Antipsychotic Generations Compared

A new meta-analysis compared overall efficacy, positive and negative symptoms efficacy, other outcomes, and adverse events between the classes.¹

**Background:** A previous meta-analysis found clozapine, amisulpride, olanzapine, and risperidone more effective than conventional first generation agents.² The other atypicals were found to be similar in efficacy and side effects to conventional agents.

**Data Sources:** An updated literature search of The Cochrane Schizophrenia Group and Medline databases from August 2005 to October 2006 was undertaken.

**Study Inclusion:** Good quality double-blind randomized controlled trials comparing second generation agents to first generation antipsychotics (n=150) were included. The total sample comprised >21,000 patients with schizophrenia or related disorders. Second generation agents studied were amisulpride; aripiprazole; clozapine; olanzapine; quetiapine; risperidone; sertindole; ziprasidone; and zotepine. First generation comparators were haloperidol; chlorpromazine; perphenazine; fluphenazine; flupenthixol; thioridazine; levopromazine; zuclopenthixol; thiothixene; and others. Most studies (81%) had treatment durations of 12 weeks or less.

**Results:** Overall, clozapine, amisulpride, olanzapine, and risperidone were significantly more effective than older agents (p≤0.002). Numbers needed to treat* for these agents ranged from 6 with amisulpride to 15 with risperidone. The efficacy advantage was evident for both positive and negative symptoms (p≤0.005). The other atypicals (i.e., aripiprazole; quetiapine; sertindole; ziprasidone; zotepine) were similar to conventional agents in terms of overall efficacy and positive and negative symptoms improvements. Depressive symptom improvements were significantly better with amisulpride, aripiprazole, clozapine, olanzapine, and quetiapine, but not with the other atypicals including risperidone.

Relapse was reported in 14 of the 150 studies. Olanzapine, risperidone, and sertindole were significantly better at preventing relapse, whereas amisulpride, aripiprazole, and clozapine were not. Quality of life was assessed in 17 studies, and amisulpride, clozapine, and sertindole proved significantly better than older agents.

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All second generation agents were associated with fewer extrapyramidal effects than haloperidol, and clozapine, olanzapine, and risperidone were better than the low-potency conventional agents. Second generation antipsychotics, with the exception of aripiprazole and ziprasidone, produced significantly more weight gain than haloperidol, but not low-potency conventional agents. Only clozapine was shown to be significantly more sedating than first generation agents overall.

**Discussion:** This updated review confirms the previously reported advantages of clozapine, amisulpride, olanzapine, and risperidone, which while statistically significant, were small to medium by effect size standards. The other atypicals were equally effective as the older agents, even in terms of negative symptoms. Several meta-analyses have now shown not all of the second generation agents produce better results and thus they are not a homogeneous group. The authors suggest the classification of all second-generation agents as “atypical” be abandoned.

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


**Drug Trade Names:**
- amisulpride (not available in the U.S.)—Deniban, Solian, Sulamid;
- aripiprazole—Abilify;
- chlorpromazine—Thorazine;
- clozapine—Clozaril;
- flupenthixol (not available in the U.S.)—Depixol, Fluonxol;
- fluphenazine—Prolixin;
- haloperidol—Haldol;
- levopromazine—Lepropro;
- olanzapine—Zyprexa;
- perphenazine—Trilafon;
- quetiapine—Seroquel;
- risperidone—Risperdal;
- sertindole (not available in the U.S.)—Serdolect;
- thioridazine—Mellaril;
- thiothixene—Navane;
- ziprasidone—Geodon;
- zotepine (not available in the U.S.)—Zoleptil;
- zuclopenthixol (not available in the U.S.)—Clopixol

*Reference Guide Item.

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**Memantine Improved OCD**

Open-label add-on memantine produced response in almost half of patients with resistant obsessive compulsive disorder.¹

**Background:** There is an abundance of research suggesting glutamate dysfunction as a possible factor in OCD, but the association has not been confirmed. Two case reports suggest memantine (Namenda) may be effective in OCD.² ³ Because memantine acts on glutamate receptors, it was tested as an add-on to SSRI therapy.

