Antipsychotics and Endometrial Cancer

Prolactin-elevating antipsychotics were not associated with increased risk of endometrial cancer in a population-based study. This finding suggests that prolactin may not play an important role in endometrial cancer pathogenesis.

**Background:** A possible long-term association of prolactin-elevating antipsychotics with hormone-sensitive cancer has been primarily investigated for breast cancer. There has been very little research on endometrial cancer, although these cancers express prolactin receptors and respond to prolactin in vitro; plus prolactin levels are elevated in women with endometrial cancer. A single study found a 5-fold increase in endometrial cancer risk in women who received treatment with antipsychotics, compared with untreated women.

**Methods:** Data were extracted from the U.K. Clinical Practice Research Datalink, covering >13-million patients enrolled in British general practices. A nested case-control analysis was conducted within a cohort of all women given a first-ever prescription for an antipsychotic in 1990–2013, excluding those with a history of prolactinoma, endometrial cancer, or hysterectomy at cohort entry. To account for latency and minimize detection bias, follow-up commenced 1 year after the first antipsychotic prescription. Each case—a woman in whom endometrial cancer developed—was matched with up to 20 controls of similar age, year of cohort entry, and duration of follow-up. Antipsychotics were divided into 2 categories: prolactin-elevating (all first-generation agents plus the second-generation agents amisulpride, paliperidone, risperidone, and zotepine) and prolactin-sparing (all other second-generation agents). Exposure was defined as ≥3 prescriptions within a 12-month period. The analysis was adjusted for multiple confounders including comorbid medical conditions and use of medications that have been associated with endometrial cancer risk or that suppress prolactin levels.

**Results:** Nearly 66,000 women were given a new prescription for an antipsychotic during the study period. Prolactin-elevating antipsychotics were not associated with an elevated risk of
endometrial cancer compared with prolactin-sparing antipsychotics (adjusted odds ratio,* 1.00). Risk did not differ in subgroups stratified for duration of antipsychotic use. However, risk was slightly elevated, although nonsignificantly, in women under menopausal age and those aged ≥75 years, but decreased, again nonsignificantly, in women aged 51–74 years.

**Discussion:** Data on prolactin levels were not available for evaluation. Nevertheless, the results suggest that prolactin may merely be a mediator of estrogen-induced tumorigenesis, not an independent risk factor.

1Kil-Drori A, Yin H, Abenhaim H, du Fort G, et al: Prolactin-elevating antipsychotics and the risk of endometrial cancer. *Journal of Clinical Psychiatry* 2017;78 (June):714–719. From Jewish General Hospital, Montreal, Canada; and other institutions. **Funded by the Canadian Institute of Health Research. The authors declared no competing interests.**


**Common Drug Trade Names:** amisulpride (not available in the U.S.)—Solian; paliperidone—Invega; risperidone—Risperdal; zotepine (not available in the U.S.)—Losizopilon

*See Reference Guide.

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**Adjunctive Minocycline for Bipolar Depression**

In a pilot study, adjunctive minocycline (*Minocin*) improved depressive symptoms in patients with bipolar disorder.

**Background:** Evidence suggests that chronic low-grade inflammation may be involved in the pathophysiology of bipolar disorder and that pharmacological modulation of inflammation reduces symptoms of depression in patients with mood disorders. Minocycline is a second-generation tetracycline that readily crosses the blood-brain barrier and has antiinflammatory activities independent of its antibiotic effects.

**Methods:** The pilot study was an open-label, uncontrolled, 8-week trial of minocycline in patients with bipolar I or II disorder who were currently experiencing a major depressive episode. Patients were required to have a screening score of ≥20 on the 17-item Hamilton Rating Scale for Depression (HAM-D) and to have been experiencing depression for ≥1 month but <1 year. Those whose current depressive episode had been resistant to ≥2 drugs were excluded. All participants received 100 mg minocycline b.i.d in addition to their previous medications, which were to remain unchanged. The primary efficacy outcome was change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS). Because early life adversity is a known risk factor for bipolar disorder and has been shown to condition immune responses to danger signals, a standardized scale was also administered to assess the indirect effects of childhood trauma.

