Safety of Serotonergic Coprescription

The incidence of serotonin syndrome was low in patients who received concomitantly prescribed serotonergic antidepressants and triptan antimigraine drugs, according to an analysis of 14 years of electronic medical records from a large data registry.

Background: In 2006, the FDA issued a warning regarding the risk of serotonin syndrome with concomitant use of triptans and SSRIs or SNRIs. However, the warning was based on a small number of cases, and population-based studies were not conducted to confirm the association. In addition, based on their receptor affinity, the biological plausibility of triptans as a cause of serotonin syndrome is questionable.

Methods: The present analysis was based on the Partners Research Patient Data Registry, which includes information on >6.5 million patients receiving care in the Boston area. Patients were identified who received prescriptions for a triptan and an SSRI or SNRI in 2001–2014. Within this population, investigators searched for all cases of potential serotonin syndrome and examined the records of these patients.

Results: The number of patients who received prescriptions for triptans increased steadily during the study period. In spite of the warning, the proportion of patients who concomitantly received an SSRI or SNRI remained stable between 21% and 29%.

More than 19,000 patients received prescriptions for both a triptan and an SSRI or SNRI during the study period; 229 (0.01%) experienced extrapyramidal symptoms. Serotonin syndrome was clinically suspected in 17 of these patients. Of these, 7 cases met criteria for serotonin syndrome based on ≥1 set of standardized criteria. Detailed record review indicated that triptans had been used in close temporal association with serotonin syndrome-like symptoms in only 2 cases, but in both cases, symptoms had onset before triptans were started. Using a strict, conservative case definition, the incidence of serotonin syndrome in this population was 0.6 per 10,000 person-years. Assuming, less conservatively, that serotonin syndrome...
occurred in all 17 suspected cases, the estimated incidence was 2.3 per 10,000 person-years. No cases of serotonin syndrome, either suspected or confirmed, were life-threatening.

**Discussion:** These observations suggest there is reason to be skeptical that triptans increase the risk of serotonin syndrome beyond that associated with SSRIs and SNRIs alone. They also provide evidence that patients with affective disorders and migraine do not necessarily need to forgo treatment of 1 disorder to manage the other.

Orlova Y, Rizzoli P, Loder E: Association of coprescription of triptan antimigraine drugs and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants with serotonin syndrome. *JAMA Neurology* 2018; doi 10.1001/jamaneurol.2017.5144. From Brigham and Women’s Hospital, Boston, MA; and other institutions. Funded by Harvard Catalyst; and other sources. The authors declared no competing interests.

### Adjunctive Mifepristone in Psychotic Depression

Mifepristone, a glucocorticoid receptor antagonist that blocks the activity of cortisol, can reduce positive symptoms in patients with psychotic depression, according to a combined analysis of 5 clinical trials. Efficacy in the trials was limited to patients who had relatively high drug plasma levels.

**Background:** There are no agents specifically FDA approved to treat psychotic depression. In several studies, mifepristone produced response rates numerically superior to placebo; however, statistical significance was not consistently observed.

**Methods:** The present analysis included 5 similarly designed manufacturer-sponsored phase II or III trials. The trials enrolled patients with psychotic depression, and all but 1 trial required a score of ≥8 on the Brief Psychiatric Rating Scale (BPRS) positive symptom subscale. Following a ≥7-day washout of antidepressant and/or antipsychotic medications, 1460 participants (mean age, 45 years; 59% women) were started on an FDA-approved antidepressant and randomly assigned to 7 days of treatment with either placebo or 300, 600, or 1200 mg/day mifepristone. The primary efficacy outcome of the trials was the proportion of patients in each group who had a ≥50% decrease from baseline on the BPRS positive symptom scale at both day 7 (rapid response) and the final study visit (sustained response; days 28 or 56, depending on the study). Trough plasma levels were measured on day 7, before the final administration of the drug.

**Results:** A total of 833 patients received mifepristone, and 627 received placebo. Dropout rates were about 19% in each group. Rates of rapid, sustained response were 37% with mifepristone and 29% with placebo (p=0.004). Outcomes of mifepristone and placebo diverged statistically beginning in week 2 of follow-up and continued through week 8.

A mifepristone plasma level of 1637 ng/mL was identified as a cutoff between responders and nonresponders. Patients with mifepristone plasma levels below the cutoff did not have a higher response rate than the placebo group. Higher plasma levels were superior to placebo, with a psychotic symptom response rate of 43%, a number needed to treat* of 7, and an effect size* of 0.30. Although some patients in all dosage groups achieved high plasma drug levels, the likelihood was higher as the dosage increased: 25% with 300 mg/day, 44% with 600 mg/day, and 65% with 1200 mg/day. Change from baseline in adrenocorticotropic hormone (ACTH) and cortisol levels were significantly correlated with the day-7 mifepristone level (for cortisol, p<0.0001; for ACTH, p<0.0001).

