Reminder: Lithium/Caffeine Interaction

A 58-year-old male with bipolar disorder had been treated with lithium for 5 years. He had a recent history of decreasing lithium levels despite compliance with a medication regimen that included 900 mg/day lithium (serum levels, 0.44–0.9 mEq/L), as well as fosinopril, metoprolol, amlodipine, a statin, and insulin for hypertension, hyperlipidemia, and diabetes. The lithium dosage was increased to 1125 mg/day, but serum levels continued to be low. Two months later, he was admitted in a mixed state with a lithium level of 0.08 mEq/L. While describing his medical history, the patient reported drinking up to 3 liters/day of Coca-Cola Zero (containing a total of about 300 mg caffeine) during the previous 3 months. The lithium dosage was unchanged, and the serum level began to increase when cola consumption was stopped, reaching 0.5 mEq/L within 5 days.

The diuretic action of caffeine has been shown to increase lithium clearance and decrease serum levels. According to the authors, this patient’s excessive Coca-Cola Zero ingestion, which provided high caffeine intake, was likely responsible for his otherwise unexplained low serum lithium levels.


Drug Trade Names: amlodipine—Norvasc; fosinopril—Monopril; metoprolol—Lopressor

Valproate in Alzheimer's

In a placebo-controlled trial, prophylactic valproate did not prevent or delay the onset of agitation or psychosis in patients with Alzheimer’s disease.

Background: Treatment of agitation and psychosis in Alzheimer’s disease is generally reactive, and antipsychotics may provide some relief. However, adverse effects are problematic and the agents may increase mortality in this population. Because valproate has also been shown to
provide some relief from agitation in dementia, a controlled trial was undertaken to determine if prophylactic treatment would prevent or delay onset.

**Methods:** The trial enrolled 313 patients who met standardized criteria for Alzheimer’s disease, had Mini Mental State Examination scores of 12–20, lived in the community, and had no signs of agitation or psychosis. Patients were randomly assigned to receive double-blind valproate or placebo for 2 years. Valproate was flexibly dosed (target, 10–20 mg/kg/day). Patients were permitted to receive concomitant cholinesterase inhibitors, memantine, and antidepressants, but not other psychotropics. The primary study outcome was onset of moderately severe delusions, hallucinations, or agitation/aggression as assessed with the Neuropsychiatric Inventory, plus the physician’s judgement that these symptoms were clinically significant.

**Results:** About 60% of patients did not complete 2 years of assigned treatment; about half of these patients were either lost to follow-up or experienced the study endpoint. At baseline, more than 90% of the patients were taking a cholinesterase inhibitor, two-thirds were using memantine, and one-third had been prescribed an antidepressant.

Agitation or psychosis developed in 29 patients receiving placebo and in 25 patients receiving valproate (18% vs 16%; p=ns). Time to onset also did not differ between the groups. Rates of adverse events did not differ markedly between the 2 treatment groups, but discontinuation because of them was more common with valproate (25 vs 12 patients). Sedation scores progressively increased in the valproate group (p=0.02). Safety and tolerability of valproate were consistent with prior reports in this patient population and with the drug’s labeling.

Volumetric MRI studies were obtained at baseline and after 1 year in 88 patients. Compared with placebo, valproate was associated with greater reductions in hippocampal and whole brain volumes. These changes were not associated with cognitive or functional decline.

**Discussion:** The overall incidence of psychosis in this patient sample (17%) was less than the expected rate of about 50%. However, the reduced incidence was not a result of valproate treatment, and the authors conclude that valproate should not be used to delay or control agitation in patients with dementia.

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


Drug Trade Names:  
memantine—Namenda;  
valproate—Depakene, Depakote

*See Reference Guide.

### Antidepressants Ineffective in Patients with Dementia

Neither mirtazapine nor sertraline was superior to placebo in treating depression in patients with dementia in a large controlled trial. Although antidepressants may sometimes be indicated, the findings suggest that they should not be recommended as routine first-line therapy for depression in patients with Alzheimer’s disease.

