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Riluzole in Resistant Schizophrenia

In patients with treatment-resistant schizophrenia, higher baseline levels of glutamate metabolites (Glx) in the anterior cingulate cortex (ACC) are associated with more severe negative symptoms and poorer cognitive performance. Riluzole, licensed to treat amyotrophic lateral sclerosis (ALS), modulated Glx levels and frontal cortex connectivity in a clinical experiment.[1]

Background: Several lines of evidence have implicated glutamatergic dysfunction in schizophrenia, particularly in treatment-resistant symptoms. Existing research also suggests glutamatergic dysfunction could underlie functional disconnectivity between the ACC and the frontal cortex, contributing to at least some resistant symptoms. Riluzole lowers synaptic availability of glutamate via multiple mechanisms. The present study was conducted to test the hypothesis that administering riluzole would reduce Glx levels and increase cortical connectivity in patients with treatment-resistant schizophrenia.

Methods: Study participants were 19 outpatients with treatment-resistant schizophrenia and 18 controls with no history of mental illness. Subjects underwent MRI scans and clinical evaluation before and after a 2-day riluzole challenge. The drug was administered at a 50-mg dose every 12 hours, the dosage recommended for treating ALS. The second MRI scan was obtained 1.5 hours after the last riluzole dose, when plasma levels were expected to be at peak. MRI studies measured ACC Glx, resting ACC-functional connectivity, and regional cerebral blood flow. Schizophrenia symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), and all participants underwent neurocognitive testing.

Results: Patients with schizophrenia were receiving treatment with a variety of antipsychotics, including 9 with long-acting injectable formulations. Despite plasma antipsychotic levels in the therapeutic range for all treated patients, baseline schizophrenia symptom severity was at least moderate in 63%.

Average pre- and post-treatment Glx levels in the ACC did not differ between patients with schizophrenia and controls. Riluzole treatment did not affect ACC Glx levels in healthy controls. However, patients with schizophrenia demonstrated a decrease in ACC Glx following

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riluzole treatment. This decrease did not reach statistical significance, likely because the study was underpowered. The groups did not differ on any measure of cerebral blood flow in response to riluzole, suggesting that observed changes in Glx in patients with schizophrenia were not secondary to nonspecific changes in cerebral blood flow. Baseline frontal connectivity at 1 site located within the right anterior prefrontal cortex was lower in patients than in controls, an effect that reversed following riluzole treatment. In patients with schizophrenia, but not in controls, changes in Glx correlated inversely with changes in ACC-frontal connectivity.

In patients with schizophrenia, higher levels of baseline Glx were associated with lower scores on tests of verbal learning (p=0.002) and with elevated PANSS negative symptom scores (p=0.03). Pre-riluzole, lower connectivity between the ACC and anterior prefrontal cortex was also associated with lower verbal learning scores (p=0.04) in these patients. There were no associations between baseline PANSS positive, general, or total scores or other neurocognitive measurements.

Discussion: The finding that negative and cognitive symptoms are directly associated with Glx levels and that riluzole can modulate these levels as well as frontal cortical connectivity adds to existing evidence that glutamatergic dysfunction contributes to some symptoms of schizophrenia. A previous clinical study showed that adding riluzole to risperidone resulted in a significant improvement in negative symptoms in treatment-resistant schizophrenia,[2] but other drugs targeting glutamatergic neurotransmission have had disappointing results in treatment-resistant schizophrenia.

[1]Pillinger T, Rogdaki M, McCutcheon R, Hathway P, et al: Altered glutamatergic response and functional connectivity in treatment resistant schizophrenia: the effect of riluzole and therapeutic implications. *Psychopharmacology* 2019;236:1985–1997. doi 10.1007/s00213-019-5188-5. From King's College London, U.K., and other institutions. **Funded by the Medical Research Council; and other sources. One of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Farokhnia M, et al: A double-blind, placebo controlled, randomized trial of riluzole as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia. *Psychopharmacology* 2014; 231:533–542.

