Mirtazapine Effects in Patients with Diabetes

In a retrospective observational study of patients receiving naturalistic treatment for diabetes, mirtazapine was associated with weight gain but had no other adverse metabolic effects.

**Background:** The results of several studies have raised concern that antidepressant drug therapy is associated with increased risk of weight gain and diabetes. Weight gain is listed as an adverse effect of mirtazapine, although clinical trial results have suggested it may be transient. There is little information on the metabolic effects of this agent in patients with diabetes, who are generally excluded from antidepressant clinical trials.

**Methods:** Study subjects were patients with diabetes (n=33), referred by their endocrinologist to a psychiatrist for treatment of depression. DSM-IV diagnosis of unipolar major depressive disorder was confirmed by 2 psychiatrists. All patients received mirtazapine for ≥6 months and had baseline and follow-up data on body mass index (BMI), glucose metabolism, and lipids. Patients were individually matched for age, gender, mode of diabetes treatment, and diagnosis of dyslipidemia with diabetic controls who had not taken any psychotropic medication.

**Results:** Baseline characteristics of the 2 groups did not differ, with the exception of total cholesterol levels, which were higher in the control group. The mean patient age was 60 years, and the mean mirtazapine dosage was 24 mg/day. A total of 16 patients in each group had dyslipidemia. In each group, 8 patients received treatment with metformin, 16 with multiple oral agents, 1 with insulin, and 8 with insulin plus oral agents. Six patients in the mirtazapine group and 8 in the control group were given a prescription for an additional oral antidiabetic agent or had a dosage increase during follow-up.

After 6 months of treatment, average BMI was increased by 1 point in the mirtazapine group and by 0.3 points in the comparison group (p<0.001). The increase in BMI was not dose-related and was more pronounced in patients who were initially overweight (BMI, ≥25).

HbA1c and fasting plasma glucose decreased in both groups with no significant between-group differences. Lipid measurements, a secondary study outcome, also showed no significant
differences between patients taking mirtazapine and controls. Both groups had significant decreases in average total and LDL cholesterol. Triglycerides remained stable. HDL cholesterol increased in the comparison group only, but this change did not differ statistically from the patients who received mirtazapine. In a separate analysis limited to patients without dyslipidemia, triglycerides decreased significantly in the control group but increased slightly in the mirtazapine group.

**Discussion:** These results suggest that mirtazapine can be prescribed safely for short-term treatment of depression in patients with diabetes, but clinicians should be alert to the risk of weight gain. This is the first known study to examine mirtazapine’s metabolic effects in patients with diabetes. Longer-term studies are needed.


**Drug Trade Names:** metformin—Glucophage; mirtazapine—Remeron

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**Violent Patients: Treatment Outside the Guidelines**

In patients with schizophrenia, violence is an important indication for aggressive treatment strategies. Guidelines for schizophrenia treatment recommend a series of atypical antipsychotics as monotherapy, followed by a trial of clozapine. However, many patients continue to be violent and require additional treatment. According to a review, high-dose monotherapy and antipsychotic polypharmacy may be useful for these patients.

