In a group of patients with bipolar depression and no significant metabolic disorder, adding pioglitazone (Actos) to lithium produced earlier response and a higher rate of remission.

**Background:** The oral antidiabetic pioglitazone has incidentally been found to have antidepressant effects in patients with concomitant diabetes or metabolic syndrome and major depression or bipolar disorder. The present randomized controlled trial was undertaken to evaluate the antidepressive effects of adjunctive pioglitazone in patients receiving lithium for bipolar depression.

**Methods:** Study subjects (n=48; 15 women) had a DSM-IV-TR diagnosis of bipolar I disorder and were experiencing a current depressive episode that had not responded to a trial of lithium plus an antidepressant. Patients were required to have stable, therapeutic levels of lithium for ≥2 consecutive weeks before starting 6 weeks of double-blind, randomly assigned placebo or pioglitazone (15 mg/day for 1 week, followed by an increase to 30 mg/day). Response was defined as a ≥50% reduction in the Hamilton Rating Scale for Depression (HAM-D) score without a switch to mania or hypomania; early improvement was defined as a ≥20% reduction on the HAM-D within the first 2 weeks; and remission as a final score of ≤7.

**Results:** Of the 48 patients, 4 withdrew before receiving treatment and the remaining 44 completed the trial. The average illness duration was about 4.5 years, and patients had experienced an average of 4 previous depressive episodes. HAM-D scores averaged about 23 points at baseline and decreased by about 14 points with pioglitazone and 12 points with placebo (mean difference, 2.27; p=0.006). A total of 19 patients experienced response with pioglitazone and 16 with placebo, a statistically nonsignificant difference. Early improvement was observed in all 22 patients in the pioglitazone group and in 17 of 22 (77%) in the placebo group (p=0.048). Five patients experienced remission with pioglitazone, and 1 with placebo (23% vs. 5%), but the difference was not statistically significant. Treatment had no effect on fasting blood glucose, hemoglobin A1c, body weight, or hepatic enzymes. No patient experienced hypoglycemia, and no patient switched to mania or hypomania.
**Discussion:** Preclinical studies suggest the antidepressant effects of pioglitazone are mediated at least partly through the nitric oxide pathway and PPARγ (peroxisome proliferator-activated nuclear receptor gamma) receptors. The present results support the hypothesis that the pathophysiology of depressive disorders extends beyond the monoamine pathways. However, because participants were not tested for insulin resistance, it is possible the antihypoglycemic effects of pioglitazone may have played a role in patients’ early response to treatment.

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


From Tehran University of Medical Sciences, Iran; and other institutions. **Funded by Tehran University. The authors declared no conflicts of interest.**

*See Reference Guide.

### ADHD Medications and Pregnancy Outcomes

In a population-based cohort study, treatment with ADHD medications was associated with increased rates of some adverse pregnancy outcomes, but these were largely explained by the effects of ADHD itself.

**Methods:** Registry data were analyzed from a cohort of nearly 1 million pregnancies in Danish women over a 12-year period. The data included all diagnoses of ADHD and all prescriptions for methylphenidate or atomoxetine that were filled beginning 30 days before the estimated date of conception, until birth, stillbirth (weeks 22–28), or spontaneous abortion (before week 22). Adverse pregnancy outcomes included low birth weight (<5.5 lbs.), preterm birth (before 37 weeks), small size for gestational age (<10th percentile), Apgar scores <10 at 5 minutes, and major congenital malformations.

**Results:** The study population included 186 women who were taking ADHD medications and 275 with ADHD who did not use medications. Compared with those without ADHD, women with ADHD were younger, less well educated, lower-income, and more likely to be single and nulliparous; they also had higher rates of concomitant medication, comorbidity, and smoking.

Women with ADHD had about a 55% increased risk of spontaneous abortion compared with those without ADHD, after adjustment for maternal age, education, cohabitation, comorbidity, and comedication. This association was present regardless of medication use. Women taking ADHD medication had a significantly higher adjusted proportion of newborns with low Apgar scores than comparison women (adjusted relative risk,* 2.06), but unmedicated women with ADHD did not (relative risk, 0.99). Unmedicated women with ADHD, but not medicated women, had elevated adjusted rates of preterm births compared with controls. Other study outcomes occurred too infrequently in women taking ADHD medications to be analyzed statistically: preterm birth, small for gestational age, low birth weight, and congenital malformations.

