Sertraline and Benzodiazepine Screening

A series of 3 false-positive urine benzodiazepine screens along with contradictory information in the literature regarding the potential for sertraline (Zoloft) to interfere with the test prompted the study authors to undertake a retrospective review of benzodiazepine screens at their institution.

All positive urine benzodiazepine screens (n=522) conducted at 1 military institution using an AEROSET or ARCHITECT assay in 2007 and 2008 were reviewed. Of these screens, 160 were determined by follow up gas chromatography–mass spectrometry to be false positives. Patients with an active benzodiazepine prescription (n=62) were excluded from further analysis and the pharmacy records for the remaining 98 patients were explored for active sertraline prescriptions. A total of 26.5% of these remaining false-positive benzodiazepine urine screens were associated with sertraline use.

False-positive drug screening results can delay diagnosis and appropriate treatment. They can also undermine the therapeutic alliance between patients and clinicians. Even acknowledging the study’s limitations (e.g., retrospective nature, potential for incomplete documentation), these findings suggest sertraline may be an underreported cause for false-positive benzodiazepine screens. Although these results can not be extrapolated to all assays, literature reports have described cross-reactivity with the inactive metabolite of sertraline using other commercially available products.


Warfarin/Antidepressant Interactions

A comparison of warfarin interactions by drug information source found alarming inconsistencies between information providers. Because warfarin is so widely prescribed it is likely to be used by patients with comorbid psychiatric conditions. A recent literature review relates what is currently known from both clinical and theoretical studies about concomitant use of antidepressants and warfarin.

Continued
The FDA package labeling for SSRIs and some SNRIs include cautions about abnormal bleeding with concomitant warfarin use. The likely mechanism of the interaction is inhibition of cytochrome P-450 (CYP) isoenzymes by antidepressants. Warfarin is metabolized via the CYP 2C9, 1A2, 2C19, and 3A4 isoenzymes. The CYP 2C9 and 1A2 isoenzymes appear to be the strongest in terms of interaction relevance. Antidepressant medications (even those in the same class) have different isoenzyme inhibitory effects and those that inhibit CYP 2C9 or 1A2 are most likely to be associated with warfarin potentiation and abnormal bleeding.

**Sertraline and citalopram** appear to be the safest for use in patients taking warfarin. Although prothrombin times were elevated in patients taking these agents with warfarin, the increases were not clinically significant. **Paroxetine** appears to have an intermediate risk for warfarin interaction with a low-to-moderate risk of abnormal bleeding. **Fluoxetine and fluvoxamine** appear to have the highest potential to inhibit warfarin metabolism and increase bleeding.

**Venlafaxine and desvenlafaxine** do not appear to affect the relevant CYP isoenzymes and are assumed not to inhibit warfarin metabolism. Based on its CYP profile, **duloxetine** should also have minimal risk of warfarin interaction, but case reports have documented both increased and decreased warfarin effects with concomitant administration. Because duloxetine is among the newer agents, continued observation is needed to determine its safety in combination with warfarin. **Mirtazapine** has minimal effects on the important CYP isoenzymes and as a result, a low potential for interaction. Data on **bupropion** is scarce but it can alter prothrombin times and/or international normalized ratios (INRs) when coadministered with warfarin. The TCAs **amitriptyline** and **nortriptyline** appear to have dose-dependent effects on prothrombin time.

All patients treated with warfarin should undergo regular INR monitoring. The antidepressant/warfarin interaction may be more important for patients already taking warfarin and then adding an antidepressant. Adjustments can be made during initial warfarin titration when it is added to an existing antidepressant.


**Drug Trade Names**: amitriptyline—Elavil; citalopram—Celexa; desvenlafaxine—Pristiq; duloxetine—Cymbalta; fluoxetine—Prozac; fluvoxamine—Luvox; mirtazapine—Remeron; nortriptyline—Aventyl, Pamelor; paroxetine—Paxil; sertraline—Zoloft; venlafaxine—Effexor; warfarin—Coumadin, Jantoven

### Suicidality and Antidepressant Response

Treatment of depressive symptoms in patients with recurrent major depression or bipolar disorder was half as effective in those with a Hamilton Rating Scale for Depression (HAM-D) score indicating suicidality.

