Transdermal Estradiol for Postpartum Depression

Between late pregnancy and 48 hours postpartum estradiol levels can decrease 100-fold, and preliminary evidence has suggested that reproductive hormones may mediate postpartum depression in some women.¹ Two published studies support the use of estradiol in postpartum depression and suggest it may produce higher response rates than traditional pharmacotherapy and that response may be achieved faster.²,³ Transdermal estradiol (Alora, and others) closely resembles naturally produced estradiol and may be most effective. There is minimal passage of estradiol to breast milk, making it safe in breastfeeding. Common adverse effects include nausea; vomiting; bloating; abdominal cramps; headache; and hair loss.

Although conventional antidepressant treatments are known to be effective in postpartum depression, some women may prefer a more natural alternative. Transdermal estradiol appears to be a promising and safe option for these women, but because efficacy and safety data are limited, it can not be considered a first-line treatment. Use before well-established lactation can diminish milk production, and it should also be noted that coadministration of a progestogen is necessary with estradiol administration.

¹Moses-Kolko E, Berga S, Kalro B, Sit D, et al: Transdermal estradiol for postpartum depression: a promising treatment option. Clinical Obstetrics and Gynecology 2009;52 (September):516–529. From Western Psychiatric Institute and Clinic, Pittsburgh, Penn.; and other institutions. Funded by the NIMH; and other sources. The study authors have disclosed multiple commercial relationships that might pose conflicts of interests.


Prazosin for Behavioral Symptoms in Alzheimer’s Disease

A pilot study provides preliminary support for the use of prazosin (Minipress) to improve agitation and aggression in elderly patients with Alzheimer’s disease.¹

Background: Atypical antipsychotics for agitation and aggression are only modestly effective and have been shown to increase risks for stroke and death in elderly patients with dementia. The prescribing information for the antipsychotics includes a black box warning about the risks
in elderly patients. An open-label study found the alpha antagonist prazosin, approved for hypertension and benign prostatic hypertrophy, reduced treatment-resistant agitation in elderly patients with dementia.²

**Methods:** Study participants (n=22) were recruited from a community nursing home or the Alzheimer’s Disease Research Center at the University of Washington. All had exhibited agitation/aggression at least twice per week for ≥2 weeks and had at least moderate anxiety, tension, hostility, incooperativeness, or excitement based on a Brief Psychiatric Rating Scale (BPRS) evaluation. Patients with low blood pressure, orthostatic hypotension, uncontrolled psychosis, delirium, depression, unstable medical conditions, or a history of bipolar disorder or schizophrenia were excluded. Patients received 8 weeks of double-blind placebo or up to 6 mg/day prazosin in addition to their previous medications (including psychotropics). The primary outcome measures were the Clinical Global Impression–Improvement (CGI-I)* scale, the Neuropsychiatric Inventory (NPI), and the BPRS.

**Results:** In the modified intent-to-treat analysis of all participants with at least 1 follow-up measure, behavioral improvements were significantly greater with prazosin than placebo. By study end, NPI scores decreased from 49 to 30 in the prazosin group and from 43 to 41 with placebo (p=0.01). BPRS scores decreased from 45 to 36 with prazosin and from 44 to 41 with placebo (p<0.04). CGI-I scores at end point were 2.6 and 4.5 in the groups, respectively. Patients treated with prazosin generally improved or did not change, while 6 of 11 placebo-treated patients worsened. Substantial improvements were seen in specific items of the NPI including delusions; agitation/aggression; anxiety; apathy/indifference; disinhibition; irritability; and aberrant motor behavior.

Slightly less than half of the patients did not complete the 8-week treatment. Four prazosin-treated patients withdrew from the study: 2 because of a change in living arrangements, 1 for lower extremity edema, and 1 for continuing agitation. In the placebo group, 3 patients withdrew for continuing agitation, 1 for lower extremity edema, and 1 for rash. Neither treatment group showed clinically important blood pressure changes, but 1 prazosin-treated patient experienced dizziness on standing.

**Discussion:** Results of this study support prazosin as a promising alternative to atypical antipsychotics in elderly patients with behavioral disturbances of Alzheimer’s disease. However, because of the small sample size and the high dropout rate, they must be viewed as preliminary and require replication.

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


*Reference Guide Item.

