Asenapine Reviewed

According to a *Medical Letter* review of the recently approved atypical antipsychotic asenapine (*Saphris*), "available data on its efficacy are not impressive." Asenapine is formulated in a sublingual tablet and is approved for acute schizophrenia and manic or mixed bipolar episodes. Its receptor affinity profile is similar to other atypicals. Three placebo-controlled trials have been conducted in schizophrenia and 2 have been conducted in acute manic or mixed episodes. Results of the trials were mixed. In 2 of the schizophrenia trials, 5 mg asenapine b.i.d. was superior to placebo, but 10 mg b.i.d. was not more effective than haloperidol or placebo. In the third trial, olanzapine was significantly more effective than placebo but 5 mg asenapine b.i.d. was not. In short-term bipolar disorder studies asenapine was more effective than placebo and noninferior to olanzapine at reducing mania severity. Adverse effects included akathisia and other extrapyramidal symptoms, diminished oral sensation, somnolence, and dizziness. Asenapine can prolong the QT interval, cause weight gain, and increase prolactin levels. Concomitant use with a strong CYP1A2 inhibitor such as fluvoxamine can increase asenapine concentrations and concomitant use can increase paroxetine concentrations nearly 2-fold. Asenapine should not be used by patients with severe hepatic impairment and patients should not eat or drink for at least 10 minutes after administration. Adherence to sublingual dosing may be problematic for patients experiencing acute mania or schizophrenia.

*Asenapine (Saphris) sublingual tablets for schizophrenia and bipolar disorder. The Medical Letter 2010;52 (February 8):9–10.*

_Fatty Acids for Perinatal Depression?_

Antidepressants may be effective in perinatal depression but risks, including persistent pulmonary hypertension and poor neonatal adaptation syndrome in infants with SSRI exposure during late pregnancy, may lead women to refuse treatment. Omega-3 fatty acid depletion in pregnancy may have a role in onset of depressive symptoms and supplementation has been investigated in the prevention and treatment of perinatal depression. A literature review evaluated 6 published studies; 4 were randomized controlled trials and 2 were open-label investigations. Study samples...
were small, ranging from 15 to 89 women, and planned treatment durations ranged from 6 weeks to 4 months. Fatty acid initiation varied from 16 weeks gestation to 1 month postpartum. Use of antidepressant medication was an exclusion criteria in 5 of the studies; 1 study in postpartum depression did not evaluate concomitant medication. The Edinburgh Postnatal Depression Scale, the Hamilton Rating Scale for Depression (HAM-D), or the Beck Depression Inventory was used to measure depressive symptoms in each study.

Depression scores decreased with fatty acids in all studies and with placebo in the controlled trials. The improvements were statistically significant compared with baseline in 3 studies. A single study found more fatty acid treated women achieved HAM-D response (62% vs 27%; p=0.03) and remission (38% vs 18%; p=ns), but the study was conducted in a population with high fish consumption. Fatty acids were well tolerated. Adverse effects included foul breath, unpleasant taste, nausea, heartburn, insomnia, burping, and diarrhea; none were serious.

This literature review does not appear to resolve the issue of whether omega-3 fatty acids should be used to treat perinatal depression. The studies were limited by small samples, variable dosing, and short durations. The authors suggest the consistent decrease in depression scores coupled with the tolerability of treatment warrant further study.

Borja-Hart N, Marino J: Role of omega-3 fatty acids for prevention or treatment of perinatal depression. Pharmacotherapy 2010;30 (February):210–216. From Nova Southeastern College of Pharmacy, Fort Lauderdale, Fla. The authors did not include a statement of financial disclosure.

**Bradycardia With Aripiprazole and Ziprasidone**

Common cardiac effects of atypical antipsychotics include orthostatic hypotension and tachycardia. There have also been reports of bradycardia with clozapine, olanzapine, risperidone, quetiapine, and amisulpride. However, it may not be a class effect of atypical antipsychotics as some patients tolerate another atypical after the bradycardia resolves. A recent report extends the effect to aripiprazole and ziprasidone.