Neuroimaging studies have shown that blockade of ≥60% of D2 receptors by antipsychotic treatment is necessary to reduce psychosis; and 80% occupancy is the threshold for extrapyramidal effects in many patients. A patient whose psychotic or impulsive violence is not ameliorated with standard antipsychotic monotherapy may be experiencing pharmacokinetic failure (i.e., inability to achieve adequate receptor occupancy due to problems such as rapid metabolism, cytochrome P450 polymorphisms, poor absorption, or drug interactions). Pharmacokinetic failure is usually accompanied by a lack of side effects and should be confirmed with therapeutic drug monitoring. Effective interventions may include increasing the dose, switching to another antipsychotic monotherapy (perhaps with a different route of administration), instituting antipsychotic polypharmacy, or simply taking the antipsychotic with food. Pharmacodynamic failure (i.e., a lack of response despite adequate blood levels) may call for treatment strategies aimed at increasing D2 receptor occupancy above 80%. Each available agent has its own considerations for high dosing, which are summarized in the table below. As less is known about high-dose therapy with iloperidone, asenapine, and lurasidone, these are not included in the table. Higher doses of aripiprazole are usually not more effective, and are possibly less effective.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Dosage Range (Oral Formulation)</th>
<th>Maximum Dosage Based on Clinical Evidence</th>
<th>Considerations for High Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>300–450 mg/day</td>
<td>900 mg/day</td>
<td>Dosages &gt;550 mg/day may require concomitant anticonvulsant use to reduce risk of seizure. Increases should be made at intervals of 5–7 days.</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2–8 mg/day</td>
<td>16 mg/day</td>
<td>Very high doses are not usually well tolerated. Increases should be made at intervals of 5–7 days.</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>3–6 mg/day</td>
<td>12 mg/day</td>
<td>Increases should be made at intervals of 5–7 days.</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10–20 mg/day</td>
<td>90 mg/day</td>
<td>Increases should be made at intervals of 5–7 days.</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>400–800 mg/day</td>
<td>1800 mg/day</td>
<td>Very low risk of EPS even at high doses.</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>40–200 mg/day</td>
<td>360 mg/day</td>
<td>Must be taken with food.</td>
</tr>
</tbody>
</table>
Data supporting antipsychotic polypharmacy are somewhat limited, but this strategy appears to be common in clinical practice. Polypharmacy should likely be reserved for the subpopulation of patients for whom several antipsychotic monotherapy trials were unsuccessful and a trial of clozapine was unhelpful or could not be attempted. If polypharmacy is attempted, the choice of agents should be based on the receptor binding profiles of the drugs, and the use of agents with similar side-effect profiles should be avoided. Potential cytochrome P450 interactions should be carefully considered. Combinations that include clozapine have the most evidence for efficacy; however, when clozapine is not an option, it appears that a combination of a first- and second-generation antipsychotic is often used. If either high-dose monotherapy or polypharmacy is effective in curbing violent behavior, an attempt should be made to switch the patient to more conventional antipsychotic therapy.

Morrissette D, Stahl S: Treating the violent patient with psychosis or impulsivity utilizing antipsychotic polypharmacy and high-dose monotherapy. CNS Spectrums 2014; doi 10.1017/S1092852914000388. From the Neuroscience Education Institute, Carlsbad, CA; and other institutions. Source of funding not stated. One study author disclosed relationships with commercial sources; the other author disclosed no conflicts of interest.

Drug Trade Names: aripiprazole—A bilify; asenapine—Saphris; clozapine—Clozaril; iloperidone—Fanapt; lurasidone—Latuda; olanzapine—Zyprexa; paliperidone—Invega; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

Intranasal Oxytocin for Resistant Depression

Adding intranasal oxytocin to escitalopram resulted in rapid clinical improvement in a pilot study of patients with treatment-resistant depression.

Background: Oxytocin is involved in the regulation of emotions, and there has been speculation that dysregulation of oxytocin function is associated with some of the symptoms of depression, including social withdrawal, reduced appetite, and cognitive impairment. Preclinical evidence suggests oxytocin may influence the activity of the serotonin system, but clinical studies in depression have had mixed results.

Methods: Participants in this open-label, uncontrolled study were 6 women and 8 men with a ≥2-year history of major depressive disorder. All patients had been treated unsuccessfully with antidepressants from different classes at the maximum recommended dose (≥22 trials). During the current treatment episode, all patients had received 40 mg/day escitalopram for ≥8 weeks but continued to have a Hamilton Rating Scale for Depression (HAMD) score of ≥17. Patients were treated with adjunctive intranasal synthetic oxytocin (a single 4-IU puff per nostril, twice daily). The 4 premenopausal women received treatment beginning in the first phase of their menstrual cycle. Clinical assessment was performed weekly for 4 weeks.