**Methods**: Consecutive adults (n=82) admitted to a day hospital for treatment of severe resistant depression (50 unipolar, 32 bipolar) were included in the study. All received intravenous citalopram (not available in the U.S.) for 15 days followed by 4 weeks of outpatient therapy with oral citalopram (Celexa). Suicidal status was determined using item 3 of the HAM-D with a score of ≥3 indicating suicidality in 31 patients (38%); 13 of the patients judged to be suicidal (42%) had bipolar depression. Most patients (83%) had previously received a mood stabilizer and adjunctive treatments were continued without change.

**Results**: Baseline depression severity scores (omitting item 3) did not differ between patients who were suicidal and those who were not, but actual values were not given. At 6 weeks the HAM-D improvement in the nonsuicidal patients was almost twice that in the suicidal group: 25 points vs 13 points (p<0.001). The proportion of patients with a ≥20% improvement was also
twice as high in nonsuicidal patients (57% vs 26%; p=0.006). At study end, HAM-D item 3 scores remained elevated in the suicidal patients, and 6 patients attempted suicide in the first 2 study weeks.

Suicidal patients had a longer duration of the current episode, were more likely to have substance abuse problems and to receive a mood stabilizer, and they were younger and more likely to be unmarried. A multivariate analysis accounting for these variables found only the presence of suicidality at baseline predicted poor outcome.

**Discussion:** Although suicidal patients did improve, they still endorsed suicidality after 6 weeks of aggressive treatment. This finding underscores the need for continued monitoring of these patients.

Pompili M, Baldessarini R, Tondo L, Innamorati M, et al: Response to intravenous antidepressant treatment by suicidal vs nonsuicidal depressed patients. *Journal of Affective Disorders*. Published online August 24, 2009 at www.elsevier.com; doi 10.1016/j.jad.2009.07.018. From Sant'Andrea Hospital, Rome, Italy; and other institutions. Funded by the Bruce J Anderson Foundation; and the McLean Private Donors Psychopharmacology Research Fund. The authors disclosed no potential conflicts of interest.

### EPA for Major Depression

A double-blind placebo-controlled trial adds further support for fatty acid efficacy in major depression.

**Background:** Several studies have shown the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) alone or in combination can reduce depressive symptoms when used as an adjunct to antidepressant drugs. Less is known about their efficacy as monotherapy.

**Methods:** Patients at Massachusetts General Hospital who were ≥18 years and who met DSM-IV criteria for major depressive disorder were eligible for the study if they had a Hamilton Rating Scale for Depression (HAM-D) score of ≥18 and a Clinical Global Impression-Severity rating of at least "mildly ill." Patients with schizophrenia or psychosis, bipolar disorder, suicide risk, treatment-resistant depression, or receiving mood stabilizing treatment were excluded. A total of 41 patients (mean age, 43 years) received double-blind randomly assigned 1 g/day EPA (n=17) or placebo (n=24) for 8 weeks. The primary outcome measure was the HAM-D with response defined as a ≥50 decrease in score and remission as a score of ≤7. Both completer and intent-to-treat (ITT) analyses were conducted. Plasma fatty acid levels and omega-3/omega-6 ratios were also evaluated.

**Results:** In the 24 patients who completed the study (11 taking EPA, 13 taking placebo), the mean HAM-D score decreased from 21 to 11 with EPA (p=0.004), compared with a decrease from 21 to 16 (p=ns) with placebo. Although the between-group difference was not statistically significant, the effect size* for EPA was 0.73. Response rates were 45% and 23% in the groups, respectively with an odds ratio (OR)* for EPA response of 2.8. Remission rates were 36% and 15% with an OR of 3.1. Results in the ITT analysis were similar but slightly less robust (effect size for EPA, 0.55).

Few patients reported adverse effects: 5 in the placebo group and 2 in the EPA group. All adverse effects were gastrointestinal and mild. No patient withdrew from the study because of medication intolerance. Most patients who did not complete the protocol were lost to follow-up with no explanation available.

Seven patients (4 EPA; 3 placebo) who met response criteria chose to continue study treatments for an additional 8 weeks. Although the small sample did not allow for statistical comparisons, all patients maintained their response and none had significant worsening of depressive symptoms.
Baseline fatty acid intake and the corresponding plasma levels did not affect depression severity. However, patients with the lowest dietary fatty acid intake at baseline had the most robust response to EPA. Plasma levels of EPA increased with treatment; the omega-3/omega-6 ratio decreased and was significantly associated with treatment response.

