Budeprion XL: Market Withdrawal

FDA approval was granted for 5 generic versions of Wellbutrin XL (bupropion) 300 mg. However, each approval was based on extrapolation of bioequivalence studies comparing the 150-mg strength products to Wellbutrin XL 150 mg; no studies directly compared the 300-mg strength products. The FDA has determined that this approach is no longer appropriate to establish bioequivalence of 300-mg bupropion hydrochloride extended-release tablets to Wellbutrin XL 300 mg, and the agency is revising its guidance to the industry for how to conduct premarket bioequivalence studies in generic bupropion products.

Soon after Budeprion XL 300-mg tablets (manufactured by Impax and marketed by Teva) received approval, the FDA began to receive reports that patients who were switched from Wellbutrin XL 300 mg to a generic counterpart were experiencing reduced efficacy. The lack of efficacy appeared to be limited to the Teva product, and the FDA sponsored a bioequivalence study comparing Budeprion XL 300 mg to Wellbutrin XL 300 mg. The results show that Budeprion XL 300-mg tablets are not therapeutically equivalent to Wellbutrin XL 300 mg. They do not release bupropion into the blood at the same rate or to the same extent as Wellbutrin XL 300 mg. No safety issues were identified, but in some patients, the drug may not provide the desired efficacy. As a result, the Teva Budeprion XL 300-mg tablets will be removed from the market.

The FDA has now asked each of the other generic bupropion manufacturers to conduct their own studies to assess the bioequivalence of their 300-mg extended-release bupropion tablets to Wellbutrin XL 300 mg. Data from those studies is expected to be submitted to the FDA no later than March 2013.

FDA Update: Budeprion XL 300 mg not therapeutically equivalent to Wellbutrin XL 300 mg. Available at www.fda.gov/Drugs/DrugSafety.
Treatment of SSRI-Induced Hyperhidrosis

Excessive sweating is reported as an unpleasant side effect by about 10% of patients taking an SSRI. Prevalence appears to be highest, about 19%, with sertraline, and tolerance does not develop even with prolonged treatment. In a placebo-controlled study, the anticholinergic oxybutynin reduced sertraline-induced hyperhidrosis.

Methods: Study subjects were 145 otherwise healthy patients with major depression (mean age, 38 years; 61% women) who were experiencing hyperhidrosis associated with sertraline treatment. In addition to their sertraline (50–100 mg/day; mean, 83 mg/day), participants received randomly assigned, double-blind 5 mg/day oxybutynin or placebo for 2 consecutive weeks. Sweating was evaluated with the 4-point Hyperhidrosis Disease Severity Scale (HDSS).

Results: Study patients all had at least grade 2 hyperhidrosis (sweating tolerable but sometimes interferes in daily activities), 45 had grade 3 (sweating barely tolerable with frequent interference), and 30 had grade 4 (sweating never tolerable and permanently interferes with daily activities). Mean baseline hyperhidrosis severity was greater in men than in women, average HDSS scores were about 3 and 2.5 points, respectively. Five patients withdrew from the study because of inability to tolerate oxybutynin (n=3) or placebo (n=2).

At study end, sweating was significantly improved in both treatment groups. Improvement was greater with oxybutynin than with placebo; mean post-treatment HDSS scores were 1.78 in men and 1.38 in women, compared with placebo-group scores of 2.15 in men and 1.85 in women. Dry mouth and urinary complications were reported as adverse events by 3 patients in the oxybutynin group and by none in the placebo group.

Discussion: Previous reports of oxybutynin effectiveness for SSRI-induced hyperhidrosis have been anecdotal. As well as providing placebo-controlled evidence, the present study also suggests that the severity of SSRI-induced sweating may be greater in men than in women, both pre- and post-treatment, and that sweating is reduced after 2 weeks of placebo treatment. The latter finding may reflect patients' expectation of benefit or reduced symptoms of anxiety or depression due to antidepressant treatment.

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

Ghaleiha A, Jahangard L, Sherafat Z, Ahmadpanah M, et al: Oxybutynin reduces sweating in depressed patients treated with sertraline: a double-blind, placebo-controlled, clinical study. Neuropsychiatric Disease and Treatment 2012;8:407–412. From Hamadan University of Medical Sciences, Iran; and other institutions. This research originated as a doctoral thesis; sources of external funding not stated. The authors disclosed no potential conflicts of interest.

Drug Trade Names: oxybutynin—Ditropan, and others; sertraline—Zoloft

*See Reference Guide.

