Comparing Antidepressant Efficacy—Editor’s Note

The evidence used in meta-analyses and systematic reviews, generally considered best evidence, is usually from randomized controlled trials of paired comparisons. The conclusions are limited to these comparisons, and makes choosing the most effective treatment difficult.\(^1\) Multiple treatment meta-analysis presents results in a way that makes conclusions possible by using indirect comparisons. Although this type of evidence is useful in clinical practice, many claim that these indirect comparisons may overestimate treatment effects.

In a recent issue, we presented the results of a multiple treatment meta-analysis ranking the comparative efficacy of antidepressants.\(^2\) The analysis suggested that sertraline may be the best acute treatment, a conclusion that has generated some controversy. Several letters to the editors state that many studies included in the analysis were biased, and that examining only head-to-head comparisons left out a substantial amount of valid evidence from placebo-controlled comparisons. Some believe the data should have been interpreted more cautiously.\(^3\) In addition, the American College of Physicians conducted a similar study, but came to a substantially different conclusion: that efficacy differences can not be used to guide antidepressant selection, rather choices should be based on cost and patient preferences.\(^4\) According to the researchers who conducted the multiple treatment meta-analysis, “standard thinking has become that most antidepressants are of similar average efficacy and tolerability” and their study was conducted to alleviate the uncertainty felt by physicians when faced with a number of apparently effective antidepressants. In addition, these researchers have recently conducted Cochrane Reviews of sertraline and escitalopram (judged in the initial report to be a second best) and summaries are included in this issue.


**References**

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Sertraline Vs Other Antidepressants

A Cochrane review suggests sertraline may be more effective and better tolerated than many other antidepressants and should be considered a "strong candidate" for the first-line of therapy for major depression. However, this conclusion was based on admittedly low-quality evidence.

**Methods:** This analysis included 59 randomized trials of sertraline compared directly to another antidepressant. Study participants were adults with major depression and most were outpatients with moderate-to-severe symptoms. Response was defined as a ≥50% or greater improvement on any standardized depression rating scale or a rating of "much improved" or "very much improved" on the Clinical Global Impressions-Improvement scale during acute treatment of 6–12 weeks.

**Results:** Although most differences were not statistically significant, many efficacy, safety, and tolerability comparisons favored sertraline. Among the few statistically significant findings: sertraline was superior to imipramine at producing acute remission and inferior to amitriptyline at reducing depressive symptoms. Sertraline was more effective than fluoxetine (odds ratio* for response, 0.73; p=0.007) but not the other SSRIs. Sertraline had comparable efficacy to maprotiline, St Johns wort, and newer antidepressants representing various drug classes. Its efficacy was inferior to that of mirtazapine (odds ratio for response, 1.40; p=0.05).

Sertraline had better acceptability or tolerability than amitriptyline, imipramine, paroxetine and mirtazapine and was less acceptable than bupropion ("acceptability" is measured by treatment withdrawal for any cause, while "tolerability" refers to withdrawal because of side effects). Sertraline was associated with a higher incidence of diarrhea than several other agents, but no other distinct pattern of side effects was evident.

Many of the studies, particularly those comparing sertraline with older drugs, were sponsored by the manufacturer of sertraline. The investigators judged the overall quality of the studies to be low, with incomplete reporting of outcome data in about half and selective reporting in about two-thirds, and they lacked enough evidence to determine whether publication bias had occurred.

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

Cipriani A, et al: Sertraline versus other antidepressive agents for depression. *Cochrane Database of Systematic Reviews* 2009 Issue 2. From the University of Verona, Italy, and other institutions. The Cochrane collaboration is supported by national governments, international governmental and non-governmental organizations, universities, hospitals, private foundations, and personal donations and does not accept funding from conflicting organizations such as pharmaceutical companies.

*Drug Trade Names:* amitriptyline—Elavil; bupropion—Wellbutrin; fluoxetine—Prozac; imipramine—Tofranil; maprotiline—Ludionil; mirtazapine—Remeron; paroxetine—Paxil; sertraline—Zoloft

*Reference Guide Item.

Escitalopram Vs Other Antidepressants

Escitalopram "appears to be suitable as first-line antidepressant treatment for moderate to severe major depression“ concludes a review of randomized trials conducted by the Cochrane Collaboration, an industry-independent body.

**Methods:** The analysis included 19 randomized controlled trials, and 3 unpublished studies found only in the manufacturer’s online registry. Study participants were adults with major depressive disorder; the great majority were outpatients, and both primary-care and specialist settings were represented. Most studies were 8 weeks in duration. Escitalopram was compared with 4 other SSRIs (i.e., citalopram, fluoxetine, paroxetine, sertraline) and 3 newer non-SSRI
antidepressants (i.e., venlafaxine, bupropion, duloxetine). Response was defined as a ≥50% or greater reduction in the Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Rating Scale for Depression (HAM-D).

