Mood Stabilizers, Antipsychotics, and Breastfeeding

In women taking mood stabilizers or antipsychotics for bipolar disorder, the benefits of breastfeeding generally outweigh the risks, according to a systematic literature review. However, precautions should include choosing medications with an adequate safety record, reducing exposure by combining breast milk with other sources of nutrition, and avoiding or restricting breastfeeding in premature newborns.

The postpartum period is one of high risk for new onset of bipolar disorder or for relapse, especially in women who have discontinued medication. Almost all drugs used to treat bipolar disorder are secreted into breast milk, and the risk of toxicity from these drugs could be significant. The literature was reviewed for all evidence of the effects on breastfed newborns of drugs commonly used to treat bipolar disorder. Data were collected from 56 studies—mainly case reports, case series, and small open-label studies.

General Considerations. Drugs with a high percentage of plasma protein binding are the least likely to enter breast milk. Availability is often reported as the milk/plasma (M/P) ratio—i.e., the ratio of the concentration of drug in the milk to that in the plasma. Drugs with an M/P ratio >1 may be present in milk at high concentrations. However, a high M/P ratio may not be a problem if maternal plasma levels are low. Another factor to consider is the relative infant dose, the ratio of the weight-based dose in milk to the weight-adjusted dose received by the mother. A ratio of <10% is generally considered safe. Premature and newborn infants are at greater risk to develop high plasma drug concentrations because of their immature hepatic and renal systems. Infants who are exclusively breast fed for long periods of time develop higher concentrations than those in whom breast milk is alternated with supplemental foods. The mother should take her medication immediately after breastfeeding and not before.

Specific Agents. The consensus on lithium, use of which was previously discouraged in breastfeeding women, has changed based on recent case series showing low serum levels in...
exposed infants and no clinically apparent adverse effects. Lithium levels of about one-fourth of maternal levels have been reported in breastfeeding newborns. If lithium is used, monitoring of maternal and infant lithium levels, as well as infant hydration, weight gain, muscle tone, and renal and thyroid function should be conducted.

Data on antiepileptic mood stabilizers in breastfeeding, although scarce, suggest that they are safe to use under close observation. Case reports and open-label studies have found few adverse effects of valproate, carbamazepine, and oxcarbazepine. Lamotrigine is considered "moderately safe" based on wide variability of M/P ratios and infant plasma concentrations and elevated platelet counts; there were no reports of serious adverse effects.

Among the second-generation antipsychotics, quetiapine and olanzapine are considered safe, based on numerous reports of low plasma concentrations in exposed infants. Evidence suggests the same is probably true for most other second-generation antipsychotics, but the data are extremely limited. First-generation antipsychotics are not recommended because of a lack of data.

Pacchiarotti I, Leon-Caballero J, Murru A, Verdolini N, et al: Mood stabilizers and antipsychotics during breastfeeding: focus on bipolar disorder. European Neuropsychopharmacology 2016; doi 10.1016/j.euroneuro.2016.08.008. From the University of Barcelona, Spain; and other institutions. Nine study authors disclosed financial relationships with commercial sources; the remaining 9 authors declared no competing interests.

Common Drug Trade Names: carbamazepine—Tegretol; lamotrigine—Lamictal; olanzapine—Zyprexa; oxcarbazepine—Trileptal; quetiapine—Seroquel; valproate—Depakene, Depakote

Metabolic Effects of Injectable Aripiprazole

Aripiprazole lauroxil, the long-acting injectable form of the antipsychotic, was associated with low risk of weight gain, adverse metabolic effects, and prolactin increases, according to a secondary analysis of safety data from a phase III clinical trial.

Methods: The multicenter trial was carried out in hospitalized adults with an acute relapse of schizophrenia. Participants were required to have an illness duration of ≥2 years and to have had a prior beneficial response to an antipsychotic. After receiving a test dose of aripiprazole or placebo, patients received an initial injection of 441 mg or 882 mg aripiprazole lauroxil or placebo. Patients randomized to aripiprazole lauroxil also received 15 mg/day oral aripiprazole for 3 weeks. Two additional doses of study medication were given 29 and 57 days after randomization. Efficacy results of the study were previously reported.