Results: At the first weekly assessment, patients demonstrated a significant decrease in HAMD scores from a mean of 26 at baseline to about 11 (p<0.001). Other outcomes, including anxiety and quality of life, were also significantly improved (p<0.05). All measures demonstrated stable improvement throughout the remaining weeks of treatment. The average Clinical Global Impression–Severity score* decreased from 4.3 to 2.

Discussion: Although these results appear to be positive, oxytocin should be used cautiously. It can promote aggression in some circumstances, and its effects vary depending on the individual’s genetic makeup and psychosocial status. It may also cause anxiety.

Scantamburlo G, Hansenne M, Geenen V, Legros J, et al: Additional intranasal oxytocin to escitalopram improves depressive symptoms in resistant depression: an open trial. European Psychiatry 2014; doi 10.1016/j.eurpsy.2014.08.007. From the University of Liege, Belgium. Funded by the National Fund for Scientific Research; and other sources. The authors declared no conflicts of interest.

Drug Trade Names: escitalopram—Lexapro; oxytocin, intranasal—Syntocinon

*See Reference Guide.
Levomilnacipran Reviewed

The newest SNRI, extended-release levomilnacipran, is a potentially useful addition to the treatment of major depressive disorder, according to a review. Advantages of this new option include once-daily dosing and apparently low potential for drug interactions. Its comparative efficacy versus other antidepressants has not been tested.

Levomilnacipran is the more active of the 2 enantiomers of milnacipran. The agent has greater in-vitro selectivity for norepinephrine reuptake inhibition than the other available SNRIs, a property of unknown clinical significance. It is metabolized primarily by CYP3A4 and does not have any active metabolites. Levels are increased by coadministration with the CYP3A4 inhibitor ketoconazole; hence dose adjustments are recommended if the 2 drugs are coadministered. No dosage adjustment is recommended for coadministration with a CYP3A4 inducer (e.g., carbamazepine) or substrate (e.g., alprazolam). Alcohol may interfere with the extended-release properties of levomilnacipran and may cause more rapid release of active drug and potentially accelerated absorption.

The efficacy of levomilnacipran has been investigated in 4 phase III clinical trials in adults with major depressive disorder. The trials used fixed or flexible dosages of 40–120 mg/day, lasted 8 weeks, and used the Montgomery-Asberg Depression Rating Scale (MADRS) as the primary outcome measure. In 1 clinical trial of flexible-dose levomilnacipran, rates of response (MADRS reduction of ≥50%) were not statistically superior to placebo, a result that was attributed to a high placebo response rate. In the other trials, however, MADRS responder rates with levomilnacipran were significantly greater than placebo. A pooled analysis included data from these 4 trials and a phase II trial with favorable results. This analysis found a number needed to treat* of 10 patients to achieve 1 response above that observed with placebo. Benefits of treatment were generally sustained in a 1-year open-label extension study of participants who had completed 1 of the 3 acute treatment trials, as well as in a double-blind, placebo-controlled, 24-week relapse-prevention study.

Adverse effects of levomilnacipran were those associated with SNRIs, and no new safety concerns were raised. Concomitant use with MAOIs is contraindicated, and levomilnacipran should be gradually tapered if discontinuation is necessary. Heart rate and blood pressure should be evaluated before starting treatment and monitored periodically thereafter.

Adjunctive Naltrexone for Bipolar Depression

In a small, double-blind controlled trial, the opioid antagonist naltrexone (ReVia) did not significantly elevate or stabilize mood in a group of patients with bipolar disorder.

Background: Naltrexone, approved only for treatment of alcohol and opioid dependence, has been shown to improve mood in patients with bipolar disorder and alcoholism. It is unclear whether the effects on mood are direct or secondary to reduced alcohol use. The present study was undertaken to evaluate mood changes in patients with bipolar disorder without comorbid substance use disorders.

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1Scott L: Levomilnacipran extended-release: a review of its use in adult patients with major depressive disorder. CNS Drugs 2014. doi 10.1007/s40263-014-0203-1. From ADIS Springer, Auckland, NZ. The review was conducted without external funding. The author is employed by the publisher of CNS Drugs.


