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Cariprazine in Bipolar Depression

In a phase 3 randomized trial of patients with bipolar I depression, 1.5 mg/day cariprazine was significantly more effective than placebo at reducing depression; however, a 3 mg daily dose was not statistically superior to placebo.[1] These results confirm previously reported findings for the 1.5 mg dosage, but not the higher dosage, which was significantly superior to placebo in the earlier trial with the same design and inclusion criteria.[2]

Methods: The present multicenter study enrolled adult outpatients with DSM-5 bipolar I disorder and a current major depressive episode lasting <12 months. As with the earlier study, participants were required to have a baseline 17-item Hamilton Rating Scale for Depression (HAM-D17) score of ≥20, a Clinical Global Impression–Severity (CGI–S) scale score of ≥4, and a Young Mania Rating Scale score of ≤12. Following a 7–14 day screening and washout period, patients were randomly assigned to receive double-blind fixed dose cariprazine (1.5 or 3 mg/day) or placebo for 6 weeks. Additional psychotropic drugs permitted during the study were sedative/hypnotics for insomnia; lorazepam or an equivalent benzodiazepine provided the dosage had been stable for ≥1 month prior to screening; and rescue doses of lorazepam or an equivalent benzodiazepine for agitation, restlessness, or hostility (for ≤3 consecutive days), diphenhydramine or benztropine for extrapyramidal symptoms, or propranolol for akathisia. The primary efficacy outcome was change from baseline in Montgomery Asberg Depression Rating Scale (MADRS) score. Secondary outcomes included response (i.e., ≥50% decrease in MADRS score) and remission (i.e., MADRS score ≤10).

Results: A total of 493 patients (59% women) were randomized and 81% completed the study. Adverse events led to withdrawal in 3–7% of each group. Mean baseline MADRS scores were in the moderate range and did not differ between the groups. After 6 weeks of treatment, 1.5 mg/day cariprazine was associated with significantly greater reductions in MADRS score than placebo, while 3 mg/day cariprazine was not. (See table, next page.) Effect sizes* at 6 weeks were 0.28 for 1.5 mg/day and 0.20 for 3 mg/day. Results for change in the CGI–S, the study's key secondary outcome, were similar. Rates of MADRS response (36–43%) and remission (20–26%) were not significantly different from placebo with either cariprazine dose.

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Change From Baseline to Week 6 in Primary and Key Secondary Measures of Depression			
	Baseline Score	**Mean Decrease**	**Adjusted Significance vs Placebo**
MADRS			
Placebo	31.3	12.4	—
Cariprazine 1.5 mg	31.5	14.8	p=0.04
Cariprazine 3 mg	31.4	14.1	p=0.11 (ns)
CGI-S			
Placebo	4.5	1.2	—
Cariprazine 1.5 mg	4.5	1.5	p=0.04
Cariprazine 3 mg	4.5	1.4	p=0.14 (ns)

The predominant adverse events with cariprazine were akathisia, restlessness, nausea, and fatigue, affecting 2–10% of patients. Treatment-emergent mania occurred in <2% of patients in the 1.5 mg/day cariprazine and placebo groups and in no patients who received the higher cariprazine dosage. Average weight gain in the 2 cariprazine groups was negligible.

Discussion: In contrast to the earlier study, the 3 mg/day dosage of cariprazine was not significantly superior to placebo. The researchers suggest this may be attributed to a large placebo response rate (36%). Although the combined MADRS effect size for 1.5 mg cariprazine in the 2 trials is small (0.28), the difference from placebo of 2.5 points is considered clinically significant.

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

[1]Earley W, Burgess M, Khan B, Rekeda L, et al: Efficacy and safety of cariprazine in bipolar I depression: a double-blind, placebo-controlled phase 3 study. *Bipolar Disorders* 2019; doi 10. 1111/bdi.12852. From Allergan Plc, Madison, N.J.; and other institutions. **Funded by Allergan; and Gedeon Richter. All study authors disclosed financial relationships with commercial sources including Allergan.**

[2]Earley W, et al: Cariprazine treatment of bipolar depression: a randomized double blind placebo-controlled phase 3 study. *American Journal of Psychiatry* 2019; doi 10.1176/appi.ajp.2018.18070824. See *Psychiatry Drug Alerts* 2019; 33 (April):28–29.

