Desipramine Safety Update

New safety information has been added to the prescribing information for desipramine (Norpramin). The updated label now states "extreme caution should be used when this drug is given to patients who have a family history of sudden death, cardiac dysrhythmias, and cardiac conduction disturbances; and that seizures precede cardiac dysrhythmias and death in some patients." The label also warns that rates of death associated with desipramine overdose are higher than those of other tricyclic antidepressants. Additional information has been added to help identify and manage overdose.

FDA MedWatch Alert: Available at www.fda.gov/MedWatch.

Antipsychotics and Pregnancy Outcome

In a population-based study, antipsychotic drug exposure during gestation did not appear to adversely affect fetal growth, but the rate of preterm births was increased with typical antipsychotic use.¹

Methods: All medical claims from Taiwan’s national health insurance program and all birth certificates issued between 2001 and 2003 comprised the dataset for the study. The study matched each of 696 mothers with a confirmed diagnosis of schizophrenia with 5 control mothers for age, year of delivery, hypertension, and diabetes. The mothers with schizophrenia included 190 who received monotherapy with a typical antipsychotic for more than 30 days during gestation, 46 treated with an atypical agent, and 454 who were not treated with an antipsychotic. The analysis took into account the potentially confounding variables of infant gender and parity, as well as maternal and paternal age, marital status, education, and income.

Results: The risk of preterm delivery was significantly increased in women with schizophrenia who used a typical antipsychotic during pregnancy. Compared with the control group, the adjusted odds ratio* for preterm birth was 2.46 (p<0.001). The rate was also higher than in women who took atypical agents (18% vs 12.5%). Rates of all low birth weights and of infants...
who were small or large for gestational age were not increased significantly in women who used typical agents. Atypical antipsychotics were not associated with increased rates of any poor outcome, compared to rates in unmedicated women. Rates of all of these adverse outcomes were lower in the control subjects than in the unmedicated schizophrenic women, although not all differences were statistically significant.

**Discussion:** These results confirm that maternal schizophrenia increases the risk of adverse pregnancy outcomes, and suggest the use of antipsychotic medication confers little additional risk. The rationale for the high rate of typical antipsychotic use in these pregnant women is unclear. One reason may be concern about the effects of atypical agents on maternal weight and glucose tolerance. A previous report suggesting these agents might result in large-for-gestational-age infants was not supported by the present results.

**Editor's Note:** Previous reports show fetal risks vary among the atypical antipsychotics. Olanzapine, which is associated with the greatest rate of medication transfer to the fetus, may be less safe than other atypicals particularly in terms of low birth weight risk. In the present study, 13 of 46 women (28%) exposed to atypicals during pregnancy received olanzapine; other atypicals included clozapine (n=5), quetiapine (n=7) zotepine (n=5), and risperidone (n=16). Outcomes were evaluated by antipsychotic class only and not with individual agents.

---

1. Lin H-C, et al: Maternal schizophrenia and pregnancy outcome: does the use of antipsychotics make a difference? *Schizophrenia Research* 2010;16:55–60. From Taipei Medical University, Taiwan, and other institutions. The study was conducted with no external funding. The authors declare they have no conflicts of interest.


**Drug Trade Names:** clozapine—*Clozaril*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*; zotepine (not available in the U.S.)—*Nipolept, and others*

*Reference Guide Item.

---

**Antiepileptic Drugs, Suicide Attempts Unrelated?**

A pharmacoepidemiologic study found no evidence that antiepileptic drugs increased the rate of suicide attempts in patients with bipolar disorder.1

**Methods:** Nearly 48,000 patients diagnosed with bipolar disorder between 2000 and 2006 were identified from a managed care claims database. The frequency of suicide attempts (identified by ICD codes in medical claims) in the year following diagnosis was compared in nearly 14,000 patients prescribed antiepileptic monotherapy, about 2,500 receiving lithium monotherapy, and a comparison group of more than 25,000 not prescribed these drugs (nearly half of whom received no CNS medication). Suicide attempt rates were also compared in each patient in the year before and at least 1 year after diagnosis. Information on the lethality of suicide attempts was not available.

