Lamotrigine Dosing in Pregnancy

According to results of an observational study, women taking lamotrigine (Lamictal) for treatment of bipolar disorder may experience declining serum drug levels during pregnancy because estradiol increases lamotrigine clearance. These women also risk lamotrigine toxicity after delivery as drug clearance normalizes rapidly.

**Background:** Lamotrigine has a favorable reproductive safety profile compared with other anti-convulsants and is a preferred option for women of childbearing age. However, there is little data available regarding therapeutic dose monitoring during pregnancy in women with bipolar disorder.

**Methods:** The 8 women in this case series all had a diagnosis of DSM-IV bipolar I disorder that was treated with lamotrigine. They all chose to continue the drug throughout pregnancy and were recruited at or before 20 weeks’ gestation. Steady-state serum trough lamotrigine levels were measured as close as possible to weeks 20, 30, and 36 of gestation and at postpartum weeks 2, 12, and 30. Infant lamotrigine levels were measured 2–4 weeks after delivery.

**Results:** All infants were delivered full-term and healthy, and all were free of congenital malformations and developmentally normal. Lamotrigine dosages ranged from 100 to 300 mg/day. Of the 8 mothers, 6 received additional psychotropics (e.g., SSRIs, SNRIs, antipsychotics, benzodiazepines) at some point during pregnancy. Four patients required a lamotrigine dose increase after symptom worsening during the late second or third trimester.

Lamotrigine level-to-dose ratios were highly variable among patients and within patients throughout pregnancy and afterward. In general, level-to-dose ratios were lower during pregnancy than in the postpartum period. Compared with the early third trimester, postpartum lamotrigine serum levels increased an average of 172% (range 24–428%) within 5 weeks. At delivery, the mean umbilical cord lamotrigine level was 66% of the maternal level. In breastfed infants, the mean lamotrigine level was 33% of the maternal level.
**Clinical Implications:** Although no therapeutic level has been established for lamotrigine, studies of women with epilepsy indicate that maintaining preconception serum levels during pregnancy decreases the risk for recurrent seizures. The authors recommend titrating lamotrigine to the optimal therapeutic dosage and obtaining a serum level before a planned pregnancy (or as early as possible if the woman presents during pregnancy). During follow-up visits, symptoms should be assessed with the Young Mania Rating Scale, the Montgomery-Asberg Depression Rating Scale, or other self-report tools. Serum lamotrigine levels should be checked every 4 weeks, and if necessary the dosage increased by 20–25% to maintain target levels or reduce symptoms. In women who have had multiple (≥4) increases, the dosage should be decreased by 20–25% immediately after delivery to prevent lamotrigine toxicity. The serum level should be checked every 1–2 weeks in all patients and the dosage adjusted until the level returns to the pre-pregnancy baseline.

Clark C, Klein A, Perel J, Helsel J, et al: Lamotrigine dosing for pregnant patients with bipolar disorder. *American Journal of Psychiatry* 2013;170 (November):1240–1247. From Northwestern University Feinberg School of Medicine, Chicago, IL; and other institutions. **Funded by the NIMH. The authors declared no competing interests.**

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### Serotonin Antagonists for Neuroleptic-Induced Akathisia

Drugs with 5-HT$_{2A}$ receptor antagonist activity are highly effective in treating neuroleptic-induced akathisia, according to results of a systematic review and meta-analysis. The small number and size of the available clinical trials may be a limitation, however, the statistically significant result indicates these drugs have a clear and substantial benefit.

**Background:** Propranolol is considered first-line treatment for neuroleptic-induced akathisia. However, the effectiveness of this drug is limited by adverse effects (e.g., hypotension, bradycardia), contraindications (e.g., diabetes, bronchial asthma), and drug interactions based on its CYP450 activity. Limited evidence supports use of anticholinergics and benzodiazepines, but additional options are needed. The antagonism of the atypical antipsychotics at 5-HT$_{2A}$ receptors appears to account for their low incidence of extrapyramidal symptoms, so several studies have examined the effects of serotonin antagonists for treatment of akathisia.