Results: A total of 622 patients received ≥1 dose of study medication. Patients had a mean age of about 40 years, two-thirds were men, and 40% were black or African American. Baseline body mass index averaged 27–28 kg/m²; about one-third of the patients were overweight and another third were obese at the start of treatment.

Mean body weight increased by <2 lbs in the groups receiving active medication and did not change in the placebo group. About 9–10% of the groups receiving aripiprazole lauroxil and 6% of the placebo group gained ≥7% of their initial body weight. There were no clinically relevant changes from baseline in glucose, HbA1c, or lipid parameters. In the aripiprazole lauroxil groups, mean total cholesterol, LDL cholesterol, and triglyceride levels decreased by 5–8%. Both doses of aripiprazole lauroxil, but not placebo, were associated with mean decreases in prolactin; these reductions occurred in both men and women and were judged to be clinically meaningful. Of the patients with high baseline prolactin levels, 61% and 42% of those in the low- and high-dose aripiprazole groups, respectively, had levels in the normal range at the last assessment.
Metabolic changes were reported as an adverse event in 6 patients receiving aripiprazole lauroxil (increases in glucose or triglycerides, hyperlipidemia, and 1 case of hypoglycemia probably unrelated to medication) and in 2 patients in the placebo group. Weight increase was reported as an adverse event in 11 patients (<3%) receiving aripiprazole lauroxil.

Discussion: These results suggest aripiprazole lauroxil limits weight gain and other risks commonly encountered with antipsychotic treatment. The metabolic safety and tolerability of this agent is similar to that reported in studies of the oral form of aripiprazole.

1Nasrallah H, Newcomer J, Risinger R, Du Y, et al: Effect of aripiprazole lauroxil on metabolic and endocrine profiles and related safety considerations among patients with acute schizophrenia. Journal of Clinical Psychiatry 2016; doi 10.4088/JCP.15m10467. From St. Louis University School of Medicine, MO; Florida Atlantic University, Boca Raton; and Alkermes, Inc., Waltham, MA. Funded by Alkermes, Inc. All study authors disclosed financial relationships with commercial sources, including Alkermes.


Common Drug Trade Names: aripiprazole—Aabilify; aripiprazole lauroxil—Aristada

Hormonal Contraception and Depression Risk

Women using hormonal contraceptives had an increased incidence of depression in a population-based longitudinal study. Risk varied with different types of contraceptive and was especially pronounced in adolescents.

Methods: The Danish Sex Hormone Register Study is an ongoing cohort study of all women living in Denmark. The present analysis included women who were aged 15–34 years between 2000 and 2013. Those with a diagnosis of depression before 2000 or their 15th birthday were excluded, as were women with other psychiatric diagnoses and those with contraindications to hormonal contraceptives. Users of any type of prescription hormonal contraceptive were compared with non-users of any contraceptive. The study used 2 outcome measures for depression onset: first prescription of an antidepressant medication and a diagnosis of depression on discharge from an inpatient or outpatient psychiatric hospital.

Results: The study population included >1 million women followed for a mean of 6.4 years. More than 55% of women used a hormonal contraceptive during this period. A total of about 133,000 received a prescription for an antidepressant, and 23,000 received a discharge diagnosis of depression.

In users of hormonal contraceptives, the incidence of first use of an antidepressant was 2.2 per 100 person-years and of a depression diagnosis was 0.3 per 100 person-years. In non-users, the corresponding rates were 1.78 and 0.28 per 100 person-years. Relative risks* for antidepressant prescriptions differed according to contraceptive type. (See table.) Relative risks for a discharge diagnosis were slightly lower or similar.

<table>
<thead>
<tr>
<th>Relative Risk of Antidepressant Prescription in Women Using Hormonal Contraception Compared with Non-Users</th>
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<tr>
<td><strong>Contraceptive Type</strong></td>
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<tr>
<td>Combined oral</td>
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<tr>
<td>Progestin-only</td>
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<td>Transdermal patch (norelgestromin)</td>
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<tr>
<td>Vaginal ring (etonorgestrel)</td>
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<tr>
<td>Implant</td>
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<td>Levonorgestrel intrauterine system</td>
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<td>Medroxyprogesterone acetate depot</td>
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Relative risks of depression decreased with increasing age for most commonly used contraceptives. Risks were highest in adolescents aged 15–19 years, with a relative risk of 1.8 for combined oral contraceptives and parallel elevations for other types. Adolescents using non-oral types had 3 times the risk, compared with nonusers in their age group. Risks increased with increasing duration of contraceptive use, peaking at 6 months of use and then declining to background levels after about 4 years.