Common Drug Trade Names*: benztropine—*Cogentin*; cariprazine—*Vraylar*; lorazepam—*Ativan*; propranolol—*Inderal

***See Reference Guide.**

Brexanolone Vs SSRIs for Postpartum Depression

According to the results of a manufacturer-sponsored network meta-analysis, brexanolone (*Zulresso*) appears to be superior to SSRIs at improving postpartum depression in the initial weeks after treatment.

Background: Brexanolone, currently the only FDA-approved treatment for postpartum depression, requires medically supervised infusion over a 60-hour period. SSRIs, which are not specifically indicated for postpartum depression, are the most commonly used medications. However, a recent review concluded that the evidence base for SSRI treatment of postpartum depression is weak.

Methods: Brexanolone had been investigated by the manufacturer in 3 randomized clinical trials. The present analysis was limited to patients receiving a 90 µg/kg/hour brexanolone infusion; their data were merged to constitute a single study arm. A systematic review was conducted to identify all clinical trials of other pharmacological therapies and combined pharmacotherapy

and psychotherapy. Outcomes of interest were the Hamilton Rating Scale for Depression (HAM-D) and the self-reported Edinburgh Postnatal Depression Scale (EPDS). The network meta-analysis technique was modified to accommodate the additional care sometimes offered in the placebo groups and the first assessment time point of 60 hours for brexanolone, versus 6–12 weeks for oral antidepressants. Due to mixed study designs, most notably in the placebo arms of the trials, comparisons between brexanolone and placebo were conducted using matching-adjusted indirect comparisons* (MAICs). The analysis compared results at day 3, week 4, and the end of follow-up, which ranged from 30 days to 18 weeks. For studies where first observation was later than day 3 or week 4, linear interpolation* methods were used to impute the missing values.

Results: The meta-analysis included 6 clinical trials comparing an SSRI or combination treatment with placebo and the 3 brexanolone trials. There was no evidence of heterogeneity in the studies. In adjusted analyses, brexanolone was superior to SSRIs at day 3, with a mean difference in change from baseline of about 13 points on the HAM-D and 8 points on the EPDS (a significant difference based on confidence intervals*). Brexanolone continued to be significantly superior at week 4, although with smaller margins: about 6–8 points on the HAM-D and 6–7 points on the EPDS. At the last follow-up, when SSRIs were expected to have reached their maximum efficacy, brexanolone was no longer statistically superior on the HAM-D, but remained significantly superior on the EPDS.

Discussion: Acknowledging the limitations of indirect treatment comparisons and of the available evidence base, the study results suggest that compared with SSRIs, brexanolone produces larger improvements in postpartum depression on both patient- and clinician-reported measures very early in treatment. At the last observation time point (when all treatments are assumed to have the opportunity to reach optimal efficacy) improvement were similar and not significantly different between brexanolone and SSRIs.

Cooper M, Kilvert H, Hodgkins P, Roskell N, et al: Using matching-adjusted indirect comparisons and network meta-analyses to compare efficacy of brexanolone injection with selective serotonin reuptake inhibitors for treating postpartum depression. *CNS Drugs* 2019;33:1039–1052. doi 10.1007/s40263-019000672-w. From BresMed Health Solutions Ltd., Sheffield and Manchester, U.K.; and Sage Therapeutics Inc., Cambridge, MA. **Funded by Sage. All study authors disclosed potentially relevant financial relationships.**

***See Reference Guide.**

Osteoporotic Fracture Risk with Risperidone

Risperidone was not associated with increased risk of osteoporotic fracture in a nationwide cohort study of patients receiving antipsychotic medication.