An otherwise healthy 18-year-old female with bipolar disorder was admitted with mania and delusions. Heart rate, blood pressure, and laboratory analyses were within normal limits. She was started on 80 mg/day ziprasidone but asymptomatic sinus bradycardia developed after the second dose. Ziprasidone was continued and her vital signs were monitored. The following day ziprasidone was increased to 120 mg and the patient experienced lightheadedness and her heart rate fell to between 31 and 35 bpm. Bradycardia resolved, but ziprasidone was reduced to 80 mg/day and the patient was discharged. She was readmitted 3 months later after medication noncompliance and started on 15 mg/day aripiprazole and lithium to stabilize mood. After an increase to 20 mg aripiprazole, the patient again experienced bradycardia that resolved with treatment. Because of the recent experience with ziprasidone, aripiprazole was stopped. The patient’s mania was controlled with lithium monotherapy with no further episodes of bradycardia.

According to the Naranjo Probability Scale,* it is probable that bradycardia was associated with ziprasidone and aripiprazole. All reported cases of atypical antipsychotic-induced bradycardia resolved with medication discontinuation and none had long-term consequences. The mechanism that underlies the reaction is unknown.


**Drug Trade Names:** amisulpride (not available in the U.S.)—Solian, Sulamid; aripiprazole—Abilify; clozapine—Clozaril; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

*Reference Guide Item.*
Antidepressant Exposure and Infant Development

Results of a large cohort study suggest antidepressant exposure during late pregnancy affects motor development, especially in male offspring.

Information on depression and antidepressant use during pregnancy was collected from nearly 82,000 women who participated in a Danish national study of pregnant women and their offspring. Women completed prenatal interviews at 17 and 32 weeks of pregnancy. Follow-up interviews 6 and 19 months after delivery collected information on antidepressant use after 32 weeks gestation as well as attainment of developmental milestones by the offspring. A total of 24 milestones such as head control, ability to sit unsupported, motor development, attention, and language development were evaluated.

A total of 415 mothers reported using antidepressants (84% SSRIs) during pregnancy and another 489 reported experiencing depression but did not use psychotropic medication. Women with depression (regardless of treatment) had greater consumption of alcohol and tobacco than women without depression; rates were higher with untreated than treated depression. Antidepressant users were slightly older than women with untreated depression. Children exposed to antidepressants late in gestation showed small delays in gross motor development at 6 months, compared with offspring of mothers with untreated depression. Antidepressant-exposed boys were 3 times less likely to sit without support than unexposed boys; the difference was less pronounced among girls. At 19 months of age, exposed children had caught up to their unexposed peers in terms of motor development but were significantly less likely than unexposed children to be able to occupy themselves for >15 minutes.

Pedersen L, Henriksen T, Olsen J: Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. *Pediatrics.* Published online February 22, 2010 at www.pediatrics.org; doi 10.1542/peds.2008-3655. From Aarhus University, Denmark; and the University of California, Los Angeles. *Funded by the Lundbeck Foundation, an independent foundation supported by the pharmaceutical company Lundbeck; and the National Danish Research Foundation. Two of the study authors disclosed commercial relationships with Lundbeck; the third author disclosed no potential conflicts of interest.*

Bipolar Depression Algorithm

The Psychopharmacology Algorithm Project at the Harvard South Shore Program (PAPHSS) includes algorithms for depression, anxiety with comorbid drug abuse, and schizophrenia. The algorithms are available on the PAPHSS website (www.mhc.com/Algorithms/) in an interactive format that includes recommendations as well as rationale for the choices and supporting evidence. The bipolar depression project has been updated and was discussed in a recent report.