**Results:** There were no differences in the rates of suicide attempts between patients prescribed an antiepileptic and those prescribed lithium or the comparison group. Rates were 13/1000 patient-years in patients who did and did not receive antiepileptics. Probably reflecting the natural course of bipolar disorder, the frequency of suicide attempts in antiepileptic-treated patients was significantly higher before the diagnosis (72/1000 patient-years) than in the post-diagnosis year (13/1000 patient-years). The pretreatment rate of suicide attempts was 5 times higher in patients who eventually received an antiepileptic drug than in those who received no medication, suggesting these agents may be used in more severely impaired patients.
Discussion: The finding of a large post-treatment reduction in suicide attempts suggests antiepileptic drugs may have a protective effect against suicide, a finding which has been previously reported for these agents and for lithium. However, this observation conflicts with a recent FDA report based on a meta-analysis of clinical trials that found a significant increase in suicidality in patients receiving antiepileptics.\(^2\) The difference may be explained by the FDA’s use of a broader patient population (including those taking anticonvulsants for pain or epilepsy) and the inclusion of suicidal ideation and behavior among their outcomes.

\(^1\)Gibbons R, Hur K, Brown C, Mann J: Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. Archives of General Psychiatry 2009;66 (December):1354–1360. From the University of Illinois at Chicago; and other institutions. Funded by the NIMH; and the Agency for Healthcare Research and Quality. The study authors disclosed commercial relationships that might pose conflicts of interest.


**Antipsychotic Mortality in Nursing Homes**

Conventional and atypical antipsychotics have been associated with increased mortality in patients with dementia, and the FDA has issued public health warnings about the risks. However, evidence for comparative safety of the classes has been mixed. In addition, most studies have evaluated only outpatients and none compared specific agents.

**Methods:** An observational study was undertaken that included 9729 nursing home residents in Italy who were treated with an antipsychotic for dementia. Patients were aged ≥65 years and those with schizophrenia or taking multiple antipsychotics were excluded. A total of 6524 patients received an atypical antipsychotic, mainly risperidone (n=4406) and olanzapine (n=1563); and 3205 received a conventional agent, most commonly haloperidol (n=1413) or a phenothiazine (n=546). Death in the 6 months following the initial prescription was the outcome of interest.

**Results:** Within 6 months of beginning antipsychotic therapy, 1907 patients died. After adjustment for confounding factors such as comorbid conditions and concomitant medications, the rate of death was higher with conventional agents than atypicals (hazard ratio,\(^*\) 1.26). Compared with risperidone, the most commonly used atypical, the adjusted hazard ratios for death were 1.31 for haloperidol, 1.17 for phenothiazines, and 1.32 for other conventional agents. No atypical agent differed significantly from risperidone.


*Drug Trade Names:* haloperidol—*Haldol*; risperidone—*Risperdal*; olanzapine—*Zyprexa*

*Reference Guide Item.*

**Depot Olanzapine Prevented Relapse**

Patients with schizophrenia who achieved stability with oral olanzapine (*Zyprexa*) maintained their stability for 6 months after switching to long-acting injectable olanzapine (*Zyprexa, IM*). Both 2- and 4-week injection intervals were effective. Although rare, a postinjection delirium/sedation syndrome is possible and the authors suggest patients be monitored for the reaction for 3 hours after each injection.

**Methods:** Outpatients aged 18–75 years were switched from a previous antipsychotic to 10–20 mg/day oral olanzapine for 4–8 weeks. Patients who were judged stable with oral olanzapine were then randomized to 24 weeks of continued oral medication or switched to
long-acting intramuscular injections. Patients received their optimized oral dose (n=322), or injection doses considered very low (45 mg every 4 weeks; n=144), low (150 mg every 2 weeks; n=140), medium (405 mg every 4 weeks; n=318), or high (300 mg every 2 weeks; n=141). All patients received double-blind active or dummy oral tablets daily and active or dummy injections biweekly. Time to exacerbation of psychosis was the primary outcome.