**Results:** Of the 27 patients (mean age, 42 years; 13 men) in the intent-to-treat analysis, 12 had a diagnosis of bipolar I and 15 had a diagnosis of bipolar II disorder. Most patients (n=22) were receiving combinations of anticonvulsants and atypical antipsychotics. The mean duration of the current depressive episode was about 22 weeks. Adverse events—i.e., emergent mania with psychotic features, severe abdominal pain, hyperpigmentation, hives, fever and joint pain, esophageal swelling, and emergent hypomania in 1 patient each—lead to withdrawal of 7 patients by the investigators. A total of 19 patients completed treatment as planned.

Patients showed a significant reduction in mean MADRS score during treatment (effect size,* 0.835; p<0.001). Secondary efficacy measures also indicated significant depression improvement: the HAM-D (effect size, 0.949; p<0.001), the Clinical Global Impression (CGI)–Severity scale (effect size, 1.09; p<0.001), and the CGI–Improvement scale (effect size, 0.557; p=0.041). Improvement was evident at the first week post-baseline and remained significant throughout treatment. Response rates (≥50% decrease in HAM-D or MADRS score) ranged from 22% to 33% depending on the measure.
A subset of 20 study participants completed neurocognitive testing. There was a significant decline in verbal memory from baseline, which was limited to patients whose depression did not improve during the study. Psychomotor speed improved only in those whose depressive symptoms were ameliorated. The 19 patients with a history of early-life adversity showed significant improvement in depression throughout treatment, while those without early adversity showed no change.

Although 2 patients had emergent mania/hypomania, overall symptom ratings for mania in the study group did not worsen. Eight patients had worsening of suicidal ideation, which persisted in 4. Treatment had mixed effects on circulating inflammatory cytokine levels.

**Discussion:** The potential for antiinflammatory treatments to improve depression is supported by preclinical studies and other preliminary clinical evidence. Despite significant improvement in depressive symptoms in study patients, many did not achieve treatment response with minocycline; the results need to be replicated in more rigorous studies.

Soczynska J, Kennedy S, Alsuwaidan M, Mansur R, et al: A pilot, open-label, 8-week study evaluating the efficacy, safety and tolerability of adjunctive minocycline for the treatment of bipolar I/II depression. *Bipolar Disorders* 2017;19 (May):198–213. From the University of Toronto, Canada; and other institutions. Funded by the Mood Disorders and Psychotherapy Unit of the University of Toronto; and other sources. Seven of 10 authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.

*See Reference Guide.*

**Brexanolone for Postpartum Depression**

In a multicenter, placebo-controlled trial, brexanolone (a proprietary form of an endogenous neurohormone believed to be involved in postpartum depression) significantly improved symptoms of postpartum depression.1

**Background:** The neurohormone allopregnanolone—a GABA receptor modulator and a major metabolite of progesterone—increases throughout pregnancy and decreases rapidly upon childbirth. Failure of GABA receptors to adapt to the decrease in allopregnanolone is hypothesized to contribute to postpartum depression. Brexanolone is a formulation of allopregnanolone that can be administered intravenously to produce stable serum concentrations equivalent to third-trimester levels. A small proof-of-concept study suggested potential efficacy in postpartum depression.2

**Methods:** Study subjects were 21 women currently experiencing a major depressive episode with onset during the third trimester or within 4 weeks after delivery. Participants had to be within 6 months postpartum at the time of enrollment and to have a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥26, indicating severe depression. Patients were allowed to continue any ongoing antidepressants while receiving the study drug but were required to suspend breastfeeding during treatment and for the following 12 days. Women were randomly assigned to receive brexanolone or placebo in a continuous 60-hour infusion during inpatient care and were then followed as outpatients for a total of 30 days. The primary study outcome was change from baseline to 60 hours in HAM-D score. Secondary outcomes included response (≥50% reduction in HAM-D score) and remission (HAM-D score, ≤7).

**Results:** Mean baseline HAM-D scores were 28 and 29 in the brexanolone and placebo groups, respectively. Following infusion, women who received brexanolone experienced a mean 21-point reduction in HAM-D score, compared with an 8.8-point reduction in the placebo group (mean difference, 12.2 points; p=0.0075; effect size,* 1.2). Significant differences in the HAM-D between groups first appeared at the 24-hour assessment and persisted at the 7- and 30-day follow-up evaluations.
Response rates did not differ significantly between the active-treatment and placebo groups immediately following infusion (7 vs 4 women, respectively). However, the difference reached significance at 72 hours (80% vs 27%; \(p=0.037\)) and persisted at 7 days (80% vs 20%; \(p=0.033\)). Remission occurred within 60 hours in 7 of 10 patients receiving brexanolone and in 1 of 11 receiving placebo (odds ratio, \(23.33; p=0.036\)).