**Results:** In 6 studies with a total of more than 1,800 participants, escitalopram was superior to citalopram at producing response within 6–12 weeks (odds ratio* [OR], 0.67; p=0.006). Escitalopram was also associated with higher rates of acute-phase remission (OR, 0.57; p=0.02) and symptom reduction than citalopram. The 2 agents had similar response rates in the single follow-up study of 357 patients observed for 16 to 24 weeks.

Escitalopram did not differ significantly in terms of response or remission from the other SSRIs or the newer non-SSRI agents. However, it produced a significantly greater reduction in depressive symptoms than fluoxetine (p=0.02), but not the other agents. The tolerability of escitalopram was similar to the other agents. However, it was associated with lower rates of dry mouth, dizziness, nausea, and possibly irritability compared with duloxetine; diarrhea was less common than with sertraline; constipation, dry mouth, and insomnia occurred less often than with bupropion; and nausea and sweating were less common than with venlafaxine.

**Discussion:** The investigators warn that the data are not sufficient (almost one-third of the trials analyzed used citalopram as the active comparator) to make judgments about comparative efficacy. With the exception of citalopram and fluoxetine, there may have been too few studies with each comparator to identify small but possibly meaningful differences. Clinically important outcomes, such as treatment satisfaction, and return to normal functioning, were not reported. Because the great majority of comparative trials were sponsored by the manufacturer of escitalopram, the possibility of sponsorship bias, cannot be ruled out.

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

Cipriani A, Santilli C, Furukawa T, Signoretti A, et al: Escitalopram versus other antidepressive agents for depression (review). Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.:CD006532. DOI: 10.1002/14651858.CD006532.pub2. From the University of Verona, Italy. The Cochrane collaboration is supported by national governments, international governmental and non-governmental organizations, universities, hospitals, private foundations, and personal donations and does not accept funding from conflicting organizations such as pharmaceutical companies.

**Drug Trade Names:**
- bupropion—Wellbutrin
- citalopram—Celexa
- duloxetine—Cymbalta
- escitalopram—Lexapro
- fluoxetine—Prozac
- paroxetine—Paxil
- sertraline—Zoloft
- venlafaxine—Effexor

*Reference Guide Item.

**Add-On Folic Acid in Mania**

A small controlled trial found that adding folic acid supplements to valproate (Depakene) therapy improved manic symptoms in patients with bipolar disorder.¹

**Background:** A link between low folate levels and mood disorders, specifically major depression and both phases of bipolar disorder, has been reported,² and a recent study showed supplementing antidepressants with folic acid had positive effects.³ However, folic acid supplementation has not previously been investigated in the manic phase of bipolar disorder.

**Methods:** Patients admitted to a university-based psychiatric hospital in Iran were eligible for the study if they had a confirmed diagnosis of mania. The 88 patients were randomly assigned to receive valproate plus double-blind 3 mg/day folic acid supplements or placebo. The Young Mania Rating Scale was administered at baseline and after treatment weeks 1, 2, and 3.

**Results:** Manic symptoms improved significantly in both groups with significant differences seen at week 3. In patients who received valproate plus folic acid the mean YMRS scores decreased from 34 at baseline to 7 after 3 weeks (p<0.001). In the group that received valproate plus placebo the scores were 35 at baseline and 10 after 3 weeks (p<0.001). The between-group
difference in improvement significantly favored adjunctive folic acid (p=0.005). The improvements were restricted to the language/thought disorders (p=0.003), irritability (p<0.001), thought content (p=ns), and disruptive-aggressive behavior domains  (p=ns).

**Study Rating**—14 (82%): This study met most criteria for a controlled trial, but study limitations and potential bias were not discussed and the source of funding was not stated.


*Reference Guide Item.*

### Acute Bipolar Disorder Guidelines: Mania

The British Association for Psychopharmacology recently updated their guidelines for treatment of bipolar disorder. A summary of their key recommendations for acute treatment of manic or mixed episodes is presented below.

For patients with previously untreated severe manic or mixed episodes, the guidelines recommend an oral antipsychotic or valproate because they have rapid antimanic effects. Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone have been shown to be effective monotherapy for mania. Amisulpride, clozapine, sulpiride, and zotepine may also be effective, but there is less evidence supporting their use. The lowest effective dose should be used and patients should not be overmedicated to obtain a sedative effect. Rather, an adjunctive benzodiazepine (e.g., clonazepam, lorazepam) should be used to promote sleep in agitated patients. Atypical antipsychotics have a more favorable adverse effect profile in the short-term and may be preferable to conventional agents; some are available in parenteral formulations that may be particularly useful in emergency situations. Previously prescribed antidepressants should be tapered and discontinued. For less severe mania, lithium, valproate, or carbamazepine can be used. Oxcarbazepine is also an option when interactions with other drugs are a concern.