**Methods:** The reviewers searched for all randomized trials, with either an active or placebo control, using serotonin receptor antagonists to treat neuroleptic-induced akathisia. They identified 6 trials of 4 different agents: cyproheptadine; mianserin; mirtazapine; and trazodone. The studies had little heterogeneity, and there was low risk of publication bias.

**Results:** In a head-to-head comparison of cyproheptadine and propranolol, 30 patients received randomized study medication for 4 days and were observed for another 3. The 2 drugs had similar effects on akathisia. Symptoms worsened on day 4 when cyproheptadine was stopped. The remaining 5 trials were placebo-controlled and lasted from 5 to 7 days. The antidepressant mianserin was superior to placebo in 2 studies with a total of 67 subjects. Mirtazapine was superior to placebo in 2 trials that included a total of 86 patients. One of these studies also included a propranolol arm; mirtazapine and propranolol were equally effective, but mirtazapine was better tolerated. In the final study, in 13 patients, the antidepressant trazodone was superior to placebo.

All 6 studies used the Barnes Akathisia Rating Scale (BARS) as the primary outcome measure, with response defined as a reduction of ≥2 points. In the pooled data from the 6 studies, 5-HT$_{2A}$ antagonists were associated with about 7 times the likelihood of response as placebo (relative risk,* 7.1; p<0.0001). Of the 86 patients who received serotonin receptor antagonists in the 6 studies, 26 experienced remission (5 times the rate in the placebo group). Because of the small number of studies, differences in efficacy among the serotonin antagonists could not be detected.
Two studies reported no adverse effects, and 2 reported only sedation. The drugs had no effect on the severity of psychotic symptoms. Based on the existing literature, mirtazapine appears to have a more favorable side-effect profile than the other agents studied. The authors recommend low-dose mirtazapine over propranolol as first-line treatment for neuroleptic-induced akathisia. The studies provide no guidance on how long treatment should be continued.

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

Laoutidis Z, Luckhaus C: 5-HT2A receptor antagonists for the treatment of neuroleptic-induced akathisia: a systematic review and meta-analysis. *International Journal of Neuropsychopharmacology* 2013; doi 10.1017/S1461145713001417. From Heinrich Heine University, Dusseldorf, Germany. Source of funding not stated. The authors declared no competing interests.

**Drug Trade Names:** cyproheptadine—Periactin; mianserin (not available in U.S.)—Norval, Tolvan; mirtazapine—Remeron; propranolol—Inderal; trazodone—Desyrel, Oleptro, Tri lodine

*See Reference Guide.

### Add-on Benzoate for Schizophrenia

Adjunctive treatment with benzoate improved negative symptoms and had modest cognitive benefits in patients with schizophrenia. Benzoate, a natural constituent of foods and a commercial food preservative, inhibits D-amino acid oxidase (DAAO) and may increase amino acid levels and N-methyl-D-aspartate (NMDA) function in the CNS.

**Methods:** This 6-week randomized, placebo-controlled trial was conducted at 2 hospitals in Taiwan. Participants had residual symptoms of schizophrenia, with Positive and Negative Syndrome Scale (PANSS) scores of ≥60, despite stable ongoing antipsychotic treatment. Based on results of a previous dose-finding trial, active treatment consisted of 1000 mg/day benzoate in divided doses. The primary study outcome was the PANSS total score, measured at 2-week intervals. Secondary clinical outcomes were negative symptoms, overall illness severity, depressive symptoms, and quality of life. Patients also were administered a battery of neurocognitive tests at baseline and after treatment. The tests measured 7 different cognitive domains and were analyzed as a composite score both including and excluding the social cognition domain. (Excluding this domain is considered preferable if the drug is thought to have effects limited to nonsocial domains of cognition.)

**Results:** Fifty-two patients received randomized treatment. Benzoate or placebo was added to atypical antipsychotics in about half of patients and to conventional neuroleptics in about half. Patients had a mean age of 37 years and a mean of 3 lifetime hospitalizations. Five patients did not adhere to the study protocol (1 benzoate, 4 placebo) and were removed from the study.

