Adjunctive Minocycline for Negative Symptoms

In a placebo-controlled trial, the addition of minocycline to risperidone improved negative symptoms in early-stage schizophrenia.

**Background:** Minocycline is a second-generation tetracycline with apparent neuroprotective effects. It reportedly blocks the activation of microglia, preventing the release of cytokines that are believed to contribute to schizophrenia. Minocycline also helps to maintain normal glutamatergic neurotransmission. Although the exact mechanism is unknown, results of animal studies and several human trials suggest minocycline may be useful against negative symptoms of schizophrenia.

**Methods:** Study participants (n=92) were aged 18–40 years (mean age, 27 years), within 5 years of a diagnosis of schizophrenia (mean duration, about 2 years), and receiving stable doses of risperidone. Because of the teratogenic potential of minocycline, women planning a pregnancy and those who were already pregnant or lactating were excluded. Participants were randomly assigned to receive 200 mg/day minocycline or placebo for 16 weeks. The primary efficacy measure was change from baseline on the Scale for the Assessment of Negative Symptoms (SANS), with negative symptom response defined as a ≥50% reduction in this measure. Patients were also administered a battery of tests to assess 8 different domains of cognition.

**Results:** A total of 63 patients (30 in the minocycline group and 33 in the placebo group) completed the full 16 weeks of treatment; 12 of the 16 patients who did not complete the protocol were either lost to follow-up (n=7) or changed their antipsychotic (n=5). The intent-to-treat* efficacy analysis included 79 patients (30 women) who completed ≥4 weeks of treatment.

Both treatment groups showed marked improvement in negative symptoms. However, decreases in SANS scores were significantly greater in the minocycline group than the placebo group at weeks 8, 12, and 16. Mean baseline SANS scores were 60 and 61 in the minocycline and placebo groups, respectively. At week 16, the minocycline patients had an average 27-point
decrease in SANS score, compared with 13 points in the placebo group (p<0.001). At week 16, 44% of the minocycline group and 10% of the placebo group met negative symptom response criteria (p<0.05). Positive and Negative Syndrome Scale negative symptom scores and Clinical Global Impression–Severity scores also reflected significantly greater improvement with minocycline. There was no treatment-related difference in positive symptoms. Cognitive function improved in both groups, and minocycline was associated with a slightly larger improvement in attention. The frequency and type of side effects did not differ between the 2 groups.

**Discussion:** The results of this study suggest that minocycline may be a promising option for adjunctive treatment of negative symptoms in early schizophrenia. However, because the study sample was small, the treatment duration was short, and patients were not followed after minocycline discontinuation to evaluate sustained improvement, additional research is needed.

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

Liu F, Guo X, Wu R, Ou J, et al: Minocycline supplementation for treatment of negative symptoms in early-phase schizophrenia: a double-blind, randomized, controlled trial. Schizophrenia Research 2014; doi 10.1016/j.schres.2014.01.011. From Central South University, Changsha, China; and other institutions. Funded by the National R&D Special Fund for Health Profession; and other sources. The authors declared no conflicts of interest.

Drug Trade Names:   minocycline—Minocin;   risperidone—Risperdal

*See Reference Guide.

### Olanzapine Monotherapy for Bipolar Depression

In a placebo-controlled study, olanzapine monotherapy was effective for treating depression in patients with bipolar I disorder.

**Methods:** Study participants were outpatients with DSM-IV bipolar I disorder, who were experiencing a depressive episode and had Montgomery-Asberg Depression Rating Scale (MADRS) scores of ≥20 and Clinical Global Impression–Severity* (CGI-S) ratings of ≥4. After a 7–14 day washout period, patients were randomly assigned to 8 weeks of treatment with olanzapine, flexibly dosed up to 20 mg/day, or placebo. The primary study endpoint was change in MADRS total score from baseline to week 8.

**Results:** A total of 68 patients (mean age, 29 years; 40 women) were randomly assigned and began study treatment. Four patients discontinued treatment after onset of mania (1 in the olanzapine group and 3 in the placebo group), and 7 were lost to follow-up. All randomized patients were included in the efficacy analysis, regardless of study completion. The mean olanzapine dosage was 14 mg/day.