Discussion: Results of this study are consistent with the hypothesis that progesterone is involved in the etiology of depression. Progesterone dominates combined contraceptives. The high rates of depression in women using the transdermal patch and vaginal ring are probably a function of the dose rather than the route of administration. Risk of depression was also particularly high in women using progestin-only products. Progesterone metabolites influence the GABA receptor complex, the major inhibitory system in the CNS, and progestins, particularly if exogenous, increase levels of monoamine oxidase, which degrades serotonin.

Skovlund C, Mørch L, Kessing L, Lidegaard O: Association of hormonal contraception with depression. JAMA Psychiatry 2016; doi 10.1001/jamapsychiatry.2016.2387. From the University of Copenhagen, Denmark. Funded by the University of Copenhagen; and the Lundbeck Foundation. Two study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.

Common Drug Trade Names: ethinyl estradiol-norelgestromin patch—Evra; etonorgestrel-ethinyl estradiol vaginal ring—NuvaRing; levonorgestrel implant—Norplant; levonorgestrel intrauterine device—Liletta, Mirena; medroxyprogesterone acetate, depot—Depo-Provera

Medical Marijuana in Psychiatry

The rapidly changing legal status of medical marijuana gives rise to an urgent need to investigate its use for psychiatric indications, according to a literature review. At present, the quality of evidence supporting its use is very low.

Background: In addition to crude marijuana, 2 oral pharmaceutical cannabinoids are available in the U.S., dronabinol, approved for cachexia in HIV/AIDS, and nabilone, approved for nausea and vomiting associated with chemotherapy. Another, nabiximols, is available in Canada and some European countries as a nasal spray for treatment of multiple sclerosis. At present, no cannabinoid is FDA-approved for treatment of a psychiatric disorder.

Methods: A literature search was undertaken to identify all research articles on medical marijuana for psychiatric indications, beginning in 1980 and including conference proceedings. A total of 13 articles were identified that described medical marijuana use in Tourette's disorder, posttraumatic stress disorder (PTSD), and Alzheimer's disease.

Results: Two small, randomized, placebo-controlled trials of dronabinol in patients with Tourette's disorder have shown positive effects on some but not all measures of tic severity. Observational studies and case reports indicate many patients report improvement in tic severity with use of the oral agents or marijuana. The existing studies in Tourette's are flawed by small sample size, inconsistent results across multiple measures, possible selection bias, and other problems.

Studies of marijuana in PTSD include a randomized crossover trial of nabilone in 10 male soldiers, 2 retrospective chart reviews of nabilone in adult male offenders and in patients with nightmares, and an open-label study of adjunctive nabilone in patients with PTSD. There have also been 2 unpublished studies and a number of anecdotal reports. Marijuana appears to reduce nightmares and improve sleep in PTSD. The existing evidence is sparse
and its quality is limited by small samples and weak experimental designs, but emerging data on the effects of the endocannabinoid system on extinction learning may provide a basis for future hypothesis-driven clinical trials.

There are no randomized controlled trials of marijuana in Alzheimer's disease, but the handful of existing prospective studies show improvement in some measures of agitation and aggression with use of oral agents. These studies are limited by small sample size, lack of control groups, lack of blinding, and inconsistent results using different outcome measures. There is some evidence that the endocannabinoid system is involved in Alzheimer's disease. It is possible that the purported calming effect of marijuana is the result of nonspecific sedation. Since cannabinoids impair cognitive function in domains already affected by Alzheimer's disease, future studies should weigh their purported benefits against this impairment.

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

Wilkinson S, Radhakrishnan R, D'Souza D: A systematic review of the evidence for medical marijuana in psychiatric indications. *Journal of Clinical Psychiatry* 2016;77 (August):1050–1064. From Connecticut Mental Health Center, New Haven; and other institutions. Funded by the VA; the NIMH; and other sources. All 3 study authors disclosed financial relationships with commercial sources.