Pramipexole Safety Review

Based on results of a pooled analysis, the FDA has issued a warning that the dopamine agonist pramipexole (Mirapex) may be associated with increased risk of heart failure. In clinical trials, the rate of heart failure was higher in patients treated with pramipexole than with placebo, but the difference was not statistically significant. Epidemiologic studies have also suggested increased risk. Because of limitations in the studies, the FDA has not definitively concluded that the increased risk results from pramipexole treatment; other influences may have a role. Further review is underway, and until it is completed, patients are advised to continue pramipexole as directed and to contact a healthcare professional if they experience signs of heart failure.

**Warfarin Interactions with Psychotropics**

Interactions between warfarin and psychotropic drugs are uncommon but important and probably underrecognized, according to results of a literature review.

Warfarin is prescribed in the outpatient setting for prophylaxis and treatment of thromboembolism. The primary concern of warfarin drug interactions is their resultant effect on the international normalized ratio (INR), the laboratory value that reflects the degree of anticoagulation achieved with warfarin. Drug interactions can result in sub- or supratherapeutic INRs, which can lead to thromboemboli or hemorrhagic complications, respectively. Warfarin is metabolized primarily by the CYP2C9 hepatic enzyme and to a lesser extent by CYP1A2. Psychotropic drugs that interact with these enzymes can pose risks given the narrow therapeutic window of warfarin. Psychotropics may also compete with warfarin for protein binding. In addition, SSRIs and valproate have independent effects on hemostasis.

**Antidepressants.** Fluvoxamine and fluoxetine are the antidepressants most likely to inhibit warfarin metabolism, according to a handful of published case reports. Among the SSRIs, citalopram and sertraline appear the least likely to interact with warfarin. Trazodone appears to reduce the INR in patients taking warfarin; however, the mechanism remains unclear. Other categories of antidepressant either do not affect the CYP2C9 enzyme system, or in the case of nefazodone, some tricyclics, and MAO inhibitors, inhibit the enzymes but do not appear to produce clinically significant interactions. The herb St. John's wort can induce the metabolism of warfarin, resulting in reduced INRs.

**Mood Stabilizers.** Among the mood stabilizers, carbamazepine can induce the metabolism of warfarin, leading to subtherapeutic levels. There have been apparently paradoxical reports of bruising and other hemorrhagic complications in patients taking warfarin with carbamazepine, possibly as a result of overshooting the therapeutic range. Coadministration of valproic acid with warfarin can increase warfarin plasma levels. Valproate can also directly lower platelet count and prolong thrombin time, although results of a study in patients receiving long-term valproate suggest these effects are not likely to be clinically significant.

**Antipsychotics.** Antipsychotic drugs are not metabolized via the major route of warfarin, but via the minor route, CYP1A2. Interactions are unlikely but cannot be ruled out. There have been 2 reported cases of interaction with quetiapine, possibly explained by the agent's high degree of protein binding.

**Sedatives, Hypnotics, Anxiolytics.** Benzodiazepines and buspirone have little-to-no effect on warfarin metabolism, and coadministration appears to be safe. The potential for an interaction with chloral hydrate through protein-binding exists, but it is of questionable clinical significance.

**Stimulants.** Modafinil, based on its CYP profile, has the potential to interact with warfarin, but a single study found no clinical effect on warfarin metabolism when the agents were coadministered. Methylphenidate labeling cites its potential to inhibit metabolism of coumarin anticoagulants, and mixed amphetamine salts have minor inhibitory effects on CYP iso-enzymes. Although there are no documented cases of an interaction between warfarin and methylphenidate or mixed amphetamine salts, coadministration should be undertaken cautiously.

**Cholinesterase Inhibitors.** These agents (e.g., donepezil, galantamine, rivastigmine) have not been shown to alter warfarin pharmacokinetics or pharmacodynamics. Co-administration with warfarin appears to be safe.
### Discussion

Interactions between psychotropics and warfarin can be serious, as INRs outside the therapeutic range can lead to bleeding or thromboembolic complications. The need for anticoagulation in patients already receiving psychiatric treatment may necessitate a change in psychotropic medication. Patients should be monitored closely and INR values assessed regularly not only when a psychotropic is added but also when one is withdrawn.