Mean MADRS total score decreases were significantly greater in the olanzapine group than in the placebo group, and improvement in the olanzapine group was evident at the 1-week assessment. Scores differed significantly between the 2 groups in every follow-up week. By week 8, the mean score in the olanzapine group had decreased from 29 to 15, compared with a decrease from 28 to 21 with placebo (14 vs. 7 points; p<0.001). Olanzapine was also statistically superior to placebo with regard to the secondary study endpoints: the CGI–Severity and Improvement scales and the Hamilton Rating Scale for Depression. After 8 weeks, the proportion of responders (≥50% MADRS improvement) was 50% (17 of 34 patients) in the olanzapine group and 21% (7 of 34) in the placebo group (p=0.011). Remission (final MADRS of ≤12) occurred in 12 olanzapine-treated patients and 4 placebo-treated patients (35% vs. 12%; p=0.022).

Adverse effects of olanzapine included dry mouth, headache, and increased weight and appetite. Patients gained an average of 7 lbs. with olanzapine and did not gain weight with placebo (p<0.001). Olanzapine was also associated with significant adverse changes in fasting glucose, total cholesterol, HDL and LDL cholesterol, and triglycerides.
**Discussion:** Currently the olanzapine–fluoxetine combination is FDA-approved to treat bipolar I depression. In previous studies, olanzapine monotherapy was somewhat less effective than the combination. The relatively large effect in the present study may be attributable to the high average olanzapine dose.

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

Wang M, Tong J-H, Huang D-S, Zhu G, et al: Efficacy of olanzapine monotherapy for treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Psychopharmacology* 2014; doi 10.1007/s00213-014-3453-1. From the First Hospital of China Medical University; and other institutions, Shenyang, China. **Funded by the Scientific Research Fund of Liaoning Science and Technology Agency; and the Scientific Research Fund of the First Hospital of China Medical University. The authors declared no conflicts of interest.**

*Drug Trade Names:* olanzapine—Zyprexa; olanzapine–fluoxetine—Symbyax

*See Reference Guide.*

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**Lurasidone Monotherapy for Bipolar Depression**

In a manufacturer-sponsored, phase-III randomized trial, lurasidone (Latuda) monotherapy significantly improved symptoms of bipolar I depression, with minimal effects on weight, lipids, and glycemic control.

**Methods:** The multinational study was conducted in outpatients, aged 18–75 years, with bipolar I disorder who were experiencing an episode of major depression of 4 weeks to 12 months' duration, with or without rapid cycling. Those who demonstrated treatment-resistance (i.e., nonresponse to an adequate trial of ≥3 antidepressants with or without mood stabilizers) during the current episode were excluded, as were patients with psychotic features. Following a ≥3-day washout, participants were randomly assigned to receive 6 weeks of double-blind treatment with either placebo or lurasidone at 20–60 mg/day or 80–120 mg/day. Dosages were freely adjusted within the assigned range. The primary efficacy measure was the Montgomery-Asberg Depression Rating Scale (MADRS).

**Results:** A total of 485 patients (57% women) were randomly assigned to treatment and received ≥1 post-baseline assessment. Average lurasidone doses were 32 mg in the lower-dose group and 82 mg in the higher-dose group. Patients had a mean baseline MADRS score of 30. About 75% of patients in all 3 groups completed the study. Common reasons for study discontinuation included adverse effects (n=32), insufficient response (n=30), and loss to follow-up (n=19).

In the intent-to-treat population, the average decrease from baseline to week 6 in the MADRS total score was identical in the 2 lurasidone groups: 15.4 points, versus 10.7 points for placebo (p<0.001; effect size,* 0.51 for both comparisons). Decreases in the Clinical Global Impression–Severity* score were also greater with lurasidone: 1.8 and 1.7 points, respectively, compared with 1.1 for placebo (p<0.001; effect size about 0.50). Both lurasidone doses were associated with significant improvement in the core depressive symptoms measured with the MADRS-6 subscale. Response (≥50% improvement in MADRS total score) occurred in 51% and 53% of patients in the high- and low-dose lurasidone groups, respectively versus 30% of the placebo group, for a number needed to treat* (NNT) of 5. Remission occurred in 40% and 42% of the high- and low-dose lurasidone groups, respectively versus 25% of those in the placebo group (NNT, 7). Time to response and improvement in anxiety symptoms were also significantly better in the lurasidone groups.

Adverse events were similar in the 3 groups, with nausea and headache being the most commonly reported (59% and 58%, respectively). Treatment-emergent mania occurred in 3.7% of the lower-dose lurasidone group, 1.9% of the higher-dose group, and 1.9% of the placebo group. Extrapyramidal symptoms occurred somewhat more often with lurasidone than placebo, and average prolactin levels were increased slightly. The groups did not differ in other
laboratory measures or in ECG assessments. Patients in the lower-dose group gained about 1 lb. of body weight, while weight was unchanged with higher-dose lurasidone and placebo.