Background: Compared with other second generation antipsychotics, risperidone causes greater and more frequent prolactin elevations, which are associated with reduced bone mineral density. The present study was conducted to address concerns that drug-related prolactin elevations may increase fracture risk.

Methods: Data from Swedish national medical registries were analyzed for a cohort of patients prescribed risperidone, another second generation antipsychotic, or a first generation antipsychotic in the previous 12 months. Patients prescribed paliperidone, the active metabolite of risperidone, were not included in the analysis. Exposed patients were those who filled ≥2 consecutive prescriptions (to rule out those who received an initial prescription but probably never started the medication). Subjects were prescribed antipsychotic medication between 2006 and 2014 and were followed through the end of 2014. Patients whose antipsychotic was changed or who had an additional agent added were excluded. The primary study outcome, osteoporosis-related fracture, was empirically defined as a non-open hip/femur fracture

occurring in the absence of major trauma or bone metastases that occurred ≥6 months after starting antipsychotic treatment. The reference group for the comparison was patients receiving a second generation antipsychotic other than risperidone. The analysis was stratified by patient age and adjusted for multiple confounders, including psychiatric diagnoses, somatic conditions and medications associated with elevated levels of prolactin, and additional factors from a fracture risk assessment tool.

Results: The cohort included >38,000 patients exposed to risperidone, >60,000 exposed to other second generation agents, and >17,000 prescribed first generation antipsychotics. Mean age of first antipsychotic exposure differed considerably: 68 years in the risperidone group, 63 years for other second generation agents, and 44 years for first generation agents.

As expected because of their prolactin effects, risk of osteoporotic fractures was moderately elevated in users of first generation antipsychotics. However, compared with other second generation agents, risk of osteoporotic fractures was not elevated with risperidone. (See table.) Risk estimates were similar in antipsychotic naive patients and those who had received prior antipsychotic therapy. (See table.) Rates of non-hip/femur fractures, a secondary study outcome, were similar between users of risperidone and other second generation agents and moderately elevated in users of first generation agents who were aged >65 years.

Risk of Non-Open Femur Fractures by Antipsychotic Medication

Medication	Person-years of follow-up	Number of events	Adjusted hazard ratio*
All patients			
Risperidone	70,831	1269	1.04
First generation antipsychotics	36,804	443	1.04
Treatment-naive patients			
Risperidone	61,774	1177	1.04
First generation antipsychotics	34,725	426	1.25
Reference group is users of non-risperidone second generation antipsychotics			

Discussion: Because antipsychotic drug choices differ by indication, risk factors for osteoporotic fractures may also differ between medication groups. In this study, risperidone was preferentially prescribed for patients with dementia, first generation antipsychotics for those with schizophrenia, and other second generation agents for unipolar or bipolar disorders.

Clapham E, Boden R, Reutfors J, Svennson T, et al: Exposure to risperidone versus other antipsychotics and risk of osteoporosis-related fractures: a population-based study. *Acta Psychiatrica Scandinavica* 2019; doi 10.1111/acps.13101. From the Karolinska Institute, Sweden; and other institutions including Janssen Global Research and Development Epidemiology, Titusville, N.J. **Funded by Janssen. Two of 8 study authors are employees of Janssen (manufacturer of risperidone); the remaining authors declared no relevant financial relationships with commercial sources.**

Common Drug Trade Names*: paliperidone—*Invega*; risperidone—*Risperdal

***See Reference Guide.**

BMI and Ketamine Response in Depression

A secondary analysis of open-label trial data suggests that ketamine efficacy in patients with treatment-resistant depression is affected by body mass index.[1]

Background: An APA consensus statement, which provided guidance on the use of ketamine for the treatment of depression, noted that dose adjustments may be necessary for patients with a BMI of ≥30, in whom greater hemodynamic changes were observed.[2] Ketamine dosing based on ideal, as opposed to actual, body weight has been proposed. However, a study in adolescents that used the ideal weight dosing strategy found it to be ineffective.