**Methods:** Subjects (n=15; mean age, 37 years) with resistant OCD were recruited from the Stanford University OCD clinic and online advertisements. All had been treated with a stable dose of an SSRI, venlafaxine, or clomipramine for ≥12 weeks but continued to have a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥18 indicating moderate symptoms. Patients with dementia, psychotic illness, suicidal depression, and eating disorders were excluded. Six patients had also received an atypical antipsychotic without response. Memantine was added to patients’ existing regimens and increased to 10 mg b.i.d. Response was defined as a ≥25% decrease in Y-BOCS score plus a Clinical Global Impression-Improvement (CGI-I) rating of “much improved” or “very much improved” after 12 weeks of treatment. One subject was disqualified because of a protocol violation, and the remaining 14 patients were included.

**Results:** Six of the 14 patients (43%) met response criteria at study end. Y-BOCS scores in responders decreased from a baseline mean of 27 to 13 (46%). All patients who responded to treatment did so by the end of treatment week 4. Patients who did not meet response criteria had minimal improvement; the mean Y-BOCS score in these patients decreased from 30 to 29.
Responders had undergone fewer failed trials (1.5 vs 3.8) and had less severe symptoms at baseline (mean Y-BOCS scores 24 vs 30). Adverse effects were mild-to-moderate and transient, and no patient withdrew from the study because of them.

**Discussion:** Memantine produced response in nearly half of the patients in this study, suggesting that modulating glutamate may be a viable treatment option in resistant OCD. In addition, memantine may have tolerability advantages over riluzole (another glutamate-modulating agent with preliminary evidence of efficacy) because it does not usually require liver function testing. Because of study limitations, including the open-label design, further study is needed.

1 Aboujaoude E, Barry J, Gamel N: Memantine augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. *Journal of Clinical Psychopharmacology* 2009;29 (February):51–55. From Stanford University School of Medicine, Calif. Funded by Forest Labs. All of the study authors have received research funding from Forest Labs and other pharmaceutical industry sources.


*Drug Trade Names:* clomipramine—*Anafranil*; memantine—*Namenda*; riluzole—*Rilutek*; venlafaxine—*Effexor*

### Triptorelin for Male Hypersexuality

Treatment with the long-acting gonadotropin-releasing hormone analog triptorelin (*Trelstar*) controlled nonparaphilic hypersexuality in a group of men. Continuous treatment was necessary as symptoms recurred with discontinuation.

**Background:** Nonparaphilic hypersexuality is not a recognized disorder in the DSM-IV. It is generally characterized by excessive and continued engagement in conventional sexual activities with no aberrant behavior. Observational studies have shown agents that lower testosterone levels may be useful in controlling hypersexuality.

**Methods:** Participants were 76 men aged 18–75 years (mean age, 44 years) experiencing uncontrolled hypersexuality for \(\geq 6\) months despite pharmacological treatment. All received open-label monthly intramuscular injections of 3.75 mg triptorelin. Participation was voluntary, and patients gave informed consent and could withdraw from the study at any time. Frequency of sexual attempts was the primary outcome. Changes in hormone levels, testicular volume, and bone mineral density (BMD) were also evaluated. Most patients (79%) were treated for \(\geq 2\) years.

**Results:** All subjects (n=68) who received at least 6 triptorelin injections demonstrated significant improvement in hypersexuality that was evident as early as 3 months after starting treatment. Maximal improvements were evident between 4 and 8 months. The mean number of sexual attempts decreased from 8 per day at baseline to 4.2 per week at 6 months and further declined to <1 per week with continued treatment up to 24 months. Patients who stopped triptorelin began to experience a gradual increase in sex drive within 3 months of stopping treatment and according to their partners, most were at intolerable levels within 6 months.

Hormone levels began to decrease after 2 monthly triptorelin injections, and serum follicle-stimulating hormone and luteinizing hormone declined continuously as treatment progressed. Reproductive capacity (ascertained by semen analysis) was hampered in treated men due to testicular atrophy. After 24 months these effects were not completely reversible. BMD was also significantly reduced, and 11 patients (16%) required calcium and vitamin D supplementation.

Most adverse effects of triptorelin were associated with androgen deprivation. These included hot flashes (32%); injection site pain and weight gain (9% each); back pain, asthenia, muscle
tenderness, decreased hair growth (7–8% each); and increased liver enzymes (3–5%). Most were mild-to-moderate.

Discussion: These results support triptorelin as an effective way to control hypersexuality that has not improved with other treatments. However, continuous treatment is necessary and reproductive concerns should be considered.


Atypical Antipsychotics in Pregnancy: Update

Decisions regarding antipsychotic treatment during pregnancy must balance the risks of fetal injury and the maternal and fetal risks associated with untreated illness. Because research examining the safety of atypicals in pregnancy is scarce, the Psychiatry Drug Alerts editors have put together a summary of the recent evidence along with new data from a case series.