Brexanolone was well tolerated, and no serious adverse events or treatment discontinuations were reported. Common adverse events with brexanolone included dizziness (n=2), somnolence (n=2), sedation (n=1), and sinus tachycardia (n=1). At baseline, 2 patients in the brexanolone group reported active suicidal ideation with a plan; neither patient continued to have suicidal ideation during or after infusion.

**Discussion:** This study is the initial placebo-controlled trial in the ongoing clinical development program of brexanolone. Potential advantages of the treatment, relative to conventional antidepressants, include its large effects and rapid onset of action.

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


*See Reference Guide.

### Psychostimulants in Depression

Psychostimulants may reduce depressive symptom severity in patients with major depressive disorder or bipolar disorder, according to a meta-analysis of clinical trials.

**Background:** Stimulants and agents with stimulant-like activity are frequently prescribed off-label for adults with mood disorders. Their use is often empirical—i.e., they are prescribed for target symptoms that are frequent complaints in patients with depression, such as fatigue and apathy.

**Methods:** The analysis was based on a comprehensive search of English-language reports published before January 2016. Included were all randomized placebo-controlled trials of any FDA-labeled stimulant in adults with clinically significant depressive symptoms as part of major depressive disorder or bipolar disorder. Studies limited to patients with bipolar disorder were excluded. Stimulants were used as either adjunctive therapy or monotherapy and included armodafinil/modafinil, amphetamine, dextroamphetamine, lisdexamfetamine, and methylphenidate. The analysis included 21 studies with a total of 1900 patients (mean age, 44 years) who received treatment with a stimulant and 1823 controls (mean age, 43 years). The primary endpoint was investigator-identified response, measured in each study with a standardized rating scale for depression.

**Results:** Stimulant treatment was associated with a greater response rate for depressive symptoms than placebo (odds ratio [OR]* for response, 1.41; \(p=0.003\)). Response rates did not differ between patients with unipolar depression and those with bipolar disorder. In 10 studies with a total of nearly 2200 subjects, modafinil/armodafinil was superior to placebo (OR, 1.47; \(p=0.0002\)). Dextroamphetamine was statistically superior to placebo (OR, 7.11; \(p=0.04\)), but the comparison was based on a single, 2-week study in 22 patients. Other agents were numerically but not statistically superior to placebo. The analysis showed that adjunctive stimulants were associated with higher response rates than adjunctive placebo (OR, 1.39), but stimulant
monotherapy was not superior to placebo. In the few studies that reported data on mania, the incidence of manic or hypomanic induction was similar in patients receiving stimulants and controls.

**Discussion:** While these results suggest adjunctive psychostimulants may improve symptoms of depression, the analysis did find evidence of publication bias, and strong conclusions about their efficacy cannot be drawn. The pharmacodynamic profile of stimulants suggests that their clinical effects may be centered in specific symptom domains or dimensions, such as cognitive-emotional and neurovegetative symptoms.

**Study Rating*—16 (89%):** This study met most criteria for a systematic review /meta-analysis; however, the source of funding was not stated.

McIntyre R, Lee Y, Zhou A, Rosenblat J, et al: The efficacy of psychostimulants in major depressive episodes: a systematic review and meta-analysis. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000723. From the University of Toronto, Canada; and other institutions. Source of funding not stated. Four of 9 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.

**Common Drug Trade Names:** amphetamine—Evekeo; armodafinil—Nuvigil; dextroamphetamine—Dexedrine; lisdexamfetamine—Vyvanse; methylphenidate—Ritalin; modafinil—Provigil

*See Reference Guide.

### Metformin in Alzheimer's Disease

Treatment with metformin (*Glucophage*) showed promising effects on cognition and biomarkers of Alzheimer's disease in a placebo-controlled pilot study.