The bipolar depression report emphasized the importance of confirming the diagnosis prior to beginning algorithm-based treatment. Patients with depression for whom a “pre-bipolar” state should be considered include those with a family history of bipolar disorder; younger age at onset; family history of suicide; poor response to antidepressants; history of treatment-emergent suicidality, agitation, or irritability; or postpartum psychosis. These patients may be more appropriately treated for bipolar disorder than unipolar depression. Once the diagnosis is established, the following sequence is suggested.

1. **Is urgent ECT needed?**

ECT is indicated for patients with catatonia, severe suicidality, or insufficient oral intake, for pregnant women, and when rapid response is essential.

2. **Are psychotic symptoms present?**

If present, start an antipsychotic. Atypicals are preferred because of the risk for tardive dyskinesia with conventional agents. The strongest evidence supports quetiapine, but other atypicals can be considered. Olanzapine is not recommended for first-line treatment.
3. Is the patient currently taking a mood stabilizer?
If so, evaluate and adjust dosage as necessary. If not, a mood stabilizer should be added. Lithium and quetiapine appear to be the best choices, with a slight preference for lithium. Lamotrigine may also be an option, but the evidence for its use is inconsistent. The olanzapine–fluoxetine combination is another FDA-approved possibility, but long-term metabolic effects may be problematic and the long half-life of fluoxetine metabolites can prolong manic episodes in the case of switching. Limited evidence exists for aripiprazole, ziprasidone, and risperidone. Valproate should be avoided in women of childbearing potential because it is teratogenic, and the evidence is insufficient to recommend carbamazepine or oxcarbazepine.

4. Has depression persisted despite mood stabilizer or quetiapine therapy?
Evaluate medication adherence and therapeutic levels and adjust as necessary. Carbamazepine, lithium, quetiapine, and valproate all have antimanic effects and the ineffective treatment should be replaced with an alternate agent from among these. Adding an agent without antimanic efficacy (e.g., lamotrigine) is also reasonable. See the online algorithm for specific options.

5. Should an antidepressant be added?
Use of antidepressants in bipolar disorder is controversial because of the risk for manic switching and long-term destabilization. They should not be used in patients with rapid cycling. The risks may vary by agent, and bupropion appears to have the lowest potential. There is no clear evidence for superiority of any one antidepressant; however, agents with adrenergic properties (e.g., venlafaxine and TCAs) should be avoided. Patients should undergo trials of lithium, quetiapine, and lamotrigine before antidepressants are considered. If an antidepressant is to be added, it should only be used in combination with a mood stabilizer. The optimal duration of antidepressant therapy has not been determined.

6. Does the depression remain refractory to treatment?
A trial of ECT should be considered. Other options at this stage include aripiprazole, clozapine, modafinil, omega-3 fatty acids, pramipexole, and topiramate, but none are supported by high-quality evidence.

Algorithms can be helpful in treatment decision making, but the authors caution they should not replace good clinical judgment.


Drug Trade Names: aripiprazole—Abilify; bupropion—Wellbutrin; carbamazepine—Epitol, Tegretol; clozapine—Clozaril; fluoxetine—Prozac; lamotrigine—Lamictal; modafinil—Provigil; olanzapine—Zyprexa; olanzapine–fluoxetine—Symbyax; oxcarbazepine—Trileptal; pramipexole—Mirapex; quetiapine—Seroquel; risperidone—Risperdal; topiramate—Topamax; valproate—Depakene, Depakote; venlafaxine—Effexor; ziprasidone—Geodon

Combination Therapy for Bipolar Maintenance

National Institute for Health and Clinical Excellence (NICE) guidelines recommend patients with bipolar disorder who have frequent relapses while receiving lithium be switched to valproate (Depakote). The Bipolar Affective disorder: Lithium/ANtiConvulsant Evaluation (BALANCE) has found combined lithium and valproate to be more effective than valproate alone at preventing relapse.