Long-term treatment of bipolar disorder typically consists of lithium, carbamazepine, or valproate, and in some cases an atypical antipsychotic. In patients receiving long-term maintenance who experience a manic or mixed episode the clinician should determine if the episode is due to noncompliance. If so, a regimen with better tolerability can be considered. If the patient is compliant with medication but experiences an acute episode, optimal dosing should be ensured. For lithium, the guidelines recommend serum levels in the range of 0.5 to 1 mEq/L. If optimal dosing has been established, adding valproate or an antipsychotic may be helpful. Clozapine or ECT can be considered for treatment-resistant symptoms.

Medications used solely for short-term acute treatment should be tapered (usually over 2 weeks) and discontinued when symptoms remit, and patients should be moved to a maintenance regimen (to be discussed in an upcoming summary). Hypnotics, sedatives and other agents used purely for symptomatic effect should be discontinued as soon as the target symptom improves.

Before initiating lithium, the panel recommends evaluating glomerular filtration rate and thyroid function. They maintain that in most cases lithium is best given as a single nightly dose. Adverse effects include tremor; polyuria; weight gain; cognitive difficulty; sedation; impaired coordination; GI distress; hair loss, benign leukocytosis; and psoriasis. These can often be managed with a dosage reduction or change in administration schedule.
With valproate, special attention should be given to hepatic, hematological and bleeding abnormalities, and liver function. Recommended serum valproate levels range from 50 to 125 mcg/mL. GI pain, transaminase elevation, tremor, and sedation are common adverse effects; others include hair loss, increased appetite and weight gain. Rare but potentially fatal cases of irreversible hepatic failure, agranulocytosis, and hemorrhagic pancreatitis have been reported.

Blood dyscrasias and liver disease should be assessed before starting carbamazepine, and liver function, blood cell counts and creatinine should be monitored. Carbamazepine can reduce efficacy of antipsychotics, antidepressants, and oral contraceptives. Fatigue, nausea, diplopia, blurred vision, and ataxia are the most common dose-related adverse effects. Skin rash, leukopenia, liver enzyme elevations, thrombocytopenia, and hyponatremia are also possible.
Although rare, agranulocytosis, aplastic anemia, serious thrombocytopenia, hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and pancreatitis have been reported.

The panel recommends that clinicians should refer to individual prescribing information for atypical antipsychotics and monitor emerging evidence.

The consensus group acknowledges that "guidelines are systematically derived statements that are aimed at helping individual patient and clinician decisions. The principal recommendations given here usually apply to the average patient” and may not be valid in all clinical situations. In addition, they state that product licenses are designed mainly to limit the actions of manufacturers not individual clinicians, and they acknowledge that some of the uses discussed are off-label.

**Editor’s Note:** The American Psychiatric Association Practice Guideline for the treatment of patients with bipolar disorder was created more than 5 years ago and has not been updated to ensure that it reflects current knowledge and practice. In accordance with national standards, the guideline "can no longer be assumed to be current." A new edition is in development and publication is expected in December 2009.

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**Medication Plus CBT for Insomnia**

Combining zolpidem (*Ambien*) with cognitive behavioral therapy produced modestly better short-term outcomes than CBT alone in patients with persistent insomnia. However, those who stopped taking zolpidem regularly and continued CBT fared better long-term.

**Methods:** Patients aged ≥30 years with primary insomnia that caused substantial distress or daytime impairment were randomized to receive CBT alone (n=80) or CBT plus 10 mg zolpidem nightly (n=80) for 6 weeks. Psychiatric disorders were evaluated using a structured interview and those with a lifetime diagnosis of a psychotic or bipolar disorder were excluded; patients with major depression were not excluded provided they were currently receiving treatment and symptoms were in remission. After completing the acute phase, patients received randomized maintenance therapy for 6 months. Those who had received CBT alone either continued CBT (n=38) or received no additional treatment (n=37). Those who had received CBT plus zolpidem were randomized to CBT alone (n=37) or to CBT plus as-needed zolpidem (n=37). CBT sessions were weekly during acute treatment and monthly during maintenance. Patients kept sleep diaries and underwent sleep laboratory evaluations at baseline, 6 weeks, and 6 months. The Insomnia Severity Index (ISI) was used as an additional objective measure. The latter 2 assessments were performed by blinded raters.