**Background:** Insulin resistance has been associated with Alzheimer’s-like biomarkers, reduced activation of cerebrocortical insulin receptors, and decreased cerebral glucose metabolism that correlates with memory impairment. Clinical trials with intranasal insulin and other antidiabetic drugs in patients with Alzheimer’s disease have had mixed results. Treatment with metformin, an insulin sensitizer, is a promising alternative approach, avoiding the risks of chronic insulin administration.

**Methods:** Study participants were patients aged 55–80 years with a diagnosis of mild cognitive impairment or early dementia due to Alzheimer’s disease, and with no history of diabetes or prediabetes. Eligibility criteria included fasting glucose <110 mg/dL or HbA1c <6.0, at least 1 positive biomarker for Alzheimer’s disease, a lack of evidence for vascular dementia, and a baseline Mini-Mental State Examination (MMSE) score >19. Patients taking a cholinesterase inhibitor were allowed to continue on a stable dose. Study treatment consisted of 8 weeks of randomly assigned metformin (titrated to 1000 mg b.i.d. or maximum tolerated dose) or placebo, followed by 8 weeks of the crossover treatment. Outcomes in this exploratory trial included cerebrospinal fluid (CSF) sampling, magnetic resonance imaging (MRI) to assess cerebral blood flow in specified regions, and testing with the Alzheimer’s Disease Assessment Scale-cognitive subscale, computerized neuropsychological assessments, the Geriatric Depression Scale, and the Dementia Severity Rating Scale.

**Results:** Study participants (n=20; 9 women) had a mean age of 70 years and baseline MMSE scores averaging 26. After 8 weeks of active treatment, metformin was detectable in CSF at average levels of about 10% of mean fasting plasma levels. There were no changes in CSF markers of Alzheimer’s disease. Functional MRI studies showed no statistically significant treatment effect in any of the predefined regions of interest, but patients who completed scans before and after both metformin and placebo exposure (n=17) showed a significant increase in superior and middle orbitofrontal cerebral blood flow with metformin but not placebo (p<0.05 for both regions). Cognitive testing showed a statistically significant improvement in 1 measure of executive function after metformin treatment (p<0.05).
Statistical trends favoring metformin were observed on measures of learning and memory, but not language or motor speed.

Common adverse effects of metformin were anorexia, diarrhea, nausea, hypoglycemia, and weight loss. Transient lactic acidosis developed in 2 patients. Metformin was not associated with changes in plasma glucose or insulin, depression, or functional status.

**Discussion:** Regardless of important limitations, including the small sample and crossover without a washout period, results of this study indicate that metformin crosses the blood-brain barrier and may improve executive function in patients with Alzheimer’s dementia. Additional studies appear to be warranted.

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


*See Reference Guide.

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**Antipsychotics: Real-World Effectiveness Compared**

According to a registry-based observational study, among available antipsychotics, oral clozapine and long-acting injectables (LAIs) are associated with the lowest rates of rehospitalization and treatment failure.

**Methods:** Study data were collected from Swedish national health care databases for all patients aged 16–64 years with a diagnosis of schizophrenia between mid-2006 and 2013. The primary study outcomes were psychiatric rehospitalization and treatment failure, a composite outcome that included rehospitalization, discontinuation or switch to another medication, or death. The rate of each outcome was compared within individual patients during outpatient treatment with different antipsychotics versus periods of non-use of the same antipsychotic or no antipsychotic use. The analyses were adjusted for time-dependent covariates, such as the order of treatment and time since diagnosis.

**Results:** Of nearly 30,000 patients followed for a mean of 6 years, 44% were rehospitalized and 72% experienced a treatment failure. In within-patient comparisons (periods of use vs non-use of medication), the lowest rates of rehospitalization were found for oral clozapine (hazard ratio [HR],* 0.53) and for LAI paliperidone, zuclopenthixol (not available in the U.S.), perphenazine, and olanzapine (HRs, 0.51–0.58). Oral flupenthixol (not available in the U.S.) and quetiapine were associated with the highest rates of rehospitalization (HRs, 0.92 and 0.91, respectively). When compared with oral olanzapine, the most frequently used antipsychotic, risk of rehospitalization was significantly lower with LAI zuclopenthixol and oral clozapine (HRs, 0.83 and 0.84, respectively); oral flupentixol, quetiapine, and haloperidol had significantly higher risk (HRs, 1.28–1.46).