**Results:** By study end, 7% of patients who received oral olanzapine had an exacerbation of psychotic symptoms, compared with 5–10% of the medium- and high-dose depot groups, 16% of the low-dose group, and 31% of the very-low dose group. With the exception of the very-low dose group, differences between the injectable dosage groups were not statistically significant. The injection interval (i.e., 2 or 4 weeks) did not appear to affect stability of symptoms. Patients in all groups except the very-low dose injections had mean Positive and Negative Syndrome Scale (PANSS) scores in the mid 50s, indicating adequate symptom control at 24 weeks.

Local reactions at the injection site were the only adverse effects more common with the injectable olanzapine formulation. Excessive sedation and delirium consistent with olanzapine overdose developed in 2 patients after possible inadvertent intravascular injection. Both were hospitalized for management and recovered fully. Other local site reactions (e.g., pain, swelling) occurred in 3% of patients. Metabolic effects of the oral and depot formulas appeared to be similar and were consistent with the known effects of olanzapine.

**Study Limitations:** The selection of patients who had already responded to oral olanzapine may have introduced a bias in favor of the oral formulation and could have reduced the adherence-related advantages of the depot formulation. Also, these highly selected patients may differ from those for whom depot medication is typically prescribed.

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


*Reference Guide Item.

## Bromocriptine for Hyperprolactinemia

The dopamine-receptor agonist bromocriptine is established as a treatment for hyperprolactinemia in women, but there have been concerns that it can worsen underlying psychiatric symptoms in patients with antipsychotic-associated hyperprolactinemia.

**Methods:** Women aged <45 years with schizophrenia who had drug-induced hyperprolactinemia (prolactin level >25 ng/mL) and amenorrhea were enrolled in the single-blind multicenter placebo controlled bromocriptine trial. All had been receiving antipsychotics (atypicals, 21 patients) for >1 year and psychotic symptoms were controlled. The 60 participants received randomized placebo or bromocriptine at 2.5, 5, or 10 mg/day for 8 weeks. Antipsychotic dosage adjustments were not permitted. Prolactin and other hormone levels were measured at baseline and after 4 and 8 weeks of treatment.

**Results:** Mean baseline prolactin levels ranged from 94–148 ng/mL. Compared with placebo, bromocriptine significantly reduced serum prolactin at 4 weeks, but levels remained well above the cutoff for hyperprolactinemia (90–100 ng/mL) and did not differ by 8 weeks. There were no significant differences in prolactin changes among the bromocriptine dosages.
Six of the 45 women who received bromocriptine resumed menses. Other hormone levels (e.g., follicle-stimulating hormone, estrogen) were not significantly changed during the study.

Psychiatric symptoms did not worsen in any treatment group. Moreover, there was a significant trend toward decreasing total Positive and Negative Syndrome Scale scores with all treatments. Adverse effects of bromocriptine included nausea (n=7), vomiting (n=5), and postural hypotension (n=2).

**Discussion:** Animal studies suggest that at low doses (2.5 and 5 mg) bromocriptine increases dopamine levels, while a higher dose (10 mg) decreases dopamine. Given that the mechanism of action appears to be dose-related, establishing the dose-response effect in humans is important to proper prescribing. These results suggest that regardless of the dose bromocriptine reduces, but does not normalize, prolactin levels without worsening psychosis.

**Study Rating*—13 (76%):** This study met many of the criteria for a randomized controlled trial, but medication administration was single-blind and the source of funding was not stated.


**Drug Trade Names:** bromocriptine—Cycloset, Parlodel

---

**Racial Differences in Ziprasidone Efficacy?**

Medication response can differ in racial and ethnic patient subgroups and studies have indicated differences in treatment outcomes. These variations may be based on genetic differences, environmental or dietary factors, or physician prescribing practices. Although research has suggested black patients may respond to older antipsychotics and antidepressants differently than other racial groups, there has been little study of differential atypical antipsychotic efficacy.