**Background:** Depression is common in dementia, affecting >20% of patients. Antidepressants are commonly used to treat depression in dementia. While the practice is in accordance with expert recommendations, it is supported by weak or inconsistent evidence.

**Methods:** This multicenter trial was carried out in 9 U.K. geriatric psychiatry services. Patients (n=326; mean age, about 80 years) were evaluated by their referring psychiatrists and met stan-
standardized criteria for possible or probable Alzheimer’s disease, as well as depression of at least 4 weeks' duration. All were judged to need antidepressant treatment. Depression severity was measured with the Cornell Scale for Depression in Dementia (CSDD). Patients were randomly assigned to receive double-blind mirtazapine (target dosage, 45 mg/day), sertraline (target dosage, 150 mg/day), or placebo for 39 weeks. The dosage was adjusted initially based on the CSDD score and eventually according to clinician judgment. Actual mean dosages for patients who completed treatment were 95 mg/day sertraline and 30 mg/day mirtazapine.

Results: In the intent-to-treat analysis, neither mirtazapine nor sertraline differed from placebo at 13 weeks with regard to the primary outcome measure, CSDD score. Average CSDD scores decreased by 4–6 points in all groups (from baseline means of 13–14), with the largest absolute decrease occurring with placebo. At 39 weeks, the initially observed improvements were sustained. The 3 treatments did not differ in most secondary outcomes for patients (e.g., cognition, behavioral problems, or quality of life) or their caregivers (e.g., quality of life, mental health). There was no subgroup that benefitted significantly from antidepressant drug treatment. Adverse events were reported in 26% of the placebo group and in >40% of each active treatment group. The most common adverse effects were GI reactions with sertraline and drowsiness and sedation with mirtazapine. Withdrawal rates ranged from 24% to 35%, but there were no significant differences between the groups at 39 weeks.

Discussion: According to an accompanying editorial, the design of the present study mimicked clinical practice, with a representative patient population and using the most commonly prescribed antidepressants. The findings support a stepped care approach, with perhaps 13 weeks of watchful waiting, followed by low-intensity psychosocial interventions, and then by more intensive interventions. Antidepressant use should not necessarily be abandoned in patients with dementia. Trials may be warranted for some patients if psychosocial interventions fail or if depression is severe.

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


Drug Trade Names: mirtazapine—Remeron; sertraline—Zoloft

*M See Reference Guide.

Methylene Blue and Linezolid Warnings

Serious central nervous system toxicity, including serotonin syndrome, has been reported when methylene blue or linezolid was administered to patients receiving serotonergic psychiatric medications.1,2 Methylene blue and linezolid are reversible MAOIs. Methylene blue is used in emergency settings to treat methemoglobinemia, vasoplegic syndrome, encephalopathy, and cyanide poisoning. It is also used as a contrast agent in therapeutic and diagnostic imaging procedures. Linezolid is an antibacterial used to treat infections, including pneumonia and methicillin-resistant Staphylococcus aureus (MRSA). Concomitant use of methylene blue or linezolid and a serotonergic agent (e.g., SSRIs, SNRIs, TCAs) can lead to toxic serotonin build-up in the brain. Signs and symptoms of this serotonin syndrome include: confusion; hyperactivity; memory difficulty; muscle twitches; excessive sweating; shivering; diarrhea; incoordination; and fever. Complete lists of psychiatric medications that can interact with methylene blue and linezolid are available in FDA Drug Safety Communications posted at www.fda.gov.
Except in life-threatening situations, methylene blue and linezolid should not be given to patients taking a serotonergic agent. If emergency use is necessary, the serotonergic agent should be stopped immediately and the patient monitored for CNS toxicity for 2 weeks (5 weeks for fluoxetine because of its longer half life) or until 24 hours after the last methylene blue or linezolid dose. When methylene blue use is planned for an imaging or diagnostic procedure, or linezolid is considered, serotonergic agents should be discontinued 2–5 weeks before the procedure and can be reinstituted 24 hours after the last methylene blue or linezolid dose.