Results were similar for the treatment failure outcome. The lowest rates of treatment failure were observed with clozapine (HR, 0.58) and the LAI agents (HRs, 0.65–0.80). Because patients’ probability of switching from clozapine to another medication is low, the analysis was repeated without medication switching as part of the composite outcome; clozapine was still associated with the best outcome.

**Discussion:** Efficacy comparisons of antipsychotic agents are generally based on randomized controlled trials, which exclude a large proportion of patients, often because of factors that may affect treatment outcome such as treatment refusal, substance abuse, or comorbidity.
Observational studies, which are more inclusive, have shown the best results with clozapine, olanzapine, and LAI agents; however, even these studies are vulnerable to selection bias. The present study showed LAI formulations were particularly beneficial in a sub-analysis of newly diagnosed patients. Rates of psychiatric hospitalization were 40–70% higher with quetiapine than the best-performing agents, which suggests quetiapine may not be a good monotherapy option in schizophrenia.


From the Karolinska Institutet, Stockholm, Sweden; and other institutions. Funded by Janssen-Cilag. Seven of 11 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.

Common Drug Trade Names: clozapine—Clozaril; olanzapine—Zyprexa; LAI paliperidone—Invega Sustenna, Invega Trinza; quetiapine—Seroquel

*See Reference Guide.

Lithium in Pregnancy and Cardiac Malformations

In a large, Medicaid-based, retrospective cohort study, lithium use in early pregnancy was found to be associated with a modest increase in the risk of cardiac malformations in infants.¹ The results confirm an association reported in the 1970s and reflected in the product labeling of lithium, but the increase in risk was much smaller than suggested by the earlier data.

Methods: The study cohort included all Medicaid-covered pregnancies resulting in a live birth in women aged 12–55 years in 46 states and the District of Columbia in 2000–2010. Exposure was defined as ≥1 filled prescription for lithium during the first trimester and no prescriptions during the 3 months before conception, to allow for possible overlap. The primary comparison group consisted of all women with no filled prescriptions for lithium or lamotrigine (Lamictal). A second comparison group consisted of women who filled a prescription for lamotrigine (not known to be associated with increased risk of congenital malformations) during preconception or early pregnancy. Women exposed to both drugs were excluded. The primary study outcome was the presence of any cardiac malformation in the infant. A secondary outcome was right ventricular outflow tract obstruction defects, a category that includes Ebstein’s anomaly, a defect associated with lithium in early data.

Results: The cohort consisted of >1.3 million pregnancies, including 663 in women exposed to lithium in the first trimester and 1945 in women exposed to lamotrigine. After adjustment for propensity scores and other covariates (e.g., age, comorbid conditions, concomitant medications), lithium was associated with an increased overall rate of cardiac malformations compared with lamotrigine (risk ratio,* 2.25) and with use of neither medication (risk ratio, 1.65). The adjusted increase in malformations with lithium was nearly 1 case per 100 births compared with no drug exposure and 1.45 cases per 100 births compared with lamotrigine exposure. Right ventricular outflow tract obstruction defects were found in 0.6 per 100 lithium-exposed pregnancies, a somewhat higher rate than in unexposed pregnancies (risk ratio, 2.66). None of these were specifically coded as Ebstein’s anomaly.

In a dose-response analysis, risk of cardiac malformation increased with the dosage of lithium, but not lamotrigine. All cases of right ventricular outflow obstruction defect occurred with a lithium dose of >600 mg/day.

Discussion: The final report of the International Register of Lithium Babies, published in 1979, was based on 18 infants with cardiac malformations from a total of 225 exposed pregnancies.² This study lacked a control group and may have been subject to biases. Despite warnings based on these data, lithium remains first-line treatment for bipolar disorder in
women of reproductive age, based on strong evidence of its efficacy. The present study suggests the increased risk is real but smaller than previously reported, and that risk is dose-dependent.

1Patorno E, Huybrechts K, Bateman B, Cohen J, et al: Lithium use in pregnancy and the risk of cardiac malformations. NEJM 2017;376 (June 8):2245–2254. From Brigham and Women’s Hospital; and other institutions, Boston, MA. Funded by the NIMH. Six of the 8 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.


*See Reference Guide.

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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 1 group has half the risk of the other group.

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.

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 (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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