**Methods:** In a manufacturer-sponsored study, data were pooled from 4 short-term placebo-controlled trials of ziprasidone in schizophrenia and schizoaffective disorder. Patients (n=975) were aged ≥18 years, had an illness duration of ≥6 months, and had been hospitalized within the month prior to study entry. After a washout, participants were randomized to fixed-dose ziprasidone in the range of 40–200 mg/day depending on the study, or placebo for 4–6 weeks. One study included haloperidol as an active comparator. Patient ethnicity was self-reported, and ziprasidone efficacy and tolerability was compared in the self-reported black, white, and overall patient groups. Most but not all self-reported black patients were African American. Symptoms were measured using the Positive and Negative Syndrome Scale, the Brief Psychiatric Rating Scale, and other validated instruments.

**Results:** The majority of patients were white (65%), followed by black (25%) and other (10%). Comparisons across self-reported racial groups found no significant differences in improvement. The frequency of adverse events was similar in all racial groups as were rates of most individual events. Compared with baseline, self-reported black patients experienced a small but significant increase in movement disorder symptoms, but this did not differ significantly from that seen in the white or overall populations. No trends by racial group were seen in medication discontinuation.

**Discussion:** These results suggest self-reported black race has little impact on efficacy or tolerability of ziprasidone in patients with schizophrenia or schizoaffective disorder. Because
the analyses were post-hoc and racial groups were not evaluated in the individual studies, these results are preliminary and they cannot be generalized to other atypical antipsychotics.


*Drug Trade Names*: haloperidol—*Haldol*; ziprasidone—*Geodon*

### Levetiracetam Not Effective in Social Anxiety Disorder

Based on preliminary evidence suggesting levetiracetam (*Keppra*) might be an effective adjunctive treatment for anxiety disorders including PTSD and generalized anxiety disorder, a multicenter controlled trial was undertaken in social anxiety disorder.

**Methods:** Medically healthy outpatients aged 18–40 years with moderate-to-severe social anxiety disorder were recruited at 20 U.S. treatment centers. Patients with ≥2 failed medication trials for social anxiety disorder and those receiving psychotropic therapy in the week before study entry were excluded. After a 1-week placebo lead-in, participants received randomly assigned double-blind levetiracetam (n=111) or placebo (n=106) for 12 weeks. Levetiracetam was flexibly dosed in the range of 500–1500 mg b.i.d. The primary outcome measure was the Liebowitz Social Anxiety Scale (LSAS).

**Results:** Mean baseline LSAS scores were 91 in the levetiracetam group and 93 in the placebo group. At 12 weeks scores decreased to 66 and 62, respectively. Response and remission rates (based on LSAS score changes and maximum scores) did not differ between the groups. Less than 50% of patients responded to either treatment and less than 20% remitted.

**Discussion:** Levetiracetam is approved for adjunctive treatment of partial onset, myoclonic, and generalized tonic-clonic seizures. Based on these results, it can not be considered an effective monotherapy for social anxiety disorder, but its usefulness as an adjunctive treatment can not be ruled out.

**Study Rating**—16 (94%): This study met all criteria for a controlled trial except that potential limitations were not discussed.

Stein M, Ravindran L, Simon N, Liebowitz M, et al: Levetiracetam in generalized social anxiety disorder: a double-blind, randomized controlled trial. *Journal of Clinical Psychiatry*. Published online December 15, 2009 at www.psychiatrist.com; doi 10.4088/JCP.08m04949gre. From the University of California, San Diego; and other institutions. **Funded by UCB Pharma, the manufacturer of Keppra. The study authors disclosed commercial relationships with UCB Pharma and other sources that might pose conflicts of interest.**

*Reference Guide Item.*

### Targeted Pharmacotherapy in Borderline Personality Disorder

A previously published meta-analysis examined medication classes in patients with borderline personality disorder and found antipsychotics, mood stabilizers, and antidepressants to be effective for specifically targeted symptoms.¹ The present analysis examines individual agents.²