Common Drug Trade Names*: riluzole—*Rilutek*; risperidone—*Risperdal

Weight Management With Psychiatric Medication

In a retrospective study of patients attending a community weight-management program, weight loss was similar in patients taking antidepressants or antipsychotics and patients taking no medication.

Methods: Records were reviewed for patients attending a weight-management clinic with regional locations in Canada. The clinic, whose services are free, serves persons with a body mass index of ≥25 with diabetes; ≥27 with other weight-related comorbidity; or ≥30 regardless of other comorbidity. Participants were prescribed a calorie-restricted diet and were advised about diet and physical activity at regular visits with a physician or bariatric educator. For this study, weight changes were compared between patients taking antidepressants, antipsychotics, both types of drug, and no psychiatric medication.

Results: Of about 29,000 individuals enrolled in the program, >17,500 were included in the analysis. The main reasons for exclusion were failure to return to the clinic after the initial visit and use of weight-loss medications. The majority of patients (76.6%) were not receiving any psychiatric medication, 18% used antidepressants alone, 4.2% took only antipsychotics, and 11% took both types of drug. The mean duration of follow-up at the clinic was 16 months (range, 8–65 months).

Among men, initial weight did not differ according to medication use. Weight loss was also similar in the groups. After adjustment for age, initial weight, and treatment time, the largest loss (mean, 12.3 lbs) occurred in men taking both antidepressants and antipsychotics, followed

by men taking no psychiatric medication (mean, 9.5 lbs) and then those taking antidepressants only (mean, 7 lbs). Overall, about 30–36% of men lost ≥5% of their pretreatment weight, and 11–14% lost ≥10%. Men lost a similar amount of weight regardless of whether their psychiatric medications were weight-neutral or associated with weight gain.

Women who took no medication weighed less at baseline than those who took psychiatric drugs. In women, average weight loss was about 6–7 lbs, with no differences among the medication groups or between women taking or not taking medications with known weight effects. Weight loss of ≥5% occurred in 23–28% of women, and 9–12% lost ≥10% of their initial body weight.

Discussion: Individuals with psychiatric disorders are more likely to meet criteria for obesity than those without. Although the directionality of the association in unclear, weight management interventions are often necessary. The present observations suggest psychotropic medication is not a barrier to accessing or benefitting from weight management care.

Wharton S, Kuk J, Petrova L, Rye P, et al: Effectiveness of a community-based weight management program for patients taking antidepressants and/or antipsychotics. *Obesity* 2019;27 (September):1539–1544. doi 10.1002/oby.22567. From the Wharton Medical Clinic, Toronto, Canada; and other institutions. **Source of funding not stated. Three of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

SAGE-217 for Depression

The investigational GABA-A receptor modulator SAGE-217 was superior to placebo in a 14-day phase 2 study in patients with major depressive disorder.[1]

Methods: Study subjects were adults, aged 18–65 years, with a clinical interview-confirmed diagnosis of major depressive disorder and a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥22, indicating moderate to severe depression. Patients with a history of a treatment-resistant depression, bipolar disorder, suicide attempt, or schizophrenia were excluded. Participants were hospitalized for the first study week and were permitted to continue existing antidepressants at stable doses. Double-blind randomized treatment with either 30 mg/day SAGE-217 or placebo was administered for 14 days, with a single dose reduction allowed for adverse events. The primary study outcome was change in HAM-D score from baseline to day 15.

Results: The trial enrolled 89 patients with a mean baseline HAM-D score of 25. About one-fourth were receiving antidepressant treatment. The mean duration of depression was 97 days in the group receiving SAGE-217 and 146 days in the placebo group. Patients in the SAGE-217 group were older than those in the placebo group (mean age, 49 vs 38 years) and there were fewer women in the active treatment group (56% vs 68%). More than 90% of patients had experienced a previous depressive episode.