**Discussion:** Animal studies have shown methylphenidate associated with high rates of congenital anomalies, but this finding has not been replicated in humans. A few human studies suggest ADHD medications may be associated with adverse pregnancy outcomes. Confounding by indication—the contribution of risk from the underlying disease—is a persistent challenge in pharmacoepidemiological studies. The present study indicates that at least part of the increase in spontaneous abortion associated with ADHD medications may be due to the disorder itself, while low Apgar scores appear to be a direct effect of the drugs.

Bro S, Kjaersgaard M, Parner E, Sorensen M, et al: Adverse pregnancy outcomes after exposure to methylphenidate or atomoxetine during pregnancy. *Clinical Epidemiology* 2015;7:139–147. From Aarhus University and Aarhus University Hospital, Denmark. **Funded by the Danish Epilepsy Foundation. The authors declared no competing interests.**

**Drug Trade Names:** atomoxetine—Strattera; methylphenidate—Ritalin and others

*See Reference Guide.
Bipolar Disorder Treatment in Pregnancy

During pregnancy both untreated bipolar disorder and pharmacotherapy for the disorder pose risks to mother and baby. According to a comprehensive literature review, there are no risk-free treatment options, and decisions about pharmacotherapy should move beyond simply whether or not to treat, and should encompass ways to minimize potential harms.

Episodes of mania or depression recur during pregnancy in 25–30% of women with bipolar disorder. There is no evidence that pregnancy protects women with bipolar disorder from a recurrence of mood episodes, and the postpartum period is a time of high risk. A diagnosis of maternal bipolar disorder is associated with a small but statistically significant increase in risk of pregnancy complications including placental abnormalities, antepartum hemorrhages, and toxicities related to substance use. Maternal bipolar disorder is also linked to neurocognitive and psychiatric impairments in the offspring. Uncontrolled bipolar disorder is associated with behavioral risks including substance use, poor adherence to prenatal care, disruptions in family and social support structures, and suicide.

Controlled studies and published treatment guidelines generally support the use of effective maintenance treatment with mood stabilizers during pregnancy. Valproate appears to be associated with the highest risk of teratogenicity, neonatal adverse events, and neurodevelopmental difficulties. Risk increases with the valproate dose and with concomitant use of other anticonvulsants. Congenital malformation rates are lower with lithium and carbamazepine, and rates with lamotrigine are similar to background rates in the general population. There has so far not been convincing evidence that carbamazepine, lamotrigine, or lithium is associated with neurodevelopmental difficulties.

The efficacy and safety of atypical antipsychotics in pregnancy have not been well studied, and the risk of major congenital malformations is unclear. The major risks associated with these agents appear to be excessive weight gain, maternal diabetes, and gestational diabetes. In addition, all atypical antipsychotics carry an FDA warning about the possibility of extrapyramidal symptoms and withdrawal syndromes in newborns exposed during the third trimester.

Practice guidelines for the treatment of bipolar disorder during pregnancy generally agree on several points: the need to discuss reproductive and obstetric risks long before a pregnancy is planned; maximizing nonpharmacologic treatments, social supports, and regularity of sleep; use of monotherapy; avoidance of valproate in the first trimester; and use of ECT.

<table>
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<tr>
<th>Reproductive Safety of Mood Stabilizers in Bipolar Disorder</th>
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<td><strong>Drug</strong></td>
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<td>Valproate</td>
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<td>Carbamazepine</td>
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<td>Lamotrigine</td>
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for severe or refractory symptoms. Guidelines also disagree on some points: whether lithium should be continued or avoided and the degree to which atypical antipsychotic treatment is prioritized.


Drug Trade Names: carbamazepine—Epitol, Tegretol; lamotrigine—Lamictal; valproate—Depakene, Depakote

*See Reference Guide.

### Safety of SRIs in Breastfeeding

When antidepressant treatment is required in a breastfeeding woman, the SRIs with the most favorable neonatal safety profile appear to be paroxetine and sertraline, according to a systematic literature review.

**Methods:** A comprehensive literature search was undertaken to identify articles that reported data on the use during breastfeeding of any of the 6 available SSRIs or 2 SNRIs. The studies reported effects of exposure during breastfeeding on selected pharmacokinetic indices of newborn exposure (e.g., relative infant dose, milk-to-plasma ratio, infant plasma concentrations) short-term outcomes (until 6 months postpartum), and long-term outcomes.