**Discussion:** The finding that fatty acid supplements improve depressive symptoms is consistent with prior research and the study authors conclude EPA appears to be a "potentially effective monotherapy for MDD." However, because of the small sample and the low completer rate these results must be interpreted cautiously and omega-3 fatty acids should not be recommended as first-line therapy for MDD.

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

Mischoulon D, Papakostas G, Dording C, Farabaugh A, et al: A double-blind, randomized controlled trial of ethyl-eicosapentaenoate for major depressive disorder. *Journal of Clinical Psychiatry.* Published online August 25, 2009 at www.psychiatrist.com; doi 10.4088/JCP.08m04603. From Massachusetts General Hospital, Boston. *Funded by the National Center for Complementary and Alternative Medicine.* The authors have disclosed commercial relationships that might pose conflicts of interest.

*Reference Guide Item.

### Discontinuation of Injectable Risperidone

Less than half of a group of veterans administration patients started on long-acting injectable risperidone continued the medication for >18 months. Continuation rates were higher for oral antipsychotics.

**Methods:** More than 11,000 adults with schizophrenia were identified who received a new antipsychotic prescription from VA Medical Centers during a 2-month period. Pharmacy data were used to evaluate prescription renewal rates for long-acting injectable risperidone compared with oral antipsychotics.

**Results:** Long-acting injectable risperidone was not often prescribed: a total of 280 patients (2.4%) received the agent. In the first 30 days, termination rates were highest with long-acting injectable risperidone (20%) and lowest with clozapine (1.5%). At 1 year the clozapine termination rate was 15%, and 46% of long-acting injectable risperidone patients had stopped the agent. Results were similar at 18 months with 23% of clozapine-treated patients stopping the medication, compared with 55% of long-acting injectable risperidone-treated patients. Patients receiving olanzapine, risperidone, or quetiapine fell in between clozapine and injectable risperidone and those receiving aripiprazole had the highest 18-month termination rate. After adjustment for age, gender, and other confounding factors, compared with injectable risperidone, hazard ratios* for discontinuation were lower with all oral second-generation antipsychotics except aripiprazole and for all first-generation agents.

**Discussion:** Long-acting injectable agents, including risperidone, improve treatment compliance but only for the duration of time they are administered. While other factors require consideration, these results raise the possibility that the advantage in compliance may be offset by a disadvantage in durability of treatment. The added burden of having to attend a clinic session every other week, as opposed to receiving a 90-day prescription, could be another disadvantage of long-acting treatment.


**Drug Trade Names:** aripiprazole—Abilify; clozapine—Clozaril; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone, long-acting injectable—Risperdal Consta; risperidone, oral—Risperdal

*Reference Guide Item.
Donepezil in Severe Alzheimer’s Disease

Treatment of Alzheimer’s disease can be considered successful if there is improvement, stabilization, or a less than expected decline in function or behavior. Considerable research supports the efficacy of donepezil (Aricept) in mild and moderate Alzheimer’s disease, but less research has been conducted in more severely affected patients. A pooled analysis of 3 randomized controlled trials found donepezil produced small-to-medium improvements in cognitive function, activities of daily living, and global function in patients with severe Alzheimer’s disease.

Methods: Data were pooled from the intent-to-treat analyses of 3 multicenter placebo-controlled trials of donepezil in severe Alzheimer’s disease. Patients (aged ≥50 years) had imaging-confirmed disease, Mini-Mental State Examination (MMSE) scores of ≤12, and minimal functional assessment ratings indicating they required assistance with normal activities such as choosing clothing. Participants had been randomized to 10 mg/day donepezil or placebo and were followed for 8–24 weeks.

Results: Cognitive function, measured using the Severe Impairment Battery (SIB) remained stable or improved in 67% of donepezil patients, compared with 41% of placebo patients (p=0.0001). The donepezil group showed a moderate increase in SIB score (2.6 points) while the placebo group showed a decline (3.7 points); the effect size* for SIB was 0.51. Ability to perform activities of daily living decreased in both groups, but the decline was 45% larger in the placebo group (p=0.03). The effect size for donepezil on activities of daily living was 0.17, indicating a small positive effect. Global function was improved in 40% of patients treated with donepezil, compared with 27% of the placebo group (effect size, 0.26). Behavior improved in both groups, with no significant differences. Functional and behavioral improvements were greater in patients who experienced cognitive improvement or stabilization.