Mifepristone was also significantly superior to placebo at improving scores on the Hamilton Rating Scale for Depression (HAM-D), but only in patients who achieved plasma mifepristone levels above the cutoff. In these patients, HAM-D reductions ranged from 46% to 53% at the final study visit, compared with 42–48% in the placebo groups (p≤0.05). Mifepristone was well tolerated, with a comparable safety profile to placebo.
**Discussion:** Patients with psychotic depression have elevated cortisol levels, perhaps leading to overstimulation of the glucocorticoid receptor and increasing responsiveness to dopamine and glutamate. The finding of greater increases in cortisol and ACTH in the highest dosage group likely reflects increased glucocorticoid receptor antagonism. Although 4 of the 5 included studies had higher-than-expected placebo response rates, mifepristone showed clinically meaningful effects, as demonstrated by the number needed to treat, in patients who achieved therapeutic plasma levels.


*See Drug Trade Names: mifepristone—Korlym, Mifeprex

**Stimulants in Schizophrenia**

In a population-based, naturalistic study, treatment with CNS stimulants was associated with improved functional outcomes in patients with schizophrenia. However, the effect was largely confined to women.

**Methods:** Study data were collected from the Danish national registries of population, psychiatric treatment, and prescriptions. All patients with a diagnosis of schizophrenia and all exposure of these patients to CNS stimulants were identified. In a mirror-image model, the number of psychiatric hospitalizations, days of psychiatric hospitalization, and antipsychotic use were compared within individual patients for the 2-year periods before and after the initial stimulant prescription. In a whole-population analysis, psychiatric hospitalizations were compared between stimulant-exposed and unexposed patients. In this analysis, patients who stopped filling stimulant prescriptions were considered unexposed 3 months after the last prescription. In addition, patients were censored during admission to a psychiatric facility and reentered the study at discharge.

**Results:** More than 50,000 patients with schizophrenia were identified, including 1438 (nearly 3%) who received a prescription for a stimulant. The mirror-image analysis included 605 patients whose stimulant prescription was initiated after the onset of schizophrenia. Most of these patients (93%) received methylphenidate (Ritalin), and only about 30% had a comorbid ADHD diagnosis.

Stimulant use was not significantly associated with reduced psychiatric hospitalization overall. In women, the mean number of admissions was somewhat lower during stimulant use compared with before (1.33 vs 1.02 hospitalizations), but the difference was not statistically significant. However, subgroup analysis of 214 patients with a history of hospitalization in the pre-mirror-image period found stimulant effects to be significant for the whole population (3.43 vs 2.62 admissions; p=0.009), with a larger effect in women and a nonsignificant effect in men. Antipsychotic exposure, measured as the defined daily dose, was also lower during stimulant use, both overall (p=0.001) and in women (p=0.002). Rates of SSRIs and benzodiazepines use were also significantly lower in the post-stimulant mirror-image period than in the pre-stimulant period.

Average days of hospitalization could not be compared in the full mirror-image sample, as many had no history of admission in the pre-mirror-image period. However, among patients with a previous hospitalization, the number of bed-days was significantly lower in the post-stimulant period than before, both overall (78.3 vs 38.3 days; p<0.001) and in separate analyses of men and women (p<0.001 for both). In the whole-population analysis, rates of hospitalization
were lower in women during stimulant use, compared with periods of non-use (adjusted hazard ratio, 0.72).

Serious adverse effects were rare during stimulant use. Seizures or epilepsy developed in 3 patients after starting stimulant treatment, acute myocardial infarction occurred in 1 patient, and renal disease developed in 4 patients. Despite concerns that stimulants could worsen positive symptoms by increasing the availability of synaptic dopamine in the limbic system, the reductions in hospitalization suggest they did not.

Discussion: Results of previous studies suggest stimulant use may improve cognition in schizophrenia, resulting in fewer negative symptoms; but these effects have been small. The present study aimed to examine the effect of stimulants on naturalistic outcomes that reflect patient function. The stronger response to stimulants in women, which has been previously observed, may reflect mediation of the neural response by ovarian hormones. While these results are encouraging, further study is needed before stimulants can be recommended for patients with schizophrenia.