Methods: Participants in the multinational study were 330 patients aged ≥16 years for whom long-term pharmacological maintenance for bipolar I disorder was indicated. Patients with a strong preference for lithium or valproate at screening were excluded. All patients underwent a 4–8 week run-in with combined lithium and valproate. Lithium was titrated to a
target blood level of 0.4–1.0 mEq/L and valproate was administered in the range of 750–1250 mg/day. Patients were then randomized to single-blind monotherapy with either lithium or valproate or continued combination therapy and followed for up to 2 years until an emerging mood episode required treatment. In the monotherapy groups the discontinued drug was withdrawn over 4 weeks to reduce the risks associated with abrupt withdrawal.

**Results:** During follow-up 200 patients (61%) experienced a relapse that required new treatment or hospitalization. The rate was significantly lower with combined treatment (54%) than with valproate monotherapy (69%; p=0.002) but not lithium monotherapy (59%; p=ns). Hazard ratios* for relapse in the combination therapy group were 0.82 compared with lithium monotherapy and 0.59 compared with valproate monotherapy. The number needed to treat* for combination treatment vs valproate monotherapy was 7. Baseline severity and the nature of the most recent episode (i.e., manic, depressive) did not appear to affect outcomes in any group. However, the benefits of combination therapy were most pronounced for manic relapse episodes, while lithium was more effective at preventing depressive episodes.

Twenty-one patients experienced a serious adverse event: 5 during the run-in and 16 during randomized treatment. One case of polycystic ovary disease was thought be related to weight gain associated with combination treatment; no other serious adverse event was treatment-related. The potential exists for renal toxicity with lithium, and congenital malformations with valproate were not systematically evaluated.

**Discussion:** In contrast to published guidelines, this study provides evidence that combined treatment with lithium and valproate is more effective than valproate alone at preventing bipolar disorder relapse. However, it should be noted that >50% of patients receiving the most effective treatment still required additional therapy during 2 years of follow-up.

**Study Rating*—16 (94%):** Patients in this study were not blinded to treatment assignment, but investigators assessing the outcomes were masked.

Geddes J, Goodwin G, Rendell J, Azorin J-M, et al for the BALANCE investigators and collaborators: Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomized open-label trial. *Lancet* 2010;375 (January 30):385–395. From the University of Oxford, U.K.; and other institutions. Funded by the Stanley Medical Research Institute, with centers in France funded by Sanofi-Aventis. Study drugs in the UK and France were provided by Sanofi-Aventis, manufacturer of valproate and lithium products; drug provider was not specified for U.S. or Italian sites. Several study authors declared commercial relationships with Sanofi-Aventis and other pharmaceutical-industry sources.

*Reference Guide Item.

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**Phenelzine or CBT for Social Anxiety Disorder**

Research in social anxiety disorder conducted at Columbia and Temple Universities found combined treatment with phenelzine and group cognitive behavioral therapy (CBT) superior to either treatment alone and to placebo.

**Methods:** Patients aged 18–65 years with a primary diagnosis of social anxiety disorder were eligible for study provided they did not have comorbid major depression, bipolar disorder, or schizophrenia. Participants (n=128) received randomly assigned phenelzine, group CBT, combined phenelzine and CBT, or pill placebo for 12 weeks. Evaluators were blinded to medication assignment, and although all patients in the combination group received phenelzine, they believed they may have been randomized to placebo. After counseling about necessary dietary restrictions with MAOI treatment, phenelzine was started at 15 mg/day and could be titrated to a maximum of 90 mg/day. CBT was provided in weekly sessions with 4–6 participants and focused on education, cognitive skills, and exposure therapy. The primary outcome measures were the Liebowitz Social Anxiety Scale (LSAS)* and the Clinical Global Impression-Improvement* (CGI-I) scale. Patients with adequate response at 12 weeks entered a 12-week...
intensive continuation phase during which they continued randomized treatment but had fewer clinical contacts.

**Results:** Mean baseline LSAS scores ranged from 64 to 80 (indicating marked social phobia) with no significant differences between treatment groups. Combination therapy and phenelzine monotherapy were significantly superior to placebo (p=0.001 for both), but CBT alone was not. Compared with placebo, effect sizes* were large for combined treatment (1.05), medium for phenelzine monotherapy (0.6), and small for CBT (0.08).