Methods: Subject-level data were combined from 2 small open-label studies of adjunctive ketamine in adults with resistant unipolar or bipolar depression to examine associations between ketamine dose, BMI, and remission of depression. The studies included a total of 22 patients (mean age, 46 years; 77% women) who received 0.5 mg/kg ketamine infusions 2 or 3 times per week for 2 weeks. Changes in depression were assessed using the Montgomery Asberg Depression Rating Scale (MADRS). For the present analysis, participants were stratified by BMI into 4 distinct categories: 5 patients had normal weight (BMI 18.5–24.9); 6 patients were overweight (BMI 25–29.9); 5 patients had class 1 obesity (BMI 30–34.9); and 6 patients had class 2 obesity (BMI 35–39.9).

Results: Overall, patients experienced a significant improvement in MADRS score from a baseline mean of 31 to a final score of 15 ($p<0.0001$). A significant association was found between higher BMI category and remission ($p=0.03$). Remission rates increased incrementally with each BMI category: 20% in normal weight patients; 30% in overweight patients; 40% in those with class 1 obesity; and 85% in those with class 2 obesity. Additionally, the mean BMI was significantly higher in patients who achieved remission: 34 vs 28 ($p=0.05$).

Discussion: Although the very small sample size is an important limitation, the present results support an effect of BMI on ketamine response. Larger studies are needed to replicate these findings.

[1]Singh B, Bobo W, Rasmussen K, Stoppel C, et al: The association between body mass index and remission rates in patients with treatment-resistant depression who received intravenous ketamine [letter]. *Journal of Clinical Psychiatry* 2019; 80 (November/December): doi 10.4088/JCP.19l12852. From the Mayo Clinic Depression Center, Rochester, MN; and other institutions. **Funded by the Mayo Clinic. Three of 9 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Sanacora G, et al: A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.0080. See *Psychiatry Drug Alerts* 2017;31 (August):59–60.

Antiinflammatory Drugs for Depression

Results of a meta-analysis of placebo-controlled trials indicate that antiinflammatory drugs have a significant antidepressant effect, whether used as monotherapy or adjuncts to conventional antidepressants. These agents were found to be generally safe and well tolerated, with adverse events similar to placebo.

Background: Inflammation has been recognized as potential factor in the pathogenesis of major depression, and randomized controlled trials have examined the antidepressant effects of anti-inflammatory agents in the disorder. However, results have been mixed and no clear conclusions have been drawn.

Methods: A comprehensive literature search identified placebo-controlled trials of anti-inflammatory agents, published and unpublished, conducted in adults with a DSM diagnosis of major depressive disorder. Studies evaluating patients with bipolar depression were excluded. The antiinflammatory agents investigated were NSAIDs, omega-3 fatty acids, cytokine inhibitors, statins, corticosteroids, minocycline, pioglitazone, modafinil, and N-acetylcysteine (NAC). Included studies were required to report treatment effects on depression or quality of life using a standardized validated scale.

Results: The analysis was based on 31 randomized trials. Of these, 26 studies (8 monotherapy, 22 adjunctive treatment, 1 both) reported change in depression scores from baseline to endpoint in a total of 1610 patients. Quality of life was evaluated in 5 studies. About half of the studies were industry-sponsored, but no sponsor bias was detected.

Pooled data from 26 studies showed that antiinflammatory agents had a statistically significant effect on depression symptom scores relative to placebo (standardized mean difference,* 0.55; $p<0.00001$). Effect sizes were larger for adjunctive treatment than for monotherapy

(standardized mean differences, 0.7 and 0.3, respectively). Rates of response, defined as a ≥50% symptom reduction, were higher with antiinflammatory agents than placebo (pooled relative risk,* 1.52; p<0.00001). Rates of remission, variously defined on different measurement scales, were also higher with antiinflammatory drugs in the 16 studies that reported this outcome (pooled relative risk, 1.79; p<0.005). Antiinflammatory treatments had no overall effect on quality of life, but study durations were short (generally 4-12 weeks) and quality of life improvements may require a longer period to develop.