**Discussion:** In 2013, lurasidone was approved for the treatment of bipolar I depression, both as monotherapy and as an adjunct to lithium or valproate. Its efficacy in depression in this study is similar to previously reported efficacy for the other atypical antipsychotics.

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


*See Reference Guide.

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**Adjunctive Lurasidone for Bipolar I Depression**

Lurasidone (*Latuda*), added to mood-stabilizer therapy, was superior to placebo in a phase III clinical trial of patients with bipolar I depression.

**Methods:** Study participants, aged 18–75 years, were experiencing a major depressive episode associated with bipolar I depression that had not responded to ≥28 days of treatment with lithium or valproate. Entry criteria were otherwise similar to the monotherapy trial (see previous story), as were study outcome measures. Therapeutic serum mood-stabilizer levels were confirmed at the time of screening. Patients were stratified based on treatment with lithium or valproate, and then randomly assigned to 6 weeks of double-blind, flexibly-dosed lurasidone at 20–120 mg/day or placebo.

**Results:** A total of 348 patients (47% women) received randomized adjunctive treatment. Similar numbers of patients were receiving lithium and valproate. Patients had mean baseline Montgomery-Asberg Depression Rating Scale (MADRS) total scores of about 30. About 80% of enrolled patients completed the study. Common reasons for study discontinuation included adverse events (n=24), insufficient response (n=14), and loss to follow-up (n=10). The mean daily dose of lurasidone was 66 mg.

After 6 weeks, lurasidone was associated with a mean reduction in MADRS score of 17 points, versus 13.5 points for placebo (p=0.005; effect size,* 0.34). Effects of lurasidone were similar whether it was added to lithium or valproate. Response (≥50% improvement in the MADRS score) occurred in 57% of the lurasidone group and 42% of the placebo group (p=0.008; number needed to treat* [NNT], 7). Remission occurred in 50% of the lurasidone group and 35% of the placebo group (p=0.008; NNT, 7). Lurasidone was also associated with significant improvement in other secondary study outcomes: anxiety, quality of life, and functioning.

The most frequent adverse effects of lurasidone that exceeded rates in the placebo group were nausea, somnolence, tremor, akathisia, and insomnia. Serious adverse events occurred in about 1% each of the lurasidone and placebo groups. Treatment-emergent suicidal ideation occurred in 9% of the lurasidone group and 6% of the placebo group; there were no suicide attempts. About 1% of patients in each group switched to mania. Lurasidone was associated with a small increase in extrapyramidal symptoms and with minimal effects on weight, lipids, and glycemic control.

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


*See Reference Guide.
Cariprazine in Acute Schizophrenia Exacerbation

Treatment with the investigational antipsychotic cariprazine was both safe and effective in a clinical trial of patients with acute exacerbation of schizophrenia.

Methods: Participants (n=732) in this multicenter phase II trial had a DSM diagnosis of schizophrenia with a duration of ≥1 year and were experiencing an acute exacerbation of symptoms. After a ≤7-day drug washout, patients were randomly assigned to 1 of 3 different dosages of cariprazine (1.5, 3.0, or 4.5 mg/day), 4 mg/day risperidone as an active control, or placebo. Patients were hospitalized for screening and treatment but could be discharged after a minimum of 4 weeks if they were mildly ill and judged to be ready. Participants received treatment for 6 weeks, followed by 2 weeks of cross-titration, stabilization, and additional safety observation. The primary study outcome measure was the Positive and Negative Syndrome Scale (PANSS) total score.

Results: For patients receiving the 2 higher cariprazine doses, average PANSS total scores were significantly lower than the placebo group from week 1 through week 6. (See table.) In the lowest dosage group, PANSS scores differed from placebo beginning in week 2. Risperidone was also superior to placebo, but was not directly compared with cariprazine. Secondary study outcomes also improved significantly with cariprazine, including Clinical Global Impression (CGI) Severity and Improvement scores, PANSS positive and negative symptom subscales, and scores on the 16-item Negative Symptom Assessment. Rates of response, defined as a ≥30% improvement on the PANSS from baseline, were 31–36% in the cariprazine groups, 19% with placebo, and 44% with risperidone.