Nadkarni A, Oldham M, Howard M, Berenbaum I: Drug-drug interactions between warfarin and psychotropics: updated review of the literature. *Pharmacotherapy* 2012;32 (October):932–942. From Boston University Medical Center and the Boston University School of Medicine, MA. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

**Drug Trade Names:** asenapine—Saphris; buspirone—Buspar; carbamazepine—Epitol, Tegretol; citalopram—Celexa; clozapine—Clozaril; desvenlafaxine—Pristiq; donepezil—Aricept; duloxetine—Cymbalta; escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox; galantamine—Razadyne; haloperidol—Haldol; methylphenidate—Ritalin, and others; mirtazapine—Remeron; mixed amphetamine salts—Adderall; moclobemide (not available in the U.S.)—Aurorix, Manerix; mirtazapine—Remeron; nefazodone—Serzone; olanzapine—Zyprexa; oxcarbazepine—Trileptal; paroxetine—Paxil; quetiapine—Seroquel; rivastigmine—Exelon; reboxetine—Edronax; sertraline—Zoloft; trazodone—Desyrel; valproate—Depakene, Depakote; venlafaxine—Effexor.

### NSAIDs and Antidepressant Response

Data from the large NIMH-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study suggested that NSAIDs might impair the efficacy of antidepressant drug therapy. An analysis of an independent cohort and reanalysis of the STAR*D data set support the association of NSAIDs with reduced antidepressant efficacy but indicate that the effect is relatively small.¹

**Methods:** Data was analyzed from an electronic medical records system serving a large healthcare system in Boston. A total of 1528 patients with a diagnosis of major depression were identified. All patients had either achieved remission with SSRI monotherapy or remained depressed despite ≥2 courses of treatments. Exposure to NSAIDs and related drugs (COX-2 inhibitors and salicylates) was determined and classified as either chronic (≥2 prescriptions) or intermittent. The analysis was adjusted for demographic factors, medical comorbidity, and health-care utilization. A similar analysis was conducted using data from STAR*D study participants who were treated with citalopram (Celexa), the level 1 drug used in the trial. In contrast to the previous STAR*D analysis, potential sources of confounding were rigorously controlled.

**Results:** In the electronic-database cohort, NSAID exposure was significantly associated with risk for non-remission. The effect was confined to the true NSAIDs and did not extend to the related drugs. The crude odds ratio* (OR, 1.55) was reduced when the analysis was adjusted

<table>
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<tr>
<th>Warfarin/Psychotropic Interactions</th>
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<tr>
<td><strong>Increased INR</strong></td>
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<td>Venlafaxine</td>
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<td><strong>Decreased INR</strong></td>
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<td>Haloperidol</td>
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<td><strong>Unclear INR Effects</strong></td>
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<td>Lithium</td>
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<td>Mixed amphetamine salts</td>
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<td>Oxcarbazepine</td>
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¹ Source: Reference 1.
for medical comorbidity and health care utilization, which suggests that these factors have a confounding effect on the relationship between NSAIDs and antidepressant nonresponse. In the fully adjusted analysis, the association of non-remission with NSAIDs remained significant (OR, 1.31; p=0.04). Risk was increased with chronic NSAID use but not with intermittent use.

Results of the STAR*D data analysis were similar, with a significant effect for chronic NSAID use (fully adjusted OR, 1.44; p<0.01) but not for intermittent use. To better control for confounding by pain, narcotic exposure was also evaluated in the STAR*D cohort. The association between narcotic use in the absence of NSAID treatment and non-remission was similar to that for NSAIDS with an adjusted OR of 1.26. Effects of NSAIDs on response to cognitive-behavioral therapy (CBT), a level 2 treatment in STAR*D, were also analyzed; NSAID use was associated with a large increase in risk for non-remission following CBT (adjusted OR, 2.14), but the increase was not statistically significant, likely due to the small sample size.

**Discussion:** Painful physical symptoms are linked to greater depression severity and poorer outcomes. A portion of the effect of NSAIDs on antidepressant efficacy may be attributed to this phenomenon, but according to the study authors, there appears to be a more modest independent effect. They conclude that COX-2 inhibitors and salicylates appear to be preferable to NSAIDs, but the study’s modest effect sizes suggest that clinical practice should not be altered based on these results.

**Editorial:** It is possible that NSAIDs adversely affect antidepressant response. However, for several reasons, the more likely explanation for the association in the present study is residual confounding. First, the effect was seen with both antidepressants and CBT, which act through different mechanisms. In addition, a similar effect was seen with NSAIDs and narcotics, which are used for some of the same comorbid medical conditions, but act through different mechanisms. Finally, the measurement of comorbid conditions was not stringent in either cohort, and much of the variation in those conditions was likely missed. "Whether NSAIDs influence antidepressant response is by no means settled," and additional research is needed.