**Results:** A total of 104 studies were included in the analysis: 14 with citalopram; 8 with escitalopram; 21 with fluoxetine; 11 with fluvoxamine; 17 with paroxetine; 22 with sertraline; 3 with duloxetine; and 8 with venlafaxine. About one-third of those included were case reports. According to the review, only 2 cases of mild, transient adverse events were identified in the 228 infants exposed to paroxetine and 1 of the 279 infants exposed to sertraline. Exposure indices were within acceptable limits for both drugs. Moderately severe short-term effects and reduced growth curves have been reported with fluoxetine. The incidence of short-term adverse effects appears to be somewhat increased with citalopram and escitalopram, but data are limited. Very little is known about the safety of fluvoxamine, duloxetine, and venlafaxine.

**Discussion:** The neonatal safety of antidepressant use during breastfeeding remains controversial, in part because the available exposure literature includes primarily case reports and studies with small sample sizes, with reliability limited by methodological differences. In addition, the studies concentrate on measurements of exposure, such as the relative infant dose, milk drug concentration, or neonatal plasma drug concentration, rather than on the clinical relevance of exposure.

Orsolini L, Bellantuono C: Serotonin reuptake inhibitors and breastfeeding: a systematic review. Human Psychopharmacology, Clinical and Experimental 2015;30:4–20. From the United Hospital of Ancona and the Polytechnic University of Marche, Italy. Source of funding not stated. The authors declared no conflicts of interest.

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

### Antipsychotic Safety in Breastfeeding

No antipsychotic is considered entirely safe for use during breastfeeding. However, the agents are excreted into breast milk at varying concentrations and, according to a review of the limited available literature, some may be safer than others.

**Background:** On the basis of teratogenic risk, most antipsychotics are labeled as pregnancy category C;* exceptions include clozapine and lurasidone, which are labeled as category B.* These pregnancy ratings do not help guide decisions about use after birth for mothers who breastfeed. Agents with breast milk concentrations of >10% of the maternal serum level constitute significant infant exposure, which could pose dangers to the infant’s health.
Methods: A comprehensive literature search was undertaken to identify reports of antipsychotic use during breastfeeding. A total of 60 English-language articles were identified that were published between 1960 and May 2014 and evaluated an antipsychotic available in the U.S. Both first- and second-generation antipsychotics were considered.

Results: Among the first-generation antipsychotics, perphenazine, trifluoperazine, and haloperidol can be detected in breast milk but do not cause clinically apparent adverse effects in the infants. Chlorpromazine has been associated with infant drowsiness and lethargy after exposure in breast milk. Haloperidol, when administered with chlorpromazine, has reportedly caused developmental delays in 12–18-month-old children. There are no data regarding the safety of fluphenazine, loxapine, pimozide, thioridazine, or thiothixene in breastfeeding.

The second-generation agents aripiprazole, clozapine, olanzapine, quetiapine, and risperidone have all been detected in breast milk. There have been no adverse-effect reports for aripiprazole exposure in breastfed infants. Although olanzapine, quetiapine, and risperidone also appear to have no adverse effects, exposed infants should be monitored carefully for sedation, extrapyramidal symptoms, and seizures. Periodic plasma-level monitoring is recommended for olanzapine-exposed infants, and those exposed to quetiapine should be followed for potential developmental delays. Clozapine is rarely prescribed for lactating women because of the potential for bone marrow suppression. In addition, clozapine in breast milk has been associated with sedation; decreased suckling; restlessness and irritability; seizures; and cardiovascular instability in exposed infants. No data exist for the safety in lactation of the newer antipsychotics asenapine, iloperidone, lurasidone, paliperidone, and ziprasidone.

Discussion: Although this review suggests several agents may be safe for use in breastfeeding, it should be noted that even with acceptable milk concentrations (<10%) of medications that appear to be safe for neonates, developmental delays remain a possibility with exposure. A registry-based or large-scale retrospective study could clarify the developmental effects of these antipsychotic agents.


Drug Trade Names: aripiprazole—Abilify; asenapine—Saphris; clozapine—Clozaril; haloperidol—Haldol; iloperidone—Fanapt; loxapine—Loxitane; lurasidone—Latuda; olanzapine—Zyprexa; paliperidone—Invega; pimozide—Orap; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

*See Reference Guide.

Duloxetine for OCD

In a small, manufacturer-sponsored, open-label study, the SNRI duloxetine (Cymbalta) produced significant symptom reductions in a group of patients with obsessive-compulsive disorder.

