New Zolpidem Formulation for Middle-of-the-Night Waking

The FDA has approved a low-dose zolpidem sublingual tablet (Intermezzo) for as-needed treatment of insomnia characterized by middle-of-the-night waking and difficulty returning to sleep. The dosing recommendation is 1.75 mg in women and 3.5 mg in men, and the tablet should be taken once per night and only if the individual can remain in bed for ≥4 hours. The lower dosage for women is recommended because females clear zolpidem more slowly than males. Common adverse effects associated with Intermezzo include headache, nausea, and fatigue. Because the dosage is lower than standard zolpidem (Ambien), there is less risk of residual morning drowsiness, but like other sleep medicines, Intermezzo can have serious adverse effects and regular use can lead to dependence.

FDA approves first insomnia drug for middle-of-the-night waking followed by difficulty returning to sleep. FDA MedWatch Alert. Available at www.fda.gov.

Celecoxib Enhanced SSRI Response in OCD

In a randomized controlled trial, adding celecoxib to fluoxetine produced significantly greater improvement than fluoxetine alone in a group of patients with obsessive-compulsive disorder.

Background: COX-2 inhibitors reduce production of proinflammatory cytokines and rebalance immune responses. Inflammatory processes have been implicated in the pathophysiology of OCD, and anti-inflammatory drugs have been suggested as a possible treatment option.

Methods: Study subjects, aged 19–44 years (n=52; 54% female), had been referred to a psychiatry clinic for initial treatment of OCD. All had a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥21. Patients received no psychotropic drugs for ≥4 weeks before study entry, and those with autoimmune disease or recent infectious disease were excluded. Participants were randomized to 8 weeks of double-blind treatment with either 20 mg/day fluoxetine plus 200 mg celecoxib b.i.d. or 20 mg/day fluoxetine plus placebo, and all underwent Y-BOCS assessments every other week.
**Results:** Mean baseline Y-BOCS scores were 36 and 37 in the celecoxib and placebo groups, respectively. Patients who received celecoxib showed improvement significantly faster than those who received only fluoxetine (2 weeks vs 4 weeks; p<0.03); mean Y-BOCS scores were unchanged in the placebo group at 2 weeks and had decreased to about 25 in the celecoxib group (p=0.007). By 8 weeks, mean Y-BOCS scores were about 21 and 17 in the placebo and celecoxib groups, respectively (p=0.04). No clinically important adverse events were recorded. Common patient complaints were decreased appetite and stomach ache, and these did not differ between groups.

**Discussion:** SSRIs are well established as effective treatment for OCD. The results of the present study, although preliminary, suggest augmenting an SSRI with celecoxib can accelerate and modestly strengthen response. Risk of GI bleeding and peptic-ulcer disease is increased with long-term NSAID use and needs to be addressed in larger, longer-term studies.

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

Sayyah M, Boostani H, Pakseresht S, Malayeri A: A preliminary randomized double-blind clinical trial on the efficacy of celecoxib as an adjunct in the treatment of obsessive-compulsive disorder. *Psychiatry Research* 2011;189:403–406. From Jundishapur University of Medical Sciences, Ahwaz, Iran. **The study was conducted with no external funding. The authors disclosed no competing interests.**

**Drug Trade Names:** celecoxib—Celebrex; fluoxetine—Prozac

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*Tolerability of Antidepressant Strategies*

In patients with resistant depression, augmentation was not associated with more adverse effects than switching to an alternate drug.

**Methods:** Investigators analyzed data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, completed in 2004. In that trial, patients first received 12 weeks of citalopram treatment. Patients who did not experience remission were then randomly assigned to 1 of 2 next-step strategies: either citalopram augmentation (with bupropion or buspirone) or switching (to bupropion, sertraline, or venlafaxine). Adverse effects were evaluated using a detailed questionnaire at 6–7 clinic visits during the 12–14 weeks of second-stage treatment. Because allowing patients some freedom in choosing their treatment could cause selection bias, the analysis was limited to pairs of patients propensity-score-matched* for characteristics associated with the likelihood of receiving antidepressant augmentation.

**Results:** Of the 1292 STAR*D patients who received either augmentation or a switch as second-stage treatment, 269 propensity-matched pairs were identified. In the propensity-matched sample, adverse effect rates did not differ between the switch and augment groups. Overall, the incidence proportion of adverse effects, calculated by dividing the number of participants who experienced any event by the total randomized population, was 0.98 in each group. There were no statistically significant differences in any specific effects, in any of the 9 organ/system categories specifically assessed, or for distressing vs less severe events.

**Discussion:** Because there is little evidence to guide the choice of second-stage antidepressant treatment, clinicians often rely on adverse-event expectations. Results of this study were unexpected and should be interpreted cautiously because propensity-matching reduced the sample size and ability to detect possible true differences and may have limited the generalizability of the results. Results may not apply to different medications and patient populations.

