Antidepressants and Breastfeeding

According to a literature review, concentrations of second-generation antidepressants vary in breastfed infants. Because they produce the lowest infant concentrations, paroxetine and sertraline may be the safest options for women who require antidepressant therapy while breastfeeding.

Postpartum depression is believed to develop in 10–15% of women after childbirth. SSRIs are first-line treatment for postpartum depression but their safety in breastfeeding has been questioned. In breastfed infants, antidepressant concentrations generally parallel maternal levels. Infant doses can be estimated based on the milk/plasma concentration ratio and the maternal dose; relative doses of <10% of the maternal dose are considered negligible. Previous reviews included literature published through 2008. The current review included newer data, and in light of the fact that TCA use has decreased in the last decade, it focused on SSRIs and other newer antidepressants.

Overall, infant exposure to antidepressants via breast milk was found to be low, suggesting that antidepressants need not be avoided in postpartum depression, particularly in women who required medication before or during pregnancy. Based on relative infant doses and plasma concentrations, paroxetine and sertraline appear to be the best choices as first-line therapy. (See table, next page.) However, the potential risk of fetal cardiac defects with intrauterine exposure should be considered before prescribing paroxetine to women likely to become pregnant. Fluoxetine and citalopram appear to be present in breastfed infants at higher relative concentrations. Moreover, these agents have been suspected of causing subtle and nonspecific adverse effects in the infants and should be reserved for second-line therapy or for women already treated with the drug before or during pregnancy. Venlafaxine appears to produce the highest relative infant doses and plasma concentrations. The other studied antidepressants were either not detected in breast milk (i.e., bupropion, fluvoxamine, duloxetine) or detected at very low concentrations (i.e., escitalopram, reboxetine, mirtazapine), but the small numbers of mother/infant pairs evaluated make those findings less certain.
When treating postpartum depression, the risks for the infant of untreated maternal depression must be weighed against the risks of antidepressant exposure. These results, as well as those of the previously published reviews, support new or continued antidepressant use in postpartum depression, although psychotherapy and other nonpharmacological therapies may be useful for moderate symptoms. These results provide additional support for paroxetine and sertraline as first-choice therapy. The authors note that because of the long half lives of antidepressants, timing maternal dosing around infant feeding and pumping and discarding milk near maternal peak concentration have little value as a means to reduce infant exposure.

Berle J, Spigset O: Antidepressant use during breastfeeding. Current Women’s Health Reviews 2011;7:28–34. From Haukeland University Hospital, Bergen, Norway; and other institutions. Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.

**Drug Trade Names:** bupropion—Wellbutrin; citalopram—Celexa; duloxetine—Cymbalta; escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox; mirtazapine—Remeron; paroxetine—Paxil; reboxetine (not available in the U.S.)—Edronax, Vestra; sertraline—Zoloft; venlafaxine—Effexor

### Adjunctive Lamotrigine for OCD

In a placebo-controlled trial, adjunctive lamotrigine (*Lamictal*) was effective in patients with obsessive-compulsive disorder resistant to SRI therapy.

**Methods:** Study participants (n=40; 16 males) met DSM-IV-TR criteria for OCD and demonstrated persistent symptoms, with a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of ≥16, despite at least 12 weeks of SRI therapy. Mean ages were 34 and 39 years in the lamotrigine and placebo groups, respectively. Background SRIs included fluvoxamine (n=9), fluoxetine (n=7), sertraline (n=9), citalopram (n=6), and paroxetine (n=9); mean treatment durations were 16–18 weeks. Active adjunctive treatment consisted of 16 weeks of double-blind fixed-dose lamotrigine, increased weekly in 25-mg/day increments, to a maximum of 100 mg/day, or placebo. Response was defined as a >25% decrease in Y-BOCS score.