On day 15, the mean HAM-D score decrease was significantly greater in the SAGE-217 group than in the placebo group (17 points vs 10 points; $p<0.001$). Scores diverged statistically as early as the third day of treatment. Clinical Global Impression–Improvement ratings indicated 79% of patients in the SAGE-217 group were much or very much improved, compared with 45% of the placebo group (odds ratio,* 8.6). Differences in other secondary outcomes, including anxiety and alternative measures of depression, also favored the investigational drug. The percentage of patients meeting remission criteria (i.e., HAM-D score of ≤7) was 64% in the SAGE-217 group and 26% in the placebo group (odds ratio, 5.3).

Patients and clinicians remained unaware of treatment assignment during an additional 2 weeks of medication-free follow-up. By day 28, a new antidepressant had been initiated in 3

patients in the SAGE-217 group and 11 in the placebo group. HAM-D scores remained at ≤7 in 52% and 28% of patients, respectively. On the last follow-up occasion at day 42, between-group differences in remission were no longer statistically significant (45% vs 33%). The most common adverse events with SAGE-217 were headache (18%), dizziness (11%), nausea (11%), and somnolence (7%). Rates in the placebo group were 16% for headache and 2% for each of the other common adverse effects.

Editorial:[2] SAGE-217 had an effect size similar to existing antidepressants but a more rapid onset of action, although not as rapid as glutamate modulators like ketamine (*Ketalar*). Other advantages of SAGE-217 are oral administration and a relatively benign adverse effect profile. This trial was designed to confirm results of a previous preliminary 14-day study, but was not powered to investigate longer treatment durations. Based on the finding that between-group differences in efficacy narrowed after completion of treatment, it is likely that the drug would need to be administered for more than 14 days. Important remaining questions are the effects of SAGE-217 in patients with treatment-resistant depression and whether future studies will fail to confirm these promising phase 2 results, as has been the case with other investigational drugs that target nonmonoamine neurotransmitter systems.

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

[1]Gunduz-Bruce H, Silber C, Kaul I, Rothschild A, et al: Trial of SAGE-217 in patients with major depressive disorder. *NEJM* 2019;381 (September 5):903–911. doi 10.1056/NEJMoa1815981. From Sage Therapeutics, Cambridge, MA; and other institutions. F**unded by Sage Therapeutics. Thirteen of 14 study authors disclosed relevant financial relationships with commercial sources including Sage Therapeutics; the remaining author declared no competing interests.**

[2]Coccaro E: New hope for patients with major depressive disorder? [Editorial]. *NEJM* 2019;381 (September 5):980–981. doi 10.1056/NEJMe1907638. From the University of Chicago, IL. **The author disclosed potentially relevant financial relationships.**

***See Reference Guide.**

Istradefylline for Parkinson's Disease

The course of Parkinson's disease is characterized by off periods when existing treatment with levodopa–carbidopa becomes less effective and patients experience worsening of motor symptoms. The FDA has approved a new agent, istradefylline, for use as an add-on treatment during these off periods. In clinical trials with >1100 patients, those who received 12 weeks of istradefylline experienced significant decreases in daily off time, compared with those who received placebo. Common adverse effects of istradefylline included dyskinesia, dizziness, constipation, nausea, hallucinations, and insomnia. If psychotic behavior or impulsive/compulsive behaviors develop, istradefylline should be reduced or discontinued. Use of the agent during pregnancy is not recommended, and women with childbearing potential should be advised to use adequate contraception.

FDA News Release: FDA approves new add-on drug to treat off episodes in adults with Parkinson's disease. Available at www.fda.gov/news-events/press-announcements/fda-approves-new-add-drug-treat-episodes-adults-parkinsons-disease.