Subgroup analyses (see table) revealed significant antidepressant effects for NSAIDs and omega-3 fatty acids; effects of statins and minocycline were also significant, but there were few studies which could lead to imprecise estimates of their efficacy.

Subgroup Analyses of Antiinflammatory Agents Vs Placebo

Variable	Number of Trials	Number of Patients	Standardized Mean Difference	Significance
Treatment Type				
Monotherapy	8	569	0.30	p=0.03
Adjunctive therapy	18	1041	0.70	p<0.00001
Type of Antiinflammatory Agent				
NSAID	4	121	0.76	p<0.0001
Omega-3 fatty acids	12	746	0.35	p=0.008
Statin	3	166	0.65)	p<0.0001
Minocycline	3	151	0.79	p=0.002
Pioglitazone	1	40	2.09	p<0.00001
Modafinil	2	179	0.78	p=0.27
Study Population				
Trials including only women	5	179	0.49	p=0.06
Trials including women and men	21	1431	0.56	p<0.00001

The only treatment-related difference in adverse effects was an increase in gastrointestinal effects that was limited to statins and NAC. Serious effects of potential concern, such as rhabdomyolysis with statins, were not detected.

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

Bai S, Guo W, Feng Y, Deng H, et al: Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised clinical trials. *Journal of Neurology, Neurosurgery, and Psychiatry* 2019; doi 10.1136/jnnp-2019-320912. From Huazhong University of Science and Technology, China. **Funded by the National Natural Science Foundation of China. The authors declared no competing interests.**

Common Drug Trade Names*: minocycline—*Minocin*; modafinil—*Provigil*; pioglitazone—*Actos

***See Reference Guide.**

Esketamine Approval Concerns

With its novel mechanism of action, the newly-approved esketamine nasal spray has garnered considerable interest in the psychiatric community. However, a recent commentary by a member of the Psychopharmacologic Drugs Advisory Committee suggests that FDA approval alone is insufficient evidence to support prescribing the new agent, and that a review of the documents used in the recommendation process raises some important concerns.[1]

First, in the esketamine clinical trials the definition of treatment resistance was broad. Specifically, the requirement for treatment failure with any 2 antidepressants allowed for inclusion of patients in whom only SSRI trials were unsuccessful and patients were not required to have

undergone unsuccessful psychotherapy. This broad definition may have led to a study population with less severe treatment resistance than typically encountered in practice. In addition, a short-term phase 3 trial[2] found the mean decrease from baseline in Montgomery-Asberg Depression Rating Scale score was 21 for esketamine, compared with 17 for placebo, a relatively small difference despite that the statistical significance (p=0.02; effect size, 0.3). Furthermore, inclusion in a randomized withdrawal trial[3] was restricted to patients who had achieved remission with esketamine in a short-term trial, potentially creating a population that was statistically more likely to respond to the drug. Results were no longer significant (p=0.48) in an analysis that removed an outlier study site with a 100% relapse rate in the placebo group. Although esketamine appears to be effective, meta-analysis of 3 clinical trials produced an effect size of 0.28, which is similar to that reported for the olanzapine–fluoxetine combination, and lower than those reported for the approved adjunctive treatments aripiprazole and quetiapine (0.35 and 0.40, respectively). Finally, although rapid onset of response has been suggested, in studies that could evaluate response timing, rapid response was achieved by about 10% of esketamine treated patients.

Editor's Note: The trials discussed above were covered in recent issues of *Psychiatry Drug Alerts*. Although our reports noted the limitations, given the publicity esketamine has been receiving as a potential "blockbuster," the present editorial is included to ensure that we present a balanced picture with regard to the drug so that our readers can form an opinion based on all of the evidence.