Minocycline plus Aspirin for Bipolar Depression

In a preliminary randomized trial, the combination of minocycline (Minocin) plus aspirin was effective as adjunctive treatment of bipolar depression. Neither of the 2 antiinflammatory agents was effective without the other.

Background: Given the few safe and effective options for treating bipolar depression, interest in drugs with antiinflammatory activity is increasing. Aspirin and minocycline were investigated because they are well tolerated, penetrate the brain, and act by different antiinflammatory mechanisms.

Methods: Study subjects were adults with bipolar disorder type I, II, or NOS, with a current major depressive episode lasting ≥4 weeks and of at least moderate severity, who were receiving stable ongoing medication. Participants received randomized, double-blind treatment for 6 weeks with 100 mg minocycline b.i.d. plus aspirin placebo; 81 mg aspirin b.i.d. plus minocycline placebo; both active agents; or double placebo. Midway through the study design, an interim analysis revealed that the double-treatment and double-placebo groups were separating statistically, but that the 2 single-agent groups were not, and no new patients were enrolled in the 2 single-agent groups. The primary study outcome was durable response, defined as a >50% decrease in Montgomery-Asberg Depression Rating Scale score for the final 2 study visits. Levels of interleukin-6 (IL-6) were measured to assess inflammation, and the Young Mania Rating Scale (YMRS) was used to evaluate whether minocycline and/or aspirin would precipitate hypomania or mania.

Results: A total of 99 patients with an average age of about 41 years (75% women) were randomized: 37 with bipolar I disorder, 57 with bipolar II disorder, and 5 with bipolar disorder NOS. A total of 31 patients received minocycline plus aspirin, 30 received double placebo, and 19 patients each received minocycline plus placebo or aspirin plus placebo. Mean baseline MADRS scores ranged from 26 to 29 and did not differ between groups. Patients receiving both active agents had a higher response rate than the placebo group: 44% versus 21% (odds ratio,* 2.93; p=0.034; number needed to treat,* 4.7). When groups receiving active agents were combined, the 2 groups that received aspirin had a significantly higher response rate than those who received
placebo (odds ratio, 3.67; p=0.019), but no such effect occurred for the minocycline groups. Response to minocycline was associated with higher initial interleukin-6 (IL-6) levels and with greater IL-6 decreases during treatment. One patient in the minocycline–aspirin group experienced hypomania during the study. There was no difference between groups in YMRS scores.

**Discussion:** These results provide preliminary evidence that aspirin and minocycline may be effective adjunctive therapies for the treatment of bipolar depression. Additional study appears to be warranted.

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

Savitz J, Teague T, Misaki M, Macaluso M, et al: Treatment of bipolar depression with minocycline and/or aspirin: an adaptive, 2×2 double-blind, randomized, placebo-controlled, phase IIa clinical trial. *Translational Psychiatry* 2018; doi 10.1038/s41398-017-0073-7. From the Laureate Institute for Brain Research, Tulsa, OK; and other institutions. Funded by the Stanley Medical Research Institute; and the Laureate Institute for Brain Research. Five of 11 study authors disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.

*See Reference Guide.

### Fluvoxamine Augmentation in Schizophrenia

Augmentation of risperidone with fluvoxamine improved cognitive function and negative symptoms in a small randomized trial in patients with schizophrenia.

**Background:** Fluvoxamine is a candidate drug for improving cognitive function because of its affinity for the sigma-1 receptor, which is believed to be involved with cognitive impairment in schizophrenia. Previous studies have evaluated both cognitive- and negative-symptom effects of adjunctive fluvoxamine in schizophrenia with mixed results.

**Methods:** The study enrolled 68 inpatients (46 men) with chronic schizophrenia (DSM-5) who were receiving risperidone as maintenance treatment. Patients were aged 19–61 years (mean age, 42 years) and free of dementia, depression, and extrapyramidal symptoms. Participants were randomly assigned to receive fluvoxamine (50 mg/day for 2 weeks and then increased to 100 mg/day) or placebo. Fluvoxamine was tapered between weeks 8 and 10. Patients were evaluated with the Scale for the Assessment of Negative Symptoms (SANS) and Positive Symptoms (SAPS), the Wechsler Memory Scale (WMS), and the World Health Organization Quality of Life scale.