**Common Drug Trade Names:** dronabinol—Marinol; nabilone—Cesamet; nabiximols (not available in U.S.)—Sativex

*See Reference Guide.

### Antimanic vs. Antipsychotic Drugs in Bipolar Disorder

Results of a population-based comparative effectiveness study suggest that lithium and valproate are superior to second-generation antipsychotics as initial therapy for manic episodes.

**Background:** Results of randomized controlled trials, conducted in carefully selected patients and under strict conditions, indicate that second-generation antipsychotics are equivalent to or superior in efficacy to conventional antimanic agents. However, little is known about their comparative effectiveness in real-world settings, an important issue due to the cardiometabolic effects of some second-generation agents, as well as their higher costs.

**Methods:** Using nationwide claims data from the Department of Veterans Affairs (VA), spanning 2003–2010, efficacy was compared between second-generation antipsychotics and conventional antimanic agents in nearly 28,000 patients with bipolar disorder type I, type II, or NOS, who were started on either class of drug or both. The analysis was limited to the 5 most common second-generation antipsychotics: aripiprazole; olanzapine; quetiapine; risperidone; and ziprasidone. Antimanic agents included lithium, valproate, and carbamazepine or oxcarbazepine. The primary outcome measure was hospitalization for any cause during the year following the first prescription. The analysis was adjusted for an extensive list of covariates.

**Results:** Study participants had an average age of 45 years, and 17% were women. Patients with psychosis were more likely than others to receive a second-generation antipsychotic, and those with substance use disorders, psychosis, antidepressant use, and prior hospitalization were more likely to receive combination therapy, but the analysis was adjusted for these differences.

Compared with patients receiving second-generation antipsychotic monotherapy, rates of all-cause hospitalization were significantly lower in those receiving lithium (odds ratio [OR], 0.82) or valproate (OR, 0.85). The combination of a second-generation antipsychotic plus valproate was associated with a higher likelihood of all-cause hospitalization than second-generation antipsychotics alone (OR, 1.32). Comparative rates of mental health hospitalization paralleled these results, while rates of medical-surgical hospitalization were
similar among the treatment groups. Compared with second-generation antipsychotics, time to hospitalization was significantly shorter for lithium (hazard ratio [HR],* 0.86; p<0.0004) and valproate (HR, 0.87; p<0.0001).

An exploratory head-to-head analysis of second-generation antipsychotics, using risperidone as the reference treatment, showed that aripiprazole was associated with a significantly lower likelihood of all-cause hospitalization (HR, 0.69). The other drugs—olanzapine, quetiapine, and ziprasidone—did not differ from risperidone.

Discussion: Although the study is subject to the limitations of observational study designs, the results suggest that lithium or valproate, rather than second-generation antipsychotics, could be considered for initial antimanic treatment in bipolar disorder.


Common Drug Trade Names: aripiprazole—Abilify; carbamazepine—Tegretol; olanzapine—Zyprexa; oxcarbazepine—Trileptal; quetiapine—Seroquel; risperidone—Risperdal; valproate—Depakene, Depakote; ziprasidone—Geodon

*See Reference Guide.

**Escitalopram for Body Dysmorphic Disorder**

In a placebo-controlled relapse-prevention trial in patients with body dysmorphic disorder, 6 months of continued treatment with the SSRI escitalopram (Lexapro) significantly delayed the time to relapse.

Methods: Study participants were adults who had been experiencing DSM-IV body dysmorphic disorder for ≥6 months and who had a Yale-Brown Obsessive Compulsive Scale modified for body dysmorphic disorder (BDD-YBOCS) total score of ≥24 as well as Clinical Global Impression–Severity (CGI-S) ratings of at least “moderately ill.” All patients received treatment with open-label escitalopram for 14 weeks (phase 1), with a target dosage of 30 mg/day. Response was defined as a ≥30% reduction in the BDD-YBOCS on at least 2 consecutive assessments and through the last visit. Patients who experienced response with escitalopram were randomly assigned to 6 additional months of treatment, either with their final escitalopram dosage or with placebo after an escitalopram taper. Relapse was defined as a loss of ≥50% of previous improvement on the BDD-YBOCS, plus a final score >20 (which corresponds to meeting full diagnostic criteria) and a CGI-Improvement rating of "much worse" or "very much worse." The primary study outcome was time to relapse after the start of phase 2.

