Adjunctive Hormonal Treatment in Mania

In a randomized controlled trial, adjunctive medroxyprogesterone acetate (MPA) improved symptoms of mania in women with bipolar or schizoaffective disorder.¹

**Background:** Both tamoxifen and MPA are estrogen antagonists. Tamoxifen is also a potent inhibitor of protein kinase-C (PKC), and manic symptoms are correlated with fluctuations in this enzyme. In a previous pilot study by these researchers,² improvement in manic symptoms was observed with adjunctive tamoxifen treatment and to a lesser degree with MPA. Tamoxifen was the primary focus of the present study, and MPA was a comparison treatment to separate the effects of PKC inhibition from those of estrogen antagonism.

**Methods:** Study participants were 51 women, aged 18–65 years, with a diagnosis of bipolar disorder (n=42) or schizoaffective disorder (n=9). Despite ongoing therapy with a mood stabilizer or mood-stabilizing antipsychotic, all women were experiencing mania (i.e., Clinician Administered Rating Scale for Mania [CARS-M] score of ≥15) at study entry. The women were not taking oral contraceptives or other hormonal treatments. They were randomly assigned to adjunctive treatment with 40 mg/day tamoxifen, 20 mg/day MPA, or placebo. The CARS-M and platelet levels of PKC were measured weekly for the 4-week study.

**Results:** There were no significant baseline differences between the groups in age or diagnosis. Distribution of mood-stabilizer (>90% of patients) and antipsychotic (about 13% of patients) treatment also did not differ. The CARS-M decreased from baseline in all treatment groups, but to a greater degree and more quickly in patients who received MPA than either tamoxifen or placebo. The mean baseline CARS-M scores were 25 in the MPA group and 30 in the tamoxifen and placebo groups. By week 4, these had decreased to about 10 with MPA, 12 with tamoxifen, and 14 with placebo. The between-group difference was statistically significant (p<0.05) at week 3, but not at week 4. Mean PKC levels also decreased over time in the 2 groups receiving hormonal therapy but increased in the placebo group, although these trends were not statistically significant. PKC levels were more stable in the MPA group than the others. Estradiol levels increased in the tamoxifen group only.
Discussion: The difference between these results and the earlier pilot study may be attributed to the larger sample size of the present study, the authors say. The tamoxifen dose was relatively low to avoid inducing hot flashes. Although the pilot study also used a 40-mg dose of tamoxifen, it is possible that a treatment effect might be evident with higher doses.

The lack of a treatment effect on PKC levels was an unexpected finding. It is possible that higher serum estradiol levels might have negated the effect of PKC inhibition in the tamoxifen group. Alternatively, MPA might affect mania via pathways other than PKC inhibition.

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

1Kulkarni J, Berk M, Wang W, Mu L, et al: A four week randomised control trial of adjunctive medroxyprogesterone and tamoxifen in women with mania. *Psychoneuroendocrinology* 2014; doi 10.1016/j.psyneuen.2014.02.004. From Monash University and Alfred Hospital, Melbourne, Australia; and other institutions. Funded by the Stanley Medical Research Institute; and the National Health and Medical Research Council. The authors disclosed no financial relationships with commercial sources.


Drug Trade Names: medroxyprogesterone acetate—Provera; tamoxifen—Nolvadex

*See Reference Guide.

### Antipsychotic Dose Adjustments in Nonsmokers

According to results of a meta-analysis, doses of olanzapine and clozapine should be reduced by 30% and 50%, respectively, in nonsmokers to obtain equivalent drug concentrations to smokers.

**Background:** About 60–90% of patients with schizophrenia are smokers. Cigarette smoke increases the activity of CYP1A2, which metabolizes both olanzapine and clozapine. Numerous studies have reported higher concentrations of these drugs in nonsmokers than in smokers, but there has been no definitive agreement regarding a dose adjustment in nonsmokers.

**Methods:** Investigators combined data from all available studies of the effects of smoking on the disposition of olanzapine and clozapine under steady-state dosing in human subjects. Studies were required to be published in English-language peer-reviewed journals and to report outcomes as mean plasma concentration-to-dose (C/D) ratios (calculated as plasma concentration [ng/mL] divided by daily dosage).