Cardiovascular Safety of Antidepressants

According to an epidemiologic study, cardiovascular risks of most available antidepressants are comparable to that of paroxetine, an agent considered to have a favorable cardiovascular profile.

Background: Some antidepressants have been listed on the University of Arizona’s Center for Education and Research and Therapeutics (CERT) roster of potentially arrhythmogenic drugs, based on ECG markers of risk. The present study evaluated the comparative cardiovascular safety of antidepressants.

Methods: Medicaid claims data were analyzed from 5 large states (about 35% of the Medicaid population) from 1999 to 2003. Antidepressant use was identified in nearly 3.4 million patients, and unadjusted rates of sudden cardiac death or ventricular arrhythmia resulting in hospital presentation were then derived for each antidepressant. After adjustment for demographic and illness factors as well as history of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, hazard ratios for adverse sudden cardiac death and ventricular arrhythmia were calculated for each agent. Concomitant use of drugs that affect antidepressant metabolism was also analyzed. In order to avoid confounding by indication, the study did not include an untreated control group.

Results: During nearly 1.3 million person-years of observation, 4222 incident cardiovascular events occurred. Agents with >30 events (n=13) were included in the analysis. The incidence of cardiovascular events did not differ between paroxetine, which was used as the reference because of its limited effects on the QT interval, and most other agents. Drugs representing all classes—other SSRIs, tricyclics, trazodone, venlafaxine, nefazodone, and lithium—were comparable in safety to paroxetine with hazard ratios* (HRs) of 1.0–1.2. Mirtazapine was associated with a slightly higher risk (HR, 1.26), and bupropion with a lower risk (HR, 0.8). However, mirtazapine was prescribed more often than other agents for elderly patients with multiple illnesses. Although the data were adjusted for these factors, it is possible that the adjustment did not remove all bias or that the association was a chance finding.

Discussion: The results of this study suggest that the cardiac safety of available antidepressants is comparable and there are no large differences in their potential to cause sudden cardiac death or ventricular arrhythmia.


Drug Trade Names: bupropion—Wellbutrin; mirtazapine—Remeron; nefazodone—Serzone; paroxetine—Paxil; trazodone—Desyrel; venlafaxine—Effexor

*See Reference Guide.
Contraception in Women with Schizophrenia

Lifetime rates of unwanted pregnancies and sexually transmitted diseases (STDs) are higher than population norms among women with serious persistent mental illnesses including schizophrenia. However, rates of contraceptive use in this population are low, in part because patients may believe themselves infertile when menstrual periods are absent or irregular because of antipsychotic-induced hyperprolactinemia. In addition, medication compliance may be particularly problematic for patients with schizophrenia. Comprehensive care for these patients should include contraceptive counseling.

Because they require little attention, long-lasting contraceptive methods, particularly intrauterine devices, have been recommended as the best option for women with chronic illness. Other longer-term options include depot progesterone injections and tubal ligation. Women should be reminded that none of these methods provide STD protection. The patient’s competence to understand and consent to tubal ligation must be ensured before surgical intervention is recommended.

Traditional oral contraceptives are effective, but compliance can be challenging. They also have clinically important interactions with many drugs used in psychiatry including antiepileptics and several antipsychotics. In some cases, contraceptive efficacy is reduced. In others, competing cytochrome P450 metabolism can lead to reduced effectiveness of psychiatric medication. Women with schizophrenia who smoke, are overweight, or have diabetes, migraine, cardiovascular disease, or a family history of breast cancer should not be offered oral hormonal contraceptives as risks of thrombosis, other adverse cardiac events, and possibly breast cancer are increased.

Hormonal contraception is also available in skin patches; transdermal gels and sprays; subdermal implants; and vaginal rings. These formulations bypass the liver and do not cause drug interactions via CYP450 metabolism. Female barrier methods (e.g., cervical caps) and natural family planning may be difficult for women with schizophrenia to manage.