Results: Of 100 patients who received escitalopram in phase 1, 60 completed treatment and achieved response after a median of 8 weeks and at a median final escitalopram dosage of 26 mg/day. Response rates did not differ significantly between the 26 patients with delusional beliefs and the 74 without these beliefs.

Of the 60 responders, 58 entered the randomized withdrawal phase. Time to relapse was significantly longer with continued escitalopram than with placebo (hazard ratio,* 2.72; p=0.049). By the end of phase 2, 18% of the escitalopram group and 40% of the placebo group had experienced a relapse. One-third of the escitalopram-treated patients experienced further decreases in psychiatric symptoms during phase 2.

Discussion: Results of the few previous pharmacotherapy studies in body dysmorphic disorder, all with small sample sizes, suggest SRIs are effective, a result confirmed in phase 1.
of the present trial. No dose finding studies have been conducted, but the results of the present study and others suggest relatively high SRI doses may be necessary to treat body dysmorphic disorder.

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

Phillips K, Keshaviah A, Dougherty D, Stout R, et al: Pharmacotherapy relapse prevention in body dysmorphic disorder: a double-blind, placebo-controlled trial. *American Journal of Psychiatry* 2016;173 (September):887–895. From Brown University, Providence, RI; and other institutions. **Funded by the NIMH. Four study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

*See Reference Guide.

### Sertraline and Post-TBI Depression

In a placebo-controlled trial, low-dose sertraline (*Zoloft*) prevented depression when started within a few weeks following traumatic brain injury.

**Methods**: Study participants were adults, aged 18–85 years (40% women), who had a closed TBI of any severity. They were required to be free of depression at baseline and to have complete recovery of posttraumatic amnesia within 4 weeks of the injury. Those with a history of mood disorder were required to be in full remission for at least the previous year, and those already taking antidepressants were excluded. Participants were randomly assigned to receive 100 mg/day sertraline or placebo for 24 weeks. The primary study outcome was onset of a depressive episode identified using the Mini-International Neuropsychiatric Interview.

**Results**: Of >1000 patients with a TBI who were screened for the study, about half met eligibility criteria. The most common reason for exclusion was a diagnosis of drug/alcohol use disorder. Of about 500 eligible patients, 80% refused to participate, including 120 who were unwilling to add another drug to the ones they were already taking and 30 who would not consent to potential placebo treatment and started antidepressant therapy outside the study. The remaining 94 patients (46% women; average age, 50–55 years) were enrolled, most within 3–4 weeks after the TBI. According to Glasgow Coma Scale ratings, the injury was mild in nearly 80% of the patients and severe in 10%.

Nearly half of all patients did not complete 24 weeks of treatment. Withdrawal rates were similar across groups, and all patients who received any randomized treatment were included in the analysis. Depression developed in 27 patients (29%) during the 24 weeks of follow-up. Incident depression was significantly less likely to occur in sertraline-treated patients for whom the number needed to treat* to prevent 1 depressive episode was 5.9 (p=0.03). Given that SSRIs can enhance neuroplasticity, neuropsychiatric tests for attention, memory, and executive function were administered to patients who did not develop a mood disorder. No differences were found between the sertraline and placebo groups.

**Discussion**: These observations suggest sertraline may be effective in preventing depression when administered early after a brain injury. Given the study’s limitations, including small sample size and the predominance of mild TBI, the results should be viewed as preliminary until they can be replicated.

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

Jorge R, Acion L, Burin D, Robinson R: Sertraline for preventing mood disorders following traumatic brain injury; a randomized clinical trial. *JAMA Psychiatry* 2016;73 (October):1041–1047. From Baylor College of Medicine, Houston, TX; and other institutions. **Funded by the NIH. Two study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

*See Reference Guide.
**Reference Guide**

**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 1 group has half the risk of the other group.

**Number Needed to Treat:** Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

**Odds Ratio:** A comparison of the probability of an event in 2 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.

**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 are posted at www.alertpubs.com.

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