**Results:** The olanzapine analysis was based on 7 studies including 652 smokers and 442 nonsmokers with schizophrenia or other psychiatric disorders. The C/D ratio was significantly lower in smokers than in nonsmokers, with a mean C/D ratio difference of −0.75 (p<0.00001). Smoking increased olanzapine clearance by 55%. Previous research indicates that the clinical efficacy of olanzapine is clearly associated with the plasma drug concentration, with a therapeutic range of 20–50 ng/mL. The standard doses of olanzapine in Japan, where the analysis was conducted, are 10 and 20 mg/day. To achieve equivalent concentrations in nonsmokers, the dosages would need to be reduced by 30%, to 7 and 14 mg/day.

The 4 studies of clozapine included 120 smokers and 76 nonsmokers with schizophrenia or other psychiatric disorders. The C/D ratio was significantly lower in smokers, with a mean difference of −1.11 (p<0.00001). It should be noted that clozapine pharmacokinetics vary widely among patients, and the relationship of clozapine concentrations to clinical outcomes is controversial. It has been reported that clozapine dosages must be regulated carefully during smoking cessation. The usual clozapine dosages in Japan—200 and 400 mg/day—would be halved in nonsmokers.

**Discussion:** Other factors, including gender, age, comedication, and genotype, can affect the disposition of both olanzapine and clozapine. The authors caution that data in the present
analysis was insufficient to evaluate the effects of these factors, and the influence of smoking on antipsychotic doses may vary in different populations such as the elderly and other diagnostic subgroups.

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

Tsudo Y, Saruwatari J, Yasui-Furukori N: Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine. *BMJ Open* 2014; doi 10.1136/bmjopen-2013-004216. From Kumamoto University; and Hirosaki University School of Medicine, Japan. Funded by the Japanese Ministry of Education, Science, Sports and Culture. The authors disclosed no competing interests.

**Drug Trade Names:** clozapine—Clozaril; olanzapine—Zyprexa

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**Venlafaxine for Hoarding Disorder**

Extended-release venlafaxine was effective and well tolerated in a small open-label study of patients with hoarding disorder.¹

**Methods:** Study participants were 24 adults (mean age, 52 years; range, 33–61 years; 21 women), recruited by advertising or clinically referred, who met DSM-5 diagnostic criteria for hoarding disorder as their primary, most distressing or impairing condition. All patients received 12 weeks of venlafaxine treatment, initially titrated over 3 weeks to a target of 225 mg/day. The venlafaxine could be increased to a maximum of 300 mg/day or reduced if clinically indicated. Other drugs, cognitive behavioral therapy (CBT), and help from professional organizers or other third parties were not permitted. The severity of hoarding-disorder symptoms was evaluated at baseline and the end of treatment using 2 different scales. The UCLA Hoarding Severity Scale (UHSS) has 3 component factors: 1) associated features and functional impairment; 2) clutter and social impairment; and 3) excessive acquisition, distress with discarding, and the need to save possessions. The Saving Inventory-Revised (SI-R) has 3 subscales that measure difficulty discarding, excessive clutter, and compulsive acquisition. Response was defined as a ≥30% decrease in scores on both of these scales and a rating of at least "much improved" on the Clinical Global Impression–Improvement Scale.²

**Results:** Except for 1 patient who moved away, all participants completed the 12 weeks of treatment. The mean final venlafaxine dosage was 204 mg/day. At week 12, compulsive hoarding symptoms had decreased by an average of 36% on the UHSS (p<0.0001) and by 32% on the SI-R (p<0.001). The effect sizes² were large: 1.98 for the UHSS and 1.68 for the SI-R. Statistically significant decreases were observed for all 3 symptom clusters of both the UHSS and the SI-R. Sixteen patients were classified as treatment responders. Large improvements were also observed in secondary study outcomes of depression, anxiety, obsessive-compulsive symptoms, and overall functioning.

**Discussion:** Venlafaxine was selected for study in part because of its tolerability in older patients. Taken together with these authors' previous reports of the efficacy of paroxetine,² the results indicate that SNRI or SSRI therapy may be as effective for hoarding as for non-hoarding obsessive-compulsive disorder.

¹Saxena S, Sumner J: Venlafaxine extended-release treatment of hoarding disorder. *International Clinical Psychopharmacology* 2014; doi 10.1097/YIC.0000000000000036. From the University of California San Diego School of Medicine. Funded by the NIMH; and other sources. The authors disclosed no conflicts of interest.