**Results:** Of the 40 patients enrolled, 33 completed the study. Three in the lamotrigine group dropped out, including 1 with a drug-related skin rash; and 4 discontinued in the placebo group, including 2 who were withdrawn for lack of efficacy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate Number of Mother/Infant Pairs Studied</th>
<th>Relative Infant Dose (%)</th>
<th>Relative Infant Plasma Concentrations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>119</td>
<td>0.5–3</td>
<td>Not detected</td>
</tr>
<tr>
<td>Sertraline</td>
<td>145</td>
<td>0.5–3</td>
<td>Not detected</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>149</td>
<td>&lt;12</td>
<td>Up to 80</td>
</tr>
<tr>
<td>Citalopram</td>
<td>80</td>
<td>3–10</td>
<td>Up to 10</td>
</tr>
<tr>
<td>Bupropion</td>
<td>20</td>
<td>2</td>
<td>Not detected</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>12</td>
<td>&lt;2</td>
<td>Not detected</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>6</td>
<td>&lt;1</td>
<td>Not detected</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>12</td>
<td>3–6</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>4</td>
<td>1–3</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>11</td>
<td>0.5–3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>23</td>
<td>6–9</td>
<td>Up to 30</td>
</tr>
</tbody>
</table>
Adjunctive lamotrigine reduced Y-BOCS total scores from 27 to 18, while scores in the placebo group increased very slightly (p=0.003). Both obsessions and compulsions were significantly improved with lamotrigine compared with placebo (p=0.004 and p<0.0001, respectively). Hamilton Rating Scale for Depression scores were also improved with lamotrigine, but the difference was not significant compared with placebo. A total of 17 lamotrigine-treated patients (85% of patients randomized to the drug; 100% of those who completed treatment) met criteria for response. Of these, 10 (50%) had a partial response (25–34% improvement) and 7 had full response (≥35% improvement). No patient in the placebo group met response criteria.

Discussion: About half of patients with OCD do not respond to first-line treatment with SRIs. Evidence supports the efficacy of adjunctive therapy with several second-generation antipsychotics and some anticonvulsants. Lamotrigine has been the subject of few previous investigations in OCD, and results have been conflicting. It has been associated with less cognitive dysfunction than other anticonvulsants. The present study suggests lamotrigine augmentation may be a valid strategy in SRI-resistant OCD. However, the results should be considered preliminary due to the study’s small sample size and short duration.

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

Bruno A, Mico U, Pandolfo G, Mallamace D, et al: Lamotrigine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. Journal of Psychopharmacology 2012; doi 10.1177/0269881111431751. From the University of Messina, Italy; and other institutions. This study was conducted without funding. The authors declared no conflicts of interest.

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

*See Reference Guide.

More Support for Ketamine in Depression

In a randomized controlled trial in a group of patients with treatment-resistant major depression, a single dose of ketamine improved depressive symptoms over the course of 4 weeks. However, following the ketamine infusion with oral riluzole did not enhance outcomes.

Background: The N-methyl-D-aspartate antagonist ketamine has been shown to have rapid antidepressant effects in patients with treatment-resistant major depression. The effects have been reported to last for about 1 week. The present study was undertaken to assess the extent and course of improvement with ketamine and to determine if riluzole, another glutamatergic modulator, could potentiate the antidepressant effects of ketamine.

Methods: Study subjects were 42 inpatients (mean age, 47 years) with treatment-resistant depression. All patients had undergone unsuccessful treatment with ≥2 previous antidepressant trials and had a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥22 despite >4 weeks of current adequate treatment. Following a 2-week medication-free period, all participants received an open-label infusion of 0.5 mg/kg ketamine over 40 minutes. Several hours after the infusion, they were randomized to receive double-blind placebo or 100–200 mg/day riluzole for 4 weeks. Depression was rated 40, 80, 120, and 230 minutes after ketamine infusion, and then daily for the 28 days of randomized treatment.

Results: The hypothesis that riluzole would potentiate ketamine response was not supported by the study results. There was not a significant difference between the riluzole and placebo groups at any time point. However, all patients experienced a statistically significant improvement in depressive symptoms following the ketamine infusion. Throughout randomized treatment, mean MADRS scores were significantly lower than baseline values in both treatment groups (from 33 to 20 at day 1, to 22 at day 7, and to 26 at day 28; p<0.001). Hamilton Rating
Scale for Depression scores followed a similar pattern with a reduction from 21 at baseline to 12–13 at days 1 and 7, and to 16 at day 28 (p<0.001). Effect sizes* ranged from 1.02 on day 2 to 0.46 on day 28. Treatment response (≥50% improvement in MADRS score) was seen within 230 minutes of the infusion in 17 patients (40%). For the majority of patients, response persisted for <1 week. (See table.) Perceptual disturbances, drowsiness, confusion, BP and pulse elevations, and dizziness occurred with the ketamine infusion, but all resolved within 80 minutes.