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**Modafinil-Associated Psychosis—Reminder**

A 25-year-old female with a 10-year history of narcolepsy characterized by excessive daytime sleepiness and sleep paralysis had been treated with methylphenidate for 5 years with partial symptom resolution.¹ Modafinil, titrated to 300 mg/day, produced marked symptom improvement, but she experienced transient dry mouth and tachycardia during the first 5 days of treatment. About 6 months after starting modafinil she began to experience visual and auditory
hallucinations and delusions of reference. Modafinil was stopped and the psychotic symptoms resolved. Because the narcolepsy worsened, modafinil was restarted with every other day dosing. Hallucinations occasionally recurred but the patient learned through psychoeducation to cope with them.

There have been 5 other reported cases of hallucinations with modafinil: 2 in patients with narcolepsy (including 1 reported in the May 2002 issue of Psychiatry Drug Alerts)\(^2\) and 1 each in patients with schizophrenia, mood disturbance and substance abuse, and a healthy volunteer. Although it is not clear how modafinil contributes to the psychotic symptoms, the authors believe it may be related to the dopaminergic effects of the drug.


### Antipsychotic Augmentation in MDD

A meta-analysis of placebo-controlled trials confirms the efficacy of atypical antipsychotic augmentation in nonpsychotic major depressive disorder (MDD).\(^1\)

**Methods:** Results of all double-blind placebo-controlled trials comparing antidepressant augmentation with an atypical and placebo (n=16) were assessed. The studies included nearly 3500 patients who received olanzapine (n=586), risperidone (n=211), quetiapine (n=677), aripiprazole (n=540), or placebo (n=1466). No studies of clozapine, paliperidone, or ziprasidone were identified. Trial durations ranged from 4 to 12 weeks.

**Results:** Compared with placebo, the odds ratio (OR)* for response with an atypical was 1.69 (p<0.00001) and the number needed to treat* was 9. Odds ratios varied by agent from 1.39 to 2.07 with no significant differences between them. The overall OR for remission was 2.0 (p<0.00001) with a number needed to treat of 9. Pooled remission rates were 31% for atypicals and 17% for placebo. In 14 of the 16 studies patients continued the same antidepressant. When the 2 studies in which the antidepressant was switched concurrently with augmentation were excluded from the analysis, the results were not substantially changed.

More patients receiving an atypical than placebo discontinued their study medication (OR, 1.3; p=0.004) and rates did not differ by agent. Discontinuation for adverse effects was associated with an OR of 3.9, and the number needed to harm* was 17.

**Discussion:** Antipsychotic augmentation is clearly effective in nonpsychotic MDD. However, adverse effects including weight gain and potentially serious metabolic changes can occur. Because of these risks, antipsychotic augmentation was placed after lithium and thyroid agents in the Texas Medication Algorithm.\(^2\)

**Study Rating*—16 (89%):** This study met all criteria for a meta-analysis except that individual study quality was not assessed.

\(^1\)Nelson J, Papakostas G: Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. American Journal of Psychiatry 2009;166 (September):980–991. From the University of California, San Francisco and other institutions. The study was conducted with no external funding. Both study authors disclosed commercial relationships that might pose conflicts of interest.

\(^2\)The Texas Medication Algorithm Project: Algorithm for the treatment of major depressive disorder. Available at www.dshs.state.tx.us/mhprograms/TMAP.shtm.

Drug Trade Names: aripiprazole—Abilify; clozapine—Clozaril; olanzapine—Zyprexa; paliperidone—Invega; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

*Reference Guide Item.
Olanzapine Plus Sertraline in Psychotic Depression

Combining olanzapine and sertraline was more effective than atypical antipsychotic monotherapy in a controlled trial of patients with psychotic depression.

Background: About 15–20% of patients with major depression have psychotic features, which are associated with poor outcome, longer time to recover, and more residual disability than nonpsychotic depression. Prevalence is reportedly higher in elderly patients. Recommended treatments for psychotic depression are ECT or the combination of an antidepressant and an antipsychotic. The present study evaluated the combination of olanzapine and sertraline because both have antidepressant effects and sertraline has been effective in psychotic depression.

Methods: After a taper of previous psychotropic medications, patients (n=259) at 4 academic medical centers were stratified by age (i.e., 18–59 years, ≥60 years) and randomized to 12 weeks of olanzapine plus sertraline or olanzapine plus placebo. All patients had a Hamilton Rating Scale for Depression (HAM-D) score of ≥21 and at least 1 clearly defined delusional belief. Olanzapine was titrated to a target dose of 15–20 mg/day and sertraline to a target of 150–200 mg/day. Patients were evaluated weekly for the first 6 weeks and then biweekly for the remainder of the study. Remission, the primary outcome, was defined as a HAM-D score of ≤10 at 2 consecutive assessments along with the absence of delusions.