The mean PANSS score decreased from about 90 to 72 in patients who received benzoate and from 87 to 81 in the placebo group (effect size,* 1.53; p<0.001). Benzoate was also associated with significant improvement in positive symptoms (effect size, 1.69; p<0.001), negative symptoms (effect size, 1.19; p<0.001), and the other clinical outcomes (effect sizes between 0.74 for depression and 1.5 for quality of life). A post-hoc analysis showed that the effects of benzoate were similar in patients who received risperidone and haloperidol, the 2 most frequently used baseline antipsychotics.

Benzoate also had a modest, but statistically significant, positive effect on cognition, in general and specifically in processing speed and visual memory, regardless of whether social cognition was included in the composite score. The improvement in cognition was independent of changes in psychopathology. Benzoate was well tolerated and had no notable side effects.

**Discussion:** Results of many studies suggest glutamatergic hypofunction may be involved in schizophrenia, but the development of drugs that target this mechanism has had poor or mixed
results. Benzoate, which occurs as benzoic acid in milk and other animal and plant foods, is recognized as a safe food additive and widely used in food manufacturing. Benzoate has high CNS bioavailability compared with other agents with similar mechanisms, which may account for its apparently larger effects. Because of the potential for benzoic acid and its salts to react with ascorbic acid to form benzene, a known carcinogen, benzoate and high-content ascorbic acid should not be ingested concurrently.

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


From China Medical University Hospital, Taichung, Taiwan; and other institutions. **Funded by the National Science Council of Taiwan; and other sources. One study author disclosed financial relationships with commercial sources relevant to the study material.**

*Drug Trade Names*: haloperidol—Haldol, and others; risperidone—Risperdal, and others

**Vortioxetine for MDD**

The antidepressant vortioxetine (*Brintellix*) recently received FDA approval for once-daily treatment of major depressive disorder in adults. Lundbeck and Takeda, who co-developed the drug, anticipate the product launch by the end of 2013. As with other antidepressants, the vortioxetine label will carry a boxed warning regarding the risk of suicidal thoughts and behavior with antidepressants in children, adolescents, and young adults.

Vortioxetine has a high affinity for serotonin (5-HT) transporter binding and is a potent serotonin reuptake inhibitor; its affinity for noradrenaline and dopamine transporters is much lower or negligible. Vortioxetine is also a 5-HT₁₄ receptor agonist, a partial 5-HT₁₉ agonist, and a 5-HT₁D, 5-HT₃, and 5-HT₇ receptor antagonist. Vortioxetine has linear dose-proportional pharmacokinetics following once-daily administration, and steady states are usually achieved within 2 weeks.

Vortioxetine undergoes extensive metabolism via several cytochrome P450 (CYP) enzymes. In healthy volunteers, vortioxetine exposure was increased when the drug was coadministered with the CYP inhibitors bupropion, fluconazole, and ketoconazole, but not with omeprazole. Vortioxetine dosages should be halved when used in combination with strong CYP2D6 inhibitors (e.g., bupropion, paroxetine, fluoxetine), and the dosage should be increased when used in combination with strong CYP enzyme inducers (e.g., carbamazepine, phenytoin). Plasma concentrations of the drug are approximately twice as high in poor CYP2D6 metabolizers as in extensive CYP2D6 metabolizers. No dosage adjustments are required when vortioxetine is coadministered with warfarin or aspirin. Pharmacokinetics of birth-control drugs do not appear to be altered. Steady-state pharmacokinetics of lithium are also not affected by vortioxetine, and lithium dosages do not require adjustment. Careful monitoring is advised when starting or stopping vortioxetine in patients receiving other drugs that affect hemostasis. Given its mechanism of action and the resultant serotonin toxicity potential, individuals taking vortioxetine in combination with serotonergic agents (e.g., SSRIs, SNRIs, triptans) may develop serotonin syndrome. Concomitant use of an MAOI and vortioxetine is contraindicated, as is use of an MAOI within 3 weeks of discontinuing vortioxetine, as well as use of vortioxetine within 2 weeks of discontinuing an MAOI.