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

1 Ibrahim L, DiazGranados N, Franco-Chaves J, Brutsche N, et al: Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology* 2012; doi 10.1038/npp.2011.338. From the NIMH; and other institutions. **Funded by the NIMH. The authors disclosed no competing interests.**


**Drug Trade Names:** ketamine—*Ketalar*; riluzole—*Rilutek*

*See Reference Guide.

### CYP Inhibitor Improved Schizophrenia Response

A 50-year-old woman with a 20-year history of schizophrenia was admitted for an acute psychotic episode. She had been treated with quetiapine prior to admission, but her adherence was erratic. In addition to schizophrenia, the patient had a body mass index of >42 and impaired glucose tolerance, for which she was treated with 500 mg/day metformin. On admission, quetiapine treatment was reinstated for 7 days, but symptoms did not improve in spite of adequate serum levels. She was started on the atypical antipsychotic amisulpride (not available in the U.S.), but no substantial improvement occurred over 3 weeks. Phenotypic testing identified the patient as a CYP2D6 ultrarapid metabolizer, and a trial of haloperidol plus trazodone (to augment haloperidol-associated CYP2D6 inhibition) was added to her amisulpride; however, symptoms were not improved. A haloperidol dosage increase neither increased the serum level nor improved symptoms. Amisulpride and trazodone were stopped, and the atypical antipsychotic melperone (a butyrophenone; not available in the U.S.) was added to 30 mg/day haloperidol. After 14 days, the haloperidol plasma level increased and the patient was discharged with clear improvement.

**Editor’s Note:** Although some of the drugs used to treat this patient are not available in the U.S., the strategy of using 1 agent to inhibit or induce metabolic pathways of another agent could be a valid option for treatment-resistant schizophrenia. Most first-generation antipsychotics are metabolized via the CYP2D6 pathway, and ultrarapid metabolizers may not experience full effects of these medications. While the current case report has important limitations, including short durations between medication changes, it does suggest that augmenting a first-generation antipsychotic with an agent that inhibits CYP2D6 may be useful in resistant schizophrenia.


**Drug Trade Names:** amisulpride (not available in U.S.)—*Solian, Sulamid*; haloperidol—*Haldol*; melperone (not available in U.S.)—*Buronil, Burnil*; metformin—*Glucophage*; trazodone—*Desyrel*; quetiapine—*Seroquel*
Suicidal Behavior with Antidepressants: Longitudinal Data

Antidepressant treatment reduced suicidal thoughts and behavior in adults, largely as a consequence of resolution of depressive symptoms, according to a reanalysis of data from clinical trials of fluoxetine and venlafaxine. In children and adolescents, antidepressant use resulted in a large reduction in depression but had a neutral effect on suicide-related symptoms.

Methods: Investigators analyzed data from all available manufacturer-sponsored randomized controlled trials: 20 studies of fluoxetine (4 in youths, 12 in adults, and 4 in the elderly) and 21 adult studies of venlafaxine. A total of 9185 patients were included. This study expanded on the original FDA analyses of the same data in children and adolescents by including complete patient-level longitudinal data, which allowed a closer examination of the relationships among treatment, depression, and suicidal behavior. The data on adults and geriatric patients was not previously analyzed by the FDA.

For the present analysis, definitions of suicidal thoughts and behavior were based on single suicide items on the Hamilton Rating Scale for Depression (Item 3) in adults and the Children’s Depression Rating Scale-Revised (item 13) in youths. Depression was measured using these scales, excluding the item related to suicide. Adverse events of suicide and suicide attempts were also analyzed, but there were too few of these events (2 suicides and 20 attempts) to detect treatment-related differences.