Most patients in the donepezil (81%) and placebo (73%) groups experienced adverse effects. The most commonly reported were accidental injury, infection, and diarrhea. Anorexia, urinary tract infection, nausea, and diarrhea were the most common reasons for discontinuing donepezil, and 12% of the donepezil group and 7% of the placebo group discontinued treatment because of adverse effects. There were no clinically important changes in laboratory parameters or vital signs, and mortality rates were similar in both groups.


*Reference Guide Item.

Pharmacotherapy for Depression: Guideline Update

The Canadian Network for Mood and Anxiety Treatments (CANMAT) collaborated with the Canadian Psychiatric Association to develop evidence-based treatment guidelines for major depressive disorder in 2001. The present revision reflects advances published since then and recommendations are based on systematic reviews and meta-analyses where possible.

The new analysis reconfirms the previous guideline conclusions that newer antidepressants (SSRIs, SNRIs, and others) are safer and better-tolerated than tricyclics and MAOIs. The recommended first-line agents include most SSRIs, all SNRIs, bupropion, mianserin, mirtazapine, moclobemide, and reboxetine. Tricyclics are second-line and the MAOIs phenelzine and tranylcypromine are third-line. Because of its sedating properties, the SSRI trazodone is second-line, as are the well-tolerated selective MAO-B inhibitor selegiline transdermal and the atypical antipsychotic quetiapine.
Meta-analyses have not shown any efficacy differences among newer and older classes of antidepressants. Individual agents have shown small efficacy advantages in some meta-analyses, but not others. The highest level of evidence suggests superior efficacy for escitalopram, sertraline, and venlafaxine. However, the choice of a first-line treatment is usually based on tolerability, patient preference, and cost.

Differences in the side effect profiles of newer antidepressants and antidepressant classes have also been identified. GI side effects are more common with agents that inhibit serotonin re-uptake; nausea is less common with extended-release formulations; long-term paroxetine and mirtazapine are associated with weight gain; and abrupt discontinuation of paroxetine or venlafaxine is associated with withdrawal symptoms. Sexual dysfunction may affect up to half of patients taking an SSRI, but is not increased with bupropion, mirtazapine, and some others. Despite black box warnings, there is no clear evidence that SSRIs and newer antidepressants are associated with suicidality in adults.

For patients with nonresponsive depression, the evidence does not show a difference between within-class and between-class drug switching. The data supporting augmentation strategies is clearest for lithium and atypical antipsychotics, particularly aripiprazole, which is now approved in the U.S. for this indication. Limited evidence supports liothyronine (T3) augmentation. Augmentation with stimulants is not recommended. Only modest evidence supports antidepressant combinations.

Lam R, Kennedy S, Grigoriadis S, McIntyre R, et al: Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. *Journal of Affective Disorders* 2009;117:S26-S43. From the University of British Columbia, Canada; and other institutions. **Funded by CANMAT. The authors disclosed commercial relationships that might pose conflicts of interest.**

*Drug Trade Names:* aripiprazole—*Abilify*; bupropion—*Wellbutrin*; escitalopram—*Lexapro*; liothyronine—*Cytomel*; mianserin (not available in the U.S.)—*Lantanon, Tolvon*; mirtazapine—*Remeron*; moclobemide (not available in the U.S.)—*Aurorix, Manerix*; paroxetine—*Paxil*; phenelzine—*Nardil*; quetiapine—*Seroquel*; reboxetine (not available in the U.S.)—*Edronax, Vestra*; selegiline transdermal—*Emsam*; sertraline—*Zoloft*; tranylcypromine—*Parnate*; trazodone—*Desyrel*; venlafaxine—*Effexor*

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**Aripiprazole Efficacy in MDD and Mania**

A review of evidence suggests aripiprazole (*Abilify*) is effective in patients with major depression or manic/mixed episodes of bipolar disorder.

**Methods:** Double-blind placebo-controlled trials of aripiprazole in major depression and bipolar disorder were identified by PubMed search. Both monotherapy and adjunctive aripiprazole were considered. A total of 9 studies were found: 4 in depression (2 unipolar and 2 bipolar) and 5 in manic or mixed bipolar disorder. About 1500 patients were treated with either aripiprazole or placebo for each indication. The studies of bipolar depression used aripiprazole as monotherapy while those in patients with unipolar depression used the agent as an adjunct to an antidepressant. The primary symptom measures were the Montgomery-Asberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMRS). Response was defined as a ≥50% reduction in score on the symptom specific measure. Depression remission was defined as a MADRS score of ≤10 or ≤8 depending on the study; mania remission was a YMRS score of ≤12.