Exposure to vortioxetine does not appear to be affected by age; race; gender; mild, moderate, severe or end-stage renal disease; or mild-or-moderate hepatic impairment. However, the drug is not recommended for use in patients with severe hepatic impairment, as it has not been studied in this population.
Vortioxetine has been shown to be effective in clinical trials of acute depression, including studies limited to geriatric patients and in relapse-prevention studies. Although generalized anxiety disorder is not an approved indication for the drug, some studies have also shown positive effects of vortioxetine on symptoms of the disorder (both as acute treatment and for relapse prevention).

In clinical trials, vortioxetine in the recommended dosage range (5–20 mg/day) was generally well tolerated. Commonly reported adverse effects include nausea, constipation, and vomiting. Few patients reported sexual dysfunction with vortioxetine in clinical trials, and the comparative effects of vortioxetine and escitalopram on sexual functioning are being compared in an ongoing trial in adults with major depression. Few serious adverse effects occurred during clinical trials, but the agent was associated with left hemispheric ischemic stroke and tachycardia in long-term extension studies. Abrupt discontinuation of higher dosages (i.e., 15 and 20 mg/day) is not recommended as some patients may experience mood swings; sudden anger outbursts; headache; dizziness; and muscle tension during the week after discontinuation.


Drug Trade Names: bupropion—Wellbutrin; carbamazepine—Epitol, Tegretol; escitalopram—Lexapro; fluconazole—Diffucan; fluoxetine—Prozac; omeprazole—Prilosec; paroxetine—Paxil; phenytoin—Dilantin; vortioxetine—Brintellix; warfarin—Coumadin

**Adjunctive Mirtazapine for Negative Symptoms**

Adding mirtazapine to olanzapine therapy produced significant improvement in negative symptoms in a group of inpatients with schizophrenia.

**Methods:** Study subjects were 28 patients (mean age, 29 years; 21 men) with schizophrenia who were hospitalized for exacerbation of psychotic symptoms. Beginning on admission, all participants received 8 weeks of olanzapine monotherapy at a mean dosage of 16.5 mg/day. Patients were then randomized to double-blind add-on treatment with either placebo or 30 mg/day mirtazapine for an additional 8 weeks. Olanzapine dosages were unchanged during the second 8-week treatment phase. Positive and negative symptoms were evaluated at study entry, after 8 weeks of olanzapine monotherapy, and after 8 weeks of add-on treatment using the Positive and Negative Syndrome Scale (PANSS).

**Results:** Of the 28 patients enrolled, 20 completed 8 weeks of olanzapine monotherapy and initiated randomized treatment. Of these, 2 withdrew before completing the randomized phase (1 in each treatment group). Early discontinuations were not related to treatment. There were no significant differences between the groups in PANSS positive, negative, or total scores at study entry (before olanzapine treatment) or at randomization.

At 16 weeks, patients in the mirtazapine group demonstrated a significant decrease in mean PANSS negative symptom score from 21.5 at baseline to 15.2 (p<0.002). Scores also decreased in the placebo group (from 20.4 to 18.8), but the improvement was not statistically significant. The calculated between-group effect size* was 0.97 in favor of mirtazapine. PANSS scores for positive symptoms and general psychopathology were not significantly improved in either treatment group. Working memory deficits, evaluated using the N-back task, were also not significantly improved. No serious adverse effects were reported.

**Discussion:** Negative symptoms of schizophrenia are presumed to be associated with impaired dopamine function in the prefrontal cortex. The positive effects of mirtazapine on negative symptoms may be related to its effects on noradrenergic and serotonergic signaling, which may
increase dopamine levels in the prefrontal cortex. Previous studies have shown no significant pharmacokinetic interaction between mirtazapine and second-generation antipsychotics, suggesting the positive effects have pharmacodynamic roots. Although the study is limited by a small sample size and short duration, the positive results suggest further study of adjunctive mirtazapine for negative symptoms may be warranted.