Although contraceptive counseling may seem to be outside the typical role of the psychiatrist, many women with serious mental illness do not have a family physician, and unintended pregnancies can have negative effects on the mental and physical health of women with psychiatric illness. Contraceptive options should be revisited periodically, and partners should be included in the discussions.

Seeman M, Ross R: Prescribing contraceptives for women with schizophrenia. *Journal of Psychiatric Practice* 2011;17 (July):258–269. From The University of Toronto, Ont., Canada. Source of funding not stated. The authors declared no conflicts of interest.

Adjunctive Risperidone for PTSD

Risperidone (*Risperdal*), added to ongoing pharmacotherapy, did not reduce posttraumatic stress disorder symptoms in a controlled trial in military veterans.

Background: SRI antidepressants are indicated for treatment of PTSD, but not all patients benefit, and the agents appear to be less effective in men than in women and in chronic vs acute PTSD. In the Veterans Affairs (VA) health system, second-generation antipsychotics are often prescribed for resistant symptoms despite limited evidence of efficacy and concerns about weight gain and other adverse effects.

Methods: Study subjects (n=267; mean age, 54 years; 97% male) were veterans with service-related chronic PTSD that had not responded to ≥2 adequate SRI trials. The majority of
patients also met diagnostic criteria for major-depressive (70%) and substance-abuse disorders (63%) and were receiving services such as mental health treatment, counseling, and case management from the VA. At enrollment, patients were highly symptomatic with mean Montgomery Asberg Depression Rating Scale scores of 23 and mean Clinician-Administered PTSD Scale (CAPS) scores of 78 despite receiving an average of 3 medications. Participants were randomly assigned to double-blind treatment for 6 months with either risperidone, flexibly dosed to a maximum of 4 mg/day, or placebo. The primary outcome measure was the CAPS.

Results: Adjunctive risperidone had no effect on the primary outcome measure. Symptom scores decreased from randomization to 24-week follow-up in both groups. Remission (CAPS score of <20) occurred in 5% of the placebo group and 4% of the risperidone group. Risperidone was associated with statistically significant reductions in the CAPS subscales of reexperiencing and hyperarousal, but the changes were too small to be clinically significant. Risperidone was not superior to placebo for any of the secondary study outcomes, including quality of life, depression symptoms, and anxiety.


SSRIs Safe in Pregnancy?

Data on major congenital anomalies in offspring exposed in utero to SSRIs is conflicting. According to results of a large Finnish retrospective cohort study, use of fluoxetine or paroxetine during early pregnancy is associated with an increased risk of cardiac anomalies and citalopram use is associated with neural tube defects.

Methods: Using linked national registries of births, congenital anomalies, and drug reimbursement, >635,000 women who gave birth or terminated a pregnancy because of severe fetal anomalies between 1996 and 2006 were identified. Congenital anomalies were compared between 6976 offspring exposed to an SSRI during the first trimester (6902 live births, 30 stillbirths, and 44 terminated pregnancies) and >623,000 unexposed offspring.

Results: After adjustment for maternal factors, such as age, parity, comorbid conditions, and others, major congenital anomalies overall were not more common in SSRI-exposed offspring than in unexposed offspring (odds ratio* [OR], 1.08; confidence interval,* 0.96–1.22). However, analysis of specific defects with individual agents found associations between fluoxetine and isolated ventricular septal defects (adjusted OR, 2.03; confidence interval, 1.28–3.21). Paroxetine was associated with right ventricular outflow tract defects (adjusted OR, 4.68; confidence interval, 1.48–14.74). This finding was based on only 3 cases, but it is in line with previous study results. Citalopram use was associated with neural tube defects (adjusted OR, 2.46; confidence interval, 1.20–5.07).