Results: In the intent-to-treat analysis, remission occurred significantly more often with the combination of olanzapine and sertraline than with olanzapine plus placebo (odds ratio* [OR], 1.3; p<0.001). Remission criteria were met by 54 of the 129 patients assigned to olanzapine plus sertraline and by 31 of the 130 patients assigned to olanzapine plus placebo (42% vs 24%; p=0.002). The number needed to treat* was 5.5. The greater efficacy of olanzapine plus sertraline was evident at week 8. Treatment effects did not differ by age group.

About 55% of randomized patients completed the 12-week trial, and most patients who withdrew (75%) did so by week 6. There were significantly fewer drop outs in the olanzapine plus sertraline group (37% vs 53%; p=0.01). There were no significant differences between the groups in reasons for withdrawal or in the frequency of adverse effects. About half of patients in each treatment group gained a significant amount of weight (>6 lbs), and this was more common among younger patients (65% vs 45%; p=0.01). Older patients experienced significantly more pedal edema (13% vs 4%; p=0.01). Serious adverse effects (i.e., increased suicidal thinking or behavior) occurred in 5 patients, 4 of whom taking the active combination, and they included 1 completed suicide (p=ns). Metabolic alterations including increased cholesterol and triglyceride concentrations were a concern in both treatment groups.

Discussion: The conclusions that can be drawn from the present study are limited by the lack of an antidepressant monotherapy arm and because pre-study antidepressant therapy was not systematically evaluated. Because the remission rate with combination therapy was similar to that seen with ECT in clinical practice, the combination of olanzapine plus sertraline may be a viable option for patients with psychotic depression who object to or have difficulty obtaining ECT.

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


Drug Trade Names: olanzapine—Zyprexa; sertraline—Zoloft

*Reference Guide Item.
Antidepressants, Fetal Growth, and Preterm Birth

Because few studies have evaluated outcomes other than birth defects, the Motherisk Program at the Hospital for Sick Children in Canada evaluated fetal growth and preterm birth in pregnant women receiving antidepressants.

Methods: Motherisk is a call-in fetal teratology information service. During the initial phone contact the caller’s demographic information, medical and obstetric history, and the details of drug exposure and indication are collected. Birth outcomes of 928 women who called regarding their antidepressant use and who delivered a live infant were compared with those of 928 age- and risk-matched women who called regarding a nonteratogenic agent (e.g., acetaminophen). The most commonly used antidepressant was citalopram (n=184) followed closely by venlafaxine (n=154) and paroxetine (n=148) and then by bupropion (n=113); mirtazapine (n=68); fluoxetine (n=61); sertraline (n=61); fluvoxamine (n=52); nefazodone (n=49); escitalopram (n=21); and trazodone (n=17). Preterm birth (<37 weeks gestation) and birth weight were the outcomes of interest.

Results: There was a small but significant increase in preterm birth among women exposed to antidepressants. A total of 82 exposed infants (9%) and 50 unexposed infants (5%) were born preterm (p=0.005). The odds ratio* for preterm birth with antidepressant exposure was 1.7. Rates with individual agents were not compared. Low birth weight was not more common in exposed infants. A total of 89 (10%) and 76 (8%) of infants in the exposed and unexposed groups, respectively were born small for gestational age. The mean birth weight in both groups was 7.6 lbs.

Discussion: Although there is a small increase in risk of preterm birth, it is unclear from this study and from previous research if the increase is associated with antidepressant use or the presence of depression.

Einarson A, Choi J, Einarson T, Koren G: Adverse effects of antidepressant use in pregnancy: an evaluation of fetal growth and preterm birth. Depression and Anxiety. Published online August 18, 2009 at www.interscience.wiley.com; doi 10.1002/da.20598. From The Motherisk Program of the Hospital for Sick Children, Toronto, Canada; and the University of Toronto. Source of funding not stated.

Drug Trade Names: bupropion—Wellbutrin; citalopram—Celexa; escitalopram—Lexapro; fluoxetine—Prozac; fluvoxamine—Luvox; mirtazapine—Remeron; nefazodone—Serzone; paroxetine—Paxil; sertraline—Zoloft; trazodone—Desyrel; venlafaxine—Effexor

Congenital Heart Defects with SSRI Exposure

SSRIs have not generally been associated with major congenital malformations, but a retrospective study and several abstracts presented at scientific meetings suggested a 2-fold increase in cardiac malformations in infants exposed to paroxetine but not other SSRIs. The present prospective study confirms SSRI-associated cardiac risk.