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

Caforio G, DiGiorgio A, Rampino A, Rizzo M, et al: Mirtazapine add-on improves olanzapine effect on negative symptoms of schizophrenia [letter]. *Journal of Clinical Psychopharmacology* 2013;33 (December):810–812. From the University of Bari, Italy; and other institutions. **Funded by the Stanley Medical Institute; and Organon Italy. One study author disclosed a financial relationship with a commercial source; the remaining authors declared no conflicts of interest.**

*Drug Trade Names: mirtazapine—Remeron; olanzapine—Zyprexa*

*See Reference Guide.*

### Clozapine-Associated Hypokalemic Hypertension

A 47-year-old man with a long history of schizophrenia was admitted to a psychiatric clinic for treatment of persistent symptoms of psychosis. On admission, the patient’s general health appeared to be good and he was taking no medications. He was started on 25 mg/day clozapine, which was titrated over several days to 150 mg/day. Because plasma clozapine levels were subtherapeutic (115 ng/mL), the dosage was slowly increased to 250 mg/day. Plasma levels increased to 220 ng/mL, and hypertension and tachycardia were noted. Laboratory evaluation showed hypokalemia (serum potassium, 2.8 mEq/L; reference range, 3.5–5.0 mEq/L). Treatment with the antihypertensives perindopril and metoprolol, in conjunction with potassium supplementation, resulted in partial correction of both hypertension and hypokalemia. Clozapine was tapered and stopped, and the patient’s blood pressure and serum potassium levels normalized. Within 1 week, the antihypertensives were also stopped. The patient refused rechallenge with clozapine.

Clozapine has been associated with hypertension and other adverse cardiac effects, but hypokalemia, which can lead to arrhythmia, has not been previously reported. The exact mechanism is unknown but may be associated with clozapine-associated mineralocorticoid excess or elevated levels of catecholamines. Although without rechallenge the association cannot be confirmed, according to the Naranjo probability scale,* the hypokalemia was a "probable" effect of clozapine treatment.

Hoorn E, van der Poel M: Hypokalemic hypertension related to clozapine: a case report [letter]. *Journal of Clinical Psychopharmacology* 2013; doi 10.1097/JCP.0000000000000044. From Erasmus Medical Center, Rotterdam; and Parnassia Bavo Psychiatric Institute, Rotterdam, The Netherlands. **The authors declared no conflicts of interest.**

*Drug Trade Names: clozapine—Clozaril; metoprolol—Lopressor; perindopril—Aceon*

*See Reference Guide*

### Repeated Ketamine Infusions for Depression

In a small, open-label study, repeated infusions of the N-methyl-D-aspartate antagonist ketamine (*Ketalar*) added to ongoing antidepressant drugs produced high rates of response and remission in patients with treatment-resistant depression. The trajectory of response was highly variable, with three-fourths of patients requiring multiple infusions and about half having sustained responses.

**Methods:** Participants in this open-label study were required to have current major depression of at least moderate severity that did not remit despite ≥2 trials of antidepressants from different classes. Patients were required to be receiving stable doses of their current antidepressant and augmenting agents for ≥2 months before study entry.
Patients received ketamine infusions on a Monday-Wednesday-Friday schedule over 2 weeks. Ketamine was dosed at 0.5 mg/kg of ideal body weight and infused over 40 minutes, followed by monitoring for at least 2 hours. The Montgomery-Asberg Depression Rating Scale (MADRS) was administered at baseline, before each infusion, at several intervals during the 2-hour post-treatment observation, and then weekly for 4 weeks after the end of treatment. Response was defined as a $\geq$50% improvement in MADRS score, remission as a score of $\leq$9, and relapse as a return to $<50\%$ improvement from baseline.

**Results:** A total of 14 patients, all men, were enrolled in the study. They had a mean age of 54 years and were chronically depressed, with $>3$ lifetime episodes and a 17-month mean duration of the present episode. Baseline MADRS scores ranged from 22 to 40. Four patients had a history of suicide attempts, and 2 had received ECT.