**Methods:** Twenty-seven randomized pharmacotherapy trials judged by Cochrane standards to be of acceptable quality were included in a meta-analysis. Study samples ranged from 16 to 314 patients (total population, 1714) and durations ranged from approximately 1 to 6 months. Outcomes were overall severity of borderline personality disorder and of the following symptoms clusters: affective dysregulation; cognitive-perceptual symptoms; impulsive-behavioral dyscontrol; and interpersonal problems.
Results: In placebo comparisons, at least 1 active medication was superior for each symptom domain. Anger, a primary symptom of affective dysregulation, was significantly improved with haloperidol, aripiprazole, olanzapine, divalproex, and lamotrigine. Other affective symptoms (e.g., associated anxiety and depression, affective instability) improved with aripiprazole, olanzapine, divalproex, and amitriptyline. Cognitive-perceptual symptoms were improved with aripiprazole and olanzapine. Impulsive-behavioral dyscontrol was improved with aripiprazole, lamotrigine, and topiramate. Flupenthixol reduced suicidal behavior. Interpersonal problems responded to aripiprazole, divalproex, and topiramate. Omega-3 fatty acids improved suicidality (impulsive-behavioral dyscontrol) and depression (affective dysregulation). In general antidepressants were not helpful.

No improvements with any medication were noted in several core borderline personality disorder symptoms. These include avoidance of abandonment, chronic emptiness, identity disturbance, and dissociation. These may be more amenable to psychotherapeutic treatment.

Discussion: The American Psychiatric Association practice guidelines recommend SSRIs for affective dysregulation and low-dose antipsychotics for cognitive-perceptual symptoms.3 These guidelines are over 5 years old and in accordance with national standards, including those of the Agency for Healthcare Research and Quality’s National Guideline Clearinghouse, can no longer be assumed to be current. Findings of newer research and this meta-analysis suggest mood stabilizers or antipsychotics rather than SSRIs should be used to treat affective dysregulation in borderline personality disorder. Antipsychotics still appear to be warranted for treatment of cognitive-perceptual symptoms. Impulsive-behavioral dyscontrol should be addressed with a mood stabilizer.

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


Drug Trade Names: amitriptyline—Elavil; and others; aripiprazole—Abilify; divalproex—Depakote; fluoxetine—Prozac; flupenthixol (not available in the U.S.)—Depixol, Fluanxol; haloperidol—Haldol; lamotrigine—Lamictal; olanzapine—Zyprexa; phenelzine—Nardil; topiramate—Topamax

*Reference Guide Item.

Quetiapine Improved Executive Function

In 41 adults (34 females) with borderline personality disorder, quetiapine (Seroquel) was associated with improvement on tests of executive function during a 12-week open-label manufacturer-sponsored trial.

Twenty patients were receiving antidepressants at the start of treatment and continued them during quetiapine administration. Two-thirds experienced sedation at some point during the trial, but none reported feeling sedated during neurocognitive testing conducted at baseline and at study end. After treatment completion, patients showed significant improvement in attention and mental flexibility, better scores on a test of verbal fluency, and better mental accuracy, efficiency, and planning. Executive function is one of several impaired neurocognitive domains in borderline personality disorder. Studies of quetiapine in other psychiatric
disorders have shown mixed effects on neurocognition. The average dose, 413 mg/day, was somewhat lower than that used in bipolar disorder and schizophrenia.

Van den Eynde F, De Saedeleer S, Naudts K, Day J, et al: Quetiapine treatment and improved cognitive functioning in borderline personality disorder. *Human Psychopharmacology: Clinical and Experimental* 2009;24 (December):646–649. From University Hospital Ghent, Belgium; and other institutions. Funded by AstraZeneca, manufacturer of Seroquel. Despite clear author instructions regarding explicit statements of potential conflicts of interest, the authors did not include disclosure of potential conflicts.

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.

**Risk Ratio:** 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 (nonexposed) 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.

SPECIAL OFFER

As a subscriber, you are eligible to receive a 1-year companion subscription to **PSYCHIATRY ALERTS NOS** for $74.00—that’s $15 off the regular price.

Call Us Today at 1-800-875-0058
to Take Advantage of the Introductory Companion Price.