Methods: Data was collected on every infant born at 1 medical center between 2000 and 2007. Mothers were surveyed about prenatal antidepressant use, smoking, alcohol use, comorbid illnesses, and other medications. Any infants with a cardiac murmur 3 days after birth underwent electrocardiography and echocardiography.

Results: During the study period nearly 68,000 infants were born; 235 had been exposed to an SSRI in the first trimester: paroxetine (n=92), fluoxetine (n=66), citalopram (n=43), escitalopram (n=13), sertraline (n=8), fluvoxamine (n=4), or venlafaxine (n=39). In the control group of 67,000 infants not exposed in utero, 2537 had a persistent heart murmur and 1171 (1.7%) had confirmed congenital cardiac malformations. In the study group, 8 of 235 newborns (3.4%) had congenital
heart malformations after prenatal exposure; 4 had been exposed to paroxetine (4.3%), 2 to fluoxetine (3%) and 1 each to citalopram (2.3%) and sertraline (12.5%). Ventricular septal defect was the most common defect, affecting 6 infants, and all cases were mild. The increased prevalence of congenital malformations in the exposed infants (3.4 vs 1.6) was statistically significant (p=0.02) and the risk ratio* in exposed infants was 2.2.

**Discussion:** Although the increase in malformations was significant in exposed infants, the actual number was small. Some potentially confounding factors (e.g., race, maternal body mass index) were not evaluated and some mothers may not have reported all exposures. Based on these results and previous research, the authors judged it "appropriate to reassure the women who require treatment with SSRIs during pregnancy that the risk is small and that the possible cardiac malformations are mild and often resolve spontaneously."


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

*Reference Guide Item.

**Venlafaxine in Resistant Bipolar Depression**

An open-label crossover study found patients with resistant bipolar depression treated with venlafaxine (Effexor) monotherapy experienced significant reductions in depressive symptoms with low rates of mania induction.¹

**Background:** Most treatment guidelines for bipolar II depression recommend lithium or other mood stabilizer monotherapy and the avoidance of antidepressant monotherapy because of concerns about manic switching. However, at least 1 randomized trial found venlafaxine monotherapy to be more effective than lithium monotherapy at relieving depression without increasing risk for mania.² This report concerns the subsequent phase of that study wherein venlafaxine monotherapy was evaluated in patients with poor response to lithium.

**Methods:** Outpatients (n=83) aged ≥18 years with bipolar II disorder and a Hamilton Rating Scale for Depression (HAM-D) score of ≥18 had participated in the randomized study of lithium vs venlafaxine. Of the 40 patients assigned to lithium, 17 whose depression had not responded to 12 weeks of monotherapy (serum levels, 0.6–1.2 mEq/L) were then crossed over to open-label venlafaxine (75–450 mg/day) for an additional 12 weeks. These patients had a mean age of 40 years, mean illness duration of 23 years, and mean duration of the current depressive episode of 18 months. The primary efficacy outcome was change in HAM-D score, and manic symptoms were evaluated using the Young Mania Rating Scale (YMRS).

**Results:** Compared with baseline (after lithium treatment), depression scores significantly decreased with venlafaxine. During lithium therapy the mean HAM-D score had increased by 1 point, compared with a 11.5-point decrease with venlafaxine (p<0.0005). Numeric HAM-D values were not included in the report. Similar differences were found on the Clinical Global Impression Severity and Improvement scales, which were used secondary efficacy measures. There was no significant difference in mean YMRS scores over time with either treatment. With venlafaxine, 1 patient (6%) experienced an episode of hypomania and 3 patients (18%) experienced subsyndromal hypomania. All 4 episodes were brief and none caused the patients to discontinue venlafaxine.

Five of the 17 patients had discontinued lithium treatment in phase I of the study because of adverse effects or lack of efficacy, but none discontinued venlafaxine for adverse effects in
phase 2. One patient had experienced worsening suicidal ideation while receiving lithium, but it did not recur during venlafaxine treatment. Laboratory values and vital signs were not changed in a clinically meaningful way with either agent.

**Discussion:** Because of study limitations (e.g., short duration, small sample, open-label crossover design, lack of a placebo control) the present findings can not be viewed as definitive. However, they do add further support for antidepressant monotherapy in some patients with bipolar disorder.