**Drug Trade Names:** paroxetine—Paxil; venlafaxine, extended release—Effexor XR

*See Reference Guide.
Antipsychotic Dose Equivalents

Several methods have been developed to estimate antipsychotic dose equivalents, but none is considered a gold standard. Based on the literature, the most frequently used is the minimum effective dose method, first described in 2003 and based on fixed-dose placebo-controlled studies of 5 antipsychotics. The present systematic review refined previous methods and determined the minimum effective dose for all 10 currently available second-generation antipsychotics, plus haloperidol, the most common first-generation comparator.

Methods: The analysis is based on all available published and unpublished randomized, double-blind, placebo-controlled trials. The primary criterion for the minimum effective dose was the lowest dose that was statistically superior to placebo for the primary outcome of ≥1 trial. Various problems in trial methodology, including the increasing placebo response rate and the increasing number of failed trials, make it likely that a single positive result is a true finding. The authors also applied a more conservative criterion in a sensitivity analysis: If the minimum effective dose is supported by only a single trial, the next highest dose that was effective in another trial qualified for the secondary criterion.

Results: The analysis included 73 trials, the majority lasting 6–8 weeks. The minimum effective dose could be estimated for all currently available second-generation agents (see table), although the evidence supporting a few estimates was weak. Aripiprazole was the only drug for which ≥1 trial identified the same minimum effective dose.

Discussion: The optimal method to investigate dose equivalence is by direct comparisons, but given the large number of available atypical antipsychotics, this is unlikely to happen. The limitations of the present method should be viewed in the context of the other available methods, such as Cochrane meta-analyses or the World Health Organization’s daily defined dose (DDD) method, which also have their shortcomings. Effect sizes* for some of the compared doses were in a similar range, commonly identified as "medium", thus it is possible that lower doses may be effective.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Minimum Effective Dose</th>
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<tbody>
<tr>
<td></td>
<td>Primary Criterion</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>10 mg*</td>
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<tr>
<td>asenapine</td>
<td>10 mg</td>
</tr>
<tr>
<td>clozapine</td>
<td>300 mg</td>
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<tr>
<td>haloperidol</td>
<td>4 mg</td>
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<tr>
<td>iloperidone</td>
<td>8 mg†</td>
</tr>
<tr>
<td>lurasidone</td>
<td>40 mg</td>
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<tr>
<td>olanzapine</td>
<td>7.5 mg</td>
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<tr>
<td>paliperidone</td>
<td>3 mg</td>
</tr>
<tr>
<td>quetiapine</td>
<td>150 mg</td>
</tr>
<tr>
<td>risperidone</td>
<td>2 mg</td>
</tr>
<tr>
<td>ziprasidone</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

*Minimum effective dose calculation based on ≥3 trials.
†Minimum effective dose is 12 mg if the single study including patients with schizoaffective disorder is excluded.

Funded by the German Federal Ministry of Education and Research; and other sources. Four of 6 study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no conflicts of interest.

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

*See Reference Guide.
Ramelson for Prevention of Delirium

Results of a randomized trial indicate that the melatonin agonist ramelson (Rozerem) is highly effective in preventing delirium during acute hospitalization in elderly patients.1 The findings also suggest that melatonin neurotransmission may be involved in the pathogenesis of delirium.

Background: Delirium reportedly affects up to 56% of elderly hospitalized patients; however, no medications are FDA approved to treat it. Antipsychotics are often used, but safety is questionable. Because research has shown melatonin to be associated with reduced risk, the melatonin agonist ramelson has been suggested as an option to prevent delirium.

Methods: Study subjects, aged 65–89 years (mean age, 78 years), were hospital inpatients newly admitted for serious medical problems. Patients were excluded if they were likely to die or to be discharged within 48 hours, if they had conditions associated with cognitive fluctuation, or if they were taking medications such as antipsychotics that could affect delirium. Patients were randomly assigned to receive 8 mg/day ramelson or placebo, administered at bedtime for 7 days. The primary study outcome was the occurrence of delirium.

Results: Of >1100 patients assessed for eligibility, 67 met the study’s entry requirements and were randomly assigned to treatment. The vast majority of patients (n=964) were ineligible because they had been intubated or had a life expectancy or expected duration of inpatient treatment of <48 hours. Six patients in the placebo group and 8 in the ramelson group discontinued medication without experiencing delirium before 7 days; all were included in the analysis.