One patient withdrew after the first treatment because of low energy and irritability, and another after the second, citing dissatisfaction with the therapeutic effect. Of the remaining 12 patients, 3 met response criteria after the first ketamine infusion. After receiving at least 3 infusions, 7 patients met response criteria, 6 of whom achieved remission. After the full 6 infusions, 11 patients (92%) achieved response and 8 patients (67%) experienced remission. The average MADRS score decreased by 19 points (p<0.001) compared with baseline. Of the 11 responders, 5 remained in response throughout the 4 weeks of follow-up. The 6 patients who experienced relapse did so within an average of 16 days.

Ketamine resulted in mild increases in psychotomimetic and dissociative symptoms, but these changes resolved within 2 hours after each treatment ended. No patient experienced arrhythmia or required respiratory support during the infusions.

**Discussion:** Most previous studies of ketamine infusion have required withdrawal of background antidepressants, which may be impractical in clinical practice. The present study shows that antidepressant effects of ketamine can be achieved safely without the usual 7-day drug washout.

Shiroma P, Johns B, Kuskowski M, Wels J, et al: Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. *Journal of Affective Disorders* 2013; doi 10.1016/j.jad.2013.10.036. From Minneapolis VA Medical Center, MN; and other institutions. Funded by the Minneapolis VA Medical Center. The authors declared no conflicts of interest.

### Bupropion in Schizophrenia: Risks and Benefits

In patients with schizophrenia who receive antipsychotic treatment, the addition of bupropion is associated with little risk of emerging psychotic episodes, according to a systematic review.

Concerns about the risks of bupropion in psychosis stem from its profile of receptor activity, unique among antidepressants. Bupropion selectively inhibits dopamine and norepinephrine reuptake and is a noncompetitive antagonist at central nicotinic acetylcholine receptors. Case reports of bupropion-associated psychoses appeared after the initial launch of the drug.

A systematic review was conducted of all reports of bupropion-associated psychosis and all studies in which patients with psychosis received treatment with bupropion. Of 30 reported cases of bupropion-associated psychosis, only 2 occurred in patients concurrently taking antipsychotic medication. The patients who experienced psychosis included 13 with a previous diagnosis of a psychotic-spectrum disorder, a family history of schizophrenia, or other risk factors and 5 who had psychotic symptoms as part of a delirious state or serotonin syndrome.

All but 1 of the cases of bupropion-associated psychosis occurred with immediate- or slow-release formulations, which suggests the newer extended-release formulation is associated with lower risk. Because the 3 formulations differ in absorption time but not bioavailability, it seems absorption speed may correlate with the risk of psychotic symptoms. Psychosis has been associated with overdoses of bupropion, but psychotic symptoms have mostly occurred at doses...
within the recommended range and even with low-dose treatment, suggesting other factors such as personal susceptibility and polypharmacy may contribute to risk. Most reported cases have been associated with polypharmacy, switches in medication, or psychotropic drug use/abuse.

Other positive psychotropic effects of bupropion in schizophrenia—e.g., improvement in cognition, depression, and negative symptoms—are suggested by its mechanisms but not yet supported by clinical research. In 1 controlled study, adjunctive bupropion was inferior to placebo as an antidepressant in patients with schizophrenia and comorbid depression. With this exception, possible effects on depression have been observed as secondary outcomes in smoking-cessation studies, with no consistent results.

The review also identified patients with psychotic-spectrum disorders who received treatment with bupropion for smoking cessation (n=184) or depression (n=49). All but 9 of these patients were clinically stable on antipsychotic medications. None had emergence or worsening of psychotic symptoms. Bupropion appears effective for smoking cessation in persons with schizophrenia. However, there have been relatively few studies and little long-term data. According to 1 meta-analysis, bupropion increased quit rates 2.5-fold compared with placebo and reduced cigarette consumption in those who continued to smoke.

**Study Rating**—**14 (78%)**: This study met most criteria for a systematic review. However, individual study quality was not assessed and the source of funding was not stated.


**Drug Trade Names**: bupropion—Wellbutrin, Zyban

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**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.

**Naranjo Probability Scale**: A 10-point scale used to determine the likelihood that an adverse reaction is caused by an implicated medication. Based on scores, associations are considered doubtful, possible, probable, or highly probable.

**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.