Results: At baseline, rates of suicide risk (thoughts and behavior) were 20% in youths, 5% in adults, and 3% in geriatric patients. Among adults and older patients, rates of suicide risk were reduced by ≥50% over time in both the treated and placebo groups. Rates were lower in treated patients, but not strikingly so, beginning in the second week of treatment, and the rate of decline in suicidal risk was more rapid in treated patients than in controls. After 8 weeks, there was a 90% reduction in suicide risk in treated adults and a 79% decline in adults who received placebo. Most of the suicidal symptoms were of low severity—i.e., thoughts of death predominated over more severe ideation or behavior. In both treated and control adults, reduction in depression severity explained most of the decline in suicide risk. Results of analyses for fluoxetine and venlafaxine were similar, as were analyses in adult vs geriatric patients.

In children and adolescents, depression severity was associated with suicide risk. Depression responded to active treatment, however the effects of fluoxetine and placebo on suicide risk did not differ and were not mediated by antidepressant effects. Over 8 weeks, suicidal thoughts or behavior decreased 50% in treated youths and 61% in controls.

Discussion: These results clarify the relationship between antidepressant treatment and suicidal thoughts and behavior, particularly in adults and older adults. The findings suggest that adults whose depressive symptoms do not respond to treatment remain at higher risk for suicide, emphasizing the need to treat depression aggressively. In contrast, many youths may continue to have suicidal ideation and behavior after depressive symptoms are successfully treated. Other psychopathology, such as aggressive impulsive traits, may contribute to suicide risk in the young.


Drug Trade Names: fluoxetine—Prozac; venlafaxine—Effexor
Relative Risks of Antipsychotics in Nursing Homes

In elderly nursing home residents with behavioral disturbances of dementia, haloperidol was associated with a higher risk of death than other commonly used antipsychotics, according to a population-based cohort study. Mortality appeared to be dose related with all antipsychotics except quetiapine.

Methods: The study cohort was drawn from Medicare and Medicaid claims databases in 2001–2005 and consisted of >75,000 nursing home residents, aged ≥65 years (average ages, 82–84 years), who had a newly prescribed antipsychotic. Patients with a preexisting diagnosis of schizophrenia, bipolar disorder, or cancer were excluded. Mortality was compared among all antipsychotics prescribed with sufficient frequency to make reliable estimates: aripiprazole, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone. Risperidone, the most commonly prescribed agent, was used as the reference drug. The analysis compared deaths from circulatory, cerebrovascular, and respiratory diseases, as well as all-cause mortality within 180 days of the first antipsychotic prescription. Cancer deaths were excluded because of the potential use of antipsychotics to control nausea or augment pain medications in patients with cancer.

Results: Compared with risperidone, haloperidol was associated with a 2-fold greater mortality rate (hazard ratio [HR]* adjusted for other factors, 2.07). The effect of haloperidol was strongest during the first 40 days of treatment and subsided afterward, although it remained statistically significant. Quetiapine was associated with lower mortality (adjusted HR, 0.81), but the advantage lessened over time. No other drug differed significantly from risperidone. The increased mortality with haloperidol and decreased mortality with quetiapine were observed for all causes of death examined.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients Treated</th>
<th>Deaths</th>
<th>Unadjusted HR</th>
<th>HR Adjusted for High Dimensional Propensity Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>27,936</td>
<td>2434</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>5904</td>
<td>745</td>
<td>2.42</td>
<td>1.81</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1849</td>
<td>122</td>
<td>0.76</td>
<td>0.95</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>22,919</td>
<td>2104</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>15,776</td>
<td>1120</td>
<td>0.80</td>
<td>0.83</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1061</td>
<td>73</td>
<td>0.88</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Discussion: The FDA warns of increased mortality with antipsychotic drugs in older patients with dementia but does not distinguish among different agents. Antipsychotics are not approved for this indication but are likely to remain widely used, given the extent of behavior problems in patients with dementia and the lack of feasible alternatives. The present study underscores the importance of prescribing the lowest effective dose and monitoring patients
closely, especially in the period after the start of treatment. The study authors recommend against prescribing haloperidol in this patient population and suggest quetiapine may be the safest alternative, although this finding requires replication.

Huybrechts K, Gerhard T, Crystal S, Olfson M, et al: Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. British Medical Journal 2012; doi 10.1136/bmj.e977. From Brigham and Women’s Hospital and Harvard Medical School, Boston, Mass.; and other institutions. Funded by the Agency for Healthcare Research and Quality; and the NIMH. The study authors reported no conflicts of interest.