<table>
<thead>
<tr>
<th>PANSS Outcomes in the Last Observation Carried Forward Analysis*</th>
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<tbody>
<tr>
<td>Placebo (n=148)</td>
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<tr>
<td>1.5 mg/day Cariprazine (n=140)</td>
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<tr>
<td>3 mg/day Cariprazine (n=140)</td>
</tr>
<tr>
<td>4.5 mg/day Cariprazine (n=145)</td>
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<tr>
<td>4 mg/day Risperidone (n=138)</td>
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<tr>
<td>Dropouts</td>
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<tr>
<td>Baseline</td>
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<td>6 Weeks</td>
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Significantly more patients in the placebo group than either the cariprazine or risperidone group discontinued treatment due to insufficient response (22% vs. 7–12%; p<0.05). The most frequent adverse effects that occurred more often with cariprazine than placebo were insomnia; extrapyramidal symptoms; akathisia; sedation; nausea; dizziness; and constipation. Adverse effects did not appear to be dose-related. Cariprazine was not associated with adverse changes in prolactin, cholesterol, or fasting plasma glucose, and weight gain was intermediate between placebo and risperidone.

Discussion: Blockade of dopamine D2 receptors is believed to be a necessary action of antipsychotics. Cariprazine is a partial agonist of both D2 and D3 receptors, which may theoretically augment its antipsychotic effects relative to other agents. The drug is pharmacologically similar to aripiprazole, which also functions as a D2 partial agonist.

Durgam S, Starace A, Li D, Migliore R, et al: An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. Schizophrenia Research 2013; doi:10.1016/j.schres.2013.11.041. From Forest Research Institute, Jersey City, NJ; and other institutions. Funded by Forest Research Institute and Gedeon Richter Plc. At the time of the study, all 7 study authors were either employees of or contractors for Forest or Gedeon Richter.

Drug Trade Names: aripiprazole—Abilify; risperidone—Risperdal

*See Reference Guide.
Sexual Dysfunction with Second-Generation Antidepressants

A systematic review and meta-analysis found few differences among second-generation antidepressants in the overall incidence of sexual dysfunction. However, patterns were observed for 3 of the drugs: Bupropion was associated with generally lower risk, and escitalopram and paroxetine were associated with greater risk than some other drugs.

Methods: The meta-analysis included studies of 13 different second-generation antidepressants: bupropion; citalopram; desvenlafaxine; duloxetine; escitalopram; fluoxetine; fluvoxamine; mirtazapine; nefazodone; paroxetine; sertraline; trazodone; and venlafaxine. Both placebo-controlled trials and head-to-head randomized drug comparisons of ≥6 weeks' duration, as well as observational studies with ≥1000 participants and ≥12 weeks of follow-up, were included. All reported subtypes of sexual dysfunction (e.g., anorgasmia, loss of libido, erectile dysfunction, and others) were grouped into a single outcome. The investigators rated study quality and included only those with low or moderate risk of bias.

Results: A total of 63 studies were identified and evaluated for inclusion. Thirty-seven randomized trials, with nearly 15,000 study subjects, met the statistical criteria for inclusion in the network meta-analysis.

Most comparisons showed a similar risk of sexual dysfunction among the drugs studied. Of the 66 pairwise comparisons (55 active pairs and 11 placebo comparisons), few showed a significant difference between arms. Bupropion was associated with less risk of dysfunction than escitalopram, paroxetine, and sertraline. The incidence was significantly higher among patients treated with either paroxetine or escitalopram, compared with fluoxetine, mirtazapine, and nefazodone. Incidence was also significantly higher with paroxetine than venlafaxine.

Of the trials that reported gender-specific rates, data could be combined only for those with male-specific rates as data was insufficient to calculate rates in women only. These comparisons showed an overall incidence of sexual dysfunction of 12%, somewhat lower for fluoxetine and higher for sertraline, but generally similar for most drugs.

Discussion: The investigators urge cautious interpretation of their findings, particularly because the studies did not use consistent methods to ascertain sexual dysfunction or did not report baseline levels of sexual dysfunction. However, the results do point to 3 distinct findings: Rates of sexual dysfunction were lower with bupropion and higher with escitalopram and paroxetine.

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


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

*See Reference Guide.

Ecopipam for Tourette Tics

The selective dopamine D1 receptor antagonist ecopipam reduced tic severity in an early-phase clinical trial in patients with Tourette syndrome.

Methods: The open-label, single-arm trial enrolled adults, aged 18–63 years (mean age, 36 years; 15 men), who had a history of both motor and phonic tics for >5 years and a baseline total score of ≥20 on the Yale Global Tic Severity Scale (YGTSS). Patients with a history of depression,
psychosis, or suicidality were excluded, but those who had other mental-health disorders common in Tourette (e.g., obsessive-compulsive disorder [OCD], ADHD) were enrolled. Concomitant stable SSRI therapy was permitted. All patients received 50 mg/day ecopipam for 2 weeks, followed by an increase to 100 mg/day, if tolerated, for 6 weeks. The primary efficacy outcome was reduction from baseline in YGTSS total score.