1Gallagher P, Castro V, Fava M, Weilburg J, et al: Antidepressant response in patients with major depression exposed to NSAIDs: a pharmacovigilance study. *American Journal of Psychiatry* 2012;69 (October):1065–1072. From Massachusetts General Hospital, Boston; and other institutions. **Funded by the National Library of Medicine; and the NIMH. Several study authors disclosed financial relationships with commercial sources.**

2Shelton R: Does concomitant use of NSAIDs reduce the effectiveness of antidepressants [editorial]? *American Journal of Psychiatry* 2012;69 (October):1012–1015. From the University of Alabama, Birmingham. **The author disclosed financial relationships with multiple commercial sources, but an independent reviewer found no influence of these relationships.**

*See Reference Guide.

**Intranasal Oxytocin for Alcohol Withdrawal**

According to results of a preliminary study, intranasal oxytocin may block alcohol withdrawal symptoms in adults undergoing detoxification.

**Background:** Benzodiazepines are currently the drugs of choice for alcohol detoxification, but they may maintain sedative-hypnotic tolerance that could result in postdetoxification symptoms and increase the likelihood of relapse. Benzodiazepines can also enhance the depressant actions of alcohol, including respiratory depression, which can limit their use in outpatient detoxification. Oxytocin has been shown to block formation of alcohol tolerance and reduce withdrawal symptoms in alcohol-dependent rodents.

**Methods:** Alcohol-dependent adults were recruited through advertising and underwent telephone screening for study eligibility. Study participants were required to be aged 18–65 years, to have consumed 8–30 standard alcohol-containing drinks per day in the previous 2 weeks, and to have experienced significant withdrawal symptoms during ≥1 prior attempt to stop
drinking. Those with unstable medical or psychiatric conditions as well as those who had previously experienced alcohol-withdrawal related seizures or delirium tremens were excluded. The sample comprised 11 patients (9 men), with a mean age of 41 years who reported consuming and average of 15–18 drinks per day. On admission to the research unit, patients underwent a battery of withdrawal-symptom assessments and were then randomized to receive double-blind intranasal oxytocin or placebo twice a day for 3 days. The patients received their first intranasal medication dose (24 IU oxytocin or placebo) immediately following assessment. Patients were given 2 mg lorazepam if their Clinical Institute Withdrawal Assessment for Alcohol (CIWA) scale score exceeded 11 points. Assessments were repeated 1 hour after each lorazepam dose, and an additional 2 mg of lorazepam was administered if the CIWA score remained above 9.

**Results:** Patients in the oxytocin group required nearly 5 times less lorazepam to complete the 3-day detoxification period (mean total lorazepam doses, 3.4 mg vs 16.5 mg; p=0.0015). Mean CIWA scores were significantly lower in the patients who received oxytocin than in those who received placebo on day 1 (4.3 vs 11.8; p<0.0001) and on day 2 (3.4 vs 11.1; p=0.0015), but not on day 3 (3.1 vs 5.4; p=ns). Reductions in patient reported alcohol craving were greater with oxytocin than with placebo, but the difference was not statistically significant. Tension and anxiety were also reportedly reduced in the oxytocin group.

Because all subjects assigned to placebo but only half of those assigned to oxytocin had reported drinking ≤16 drinks per day, the analysis was repeated in this subgroup. In the oxytocin group, no lorazepam was required, while those who received placebo required a mean of 16.5 mg lorazepam to complete detoxification. CIWA scores were significantly lower in the oxytocin group throughout detoxification, and patient-reported alcohol cravings were lower, but not significantly.

**Discussion:** This appears to be the first evidence that intranasal oxytocin can block alcohol withdrawal symptoms in humans; however, because of the small sample size and other study limitations, the results must be considered preliminary. The authors also suggest investigating whether oxytocin can reduce drinking in alcohol-dependent outpatients.

**Study Rating**—18 (100): This study met all criteria for a randomized controlled trial.


**Drug Trade Names**: lorazepam—Ativan; oxytocin, intranasal—Syntocinon Spray

*See Reference Guide.

**Atypical Antipsychotics for Anorexia: Ineffective**

According to results of a meta-analysis of controlled trials, atypical antipsychotics do not affect body mass index (BMI) or eating disorder cognitions in patients with anorexia nervosa.