**Results:** Mean baseline sleep-onset latency was 37 minutes in the CBT group and 30 minutes in the CBT plus medication group. Time awake after sleep onset was 117 minutes and 129 minutes in the groups, respectively. At 6 weeks, the average decreases in sleep onset latency based on sleep diaries were 20 minutes with CBT alone and 12 minutes with CBT plus zolpidem; time awake after sleep onset was decreased by 69 and 83 minutes, respectively. Total sleep time...
decreased 6 minutes with CBT and increased by 10 minutes with combined treatment. Sleep efficiency was significantly improved in both groups.

At 6 months, there were no significant changes in sleep onset latency from the end of acute treatment in any treatment group based on sleep diaries. The CBT plus zolpidem group had a significant decrease of 16 minutes in amount of time awake after sleep onset. Total sleep time was significantly increased with continued CBT by a further 26 minutes, with no additional treatment by a further 42 minutes, and with extended CBT and medication withdrawal by a further 27 minutes. Sleep efficiency was unchanged in all groups. Treatment gains were maintained 6 months after maintenance treatment was stopped.

For both 6-week and 6-month outcomes, trends were similar with polysomnographic data, which showed a modest 6-minute decrease in sleep-onset latency with CBT and 5 minutes with combined treatment at 6 weeks. At baseline, mean ISI scores had indicated moderately severe insomnia. Treatment response was defined as a 1-category improvement or better in ISI rating (e.g., from moderate to subthreshold severity) and remission as the absence of insomnia. At 6 weeks, response rates were 60% in the CBT alone group and 61% in the CBT plus zolpidem group; remission was achieved by 40% and 44% of the groups, respectively. The remission rate was significantly higher with combined treatment than with CBT alone at 6 months: 56% vs 43% (p=0.05). Remission rates in patients receiving extended CBT after medication withdrawal improved steadily over time until the 6-month follow-up, while rates in patients who received extended CBT plus as-needed zolpidem initially increased and then decreased after treatment completion.

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

*Reference Guide Item.

Trends in Antidepressant Use

Antidepressant use rose steadily in the 1990s and appears to have declined among adults with depression according to a recent survey. Data from the Medical Expenditure Panel Surveys (MEPS) was used to investigate the recent trends in antidepressant use.

Methods: The annual MEPS survey, sponsored by the Agency for Healthcare Research and Quality, collects information from a nationally representative sample of U.S. households using 5 questionnaires to each family over 2.5 years. Information collected includes self-reports of illness and medication use. From the 2000–2004 MEPS data, nearly 18,000 individuals with self-reported depressive or anxiety disorders were identified, and >1.4 million prescription records were evaluated.

Results: During the study period 75,201 antidepressant prescriptions were filled. The percentage of Americans filling an antidepressant prescription increased from 6.6% in 2000 to 8.1% in 2004 (p<0.001). The majority of this change occurred between 2000 and 2002 (see table) and rates were relatively static from 2003 through 2004. Rates of self-reported depression also increased from 6% to 8%. In 2000, 63% of individuals with self-reported depression received an antidepressant, compared with 57% in 2004 (p<0.001). Responsible for the difference was a decrease in SSRI prescribing that was offset somewhat by an increase in prescription of newer antidepressants. Trends were similar in patients with anxiety disorders.

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<th>Year</th>
<th>% Taking Antidepressants</th>
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<tr>
<td>2000</td>
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<td>2002</td>
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Discussion: It is unclear why the use of antidepressants declined in patients with self-reported depression, but increased in the population overall. The authors suggest the finding may be based on higher rates of self-reported depression and/or more frequent use of antidepressants in anxiety disorders.


### New Treatment Options in Schizophrenia and Bipolar Disorder

The FDA has approved the atypical antipsychotic iloperidone (Fanapt) for adult schizophrenia. The approval is based on 2 short-term placebo-controlled trials that showed iloperidone reduced symptoms. The most common adverse effects are dizziness; dry mouth; fatigue; nasal congestion; orthostatic hypotension; drowsiness; tachycardia; and weight gain. As with all other atypical antipsychotics, Fanapt will carry a Boxed Warning about increased risk of death in elderly patients with dementia.

Also approved for maintenance treatment of bipolar disorder is long-acting injectable risperidone (Risperdal Consta), which was previously approved for schizophrenia in patients aged ≥13 years and for acute treatment of bipolar disorder in patients age ≥10 years. It is the only long-acting injectable antipsychotic approved as maintenance treatment (as monotherapy or adjunctively) for maintenance in bipolar I disorder. Risperdal Consta has been shown to delay mood-episode relapse and has been used as an adjunct to lithium and valproate.


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### Reference Guide

**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.

**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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