Common Drug Trade Names*: istradefylline—*Nourianz*; levodopa–carbidopa—*Sinemet

Olanzapine Discontinuation in Psychotic Depression

Combined antipsychotic and antidepressant medication is recommended for the pharmacologic treatment of psychotic depression. In a randomized discontinuation trial in patients whose symptoms responded to combined treatment, continuing the antipsychotic markedly reduced the risk of relapse over 36 weeks.[1]

Background: In the previously published STOP-PD trial, olanzapine plus sertraline was superior to olanzapine plus placebo in the acute treatment of unipolar psychotic depression.[2] Both

treatments were associated with weight gain and adverse lipid changes over 12 study weeks. The present study, the STOP-PD II trial, assessed the risks and benefits of continuing olanzapine once the depressive episode had responded to treatment.

Methods: The multicenter study recruited patients, aged 18–85 years, who met DSM-IV criteria for a major depressive episode with ≥1 associated delusion that could not be changed using reality testing. All patients were treated with open-label sertraline (target dose 150–200 mg/day) plus olanzapine (target dose 15–20 mg/day). After up to 12 weeks of acute treatment, patients were continued in the trial if they met criteria for remission (absence of delusions and hallucinations and a stable 17-item Hamilton Rating Scale for Depression [HAM-D] score of ≤10) or near remission (no delusions or hallucinations, HAM-D of 11–15 with a ≥50% reduction from baseline). After an 8-week stabilization phase, patients who still met these criteria were randomly assigned to double-blind treatment with continued olanzapine or to placebo following a 4-week olanzapine taper. During this 36-week phase, the primary study outcome was relapse, defined as either meeting DSM-IV criteria for a major depressive episode, experiencing delusions or hallucinations, a HAM-D score ≥18, or other significant clinical worsening.

Results: Of 269 patients who began open-label treatment, 74 withdrew consent or were discontinued, mainly because of insufficient response. An additional 33 patients completed acute treatment but did not experience remission. Of 162 patients who entered the stabilization phase, 126 (mean age, 55 years; 38% men) received randomized treatment with either continued or withdrawn olanzapine.

Characteristics of relapse events in patients with remitted psychotic depression±

	Sertraline + olanzapine (n=64)	Sertraline + placebo (n=62)
Total relapse events	13	34
Depression, no psychosis	5	18
Psychosis, no depression	0	1
Depression and psychosis	4	11
Suicide plan or attempt	0	3
Mania or hypomania	0	0
Psychiatric hospitalization	6	11

±Some patients experienced more than 1 event.

Relapse occurred more frequently among patients who were switched to placebo than in those who continued olanzapine (55% vs 20%; hazard ratio,* 0.25; p<0.001). Results were unchanged in analyses controlling for patient age, remission or near-remission status, and study center. The number needed to treat* with continued olanzapine to prevent 1 relapse was 2.8. The majority of relapses in the placebo group occurred within the first 12 weeks of randomized treatment, whereas relapses in the olanzapine continuation group were distributed throughout the 36-week trial.

Continuing olanzapine was associated with adverse anthropometric and metabolic changes. Patients switched to placebo lost a mean of 3.1 lb, compared with a 5.7-lb gain in those who continued receiving olanzapine (p<0.001). Waist circumference decreased by 0.8 inches with placebo and increased by 0.6 inches with olanzapine (p=0.002). Total cholesterol decreased in both groups, but to a larger extent with placebo. During the trial, statin treatment was initiated in 6 patients in each group and hypoglycemic medications were started or changed in 2 olanzapine-treated and 1 placebo-treated patient.

Discussion: While these study results suggest that continuing olanzapine after remission of psychotic depression is beneficial at 36 weeks, they do not provide an optimal duration of continuation treatment. Because the benefits must be weighed against the potential for metabolic and other adverse effects, additional study using a sequential discontinuation design appears to be warranted.

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

[1]Flint A, Meyers B, Rothschild A, Whyte E, et al: Effect of continuing olanzapine vs placebo on relapse among patients with psychotic depression in remission. the STOP-PD II randomized clinical trial. *JAMA* 2019;322 (August 20):622–631. doi 10.1001/jama2.019.10517. From the University of Toronto, Canada; and other institutions. **Funded by the US Public Health Service. Six of 12 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Meyers B, et al: A double-blind randomized controlled trial of olanzapine plus sertraline vs olanzapine plus placebo for psychotic depression: the study of pharmacotherapy of psychotic depression (STOP-PD). *Archives of General Psychiatry* 2009;66:838–847.