**Results:** A total of 18 patients began treatment, and 15 completed the 8-week protocol; 3 withdrew because of adverse events. Planned enrollment was 30 patients, and the trial was terminated early when an interim analysis showed a significant decrease in tics. In the intent-to-treat analysis,* the mean YG TSS score decreased from 30.6 at baseline to 25.3 at 8 weeks (p=0.0004). Reductions in both motor and phonic tics were significant (4.5 and 5.9 points; p=0.0004 and p=0.0056, respectively). YG TSS impairment scores and Clinical Global Impression–Severity scores also improved. Patients experienced no change in premonitory urges or symptoms of depression or OCD. ADHD symptom self-report scores were mostly in the clinical range on average at baseline and decreased by 16% after 8 weeks.

The most frequent adverse effects of ecopipam, occurring in 20–40% of patients, were sedation; fatigue; insomnia; somnolence; anxiety; headache; and muscle twitching. Akathisia developed in 1 patient. No patient experienced weight gain, in contrast to D2 receptor antagonists.

**Discussion:** Selective antagonism of the D1 receptor is a novel mechanism for reduction of tics. It is likely that Tourette tics occur via a combination of D1 and D2-related mechanism and that individual patients may respond differentially to blockade of each receptor. Controlled trials are needed.

Gilbert D, Budman C, Singer H, Kurlan R, et al: A D1 receptor antagonist, ecopipam, for treatment of tics in Tourette syndrome. *Clinical Neurorpharmacology* 2014;37 (January/February):26–30. From Cincinnati Children’s Hospital Medical Center, OH; and other institutions including Psyadon Pharmaceuticals, Inc., Germantown, MD. **Funded by Psyadon Pharmaceuticals. The authors declared no conflicts of interest.**

*See Reference Guide.

**Beta-Interferon in Early Alzheimer's**

Interferon beta-1a was well tolerated and showed modest promise in a pilot study of patients with early Alzheimer's disease.¹

**Background:** Because of its immunomodulatory and neuroprotective effects, interferon beta-1a is widely used in the treatment of multiple sclerosis (MS). The agent was shown to prevent cognitive decline in a large cohort study of patients with MS.² The similarity of some of the mechanisms involved in MS and Alzheimer’s disease led to the present investigation.

**Methods:** The study enrolled 42 patients, aged 50–75 years, who met DSM-IV criteria for Alzheimer's disease and had a Mini-Mental State Examination (MMSE) score between 20 and 26. Patients received randomly assigned, low-dose interferon beta-1a (22 mcg by subcutaneous injection 3 times per week), or placebo. Patients were treated for 28 weeks and then followed for up to 52 weeks. The primary efficacy measure was the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog).

**Results:** Interferon beta-1a was well tolerated. Only 1 patient in the active treatment group experienced an adverse effect, mild fever, that was likely attributable to interferon beta-1a. Although interferon is known to produce a transient decline in mood early in treatment, no patient reported depression as an adverse effect of treatment. Patients who received active treatment had a modest decline in serum cholesterol.

ADAS-Cog scores showed no significant progression of Alzheimer’s disease during the treatment period in either study group. Worsening of disease was evident during follow-up; however, there was a significantly smaller decline between weeks 28 and 52 in the group that
received the interferon (p=0.03). Overall effects on the MMSE followed the same pattern. Other secondary study outcomes (e.g., self-maintenance and activities of daily living) also showed improvement with interferon beta-1a between the end of treatment and the end of follow-up, but not during treatment. The Geriatric Depression Scale showed greater improvement with placebo than active treatment.

Discussion: The study was not statistically powered to detect efficacy differences between interferon beta-1a and placebo. Paradoxically, the improvement in depressive symptoms in the placebo group may have counterbalanced any positive cognitive effect of the active drug. The cholesterol-lowering effect of interferon beta-1a is a new observation and may suggest an additional mechanism for the positive cognitive effects of the drug.

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


Drug Trade Names: interferon beta-1a—Avonex, Rebif

*See Reference Guide.

Reference Guide

Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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.

Intent-to-Treat: An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone who begins treatment is included regardless of treatment completion. ITT analyses are done to avoid the effects of crossover, drop-out, and other factors that could alter the results or inflate the magnitude of effects.

Last Observation Carried Forward (LOCF): A method of data analysis in which missing data for individual patients is replaced by the last observed value of that variable.

Network Meta-Analysis: An expansion of standard meta-analysis in which treatments can be compared even if they have not been studied in head-to-head comparisons.

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 the treatment.

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.