Drug Trade Names: aripiprazole—Abilify; haloperidol—Haldol, and others; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

*See Reference Guide.

Pseudopheochromocytoma with Clozapine

A 51-year-old female with hypertension and paranoid schizophrenia was started on clozapine after several failed trials of other psychotropics. Before starting clozapine, her blood pressure (BP) had been well controlled with 2.5 mg/day enalapril, but within several months control became suboptimal and the enalapril was increased to 10 mg/day. Clozapine partially improved her psychotic symptoms, and BP remained controlled for 8 years before she presented with worsening anxiety, weight loss, dizziness, and tachycardia. She was found to be in hypertensive crisis (BP reaching 250/120 mmHg), and urinary catecholamine levels were nearly double the upper limit of the normal range. Comprehensive evaluations ruled out pheochromocytoma (a catecholamine producing tumor of the sympathetic nervous system) and other causes for the hypertension and elevated catecholamine levels, and she received a diagnosis of clozapine-associated pseudopheochromocytoma. Clozapine withdrawal was advised, but because she had a history of poor response to other antipsychotics and her symptoms were at least partially responsive to clozapine, it was continued and her antihypertensive therapy was optimized. One year later, urinary catecholamines remained elevated but BP was controlled.

Clozapine can elevate plasma noradrenaline levels, and although these elevations are largely asymptomatic, there have been 6 other reports of clozapine-associated pseudopheochromocytoma. The patients, all with refractory schizophrenia (5 males), were aged 22–44 years and had been receiving 300–900 mg/day clozapine for 2–18 months. All presented with elevated BP (143–180/100–120 mmHg) and increased levels of urinary catecholamines. Clozapine was stopped in 4 of the cases, and BP and catecholamine levels quickly normalized.


Drug Trade Names: clozapine—Clozaril; enalapril—Vasotec

Neuropsychiatric Sequelae of Glucocorticoid Therapy

Patients treated with oral glucocorticoids appear to be at increased risk for suicidal behavior, depression, mania, and other severe neuropsychiatric disorders, according to a population-based study.

Methods: Data from 424 British general practices was analyzed for an 18-year period. All adults who received a prescription for an oral glucocorticoid were included, as were 2 control groups: a random sample of all unexposed patients, and a sample of those who had the same medical diagnoses as the exposed patients but who did not receive a glucocorticoid.

Results: The database included 372,696 patients who received nearly 800,000 courses of oral corticosteroids, as well as nearly 2 million controls. Most prescriptions of oral glucocorticoids were for lower respiratory tract infection (39%) or asthma (30%). Persons taking glucocorticoids were about 2–3 times as likely to have onset of a neuropsychiatric illness as controls, depending
on the control group (hazard ratio* vs randomly selected controls, 3.26; vs controls with the same medical illnesses, 2.26). In the exposed patients, there were 19 completed suicides and 90 suicide attempts. The incidence of suicidal behavior was 5–7 times higher in exposed patients than in controls, although the overall numeric risk of suicide was low. Risk in glucocorticoid-exposed patients was increased about 6-fold for delirium/confusion/disorientation, 5-fold for mania, and about 2-fold for depression and panic disorder.

Risks were higher for the first glucocorticoid prescription than for subsequent prescriptions. For patients on their first course of therapy, the risk of any neuropsychiatric illness was 22 per 100 person-years of exposure. Higher glucocorticoid doses and a history of neuropsychiatric disorders were also associated with greater risk. Other risk factors differed among the disorders; for instance, women were more likely to experience depression, and men were more likely to experience mania or delirium-related symptoms. Patients treated for asthma were less likely than others to have neuropsychiatric sequelae, possibly because of chronic exposure to low-dose inhaled corticosteroids.

Discussion: The association of glucocorticoid therapy with psychiatric symptoms has been observed previously in clinical practice, but there has been little data on risks in the general population. The results of this study underline the need for caution in prescribing oral glucocorticoids, particularly for nonrecommended indications.


*See Reference Guide.

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.

Propensity Scoring: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.