Delirium, diagnosed using DSM-IV criteria, occurred in 1 patient in the ramelson group and 11 in the placebo group (3% vs. 32%; p=0.003). The relative risk* of delirium with ramelson was 0.09. The effect of ramelson remained statistically significant after adjustment for age, dementia, and an admitting diagnosis of infection. There were no differences in the use of rescue sleep medication or in sleep metrics between the groups. There were no adverse effects reported that were attributable to ramelson.

Discussion: Melatonin, which regulates the sleep-wake rhythm, becomes depleted in old age. In a previous controlled trial, melatonin was associated with reduced risk of delirium.2 The effect of ramelson in the present study was larger than that reported for melatonin, possibly a result of its higher potency.

1Hatta K, Kishi Y, Wada K, Takeuchi T, et al: Preventive effects of ramelson on delirium: a randomized placebo-controlled trial. JAMA Psychiatry 2014; doi 10.1001/jamapsychiatry.2013.3320. From Juntendo University, Tokyo, Japan; and other institutions. Funded by the Japan Society for the Promotion of Science. Six of the 7 study authors disclosed financial relationships with commercial sources.


*See Reference Guide.

Arrhythmia Risk in Psychiatry

Risk of cardiac arrhythmia associated with QT prolongation induced by psychotropic drugs is an important consideration in clinical practice. A guideline for managing risk of drug-induced arrhythmias has been developed jointly by the Danish Psychiatric Society and the Danish Society of Cardiology. The guideline reviews what is known about risk with individual drugs, and recommends a series of steps for managing use of the drugs associated with increased risk.

The guideline is based on evidence from 5 sources, including the FDA and the European Medicines Agency, as well as publications of “thorough QT studies,” which have been mandated by European regulators for all new drugs since 2005. QT prolongation is used as a...
marker for potentially life-threatening ventricular tachycardia. In the guideline, psychotropic medications are categorized as Class A, with no apparent risk of QT interval prolongation or Torsades de pointes; Class B, with a propensity to induce QT prolongation; and Class B*, with pronounced QT prolongation, documented cases of Torsades de pointes, or other serious arrhythmias.

In general, anxiolytics and mood stabilizing anticonvulsants are Class A agents, as are most SNRI and SSRI antidepressants. Most tricyclic antidepressants prolong the QT interval and are Class B, although reports of Torsades de pointes with these drugs are few. Lithium is Class B, and dose limitations are now recommended for citalopram and escitalopram (Class B) to limit risk of QT prolongation. Antipsychotics are a mixed category: Risks appear to be increased, dose-dependently and to a similar degree, with first- and second-generation antipsychotics.

For Class A drugs, treatment can be initiated without a cardiac risk assessment. Patients should be informed if their prescribed drug could increase arrhythmia risk. However, if treatment is urgent and the patient cannot comprehend a discussion, the drug should be started and the discussion and risk assessment postponed. Otherwise, the cardiac risk profile should be assessed before starting treatment. The risk profile includes demographic information (e.g., gender, age), personal and family history, various laboratory studies, and ECG. If risk is low, treatment can be started, followed by a re-assessment within 1–2 weeks and again after a dose increase. If there are positive indicators of risk, cardiology consultation should be sought and/or the choice of drug should be reconsidered.

Fanoe S, Kristensen D, Fink-Jensen A, Jensen H, et al: Risk of arrhythmia induced by psychotropic medications: a proposal for clinical management. European Heart Journal 2014; doi 10.1093/eurheartj/ehu100. From Copenhagen University Hospital, Denmark; and other institutions. Source of funding not stated. Two study authors disclosed financial relationships with commercial sources; the remaining authors declared no conflicts of interest.

Drug Trade Names: amitriptyline—Elavil; aripiprazole—Abilify; bupropion—Wellbutrin; carbamazepine—Epitol, Tegretol; citalopram—Celexa; clomipramine—Anafranil; clozapine—Clozaril; doxepin—Sinequan; duloxetine—Cymbalta; escitalopram—Lexapro; fluoxetine—Prozac; gabapentin—Neurontin; haloperidol—Haldol; imipramine—Tofranil; isocarboxazid—Marplan; lamotrigine—Lamictal; mirtazapine—Remeron; nortriptyline—Aventyl, Pamelar; olanzapine—Zyprexa; paliperidone—Invega; paroxetine—Paxil; pimozide—Orap; pregabalin—Lyrica; quetiapine—Seroquel; reboxetine (not available in the U.S.)—Edronax; risperidone—Risperdal; sertindole (not available in the U.S.)—Serdolect; sertraline—Zoloft; valproate—Dепаке, Depakote; venlafaxine—Effexor; ziprasidone—Geodon