A previous review of case reports, manufacturer data, and 1 prospective study found no overall association between atypical antipsychotics (i.e., clozapine, olanzapine, quetiapine, risperidone) and miscarriage, stillbirth, fetal prematurity, congenital malformations, or adverse perinatal effects. There was an increased incidence of low birth weight in exposed infants. Congenital malformations were reported in 4 of 129 cases (3%) of olanzapine use in pregnancy, but in none of the 61 reports of risperidone use or the 39 reports of quetiapine use. Among 19 women treated with clozapine during pregnancy, there were 2 reports of perinatal seizures and 1 infant had several congenital anomalies and was born prematurely. Other concerns with clozapine are agranulocytosis and orthostatic hypotension, both of which can have adverse fetal effects. Fetal exposure to ziprasidone and aripiprazole have not been reported.

A subsequent study, which quantified placental passage of antipsychotics in 54 women, found olanzapine to be associated with the greatest transfer to the fetus (72%), followed by haloperidol (66%), and risperidone (49%). Obstetric complications included preterm birth (n=4); low birth weight (n=6); high birth weight (n=3); admission to neonatal intensive care (n=6); cardiovascular complications (n=7); respiratory complications (n=12); and hypotonia (n=2). Low birth weights and intensive care admission were more common with olanzapine than with the other agents (31% each vs 0–17%) and exceeded population norms of 4–8%.

Most recently, a chart review of pregnant women treated at the Mayo Clinic between 1993 and 2007 found a total of 16 of 31,000 mothers were prescribed an atypical antipsychotic during pregnancy. In these women, quetiapine was the most commonly prescribed agent (n=10), and there were no women taking clozapine or olanzapine. Thirteen of the 16 women (81%) were already taking an antipsychotic when they conceived, and 11 (85%) continued the medication throughout pregnancy. Six of the 16 infants had no known adverse outcomes. Three were born prematurely (<37 weeks gestation), but their birth weights were consistent with their gestational age. Four infants required admission to the neonatal intensive care unit, 3 had heart murmurs, 3 had early feeding difficulty, and 1 infant had major congenital malformations (i.e., ventriculomegaly, hydrocephalus). Heart murmurs and feeding difficulties resolved before 1 year of age. Behavioral concerns developed in 2 of the infants after their third birthdays.

Discussion: Stopping treatment for a psychiatric illness because of pregnancy can pose serious dangers to both mother and fetus. Adverse effects of the medications (e.g., weight gain, diabetes, hypertension) can also lead to unfavorable pregnancy outcomes. A prepreg-
Pregnancy consultation is recommended for all women with schizophrenia who want to conceive. The patient’s history, level of psychosis, and risk of relapse without medication as well as the presence of prepregnancy risk factors should be considered when recommending a treatment course.

3 Wichman C: Atypical antipsychotic use in pregnancy: a retrospective review. Archives of Womens Mental Health. Published online January 10, 2009 at www.springerlink.com; doi 10.1007/s00737-008-0044-3. From Mayo Clinic, Rochester, Minn. No disclosure statement was included with this article.

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

**Treating Resistant PTSD: Evidence Review**

What are the evidence-based medication options when patients with posttraumatic stress disorder do not respond to or cannot tolerate SSRIs? A comprehensive review identified 64 studies that the authors graded according to the level of study evidence (see box).

**Level A Evidence:** In the treatment of PTSD, level A evidence exists only for the SSRIs, which are used as first-line treatment. None of the treatment options available when the SSRIs fail have achieved this level of evidence.

**Level B Evidence:** This level of evidence exists for risperidone, olanzapine, valproic acid, lamotrigine, and prazosin. Risperidone was investigated in 6 randomized controlled trials (RCTs), and 1 showed it to be significantly superior to placebo as monotherapy, and 3 studies showed it effective as an adjunct to SSRIs for reducing symptom severity. None of the studies found risperidone improved avoidant behavior or emotional numbness, but awakenings caused by trauma-related nightmares were reduced. Olanzapine was investigated in 2 RCTs, but the results were conflicting, with 1 study showing active treatment significantly superior to placebo, while the other did not. The outcome measures differed between these studies, and the positive effects were found in the study that employed the most commonly used measure (i.e., the Clinician Administered Posttraumatic Stress Disorder Scale). Olanzapine was also found to improve sleep patterns. Although the single RCT investigating valproic acid monotherapy did not find it to be significantly superior to placebo, a small blinded dose-ranging study showed higher doses produced marked improvement. Open-label studies and case series have also shown it to be effective as monotherapy or adjunctive treatment. Lamotrigine monotherapy produced response in 50% of patients in the only published RCT, but the number of patients was small. Prazosin has consistently been shown to improve nightmares and sleep disturbances associated with PTSD, and some studies also found it significantly more effective than placebo at reducing general PTSD symptomology.