Drug Trade Names: alprazolam—Xanax; carbamazepine—Epitol, Tegretol; levomilnacipran XR—Fetzima; milnacipran—Savella

*See Reference Guide.
**Methods:** Study subjects (n=32) were adults, aged 18–65 years, with DSM-IV-TR bipolar I or II disorder who were experiencing a depressive episode and had a Montgomery Asberg Depression Rating Scale score of ≥5. Randomized treatment with either naltrexone, titrated to 50 mg/day, or placebo was added to stable background medications. Mood symptoms were assessed weekly for 4 weeks and then at weeks 6, 8, 10, and 12 using the MADRS, the Hamilton Rating Scale for Depression, and the Young Mania Rating Scale.

**Results:** Patients in both treatment groups demonstrated small and nonsignificant improvements in mood. Improvements in symptom ratings were not significantly greater with naltrexone than with placebo at any time point during the study. The mean MADRS score, the primary outcome measure, decreased from 22 at baseline to 21 with naltrexone and to 19.5 with placebo. Naltrexone treatment was not associated with induction of mania.

**Study Rating*—17 (100%):** Although the findings were negative, the present study met all criteria for a randomized controlled trial.

Murphy B, Ravichandran C, Babb S, Cohen B: Naltrexone in bipolar disorder with depression: a double-blind, placebo-controlled study [letter]. Journal of Clinical Psychopharmacology 2014; doi 10.1097/JCP.0000000000000222. From McLean Hospital, Belmont, MA; and Harvard Medical School, Boston. **Funded by the Stanley Medical Research Institute.** One study author disclosed financial relationships with commercial sources; the remaining 3 authors disclosed no competing interests.

*See Reference Guide.

### Enhanced Fear Extinction with Methylene Blue

Methylene blue, an antidote against metabolic poisons that is available in every emergency room, is a neurometabolic enhancer in the CNS and has shown promise in improving memory retention in preclinical studies. In a small randomized placebo-controlled trial in adults with claustrophobia, methylene blue enhanced gains in fear extinction when administered after exposure training but had the opposite effect in participants who had no improvement in fear.

**Methods:** Study subjects (n=42) were university students who reported marked claustrophobia and underwent a 2-stage screening: an online questionnaire about claustrophobia, followed by face-to-face assessment in the laboratory. All participants underwent a single session of extinction training, consisting of brief psychoeducation and six 5-minute intervals of lying supine in an enclosed wooden chamber. They rated their peak fear on a 100-point visual-analog scale (VAS) after each 5-minute session. In addition to extinction training, patients received double-blind, randomized treatment with either 260 mg methylene blue in 3 divided doses (i.e., immediately following the completion of extinction training, before going to bed that night, and upon awakening the following morning) or placebo. The divided dose was intended to minimize urinary irritation and to preserve blinding. The primary study outcome was participants’ peak fear rating when exposed to the claustrophobia test chamber at a 1-month follow-up visit. To determine whether clinical response was related to improved memory or to nonspecific fear reduction, the researchers displayed lighted numbers on the wall in the extinction training chamber with no specific instructions to pay attention to them. Participants were then asked to recall the numbers 1 month later.

**Results:** Average fear ratings decreased during the training, from 73 at the first exposure (range, 20–100) to 24 at the last exposure (range, 0–90). Participants were divided into groups of low, average, and high end fear based on their fear levels at post-training, using a threshold of 1 standard deviation from the mean. In participants with low end fear, who had average ratings of zero at the end of training, methylene blue was associated with significantly lower fear ratings at 1-month follow-up (mean peak fear, 11 vs. 30 for placebo; p=0.04; effect size,* 0.76). Methylene blue had no effect on retention of the treatment effect in participants with average fear. In those with high end fear (mean VAS score of 47 at the end of exposure), methylene blue...
was associated with marginally higher fear ratings than placebo at follow-up (33 vs. 17 points; p=0.08; effect size, 0.63). Methylene blue was associated with better recall of the displayed numbers 1 month later, but recall was not related to improvement in fear, suggesting that the 2 effects of methylene blue were independent. Methylene blue was associated with few side effects other than urine discoloration and increased frequency of urination.