**Background:** Atypicals are increasingly prescribed for patients with anorexia nervosa, often as a means of increasing weight. Several rationales exist for using atypicals to treat this disorder. Serotonin activity, among the targets of atypicals, is believed to be disrupted in anorexia. Also, the eating disorder is characterized by similar irrational cognitions to schizophrenia, namely ego-syntonic abnormal beliefs marked by an acute lack of insight. Atypicals are known to have a positive effect on depression and anxiety, both of which complicate treatment of anorexia. However, given the adverse effects of atypicals, their use in anorexia nervosa should require evidence of a substantial benefit.
Methods: All available randomized controlled trials of atypical antipsychotics in adolescent or adult patients with either the restricting or binge/purging types of anorexia nervosa were identified. Eight trials were included in the analysis: 6 of olanzapine, and 1 each of risperidone and amisulpride. Control treatments were placebo in 6 studies and active drugs in the other 2.

Results: Two studies were restricted to adolescents, and the overall median age of study participants was 25 years. The median baseline BMI was 15.7 (range, 13.95–16.9). Two studies examined only the restricting type of anorexia. Compared with placebo, atypical antipsychotics had no significant effect on BMI (weighted mean difference, 0.18). This lack of effect was consistent across the included studies and did not change when the analysis was limited to studies of olanzapine, which has the greatest weight gain potential of the drugs. Analysis of secondary outcomes showed that atypical antipsychotics had no effect on drive for thinness or body dissatisfaction. Compared with placebo or active control, atypical antipsychotics were associated with increases in eating disorder symptoms and anxiety. Subgroup analyses did not reveal any differences between blinded and unblinded studies, different drug doses, or short-term (<8 weeks) vs longer studies.

Discussion: The lack of effect of atypicals, despite their known effects on weight and appetite, suggests that increasing hunger cues in patients with anorexia nervosa is not sufficient to overcome their drive for thinness. This finding is important because the weight gain side effect is one of the primary reasons physicians prescribe atypicals in anorexia.


Drug Trade Names: amisulpride (not available in the U.S.)—Solian; olanzapine—Zyprexa; risperidone—Risperdal

Quetiapine Monotherapy for Depression: Meta-Analysis

According to results of a meta-analysis of clinical trials, quetiapine (Seroquel), the only medication FDA approved to treat bipolar depression, is superior to placebo as monotherapy for acute-phase major depression. However, the rate of treatment discontinuation for adverse effects could limit its usefulness.

Methods: A comprehensive literature search identified all randomized, placebo-controlled trials of quetiapine for unipolar major depression published between 1991 and February 2012, as well as any additional studies in the drug manufacturer’s database. The studies were required to be conducted in adults (aged 18–65 years) and to use standardized rating scales for depression. Only 3 trials met all criteria and were included in the meta-analysis.

Results: The 3 published trials included a total of 1497 outpatient participants (64% women), treatment durations ranged from 8 weeks to 11 weeks, and none of the studies included patients with refractory depression. Quetiapine dosages ranged from 50 to 300 mg/day, and all 3 studies used the same efficacy outcome measures—the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS). The studies were judged to have a low risk of bias, and there was little significant heterogeneity among them.

Mean changes in HAM-D and MADRS scores were greater with quetiapine than with placebo. The response rate was significantly higher with quetiapine than placebo in the individual studies and overall (52% vs 38%; relative risk [RR],* 1.44; p<0.00001). Remission rates with quetiapine were not statistically superior to placebo in the individual studies, but they were superior in the pooled analysis (27% vs 21%; RR, 1.37; p<0.002). The pooled number needed
to treat* for quetiapine was 7.2. Although rates of treatment discontinuation did not differ between quetiapine and placebo overall, more patients withdrew from quetiapine treatment because of adverse events (RR, 2.9).

**Discussion:** The authors note that these results must be considered preliminary because of the small number of available studies, all of which were funded by AstraZeneca, the manufacturer of Seroquel. They also note that response rates to both active treatment and placebo in the present study were lower than those generally reported in antidepressant trials.

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

Maneeton N, Maneeton B, Srisurapanont M, Martin S: Quetiapine monotherapy in acute phase for major depressive disorder: a meta-analysis of randomized, placebo-controlled trials. *BMC Psychiatry* 2012;12:160; doi 10.1186/1471-244X-12-160. Published online September 27, 2012. From Chiang Mai University, Thailand; and the Brandon Lane Neuropsychiatry Clinic, Durham, U.K. This review was conducted without external funding. All study authors disclosed financial relationships with commercial sources, including 2 who received honoraria or other compensation from AstraZeneca.

*See Reference Guide.

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**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.

**Odds Ratio:** A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**Relative Risk:** The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

**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.