**Level C Evidence:** Quetiapine has improved PTSD, particularly sleep and nightmare-related symptoms, but there are no supporting randomized double-blind trials. Carbamazepine also
appears to be effective in PTSD, with the majority of patients treated in open-label studies showing at least marked improvement, but no RCTs have been conducted. In contrast, topiramate was not found to be significantly superior to placebo in 2 RCTs, but open-label studies had strikingly positive results with more than three-quarters of patients in 1 study achieving response. Levetiracetam and phenytoin significantly reduced symptom scores in open-label studies. Propranolol has been shown to reduce symptoms including intrusive thoughts, nightmares, insomnia, anger, exaggerated startle response, hypervigilance, and hyperarousal in 2 small open-label studies.

**Level D Evidence:** Little evidence exists to support clozapine or aripiprazole, but small case series suggest clozapine monotherapy improved overall psychopathology and aripiprazole augmentation improved sleep and nightmares. Anecdotal reports suggest gabapentin may have positive effects in PTSD. Transdermal clonidine produced moderate-to-marked improvement in a single study of preschool children with PTSD. Benzodiazepines have been shown to reduce PTSD-related anxiety and sleep disturbance, but in most studies PTSD specific measures were not significantly improved. Although preliminary, single open-label studies of dehydroepiandrosterone (DHEA) and lithium showed promise. Studies of opioid antagonists have been inconclusive. Tiagabine, guanfacine, and cyproheptadine were not found to be effective.


**Drug Trade Names:**
- aripiprazole—Abilify
- carbamazepine—Epitol, Tegretol
- clonidine, transdermal—Catapres-TTS
- clozapine—Clozaril
- cyproheptadine—Periactin
- gabapentin—Neurontin
- guanfacine—Tenex
- lamotrigine—Lamictal
- levetiracetam—Keppra
- olanzapine—Zyprexa
- prazosin—Minipress
- propranolol—Inderal, InoPran
- quetiapine—Seroquel
- risperidone—Risperdal
- tiagabine—Gabitril
- topiramate—Topamax
- valproic acid—Depakene, Depakote

## Antidepressants and Dementia

A large case-control study found rates of dementia were higher in patients treated with antidepressants than in the general population. Risk appeared greater early in the course of treatment and reduced with long-term treatment.¹

**Background:** Depressive disorders have been associated with increased risk for cognitive dysfunction with possible progression to dementia, and it has been suggested that antidepressants may have neuroprotective effects in this regard.

**Methods:** Linked data from Danish prescription and medical registries were used to examine the association between antidepressant use and dementia. Patients aged >40 years with at least 1 prescription for an antidepressant between 1995 and 2005 were identified. The incidence of dementia was determined for these patients (n=687,552) and for a random sample of unexposed patients (n=779,831). Dementia risk was compared in patients with 1 antidepressant prescription, >1 antidepressant prescription, and no antidepressant use.

**Results:** Compared with unexposed patients, the incidence of dementia was 3 times greater among patients with 1 antidepressant prescription. Relative risk (RR) was greater among those exposed to SSRIs than to older agents (RRs 4.74 vs 1.77). The rate of dementia diagnosis declined with continued antidepressant treatment (≥6 filled prescriptions) but not in direct relation to the number of prescriptions. Despite the decline, the incidence of dementia remained elevated compared with unexposed patients.

**Discussion:** These data show an association between continued antidepressant use and lowered dementia risk, but it could not be determined by what means the antidepressants
imparted their partial protective effects. This study was also limited by its naturalistic nature and the lack of information regarding the indication for antidepressant use and dosing.