Common Drug Trade Names*:** **olanzapine—*Zyprexa*; sertraline—*Zoloft

***See Reference Guide.**

Monotherapies for GAD

According to the results of a network meta-analysis* of monotherapies for treatment of generalized anxiety disorder, pharmacotherapy is more effective than psychological therapies, which in turn are more effective than self-help options. Among the medication classes, the strongest evidence supports use of SSRIs and SNRIs. Second-generation antipsychotics and the serotonin modulators trazodone, vilazodone, and vortioxetine were not found to be effective.

Methods: A comprehensive literature review identified all published randomized controlled trials of oral drugs, psychological therapies, and self-help interventions for treatment of GAD in adults. Studies investigating combined interventions of the drugs and/or therapies were excluded. Because there is no evidence indicating which drug or psychotherapy is the most effective among those of similar types, interventions were grouped by class for the analysis. Treatment effects were calculated as standardized mean differences (SMD)* between the active treatment and placebo interventions on validated anxiety measures.

Results: A total of 91 studies met inclusion criteria and investigated placebo comparisons with a pharmacological intervention (n=57) psychotherapeutic intervention (n=26) or self-help intervention (n=6), and 2 studies directly comparing active treatments. More than 200 unique pairwise comparisons were investigated in nearly 15,000 patients. Almost two-thirds of study participants were women, and the average study duration was about 10 weeks. The majority of medication trials (61%) were sponsored by pharmaceutical companies. While active psychological and self-help treatments were more effective than waitlist controls (SMDs, 0.06–0.40), no psychological intervention had greater effects compared with the psychological placebo. Overall, pharmacotherapies were more effective than psychological treatments.

Antianxiety Effects of Pharmacological Monotherapies in GAD

Treatment	Standardized mean difference: active treatment vs placebo
Bupropion (n=11)	1.84
Mirtazapine (n=69)	0.91
Agomelatine (n=470)	0.68
SSRIs (n=2142)	0.66
Buspirone (n=221)	0.58
Anticonvulsants± (n=1566)	0.56
SNRIs (n=1666)	0.54

±Nearly all anticonvulsant-treated patients (n=1510) received pregabalin

Bupropion and mirtazapine appeared to have the strongest antianxiety effects. (See table.) However, because very few

studies investigated these agents in small numbers of patients, the results should be interpreted cautiously. Benzodiazepines were the least effective medication class, and current guidelines do not recommend them as first-line monotherapy for GAD.

Discussion: SSRIs, SNRIs, and CBT are widely used as first-line treatments for GAD, and previous research has suggested broadly similar efficacy for pharmacological and psychological treatments. However, in the present analysis the effects of most pharmacological interventions were larger than those of psychological interventions. Although combined treatment is often recommended, it was not investigated in the study.

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

Chen T, Huang H, Hsu J, Ouyang W, et al: Pharmacological and psychological interventions for generalized anxiety disorder in adults: a network meta-analysis. *Journal of Psychiatric Research* 2019; 118:73–83. doi 10.1016/j.jpsychires.2019.08.014. From National Yang-Ming University, Taipei, Taiwan; and other institutions. **The study was conducted with no external funding. The authors declared no competing interests.**

Common Drug Trade Names: **agomelatine (not available in the U.S.)—*Valdoxan*; bupropion—*Wellbutrin*; buspirone—*BuSpar*; mirtazapine—*Remeron*; pregabalin—*Lyrica*; trazodone—*Desyrel*; vilazodone—*Viibryd*; vortioxetine—*Brintellix***

***See Reference Guide.**

First-Episode Schizophrenia Treatments Compared

According to the results of a randomized head-to-head comparison trial, risperidone may have efficacy advantages over aripiprazole and olanzapine in first-episode schizophrenia. While overall tolerability of the agents was similar, each had specific advantages and disadvantages.