Methods: Study subjects (n=20) were adults with a diagnosis of OCD confirmed by structured clinical interview at a specialized OCD clinic. Mean patient age was 30 years (range, 18–55 years), and 11 patients (55%) were women. Participants were recruited by clinical referral and advertisement. All patients began treatment with 30 mg/day duloxetine. One week later, if the patient was free of intolerable adverse effects, the dosage was increased to 60 mg/day for an additional 2 weeks, and then to 120 mg/day for the remaining 12 study weeks. The duloxetine dosage could be reduced to 60 mg/day if the higher dosage was intolerable. The primary efficacy measures were the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the Clinical Global Impression–Improvement (CGI-I)* scale. Full response was defined as a ≥25% reduction in Y-BOCS score and a CGI-I score of <3. Quality of life along with depressive and anxiety symptoms were secondary outcomes.
Results: In the intent-to-treat analysis, statistically significant decreases in Y-BOCS scores were evident beginning at week 6. The mean baseline Y-BOCS score of 27.5 was reduced to 20.5 at study end (p<0.001; effect size,* 1.2). The mean CGI-I score at the final study visit was 2.7, indicating minimal-to-much improvement. A total of 7 patients (35%) met full response criteria. Significant reductions were also found in Beck Depression Inventory (BDI) scores, but not in Beck Anxiety Inventory (BAI) scores. Quality-of-life scores were significantly improved (p=0.045).

Of the 20 patients enrolled, 12 completed the study as designed. Of the noncompleters, 2 were lost to follow-up, 1 refused medication, and 5 discontinued study treatment because of adverse effects. Although no serious adverse events were reported, nausea developed in 50% of patients, fatigue affected 41%, and sexual dysfunction occurred in 23%. In a separate completer analysis, 7 patients (58%) achieved full response, 2 achieved partial response (i.e., either Y-BOCS or CGI-I criteria), and 3 patients met neither of the response criteria.

Discussion: SRIs are first-line treatment for OCD. Although there has been little research on SNRIs for this condition, duloxetine was studied in the present trial because its additional noradrenergic effects could provide added benefit over the serotonergic-only effects of SRIs. Although limited by small sample size and unblended treatment, these results suggest that duloxetine may be an effective treatment for patients with OCD. Additional research, in the form of large-scale randomized controlled trials, appears to be warranted.


Adjunctive Pregabalin for Generalized Anxiety Disorder

Patients with generalized anxiety disorder (GAD) partially responsive to SSRI therapy showed evidence of greater clinical improvement with adjunctive pregabalin than with other approaches, according to a retrospective analysis of data from a naturalistic manufacturer-sponsored study. Although pregabalin cost more than other options, reduced costs in other health-care areas compensated for the difference.

Methods: The present report is a post-hoc analysis of a 6-month, multicenter, observational study of adults with anxiety disorder. The study included patients with GAD who had experienced partial response, defined as a Hamilton Rating Scale for Anxiety (HAM-A) score of >16 and a Clinical Global Impression–Severity* (CGI-S) score of >3, to first-line SSRIs. Patients received treatment at their psychiatrists' discretion with either pregabalin augmentation or "usual care" (i.e., switching to a different SSRI or augmentation with a different anxiolytic). Patients in the pregabalin group could also be taking concomitant benzodiazepines for a limited period of time. Study outcomes were evaluated after 6 months and included clinician-reported outcomes of anxiety (rated with the HAM-A), illness improvement (rated with the CGI-Improvement scale)*, depression (with the Montgomery-Asberg Depression Rating Scale [MADRS]), and patient-reported outcomes of sleep, disability, and quality of life. In addition, 6 months of health-care cost data were also analyzed.

Results: A total of 486 patients (325 women) were given pregabalin and 239 (159 women) received another treatment. Mean patient age was 47 years in the pregabalin group and 45 years in the usual care group. The groups were well matched demographically, but those who received pregabalin had greater severity of anxiety, depression, and overall illness at baseline than those who received usual care.
Adjunctive pregabalin was associated with greater improvements than usual care in anxiety, depression, and illness severity. (See table.) Pregabalin resulted in numerically greater improvement in all HAM-A domains, which was statistically significant for anxious mood, tension, fears, and intellectual, somatic, gastrointestinal, and autonomic symptoms. Secondary patient-reported outcomes also improved in both treatment groups after 6 months, but with statistical superiority for pregabalin in sleep problems (p<0.001), disability (p<0.0001), and global health status (p<0.001).