**Editor’s Note:** There is growing interest in neuroprotection against dementia. These investigators previously conducted a similar study using data from the same national registries and found a neuroprotective effect of lithium in patients with bipolar disorder.¹

¹Kessing L, Sondergard L, Forman J, Andersen P: Antidepressants and dementia. *Journal of Affective Disorders.* Published online January 10, 2009 at www.sciencedirect.com; doi 10.1016/j.jad.2008.11.020. From University Hospital of Copenhagen, Rigshospitalet, Denmark; and University of Copenhagen, Denmark. **No funding or conflicts of interest were declared.**


*Reference Guide Item.*

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**Metabolic Monitoring with Antipsychotics**

A follow-up to the FDA and American Diabetes Association (ADA) recommendations shows the monitoring rate of plasma lipids and glucose has slightly increased among patients receiving second generation antipsychotics. Several factors associated with increased monitoring were identified.

**Background:** Because second generation antipsychotics can cause metabolic changes, the FDA and the ADA issued a consensus statement in 2004 recommending lipid and glucose screening prior to treatment and again after 12 weeks.

**Methods:** Records from a large managed care insurance claims database were examined to identify patients who received a new prescription for a second-generation antipsychotic. Patients aged <65 years who received continuous antipsychotic therapy for ≥ 4 months were stratified to a preguideline group (n=5787) with a first prescription filled between July 1, 2000 and September 30, 2003, and a postguideline group (n=17,832) with initial prescriptions filled after March 1, 2004. Data on laboratory testing was then extracted for these patients for the periods within 40 days before or after the index prescription (baseline testing) and within 84 days after the prescription (follow-up).

**Results:** Metabolic testing increased after the guidelines were issued, but rates continued to be low. Pretreatment lipid and glucose tests were completed in about 7% and 17% of the preguideline group. After the guidelines were issued, these percentages rose to about 11% and 22%, respectively. A similar trend was seen for follow-up testing at 12 weeks, but this was even less frequent than baseline testing.

During both the pre- and postguideline periods, older age was significantly associated with metabolic monitoring. While gender had no effect on lipid testing, females were more likely than males to undergo glucose testing. Presence of pre-existing metabolic disorders was also predictive of lipid and glucose monitoring. The likelihood of monitoring was not consistently affected by the antipsychotic prescribed.

**Discussion:** While monitoring rates did increase in the postguideline period, it seems a large majority of patients (80–90%) are not receiving monitoring. Most cases of antipsychotic-associated diabetes occur within 6 months of treatment initiation.

Lamotrigine in Acute Bipolar Depression

The anticonvulsant lamotrigine is FDA approved for relapse prevention in bipolar disorder, but all 5 of the manufacturer-sponsored studies have shown it ineffective as acute treatment. Because the individual studies may have been underpowered to detect significant improvement, a meta-analysis of these studies was undertaken to attempt to clarify the acute efficacy.

Methods: The placebo-controlled trials comprised >1000 patients, and lamotrigine was dosed at 100–400 mg/day for 7–10 weeks. Response criteria was a >50% decrease in Hamilton Rating Scale for Depression (HAM-D) or Montgomery Asberg Depression Rating Scale (MADRS) score. Remission was defined as a HAM-D score of <8 or a MADRS score of <12. Patient data from all 5 trials were pooled and then response and remission rates and the number needed to treat* (NNT) were calculated.

Results: Compared with placebo, patients treated with lamotrigine had about a 25% greater likelihood of achieving response by either HAM-D or MADRS criteria. Lamotrigine did not produce a significantly higher remission rate using the HAM-D measure, but using the MADRS criteria, odds of remission were 21% higher in treated patients (p=0.02). The NNT for response ranged from 11 to 13 (an NNT of 10 is the proposed cutoff for clinical significance).

A subgroup analysis showed patients with more severe depressive symptoms (HAM-D score >24) responded better to lamotrigine than to placebo (46% vs 30%; p=0.001). Among patients with moderate depressive symptoms, response rates did not differ between lamotrigine and placebo (48% vs 45%). This lack of significance may be attributable to a high placebo response among patients with less severe depression, and conclusions must be made cautiously. Bipolar subtype did not affect treatment response.

Study Rating*—16 (89%): This study met 10 of the 11 criteria for a quality systematic review. The quality of each individual study (a key item) was not evaluated.

Geddes J, Calabrese J, Goodwin G: Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. British Journal of Psychiatry 2009;194 (January): 4–9. From the University of Oxford, U.K.; and Case Western Reserve University, Cleveland, Ohio. The trials included in the analysis were funded and conducted by GlaxoSmithKline. One study author is a member of GlaxoSmithKline’s psychiatry advisory board, and another is a coinvestigator of a study involving lamotrigine in bipolar disorder.

*Reference Guide Item.