Methods: The study was conducted at 6 major psychiatric hospitals in China. Participants had received a diagnosis of schizophrenia within the past 3 years and had received ≤4 consecutive weeks and ≤12 total weeks of prior antipsychotic exposure. Patients were randomly assigned to receive flexibly-dosed, open-label treatment with 15–30 mg/day aripiprazole, 10–25 mg/day olanzapine, or 3–6 mg/day risperidone. The full study duration was 56 weeks; the present report covers the initial 8-week acute treatment phase. Antipsychotic switches were permitted after 4 weeks if there was insufficient improvement or tolerability issues. For patients whose medication was changed, data was included only for the initial agent. Efficacy was measured with the Positive and Negative Syndrome Scale (PANSS) at weeks 4 and 8. The primary outcome was change in PANSS total score. Secondary outcomes included changes in PANSS positive, negative, and general psychopathology subscale scores, as well as response (i.e., ≥30% decrease in PANSS total score) and full response (i.e., ≥50% decrease in PANSS total score).

Results: Of 498 eligible participants, 477 patients (mean age, 25 years; 51% men) who received randomized treatment and completed ≥1 follow-up assessment were included in the analysis. A total of 91 patients withdrew from the study for insufficient efficacy: 24 in the risperidone group, 24 in the olanzapine group, and 43 in the aripiprazole group. Fewer than 10 patients in each group withdrew because of adverse effects.

Mean baseline PANSS total scores ranged from 85 to 87, and all 3 medications produced significant improvement by week 8 ($p<0.001$ for all). However, improvements were significantly larger in the risperidone group than in the olanzapine and aripiprazole groups (PANSS decreases of 39 vs 36 and 34 points, respectively; $p<0.05$). Risperidone was also associated with significantly greater improvement than aripiprazole in PANSS positive symptom scores at week 8 ($p<0.01$). Response rates were 70–75% and did not differ statistically among the treatment groups. Full response criteria at week 8 were met by 38% of patients in the risperidone group, compared with 36% of the olanzapine group (p=ns) and 27% of the aripiprazole group

(p<0.05). All 3 groups also demonstrated significant improvements in social function, with risperidone performing significantly better than aripiprazole (p<0.05).

Overall rates of adverse effects were similar with the 3 drugs. Olanzapine was associated with the largest average weight gain at week 8 (9.5 lbs vs 6.4 and 3.1 lbs with risperidone and aripiprazole, respectively; p<0.05 for both) and with the largest proportion of patients gaining ≥7% or more of their initial weight (49% vs 33% and 17%, respectively; p<0.05 for both). Olanzapine produced significantly fewer extrapyramidal symptoms than the other drugs, but significantly more psychic and "other" adverse effects. Risperidone was associated with significantly more menstrual problems than either olanzapine or aripiprazole.

Discussion: Because of its weight gain liability, olanzapine is no longer recommended in some guidelines as first-line treatment for patients with first episode schizophrenia. Based on the present findings, risperidone may be a better initial choice than aripiprazole for many patients with first-episode schizophrenia as it demonstrated greater efficacy without inferior tolerability. Aripiprazole may be preferred when preventing short-term weight gain is a priority, and olanzapine could be chosen to avoid adverse neurological effects.

Cheng Z, Yuan Y, Han X, Yang L, et al: An open-label randomised comparison of aripiprazole, olanzapine and risperidone for the acute treatment of first-episode schizophrenia: eight-week outcomes. *Journal of Psychopharmacology* 2019; doi 10.1177/0269881119872193. From Peking University, Beijing, China; and other institutions. **Funded by the Ministry of Science and Technology of China. Two of 13 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; olanzapine—*Zyprexa*; risperidone—*Risperdal

Reference Guide

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.

Network Meta-Analysis: A meta-analytic technique that can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method allows simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common.

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.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

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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