<table>
<thead>
<tr>
<th>Clinical outcomes: mean change for adjunctive pregabalin vs. usual care</th>
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<td><strong>Pregabalin</strong></td>
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<td>MADRS</td>
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Health-care resource utilization included the costs of drug treatment, medical visits and hospitalizations, and nonpharmacological care such as support groups or psychosocial therapy. Compared with baseline, both treatment groups had significant reductions in health care costs during the 6 months of adjunctive therapy. Overall costs during those 6 months were similar in the 2 groups. Increased drug costs in the pregabalin group were compensated for by reductions in the number of visits and hospitalizations.

**Discussion:** The lack of treatment randomization is an important limitation of this study, which could result in selection bias and affect the outcome. While of interest, the study results must be interpreted cautiously and randomized controlled trials are needed to replicate the findings.

Alvarez E, Olivares J, Carrasco J, Lopez-Gomez V, et al: Clinical and economic outcomes of adjunctive therapy with pregabalin or usual care in generalized anxiety disorder patients with partial response to selective serotonin reuptake inhibitors. *Annals of General Psychiatry* 2015; doi 10.1186/s12991-014-0040-0. From the Universitat Autonoma de Barcelona, Spain; and other institutions. **Funded by Pfizer. All 5 study authors declared financial relationships with commercial sources.**

*See Reference Guide.

**Acute Antidepressant Effects of Nitrous Oxide**

In a preliminary study, nitrous oxide had rapid, marked antidepressant effects in patients with refractory depression.

**Methods:** Participants in this proof-of-concept study were 20 patients (12 women) with DSM-IV-TR major depressive disorder, a baseline score of >18 on the 21-item Hamilton Rating Scale for Depression (HAM-D), failure of ≥2 adequate trials of an antidepressant during the current episode, and ≥3 lifetime failed drug trials. Each patient received randomized nitrous oxide or placebo, and then after 1 week was crossed over to the alternate treatment. Nitrous oxide was administered at a maximum concentration of 50% with oxygen, a dosage empirically based on its use in dentistry and obstetrics. The placebo was 50% nitrogen in oxygen. Patients received treatment via a face mask for 1 hour, and then were monitored for 2 hours in a recovery area. For each treatment session, the HAM-D was administered at baseline, after 2 hours, and after 24 hours. The primary outcome was change from baseline to 24 hours in the HAM-D score.

**Results:** Participants (mean age, 48 years) had an average 19-year history of major depression, with an average of 8 failed treatments. The initial mean HAM-D score of 23.5 indicated severe depression. Patients were taking an average of 2 antidepressants during the current episode, and these were continued unchanged during the study. Treatment with nitrous oxide was interrupted briefly in 2 patients and ended prematurely in 3 for transient emotional discomfort, regurgitation, claustrophobia, or nausea and vomiting. Patients received an average of 56 minutes of nitrous oxide at a mean concentration of 44%. All patients completed 60 minutes of placebo.
At the 2-hour assessment, the mean HAM-D score decreased by 4.8 points with nitrous oxide to 18.7, followed by an additional decrease to 18 at 24 hours. Average scores decreased by about half that amount after placebo treatment (p<0.001 for nitrous oxide vs. placebo). Among the individual HAM-D items, depressed mood, guilt, suicidal ideation, and psychic anxiety showed the greatest improvement with nitrous oxide. At 24 hours, 4 patients met response criteria (HAM-D decrease of ≥50%) with nitrous oxide and 1 with placebo. A total of 3 patients met remission criteria (HAM-D score ≤7) with nitrous oxide, and no patient remitted with placebo. Because of a significant crossover effect in patients who received nitrous oxide as their initial treatment (i.e., observed carryover effect—patients who received active treatment first had lower scores when starting placebo), the investigators conducted an additional analysis comparing only the results of the first active or placebo treatment. The results were essentially the same as the full analysis.

Nagele P, Duma A, Kopec M, Gebara M, et al: Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial. Biological Psychiatry 2014; doi 10.1016/j.biopsych.2014.11.016. From Washington University School of Medicine, St. Louis, MO. Funded by Washington University School of Medicine. Three study authors disclosed relationships with commercial sources; the remaining 9 authors declared no conflicts of interest.

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Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Clinical Global Impression–Severity (CGI-S) scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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.

Pregnancy Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Pregnancy Category C: Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

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

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