sedation and increased appetite. Ten patients experienced adverse effects, most frequently sedation and weight gain up to nearly 7 lbs.
**Discussion:** The results of this study suggest that adding mirtazapine to SSRI treatment may be beneficial to patients experiencing SSRI-induced sexual dysfunction. However, because the study was limited by its size, retrospective design, and lack of control group, the results must be considered preliminary.

Atmaca M, Korkmaz S, Topuz M, Mermi O: Mirtazapine augmentation for selective serotonin reuptake inhibitor-induced sexual dysfunction: a retrospective investigation. *Psychiatry Investigation* 2011;8 (March):55–57. From Firat University, Elazig, Turkey. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

**Drug Trade Names:** citalopram—*Celexa*; clomipramine—*Anafranil*; escitalopram—*Lexapro*; fluvoxamine—*Luvox*; mirtazapine—*Remeron*; paroxetine—*Paxil*; sertraline—*Zoloft*

## Treating Clozapine-Induced Sialorrhea

According to a literature review, current options for treating clozapine-induced sialorrhea are limited. Antimuscarinic medications have been the primary focus of recent research. Alpha-adrenergic and other medications have received limited attention, and botulinum toxin injections may have potential.

Sialorrhea is one of the most common clozapine side effects, reportedly occurring in 30–80% of patients. It can be a severe and disabling effect and usually develops early in the course of treatment. Nonpharmacologic options, such as chewing gum to promote swallowing, are generally insufficient. Although sialorrhea is not dose dependent, gradual titration may help prevent the effect and lowering the dose may improve symptoms.

Sublingual, low-dose atropine (available as an ophthalmic solution) is a low-cost option associated with few adverse effects. It has a short duration of action and may be associated with rebound hypersalivation. Some patients may find it difficult or confusing to administer. Although it has not been evaluated in clinical trials, sublingual atropine may be a reasonable starting point in treating sialorrhea.

Agents with antimuscarinic activity, such as benzttropine and amitriptyline, have been investigated in small clinical trials and case series. While effective, these agents have significant risks when combined with clozapine. Adding antimuscarinic agents may potentiate the anticholinergic effects of clozapine, which range from blurred vision to colon perforation, and may also adversely affect cognition. In 1 retrospective study in 60 patients, clozapine-induced sialorrhea resolved without treatment in 50% of patients, in two-thirds of those receiving benzttropine monotherapy, and in nearly all of those who received terazosin. Amitriptyline was effective in small case series but should be used cautiously because it can aggravate the anticholinergic effects of clozapine.

Alpha-adrenergic agents, such as clonidine, guanfacine, and terazosin, have received relatively little attention. Although promising, there is some concern that these agents may potentiate the hypotensive effects of clozapine. Substitute benzamide derivatives like sulpiride and amisulpride, a class of psychotropics not available in the U.S., are an effective new approach, but there are concerns about combining multiple psychoactive agents. Amisulpride provides additional antipsychotic effects to clozapine.

Injection of the parotid glands with botulinum toxin has been described in a few patients with clozapine-induced sialorrhea, as well as in those with other conditions associated with hypersalivation. A single injection reduces salivary production, with effects lasting 8–16 weeks.

Bird A, Smith T, Walton A: Current treatment strategies for clozapine-induced sialorrhea. *Annals of Pharmacotherapy* 2011; doi 10.1345/aph.1P761. From the University of Texas, Austin; and other institutions. **The authors disclosed no conflicts of interest.**

**Drug Trade Names:** amisulpride (not available in the U.S.)—*Solian, Sulamid*; amitriptyline—*Elavil, Endep, Enovil*; benzttropine—*Cogentin*; clonidine—*Catapres*; clozapine—*Clozaril*; guanfacine—*Tenex*; sulpiride (not available in the U.S.)—*Dogmatil*; terazosin—*Hytrin, Zayasel*
Tolerability of Extended-Release Quetiapine

In a trial of elderly institutionalized patients, tolerability of extended-release quetiapine (Seroquel) was similar to that of the immediate-release formulation.

Participants (n=100; mean age, 80 years) were treated for 6 weeks with randomly assigned quetiapine IR (n=32) or XR (n=68), titrated to a flexible dosage of 50–300 mg/day. Rates of mild-to-moderate adverse events were similar in both groups, the most frequent being somnolence (15–19%), sedation (7–13%), nausea (6–9%), vomiting (6–10%), and urinary tract infection (3–9%). Weight gain was minimal, and neither group had clinically significant changes in hematologic or biochemical measurements. Eosinophilia was present in 4 patients in the XR group and 1 in the IR group. Neutropenia developed in 4 patients, all in the XR group. Patients in both groups had small increases in heart rate and decreases in blood pressures, but there were no hypotension-related adverse events. Extrapyramidal symptoms did not worsen in either group.

Although quetiapine is not approved to treat agitation in older patients with dementia and carries a black box warning about increased risk of death in this patient population, both dosage forms were associated with improvements in agitation and psychosis and cognitive function did not worsen.


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**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.

**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.

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