**Discussion:** Though requiring confirmation in larger and more generalized patient groups, this finding suggests a promising treatment enhancer for exposure therapy in claustrophobia. Methylene blue should not be administered at the beginning of a desensitization session to avoid inadvertently strengthening the fear of patients who have not responded. It should be administered judiciously in patients who have achieved a significant degree of fear attenuation.

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


From the University of Texas at Austin; and Southern Methodist University, Dallas, TX. Funded by the NIH; and other sources. The authors disclosed no financial relationships with commercial sources.

*See Reference Guide.

**Alternative Adjunctive Treatments in Depression**

Clinicians often consider using off-label stimulants or stimulant alternatives as adjunctive treatment in resistant unipolar and bipolar depression; however, the evidence supporting this practice is lacking. According to a review of the limited literature, evidence supports the use of modafinil or armodafinil for augmentation in both unipolar and bipolar depression. The abuse potential of traditional stimulants and the lack of positive clinical-trial evidence make these agents less attractive.

**Background:** Stimulants, such as amphetamine and methylphenidate, activate the CNS by stimulating the release of dopamine and inhibiting its reuptake. Stimulant alternatives have other mechanisms of action. Modafinil, currently approved for excessive sleepiness associated with narcolepsy, obstructive sleep apnea, or shift-work sleep disorder, acts on various nonmonoamine neurotransmitters in the brain. Atomoxetine, approved only for treatment of ADHD, is an SNRI that acts primarily in the prefrontal cortex. Because it does not alter dopamine levels in the striatum or nucleus accumbens, it is not believed to have significant abuse potential.

**Methods:** A comprehensive literature search was undertaken to identify studies of dopaminergic stimulants (i.e., amphetamines and methylphenidate), modafinil/armodafinil, and atomoxetine for treatment-resistant unipolar or bipolar depression. Included studies were randomized controlled trials, open-label studies, or case series that were published between 1988 and 2013. Individual case reports were excluded.

**Results:** A total of 3 randomized, placebo-controlled trials and 4 open-label studies of traditional stimulants in mood disorders were identified. In 2 randomized trials, OROS methylphenidate added to ongoing antidepressant therapy was not superior to placebo. In a third controlled trial, lisdexamfetamine or placebo was added in 129 patients who had experienced a partial response to 8 weeks of escitalopram. Lisdexamfetamine was associated with a larger improvement in Montgomery-Asberg Depression Rating Scale scores (p=0.09) and significant gains in other secondary study outcomes. Patients in the open-label studies, which included 2 with both bipolar and unipolar patient populations, showed significant improvement in depression symptoms and/or global illness measures. There was no evidence of mood-state switching or stimulant abuse.

Of the newer stimulant alternatives, modafinil and its R-isomer, armodafinil, have received the most investigation, with 4 controlled trials in unipolar depression and 2 controlled trials in
bipolar depression, as well as 2 open-label studies. One of the controlled trials was terminated prematurely when 2 patients had new-onset suicidal ideation. All of the remaining studies showed positive effects of modafinil/armodafinil. The effects were particularly robust in bipolar depression: In 1 trial in 85 patients, adjunctive modafinil was effective in study subjects who had experienced a poor response to a mood stabilizer, with or without an antidepressant. Patients who received modafinil had significantly greater response rates (≥50% improvement in the Inventory of Depressive Symptomatology): 44% vs. 23% with placebo (p=0.04). In this study, modafinil did not affect measures of wakefulness or fatigue, which suggests the mood effects may be independent of its stimulant effect. None of these studies raised concerns about treatment-emergent mania regardless of mood stabilizer use.