Conclusion: In this large cohort, nearly 5 times as many infants were exposed to citalopram, fluoxetine, and paroxetine as to other SSRIs combined. The lesser used agents, escitalopram, sertraline, and fluvoxamine, were not associated with any specific pattern of congenital anomalies.

Malm H, Artama M, Gissler M, Ritvanen A: Selective serotonin reuptake inhibitors and risk for major congenital anomalies. *Obstetrics & Gynecology* 2011;118 (July):111–120. From Helsinki University Central Hospital, Finland; and other institutions. Funded by the Social Insurance Institution of Finland; and other sources. The authors disclosed no competing interests.

Drug Trade Names: citalopram—Celexa; escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox; paroxetine—Paxil; sertraline—Zoloft

*See Reference Guide.
Antidepressant Risks in the Elderly

A large population-based cohort study of antidepressant use in elderly patients found significant associations between treatment and several adverse events. TCAs appeared to be the safest agents.

Methods: Using data from a large primary care database in the U.K., >60,000 patients were identified who received a diagnosis of depression after the age of 65 years and were treated with antidepressant therapy. Data on adverse outcomes was extracted from the patient records, and hazard ratios* were calculated for specific outcomes including all-cause mortality; attempted suicide/self harm; myocardial infarction (MI); stroke/transient ischemic attack (TIA); falls; fractures; epilepsy/seizures; and hyponatremia.

Results: The mean patient age at cohort entry was 75 years, and participants were followed for an average of 5 years; two-thirds of the patients were female. SSRIs were the most commonly prescribed antidepressants, accounting for 55% of medication use. TCAs were used by 32% of patients, and because their percentage was low (14%) patients using an agent from any other class were combined into an "other" category. Many patients had concomitant medical conditions and received other medications.

After adjustment for age, gender, depression severity, and a range of other potentially confounding factors, both SSRIs and "other" antidepressants were significantly more likely than TCAs to cause adverse outcomes. SSRIs were associated with the greatest risk for MI, falls, and hyponatremia. Risks for all-cause mortality, suicide attempts/self-harm, stroke/TIA, fracture, and seizures were greater with "other" antidepressant. TCAs did not have the greatest hazard ratio for any outcome of interest. In a direct comparison of SSRIs and TCAs, SSRIs were associated with significantly higher rates of all outcomes except suicide attempt/self harm. Rates of mortality, falls, and seizures appeared to be dose-related.

Analysis of individual agents found that trazodone was associated with the highest risk for all-cause mortality and mirtazapine was associated with the highest risk for suicide attempt/self-harm. Risks for stroke/TIA, fracture, and seizures were greatest with venlafaxine. Among the SSRIs, citalopram, escitalopram, and fluoxetine were associated with significantly increased risk of hyponatremia, but paroxetine and sertraline were not.
**Discussion:** These results suggest that TCAs may be the best treatment option for depression in elderly patients. However, because of the observational nature of the study, patient characteristics that lead to prescribing of a specific drug (i.e., confounding by indication) could exist, and the results need to be confirmed in additional studies.


**Drug Trade Names:**
- citalopram—Celexa
- escitalopram—Lexapro
- fluoxetine—Prozac
- mirtazapine—Remeron
- paroxetine—Paxil
- sertraline—Zoloft
- trazodone—Desyrel, and others
- venlafaxine—Effexor

---

**Reference Guide**

**Confidence Interval:** The range in which the value of a variable in question is likely to fall, usually calculated at 95%. Confidence intervals indicate the reliability of an estimate, and a very wide interval may indicate that more data should be collected before making definite conclusions.

**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.

---

**Need CME Credits?**

As a subscriber, you can earn AMA PRA Category 1 Credits™ by reading PSYCHIATRY DRUG ALERTS and completing self-assessment exams.

Exam # 29 covering the first 6 issues of 2011 was recently released.*

It's not too late to get your copy!

For more information or to enroll, call us at 973-898-1200 or visit www.alertpubs.com.

*M.J. Powers & Co Publishers designates this enduring material for a maximum of 12 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.