**Results:** Neither treatment group showed a significant decline in positive symptoms, and scores on the SAPS did not differ between the groups at week 10. Negative symptoms scores improved significantly in both treatment groups, from baseline means of 48 and 49, respectively, to 38 and 44 (p<0.001). SANS score improvement was significantly greater with fluvoxamine than with placebo (p=0.004). Among the subdomains of the SANS, fluvoxamine was associated with improvement in poverty of speech, attention deficit, and curbing of interests, but not apathy or diminished emotional range. Patients in the fluvoxamine group had higher memory scores at baseline than the placebo group, and the difference widened over the course of the trial. At week 10, the between-group difference in WMS scores significantly favored fluvoxamine (p=0.02). Changes in quality of life scores were significantly improved with fluvoxamine compared with placebo (p≤0.001).

**Study Rating**—15 (88%): This study met most criteria for a randomized controlled trial, but the funding source was not declared.


*Common Drug Trade Names: fluvoxamine—Luvox; risperidone—Risperdal

*See Reference Guide.*
Comparative Efficacy of Antidepressants

According to the results of a systematic review and network meta-analysis including 21 different antidepressants, all antidepressants are more effective than placebo in patients with unipolar major depression, and several agents are significantly more effective than the others.\(^1\) The analysis also identified differences among the antidepressants in patient acceptability.

**Methods:** This research is an update and extension of a major meta-analysis of antidepressant efficacy and tolerability, published in 2009.\(^2\) The analysis includes all second-generation antidepressants approved in the U.S., Europe, and Japan, plus trazodone, nefazodone, and 2 widely prescribed tricyclics and was based on randomized controlled trials comparing the agents with placebo or other antidepressants as oral monotherapy in adults with major depressive disorder. The primary efficacy outcome was response, defined as a ≥50% improvement in a standardized, observer-rated depression scale score. Acceptability was measured using the rate of withdrawal for any reason.

**Results:** A total of 522 controlled trials performed between 1979 and 2016 in >116,000 patients were included. Trial durations were generally 6–8 weeks. Most of the included trials (n=421) were identified by literature search, an additional 86 were unpublished and found on clinical trial registries or pharmaceutical company websites, and 15 came from other sources. The majority of studies (78%) were funded by pharmaceutical companies. Nearly all drugs were evaluated in ≥1 placebo-controlled trial, and most were also evaluated in ≥1 head-to-head comparison.

All medications were more effective than placebo at producing a response. (See table.) Relative to placebo, amitriptyline had the highest odds ratio\(^*\) for response at 2.13. Odds ratios for other antidepressants compared with placebo ranged from 1.37 to 1.89, with wide confidence intervals. In head-to-head studies, several antidepressants—agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine—were shown to be superior to others, with odds ratios ranging from 1.19 to 1.96. The least effective drugs in head-to-head comparisons were fluoxetine, fluvoxamine, reboxetine, and trazodone. Overall, antidepressants were also more effective than placebo at inducing remission (effect size,\(^*\) 0.30; p<0.0001).

Two drugs—agomelatine and fluoxetine—were associated with a lower rate of all-cause discontinuation than placebo; however, all active drugs were associated with higher withdrawal rates for adverse events than placebo. In comparative studies, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were significantly better tolerated than other drugs, with odds ratios for dropout ranging from 0.43 to 0.77. Amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine were associated with the highest dropout rates.

### Antidepressant Efficacy Relative to Placebo

<table>
<thead>
<tr>
<th>Agent</th>
<th>Odds Ratio for Response</th>
</tr>
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<tbody>
<tr>
<td>Amitriptyline</td>
<td>2.13</td>
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<tr>
<td>Mirtazapine</td>
<td>1.89</td>
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<tr>
<td>Duloxetine</td>
<td>1.85</td>
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<tr>
<td>Venlafaxine</td>
<td>1.78</td>
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<tr>
<td>Paroxetine</td>
<td>1.75</td>
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<tr>
<td>Milnacipran</td>
<td>1.74</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1.69</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1.68</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>1.67</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1.67</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>1.66</td>
</tr>
<tr>
<td>Agomelatine</td>
<td>1.65</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>1.60</td>
</tr>
<tr>
<td>Levomilnacipran</td>
<td>1.59</td>
</tr>
<tr>
<td>Bupropion</td>
<td>1.58</td>
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<tr>
<td>Fluoxetine</td>
<td>1.52</td>
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<tr>
<td>Citalopram</td>
<td>1.52</td>
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<tr>
<td>Trazodone</td>
<td>1.51</td>
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<tr>
<td>Clomipramine</td>
<td>1.49</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>1.49</td>
</tr>
<tr>
<td>Reboxetine(^*)</td>
<td>1.37</td>
</tr>
</tbody>
</table>

\(^*\) Not available in the U.S.
Smaller and older studies generally produced larger positive effects for the active medication versus placebo. This was particularly the case for amitriptyline, bupropion, fluoxetine, and reboxetine. A “novelty” effect was observed, in which newer or experimental drugs performed better than older ones or controls. Adjusting for this effect diminished the differences among drugs. The strength of evidence supporting efficacy was moderate at best and low for a number of drugs.