### Mood Disorder Drugs in Pregnancy

Substantial pharmacokinetic changes in many commonly used antidepressants and mood stabilizers can occur during pregnancy and in the postpartum period. The following tables outline the authors’ primary recommendations for monitoring and dosing of antidepressants and mood stabilizers during pregnancy and in the postpartum period.
Metabolism of most SSRIs may be increased later in pregnancy, but this change does not occur in all women, and if it occurs, it may or may not result in altered drug levels or clinical status. The authors suggest that antidepressant drug dosing should be based primarily on the clinical presentation, augmented if possible by standardized mood-symptom questionnaires. Although not studied, one potential monitoring option is to use an individual woman’s pre-pregnancy antidepressant blood level from a time when she was euthymic as a therapeutic target.

<table>
<thead>
<tr>
<th>Table 1. Recommended Perinatal Dose Adjustments: Common Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose increase may be indicated after 20 weeks gestation</strong></td>
</tr>
<tr>
<td>Citalopram</td>
</tr>
<tr>
<td>Clomipramine</td>
</tr>
<tr>
<td>Imipramine</td>
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<tr>
<td>Paroxetine</td>
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<tr>
<td>Sertraline</td>
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</tbody>
</table>

Plasma concentrations of mood stabilizers generally decline during pregnancy and increase rapidly after delivery. In the postpartum period, the mother should be carefully monitored for adverse effects, and drug doses should be tapered to the pre-pregnancy level.

<table>
<thead>
<tr>
<th>Table 2. Recommendations for Perinatal Dose Adjustments and Therapeutic Drug Monitoring (TDM): Common Mood Stabilizers</th>
</tr>
</thead>
</table>
| **Lithium** | • TDM monthly during pregnancy and biweekly or weekly in the last month for women with unstable mood  
• TDM each trimester for euthymic women  
• Maintain lowest effective dose  
• Check maternal lithium level before and immediately after delivery and watch for change in clinical status  
• Once medically stable, restart pre-conception dosage  |

| **Lamotrigine** | • Dosage increase of about 250% is required to sustain therapeutic levels in pregnant women with epilepsy  
• Pre-conception drug levels can be used as a guide for adjusting dosage during pregnancy  
• Use lowest effective dose  
• Taper to pre-conception dose in the postpartum period  |

| **Carbamazepine** | • Monitor both free and plasma concentrations  
• Use lowest effective dose  
• Rapidly taper the dose after delivery to avoid toxicity and to maintain pre-pregnancy levels  |

| **Valproate** | • Monitor both free and total plasma concentrations  
• Baseline levels should be obtained before conception to identify optimum levels  
• Use this optimal drug level to guide dose adjustments during pregnancy  
• Use lowest effective dose (preferably <1000 mg/day)  
• Check levels at least monthly  
• Rapidly taper the dose after delivery to avoid toxicity and to maintain pre-pregnancy levels  |
Editor’s Note: The information contained in the tables is not an endorsement of the safety of these drugs in pregnancy (e.g., valproate is classified as FDA pregnancy category D*). Rather, they recommend dose adjustments should the drug be used.

Deligiannidis K, Byatt N, Freeman M: Pharmacotherapy for mood disorders in pregnancy: a review of pharmacokinetic changes and clinical recommendations for therapeutic drug monitoring. *Journal of Clinical Psychopharmacology* 2014;34 (April):244–255. From the University of Massachusetts Medical School, Worcester, and Harvard Medical School, Boston, MA. Funded by the NIH; and other sources. All study authors disclosed financial relationships with commercial sources.

Drug Trade Names: amitriptyline—Elavil; bupropion—Wellbutrin; carbamazepine—Epitol, Tegretol; citalopram—Celexa; clomipramine—Anafranil; desipramine—Norpramin, Pertofrane; desvenlafaxine—Pristiq; doxepin—Sinequan; duloxetine—Cymbalta; fluoxetine—Prozac; fluvoxamine—Luvox; imipramine—Tofranil; lamotrigine—Lamictal; mirtazapine—Remeron; nortriptyline—Aventyl, Pamelor; paroxetine—Paxil; sertraline—Zoloft; trazodone—Desyrel, Oleptro; trimipramine—Surmontil; valproate—Depacon, Depakote; venlafaxine—Effexor; vilazodone—Viibryd

*See Reference Guide

Reference Guide

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.

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 D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or 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.

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