Hansen R, Dusetzina S, Ellis A, Sturmer T, et al: Risk of adverse events in treatment-resistant depression: propensity-score matched comparison of antidepressant augment and switch strategies. *General Hospital Psychiatry* 2011; doi 10.1016/genhospsych.2011.10.001. From Harrison School of Pharmacy, Auburn University, Ala., and other institutions. **Funded by the Agency for Healthcare Research and Quality. The authors have no conflicts of interest directly related to the content of this study.**

**Drug Trade Names:** bupropion—Wellbutrin; buspirone—BuSpar; citalopram—Celexa; sertraline—Zoloft; venlafaxine—Effexor

*See Reference Guide.*
NK1 Antagonist Promising for Depression

Two clinical trials of casopitant, an investigational neurokinin-1 (NK1) receptor antagonist, provide some support to previous research suggesting the drug class may have a role in treating depression. Full receptor occupancy may be necessary for these agents to show an effect.

Background: NK1 receptors and their ligand, Substance P, are located in areas of the brain involved in the regulation of affect, and the receptor system also appears to overlap with serotonergic and noradrenergic systems of neurotransmission. Previous clinical studies with another NK1 antagonist, aprepitant (approved for prevention of chemotherapy-associated nausea and vomiting) showed no difference from placebo but suggested that antidepressant efficacy may be related to receptor occupancy. The present report describes 2 multinational, randomized, clinical trials conducted by the manufacturer of casopitant.

Methods: The 8-week trials were conducted in patients with at least moderately severe first-episode or recurrent depression, with no history of refractoriness. Change in the 17-point Hamilton Rating Scale for Depression (HAM-D) at 8 weeks was the primary outcome measure. Response was defined as a >50% decrease in HAM-D score, and remission as a final HAM-D score of <7.

One trial compared fixed-dose casopitant, 30 or 80 mg/day, with placebo in 337 patients (mean age, 41 years; 63% female). The 2 casopitant dosages were selected to provide, respectively, 90% and 95% receptor occupancy at steady-state trough levels. The second study compared forced-titration casopitant (80–120 mg/day) with 30 mg/day paroxetine or placebo in 357 patients (mean age, 44 years; 71% female). Eighty-six percent of patients receiving casopitant tolerated forced titration to 120 mg/day, the previously determined maximum tolerated dosage, by the second week of treatment, and 79% completed the study at this dosage.

Results: At 8 weeks in the fixed-dose study, the 80-mg/day casopitant dosage was associated with a nearly 3-point larger decline in HAM-D score than placebo (p=0.02). This dosage was statistically superior to placebo at all observation time points, beginning with week 1. Casopitant at 30 mg/day was numerically but not statistically superior to placebo. Response rates were 39% with the lower casopitant dosage and 40% with the higher dosage, compared with 32% in the placebo group (p=ns). Remission rates ranged from 13% with placebo to 21% with 30 mg/day casopitant (p=ns).

In the forced-titration study, both casopitant and paroxetine were numerically superior to placebo, but the differences were not statistically significant at any time point. When the analysis was limited to exclude patients with the least severe depression at baseline (HAM-D ≤20), casopitant was superior to placebo (p=0.04) but paroxetine was not. Response rates did not differ significantly between the groups (59–62%), but remission occurred in a significantly higher percentage of patients in the casopitant (52%) and paroxetine (53%) groups than in the placebo group (39%; p<0.05 for both).

Adverse-effect profiles of casopitant, paroxetine, and placebo were generally similar. Common events included headache and nausea, as well as somnolence, which was reported by 11–12% of patients who received casopitant, more than those taking paroxetine or placebo.

Discussion: The authors conclude that casopitant and other NK1 receptor antagonists merit further study in depression.


Drug Trade Names: aprepitant—Emend; casopitant—Rezonic; paroxetine—Paxil
Bupropion Improved Resistant Trichotillomania

Long-term response to SSRIs in trichotillomania is known to be inconsistent, and there is emerging evidence for a role of dopamine pathways in the disorder. Bupropion has been suggested as an effective treatment for other impulse-control disorders, such as pathological gambling, and the present case report suggests it may be useful in SSRI-resistant trichotillomania.

A 23-year-old female presented with a 6-year history of daily compulsive hair pulling. She had no comorbid mood disorders, and obsessive-compulsive disorder was ruled out. She was treated with cognitive behavioral therapy (CBT) and 20 mg/day fluoxetine, gradually increased to 80 mg/day by week 8. She experienced only mild improvement in hair pulling, and 150 mg/day extended-release bupropion was started. Over the subsequent 2 weeks, fluoxetine was tapered and discontinued. Bupropion was increased to 300 mg/day. The patient experienced mild improvement, and the bupropion was increased to 450 mg/day in divided doses. Within 1 week she reported significant improvement that was sustained with continued bupropion and CBT over 1 year. Side effects included mild and transient nausea and nervousness during the first 2 weeks of bupropion treatment.

The exact mechanism is unclear, but bupropion may improve trichotillomania by diminishing both the heightened arousal and the relief associated with the act of hair pulling. CBT is a well-established treatment for trichotillomania, and a synergistic effect can not be ruled out in this patient. Although controlled trials are needed to replicate the current findings, bupropion may be considered as an option for SSRI-resistant trichotillomania.

Rajshekhar B, Srinivasa S: Bupropion for the treatment of fluoxetine non-responsive trichotillomania: a case report. Journal of Medical Case Reports 2011;5:557. From the Rajasri Clinic, Hyderabad, India; and other institutions. The authors declared no competing interests.

Drug Trade Names: bupropion, extended-release—Budeprion SR, Wellbutrin SR; fluoxetine—Prozac

Reference Guide

Propensity Score Matching: 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.
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