1 Amsterdam J, Wang G, Shults J: Venlafaxine monotherapy in bipolar type II depressed patients unresponsive to prior lithium monotherapy. *Acta Psychiatrica Scandinavica*. Published online August 19, 2009 at www.interscience.wiley.com; doi 10.1111/j.1600-0447.2009.01462.x. From the University of Pennsylvania School of Medicine, Philadelphia; and other institutions. **Funded by The Stanley Medical Research Institute; and the Jack Warsaw Fund for Research in Biological Psychiatry. The primary study author has disclosed commercial relationships that might pose conflicts of interest; the remaining authors disclosed no potential conflicts of interest.**


### Discrepancies in Drug Interaction Sources

An examination of several trusted drug compendia and the FDA label for Coumadin (*warfarin*) found alarming differences in the reporting of drug interactions, with more than half of the entries appearing in only 1 source.

The authors compared entries for warfarin from 3 drug interaction sources (i.e., Clinical Pharmacology, ePocrates, Micromedex) and the product label. A total of 648 entries were found in the 4 sources and these included other drugs, dietary supplements, alcohol, and tobacco. Of the 648 potential interactive agents only 50 (7.7%) were common to all 4 information sources. A total of 85 entries (13%) were common to 3 sources, 143 (22%) to 2 sources, and 370 (57%) were listed in only 1 source.

These inconsistencies in drug interaction information delivery systems present a serious problem for prescribers that could lead to suboptimal patient care. Although the present review considered only warfarin, the authors suggest the same issues likely apply to all drugs and drug classes.

Anthony M, Romero K, Malone D, Hines L, et al: Warfarin interactions with substances listed in drug information compendia and in the FDA-approved label for warfarin sodium. *Clinical Pharmacology and Therapeutics*. Published online July 8, 2009 at www.nature.com; doi 10.1038/clpt.2009.95. From The Critical Path Institute, Tucson, Ariz.; and other institutions. **Source of funding not stated. The authors declared no conflicts of interest.**

### Switching Antidepressants

A recent analysis found switching antidepressants in patients with depression that does not improve with the initial treatment lacks scientific support for an advantage.

**Methods:** A systematic literature search identified 3 randomized controlled trials comparing patients who continued their initial antidepressant with patients switched to an alternate agent after nonresponse to an initial trial of 6–7 weeks. None of the studies were designed to compare the switching strategy; rather, they evaluated combination strategies but included study arms where patients remained on initial treatment or switched to alternate monotherapy. The continuation and switch study groups included a total of 395 patients.

**Results:** Switching from fluoxetine to mianserin, from nortriptyline to fluoxetine, or from venlafaxine to fluoxetine was not significantly more effective than continuing the initial treatment for an additional 6–12 weeks. Response rates ranged from 29% to 49% for the switch strategies and from 30% to 50% when initial therapy was continued. The pooled meta-analysis...
did not show a significant advantage for switching antidepressants (odds ratio* for response, 0.85; odds ratio for remission, 0.99).

**Discussion:** Because only 3 studies could be included in the analysis, the results must be interpreted cautiously. Although no study showed a meaningful advantage for switching, the strategy itself may not necessarily be ineffective. This could only be proven using a switch to placebo but this strategy is not likely to be employed because of ethical issues. Given the number of available antidepressants and thus the large number of options for switching sequences, these results can not be generalized to all agents. However they do provide some preliminary support for a trial extending initial treatment before a switch is made.

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

Bschor T, Baethge C: No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy. *Acta Psychiatrica Scandinavica*. Published online August 24, 2009 at www.interscience.wiley.com; doi 10.1111/j.1600-0447.2009.01458.x. From Jewish Hospital of Berlin, Germany; and other institutions.

Source of funding not stated and the authors did not include a disclosure of potential conflicts of interest.

**Drug Trade Names:** fluoxetine—**Prozac**; mianserin (not available in the U.S.)—**Lantanon, Tolvon**; nortriptyline—**Pamelor**; venlafaxine—**Effexor**

*Reference Guide Item.*

### 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.

**Number Needed to Harm (NNH):** A measure of how many patients need to be exposed to a risk-factor to cause harm in 1 patient who would not otherwise have been harmed. Lower NNH, indicates more attributable risk.

**Number Needed to Treat (NNT):** 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 two 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 (nonexposed) 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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