At 12 weeks, mean LSAS scores had decreased to 24 with combination therapy, to 48 with phenelzine alone, and to 63 with CBT and placebo. Scores in the CBT group remained near the upper end of the moderate severity range. CGI-I scores showed a similar pattern with scores of 1.8 with combination treatment, 2.4 with phenelzine, 2.5 with CBT. The odds ratios* for treatment response (CGI-I score of ≤2) were 5.1 with combined treatment, 2.4 with phenelzine, and 1.8 with CBT. Actual response rates were 72% with combined treatment, 54% with phenelzine, 47% with CBT, and 33% with placebo.

Results were similar at the end of the continuation phase (24 weeks), but the difference between CBT and phenelzine monotherapy narrowed somewhat. Response rates at 24 weeks were 78% with combination treatment, 49% with phenelzine, 53% with CBT, and 33% with placebo. Remission (LSAS score of ≤30) was achieved by 53% of the combination group, compared with 15–26% of the other treatment groups.

**Discussion:** Phenelzine may reduce anxiety and increase patients’ chances of successfully confronting a feared situation while skills learned in CBT sessions may in turn allow them to benefit from the exposures. In addition to the results presented here, the study included maintenance and naturalistic follow-up phases and those results will be forthcoming. Both sertraline and fluoxetine have been shown to have some efficacy in social anxiety disorder and future trials should examine an SSRI/CBT combination.

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

Blanco C, Heimberg R, Schneier F, Fresco D, et al: A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. *Archives of General Psychiatry* 2010;67 (March):286–295. From The New York State Psychiatric Institute at Columbia University, New York, N.Y.; and Temple University, Philadelphia, Penn. Funded by the NIH; and the New York State Psychiatric Institute. Several study authors disclosed commercial relationships with pharmaceutical-industry sources, and Dr. Michael Liebowitz, developer of the LSAS, is one of the study authors.

**Drug Trade Names:** fluoxetine—Prozac; phenelzine—Nardil; sertraline—Zoloft

*A Reference Guide Item.

## SSRI/Tamoxifen Mortality

A preliminary report suggested several antidepressants that inhibit cytochrome P450 (CYP) 2D6 reduce tamoxifen concentrations and may lead to cancer recurrence. A population-based cohort study now shows concurrent use of tamoxifen and paroxetine, one of the most potent CYP2D6 inhibiting SSRIs, increases risk of cancer death.

**Methods:** Prescription and cancer registry records in Canada were linked to identify a cohort of women aged >65 years with breast cancer who received a new prescription for tamoxifen and a single SSRI between 1993 and 2005. More than 24,000 women started tamoxifen treatment and 2430 women also received a single SSRI or venlafaxine and had complete data available until death or 2007. The primary outcome was breast cancer death, and all-cause mortality was also evaluated.

**Results:** Paroxetine was the most commonly prescribed SSRI (n=630) followed by sertraline (n=541), citalopram (n=467), venlafaxine (n=365), fluoxetine (n=253), and fluvoxamine (n=174). A total of 1074 women died during follow-up, including 374 as a result of breast cancer. Risk
of breast cancer death was significantly increased in women taking paroxetine with hazard ratios* (HRs) of 1.24–1.91 depending on the duration of concomitant treatment. Other SSRIs were not associated with increased risk of breast cancer death and there was a nonsignificant decrease in risk with venlafaxine. All-cause mortality was also increased with paroxetine (HRs, 1.13–1.46) but not with other antidepressants.