Atomoxetine has been evaluated for unipolar depression in 2 open trials, with positive results, and 1 placebo-controlled trial, with negative results. There have been no studies of atomoxetine in bipolar depression.

Olanzapine plus fluoxetine is the optimal treatment for bipolar depression, according to a meta-analysis. Several other treatments appeared to be effective but could not be distinguished from one another, possibly due to insufficient evidence.

**Background:** Treatment of bipolar depression is complicated by variable response and the risk of manic switching. Because guidance is generally based on strength of evidence for individual or combined drug therapies, rather than on comparative data, the present multiple-treatments meta-analysis was undertaken to identify the most effective and best-accepted drug treatments.

**Methods:** A comprehensive literature search was conducted to identify all randomized controlled trials of patients with bipolar depression treated with any drug licensed for use as psychotropic in the U.S. and Europe before April 2014, with a duration of 4–16 weeks. Outcomes were required to be assessed with a validated rating scale, and reporting had to be continuous rather than in addition to categorical outcomes. The primary efficacy outcome was change in either the Montgomery-Asberg Depression Rating Scale or the Hamilton Rating Scale for Depression score. The primary acceptability outcome was switch to mania. Studies of patients with refractory or resistant depression and those with mixed states were excluded. Combination treatments were included if the drugs were started at the same time and examined as 1 treatment. Background medications were not considered part of a combination regimen because they had failed to prevent patients’ current episode of bipolar depression. Individual drugs and some drug combinations were ranked in terms of acute efficacy and safety.

**Results:** A total of 29 studies, with >8000 participants, met criteria for inclusion. For the primary efficacy outcome, olanzapine–fluoxetine was the highest rated treatment and had an effect size of 0.56. All other active treatments were more effective than placebo, but the difference was only statistically significant for olanzapine–fluoxetine and olanzapine alone. Lamotrigine had the highest risk for manic switching, and lurasidone the lowest risk. Olanzapine–fluoxetine, followed by quetiapine, had the most optimal balance of efficacy and safety from manic switching. Olanzapine, lurasidone, valproate, and SSRIs also had a relatively favorable balance of efficacy and safety. Ziprasidone, aripiprazole, and risperidone showed no statistically signifi-
significant evidence of efficacy, but few studies investigated these agents. Olanzapine–fluoxetine also had the most favorable effects on the study’s secondary outcomes: rate of response (efficacy) and withdrawal from treatment for any reason (acceptability).

Discussion: An important limitation of the meta-analysis is the short duration of some of the studies, which may not have distinguished between patients whose depression improved and those who were in the process of switching to mania. The authors also note that patient outcomes are likely to be affected by coadministration of mood-stabilizing drugs, which was not controlled for in this analysis.

The authors recommend olanzapine plus fluoxetine as first-line therapy for bipolar depression, with olanzapine or quetiapine monotherapy as alternatives. The metabolic side effects of olanzapine remain an important consideration. Lurasidone and SSRIs may also be considered, although they performed relatively poorly compared with first-line drugs; valproate and lithium may also be worth consideration.

Taylor D, Cornelius V, Smith L, Young A: Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. Acta Psychiatrica Scandinavica 2014; doi 10.1111/acps.12343. From Maudsley Hospital, London, U.K.; and other institutions. Source of funding not stated. Two study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no conflicts of interest.

Drug Trade Names: aripiprazole—Abilify; fluoxetine—Prozac; lamotrigine—Lamictal; lurasidone—Latuda; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal; valproic acid—Depakene, Depakote; ziprasidone—Geodon

*See Reference Guide.

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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.

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.

Multiple Treatments Meta-Analysis: A method of comparison that extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common, even when direct comparisons are unavailable. For example, if in a clinical trial comparing treatment A with treatment B, option A is determined to be superior, and a separate trial in similar patients found option B superior to a third agent, option C, a network meta-analysis of these 2 trials would allow a researcher to conclude that treatment option A is more effective than option C.

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 is 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.

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