**Results:** Not all depression studies included MADRS change values, and only response and remission were evaluated. Response rates ranged from 32% with adjunctive aripiprazole in unipolar depression to 45% with monotherapy for bipolar depression. Remission rates ranged from 25% to 30%. A pooled analysis found an overall 8% increase (p=0.02) in response rate with aripiprazole and placebo and an overall 5% increase (p=ns) in remission. The improved remission rate was driven by adjunctive use, as aripiprazole monotherapy had small or negative effects on depression remission.
Mania response was also stronger with aripiprazole than placebo as was the mean difference in YMRS change (3.3 points). Overall, the response rate was 16% higher with aripiprazole than with placebo (p<0.001). Several studies did not include remission rates and this outcome was not included in the pooled analysis.

Akathisia was significantly more common with aripiprazole and affected 20–30% of patients with depression and 9–20% of those with mania. Insomnia, nausea, and restlessness were also more common with aripiprazole than placebo.

**Discussion:** Previous research supported the use of atypical antipsychotics as antimanic and antidepressant agents. However, because of a lack of published studies, aripiprazole was excluded from a previous meta-analysis. In spite of the limitations, including the heterogeneity of depression studies, the present analyses suggest aripiprazole improves depression response and mania response and remission. Depression remission may be improved in patients using aripiprazole as an adjunct to antidepressants, but not as monotherapy.

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**Long-Term Clozapine Monotherapy in Bipolar Disorder**

Add-on clozapine (Clozaril) has been effective in treatment-resistant bipolar disorder, and 1 retrospective study found the majority of enrolled patients experienced no affective episodes while receiving clozapine monotherapy for 16 months. A recently reported case supports the efficacy of clozapine monotherapy in resistant bipolar disorder and extends the follow-up period to more than 5 years.

A 33-year-old male had experienced his first episode of bipolar disorder at age 20 years. Depressive episodes often resulted in overdose or suicidal thoughts. Multiple mood stabilizer, antidepressant, and antipsychotic combinations had not controlled his symptoms. Medication compliance was reportedly good, but he was hospitalized for 11 episodes over the 8 years before being started on 1200 mg/day lithium plus 400 mg/day clozapine. Six months later the lithium dosage was reduced to 800 mg/day and at the 4-month outpatient follow-up the patient was asymptomatic. Lithium was stopped and 350 mg/day clozapine monotherapy has been continued for 66 months without recurrence of affective episodes.

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**Naltrexone for Alcoholism in Bipolar Disorder**

In a pilot study, treatment with naltrexone had moderate positive effects on some drinking measures in a group of patients with alcoholism and bipolar disorder.

**Methods:** Adult outpatients (n=50) with comorbid bipolar disorder and alcoholism were randomized to receive 50 mg/day naltrexone or placebo as an add-on to their psychotropic medications. All participants also participated in a CBT program for bipolar disorder and substance abuse. Patients with severe mood symptoms and those undergoing outpatient treatment for substance abuse (e.g., Alcoholics Anonymous ≥3 times/week) were excluded. Drinking days, heavy drinking days, alcohol craving, and mood symptoms were assessed weekly for 12 weeks.

**Results:** Forty-three patients (20 naltrexone, 23 placebo) started treatment, and 26 (14 naltrexone, 12 placebo) completed the 12-week protocol. Drinking days/week, heavy drinking days/week,
number of drinks per drinking day, and alcohol craving all decreased with naltrexone and placebo with no significant differences between groups. Effect sizes* for these outcomes ranged from 0.51 to 0.68, indicating moderate effects. Improvements in most outcomes were correlated with naltrexone adherence. Manic and depressive symptoms were not affected by naltrexone treatment. Adverse effects were similar in both groups.

Discussion: Although they did not reach statistical significance, these results suggest naltrexone may improve drinking measures in patients with bipolar disorder and alcoholism. While the study is strengthened by its placebo-controlled design, the sample was small and it may have been underpowered to detect statistical differences.

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

Brown E, Carmody T, Schmitz J, Caetano R, et al: A randomized, double-blind, placebo-controlled pilot study of naltrexone in outpatients with bipolar disorder and alcohol dependence. Alcoholism: Clinical and Experimental Research 2009;33 (November):1–7. From the University of Texas Southwestern Medical Center, Dallas; and other institutions. Funded by the NIH. The authors did not include disclosure of potential conflicts of interest.

*Reference Guide Item.

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.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

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.

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.