[1]Turner E: Esketamine for treatment-resistant depression: seven concerns about efficacy and FDA approval. *Lancet Psychiatry* 2019; doi 10.1016/S2215-0366(19)30394-3. From Portland VA Medical Center, OR. **The author declared no competing interests. While he is a member of the Psychopharmacologic Drugs Advisory Committee, he was not present at or involved in the esketamine recommendation process.**

[2]Popova V, et al: Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active controlled study. *American Journal of Psychiatry* 2019;176 (June):428–438. See *Psychiatry Drug Alerts* 2019;33 (June):42–43.

[3]Daly E, et al: Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.1189. *See Psychiatry Drug Alerts* 2019;33 (June):43–44.

Common Drug Trade Names*: aripiprazole—*Abilify*; esketamine nasal spray—*Spravato*; olanzapine–fluoxetine—*Symbyax*; quetiapine—*Seroquel

***See Reference Guide.**

Dextromethorphan–Bupropion

Therapeutic action of traditional antidepressants is often delayed. The recent approval of the intranasal N-methyl-d-aspartate (NMDA) antagonist esketamine (*Spravato*) for resistant depression provides a rapidly-acting option that acts via alternate mechanisms of action. However, because of the potential for sedation, dissociation, and abuse/misuse, use is restricted to approved healthcare settings. The investigational combination of the NMDA antagonist dextromethorphan with the norepinephrine–dopamine reuptake inhibitor bupropion (AXS-05), may provide similar effects with the benefits of oral administration and fewer adverse effects.[1]

Dextromethorphan and bupropion work synergistically by simultaneously targeting monoamines, NMDA receptors, and sigma-1 receptors. Dextromethorphan has pharmacological properties similar to those of ketamine. However, it is rapidly metabolized via cytochrome P450 2D6, and achieving therapeutic levels with oral administration is difficult. Bupropion and its metabolites inhibit CYP2D6, and coadministration with dextromethorphan significantly increases dextromethorphan exposure.

In a Phase 2, multicenter, active-controlled trial, patients with a confirmed diagnosis of moderate to severe major depressive disorder received randomly assigned, double-blind treatment with dextromethorphan–bupropion or bupropion monotherapy for 6 weeks.[2] The

dextromethorphan–bupropion combination resulted in significantly lower Montgomery-Asberg Depression Rating Scale total scores than bupropion alone as soon as week 2. Depression remitted in 26% of patients who received dextromethorphan–bupropion, com-pared with 3% of those receiving bupropion monotherapy. No dissociative/psychotomimetic events were observed. A phase 3 trial of the dextromethorphan–bupropion combination is currently underway in patients with treatment resistant depression, as well as phase 2/3 trials for the treatment of agitation associated with Alzheimer's Disease and for smoking cessation.[3]

[1]Stahl S: Dextromethorphan/bupropion: a novel oral NMDA (N-methyl-d-aspartate) receptor antagonist with multi-modal activity. *CNS Spectrums* 2019; doi 10.1017/S1092852919001470. From the University of California, San Diego. **Source of funding not stated. The author disclosed potentially relevant financial relationships.**

[2]Anderson A, et al. Efficacy and safety of AXS-05, an oral NMDA receptor antagonist with multimodal activity, in major depressive disorder: results of a phase 2, double-blind, active-controlled trial. W43. Presented at the American Society of Clinical Psychopharmacology Annual Meeting 2019; May 28-31, 2019; Scottsdale, AZ.

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Confidence Interval: The range in which the value of a variable in question is likely to fall, usually calculated at 95%. Confidence intervals indicate the reliability of an estimate, and a very wide interval may indicate that more data should be collected before making definite conclusions.

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.

Linear Interpolation: A method of estimating an unknown value using linear polynomials to construct data points within a known range of data points.

Matching-Adjusted Indirect Comparisons: A form of population-adjusted indirect treatment comparison that attempts to reduce bias in treatment comparisons by matching patient-level data from the clinical trials of one treatment to aggregate data reported for comparator trials.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Standardized Mean Difference: The difference between two normalized means - i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales, a value of 0–0.2 is considered a negligible effect, 0.2–0.5 a small effect, 0.5–0.8 a medium effect, and >0.8 a large effect.

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.

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