**Discussion:** This study is limited by a lack of information on the indication for antidepressant therapy. Some women may have been prescribed these drugs to combat tamoxifen-related hot flashes; this is particularly likely with venlafaxine. In addition, breast cancer stage was not assessed. According to the authors there is no clinical reason women with more advanced cancer would have a greater likelihood of receiving paroxetine over other antidepressants and this lack of information was not likely to bias the findings. Because paroxetine is an irreversible CYP2D6 inhibitor it may reduce or negate the long-term survival benefits of tamoxifen. Fluoxetine is also a potent CYP2D6 inhibitor and the reason for the lack of an association with breast cancer death in this study is unclear. It may be related to the relatively small number of women prescribed the agent. About 30% of women receiving tamoxifen also received an antidepressant, and because paroxetine was the most frequently prescribed antidepressant, the public health implications of these findings may be particularly important.

**Clinical Implications:** "The choice of antidepressant can significantly affect survival in women receiving tamoxifen for breast cancer." When antidepressants are necessary, use of a less potent CYP2D6 inhibitor is prudent.

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2 Kelly C, Juurlink D, Gomes T, Duong-Hua M, et al: Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. British Medical Journal. Published online February 8, 2010 at www.bmj.com; doi 10.1136/bmj.c693. From Sunnybrook Health Sciences Centre, Toronto, Canada; and other institutions. Funded by the Sunnybrook Hospital Foundation; and other sources. One study author disclosed commercial relationships relevant to the study; all other authors declared no conflicts of interest.

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

*Reference Guide Item.

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**Personality Changes with Paroxetine**

A randomized controlled trial was undertaken to determine if the effects of SSRI treatment on the personality traits neuroticism and extraversion are dependent on depression improvement or if personality changes are a direct effect of the medication and unrelated to depressive symptoms.

**Methods:** Adult outpatients with moderate-to-severe unipolar major depression were randomized to 8 weeks of paroxetine (*Paxil*; n=120), cognitive therapy (n=60), or placebo (n=60). Depression was measured using the Hamilton Rating Scale for Depression (HAM-D), and the NEO Five-Factor Inventory self-report quantified neuroticism and extraversion. Following acute treatment, patients who responded to paroxetine or cognitive therapy entered a 12-month continuation phase during which paroxetine patients were re-randomized to continued paroxetine or placebo and cognitive therapy patients could receive up to 3 booster sessions. The placebo group completed their study participation at 8 weeks and about half of the patients opted to try open-label paroxetine or another SSRI at that time.

**Results:** Both paroxetine and cognitive therapy improved depression, neuroticism, and extraversion with no differences between the groups. At 8 weeks, effect sizes* for depression improvement were 0.37 for cognitive therapy and 0.38 for paroxetine, compared with placebo, and ranged from 0.46 to 0.63 for neuroticism and extraversion. In the placebo group depression scores were substantially improved, but there was little change in neuroticism or extraversion. In a sample of 44 placebo and paroxetine patient pairs matched for depression improvement, paroxetine produced 4–7 times greater improvements in neuroticism and extraversion. Placebo
patients later treated with paroxetine showed decreases in neuroticism and improved extraversion during active treatment that they had not shown while receiving placebo. Among the 69 paroxetine responders, changes in extraversion did not affect relapse, but greater reductions in neuroticism were associated with lower risk of relapse. Changes in behavioral traits in cognitive therapy responders did not affect relapse risk.

**Discussion:** Paroxetine appears to have a distinct pharmacological effect on personality traits that is independent of depression improvement. Whether these effects extend to other SSRIs or antidepressant classes is not known.

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


*Reference Guide Item.*

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**Reference Guide**

**Clinical Global Impression-Improvement (CGI-I) Scale:** A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

**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 one group has half the risk of the other group.

**Liebowitz Social Anxiety Scale (LSAS):** A measure of social phobia severity, wherein a score of >95=very severe, 80–95=severe, 65–80=marked, and 55–65=moderate.

**Naranjo Probability Scale:** A 10-point scale used to determine the likelihood that an adverse reaction is caused by an implicated medication. Based on scores, associations are considered doubtful, possible, probable, or highly probable.

**Number Needed to Treat (NNT):** Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

**Odds Ratio:** A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

**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.