**Discussion:** The summary effect sizes for most antidepressants were relatively modest. However, several agents emerged as combining a relatively high response rate and a low dropout rate: escitalopram, mirtazapine, paroxetine, agomelatine, and sertraline.

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

1Cipriani A, Furukawa T, Salanti G, Chaimani A, et al: Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018; doi 10.1016/S0140-6736(17)32802-7. From the University of Oxford, U.K.; and other institutions. **Funded by the National Institute for Health Research Oxford Health Biomedical Research Centre** and the Japan Society for the Promotion of Science. Six of 18 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.


**Drug Trade Names:** agomelatine (not available in the U.S.)—*Valdoxan*; amitriptyline—*Elavil*; bupropion—*Wellbutrin*; citalopram—*Celexa*; clomipramine—*Anafranil*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; levomilnacipran—*Fetzima*; milnacipran—*Savella*; mirtazapine—*Remeron*; nefazodone—*Serzone*; paroxetine—*Paxil*; reboxetine (not available in the U.S.)—*Edronax*; sertraline—*Zoloft*; trazodone—*Oleptro*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Brintellix*

*See Reference Guide.

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**Injection Reactions with Paliperidone**

The recently introduced 3-month formulation of injectable paliperidone was associated with low rates of injection-site pain and reactions, according to a retrospective analysis of a phase III clinical trial. Despite a larger injection volume, the 3-month formulation had similar rates of local pain and reactions to 1-month long-acting injectable (LAI) paliperidone.

**Methods:** Safety data were analyzed from a previously published multinational noninferiority study comparing 3-month with 1-month LAI paliperidone. Patients were adults with moderately severe and worsening schizophrenia who were discontinuing other antipsychotics or who preferred injectable medications. All patients received open-label, flexible-dose, once-monthly paliperidone injections. After 17 weeks, patients who were clinically stable (i.e., a Positive and Negative Syndrome Scale score <70) were randomly assigned to continue fixed doses of 1-month paliperidone or 3-month paliperidone with placebo injections in other months. Randomized treatment continued for 48 weeks. After the first few injections (all in the deltoid), the site of injection (deltoid or gluteal) was generally at the clinician’s discretion and remained the same in each patient throughout the study, with the site switched between left and right each month. Injection site pain was assessed within 30 minutes after the injection, using a 100-point visual-analog scale. Trained observers rated injection-site reactions for induration, redness, and swelling.

**Results:** More than 1400 patients entered the open-label phase, and 1015 received double-blind treatment. During the double-blind period, 59% of patients were receiving injections in the deltoid, 30% in the gluteal muscle, and 11% in both sites.

Mean pain scores decreased from about 22 points with the first injection to 19 at the end of open-label treatment. Average scores decreased further during randomized treatment, to 18.4 with 1-month paliperidone and to 15.5 with the 3-month formulation. Pain ratings did not
differ between deltoid and gluteal injections. Treatment-emergent redness, induration, or swelling was observed in ≤6% of patients in the open-label phase and ≤5% in the double-blind phase, with no difference between the 2 formulations. Swelling and redness were generally mild. During the double-blind phase, 6% of patients in the 1-month group and 8% in the 3-month group spontaneously reported injection-site reactions. One patient had mild panniculitis at the injection site with 3-month paliperidone, and 1 had moderately severe swelling; both of these events resolved. Two patients were withdrawn from the study for injection-site pain in the open-label phase, and none in the double-blind phase.

Discussion: A dose of 3-month paliperidone has 1.75 times the volume of an equivalent dose of 1-month paliperidone. Despite little research evidence on injection volumes, most guidelines specify that deltoid injections should not exceed 2 mL, a volume that is exceeded with higher doses of 3-month paliperidone. In this study, >200 patients in both treatment groups received injections that exceeded 2 mL. These results suggest that, with proper injection technique, deltoid injections of 3-month paliperidone are well tolerated.


Common Drug Trade Names: paliperidone, monthly—Invega Sustenna; paliperidone, 3-month—Invega Trinza

Reference Guide

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Number Needed to Treat: 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 the treatment.

Odds Ratio: A comparison of the probability of an event in 2 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 are posted at www.alertpubs.com.