PSYCHIATRY DRUG ALERTS

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Folic Acid Supplements for Schizophrenia

According to a meta-analysis, folic acid supplementation may produce modest negative-symptom improvement in patients with schizophrenia.

Background: It has been suggested that folic acid may improve schizophrenia symptoms by decreasing levels of homocysteine. Various biochemical, genetic, and epidemiologic studies have linked low folic acid levels to the development of schizophrenia.

Methods: Studies were identified in the literature that were double-blind, randomized, placebo-controlled trials of folic acid or its relatives (folate, methylfolate, and folinic acid) as a supplement to antipsychotic drugs for the treatment of schizophrenia. A total of 10 trials, comprising 925 patients, were identified; none were sponsored by pharmaceutical companies. The primary outcome of the meta-analysis was improvement in total symptoms, measured using the Positive and Negative Syndrome Scale (PANSS). Other outcomes were subscales of the PANSS and tolerability (discontinuation and individual adverse events).

Results: Studies had a mean treatment duration of 14 weeks; most were small and had inconsistent results. Three trials were excluded from the analysis because they did not report sufficient data. In 3 of the 7 included trials, patients also received concomitant vitamins B_6 and B_{12}.

The 7 included studies all evaluated folic acid supplementation, and mean baseline PANSS total scores ranged from 70 to 97. While most studies showed at least a small decrease in PANSS total score (range, <1–11 points), folic acid supplementation was not superior to placebo; nor was it superior for most secondary measures. However, PANSS negative symptoms showed a larger improvement with folic acid than with placebo (standardized mean difference,* 0.25; p=0.04). Subgroup analyses indicated that concomitant vitamin B supplementation did not account for the significant difference in negative symptoms. Incidence of adverse effects did not differ between folic acid supplementation and placebo.

Discussion: The authors note several important limitations that could affect the interpretation of the study results. Sample sizes were small in the individual studies, and treatment durations

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were short. In addition, the results were not corrected for multiple comparisons, and differing national practices of food fortification with folic acid may have been an unmeasured source of error. In spite of these limitations, the present results suggest that a larger study, specifically examining the effects of folic acid on negative symptoms, may be warranted.

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

Sakuma K, Matsunaga S, Nomura I, Okuya M, et al: Folic acid/methylfolate for the treatment of psychopathology in schizophrenia: a systematic review and meta-analysis. *Psychopharmacology* 2018;235 (August):2303–2314. From Fujita Health University School of Medicine, Japan. **This study was conducted without funding. The authors declared no direct competing interests.**

***See Reference Guide.**

Adjunctive Cariprazine in Depression

In a phase II clinical trial in patients with treatment-resistant major depressive disorder, adjunctive low-dose cariprazine (*Vraylar*) showed modest benefit.[1] The study results fell short of statistical significance, perhaps as a result of small sample size, low dosage, too-gradual titration, or a large placebo effect.

Methods: Participants were adults with major depressive disorder, without psychotic features, with the current episode duration of ≥8 weeks and nonresponsive to 1 or 2 adequate antidepressant trials. After 8 weeks of treatment with an open-label antidepressant plus placebo, patients still not meeting response criteria were randomly assigned to adjunctive double-blind treatment with cariprazine or placebo for an additional 8 weeks. Cariprazine dosage ranges of 0.1–0.3 mg/day and 1.0–2.0 mg/day were based on a previously established maximum tolerated dosage of 1 mg/day in healthy individuals. (In patients with schizophrenia, dosages up to 12.5 mg/day are tolerated.) The primary study outcome was change in Montgomery-Asberg Depression Rating Scale (MADRS) score.

Results: Of 502 patients enrolled in open-label treatment, 231 were nonresponders (average age, 45 years; 69% women) and entered the randomized phase; 205 completed treatment. The frequency and causes of discontinuation were generally comparable in all 3 treatment groups.

The mean MADRS total score at randomization was 26 across the groups. In a last observation carried forward analysis,* MADRS changes were not statistically significantly different from placebo in either cariprazine group, but the higher-dose group showed a larger average reduction than the placebo group. (See table.) The higher-dose cariprazine group also demonstrated numerically, but not statistically, greater positive change in the Clinical Global Impression–Improvement scale than the placebo group, as well as numerically higher rates of MADRS response (≥50% decrease in MADRS score) and remission (MADRS score ≤10).

Improvements from Baseline to Week 16			
Outcome Measure	**Placebo**	**0.1–0.3 mg/day Cariprazine**	**1–2 mg/day Cariprazine**
Change in MADRS Total Score	-8	-7.5	-9.8
MADRS Response	26%	30%	38%
MADRS Remission	20%	22%	27%

The higher cariprazine dosage was associated with generally mild-to-moderate adverse effects: headache, restlessness, fatigue, increased appetite, insomnia, dry mouth, and constipation. One patient in this dosage group discontinued because of adverse effects. Akathisia occurred in 4 patients in the higher-dosage group.

Discussion: Although the differences between placebo and adjunctive cariprazine were not statistically significant, the 1.8-point difference between the groups in MADRS change approaches the 2-point threshold generally considered clinically relevant, and a previous trial,[2] with cariprazine dosages of up to 4.5 mg/day, showed a mean MADRS score difference of 2.2 points. Consequently, further studies to establish the optimal therapeutic dosage of cariprazine in resistant depression appear to be warranted.

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

[1]Fava M, Durgam S, Earley W, Lu K, et al: Efficacy of adjunctive low-dose cariprazine in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *International Clinical Psychopharmacology* 2018; doi 10.1097/YIC.0000000000000235. From Massachusetts General Hospital, Boston; Allergan, Madison, NJ; and Gedeon Richter Plc, Hungary. **Funded by Allergan; and Gedeon Richter Plc. All study authors disclosed potentially relevant financial relationships.**

[2]Durgam S, et al: Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. *Journal of Clinical Psychiatry* 2016;77:371–378.

***See Reference Guide.**

Adjunctive Brexpiprazole for Depression

In a randomized, multi-site trial, adjunctive brexpiprazole was effective in patients with depression that had not been adequately responsive to antidepressant drugs.

Methods: The trial enrolled patients with a current nonpsychotic major depressive episode of ≥8 weeks' duration and an inadequate response to 1–3 antidepressants during the current episode. During the first 8 study weeks, patients received open-label treatment with an investigator-selected antidepressant, plus a single-blind placebo. Inadequate response was defined using a combination of scores on the Hamilton Rating Scale for Depression (HAM-D), Clinical Global Impression–Improvement (CGI-I) scale,* and Montgomery-Asberg Depression Rating Scale (MADRS). Patients who did not meet response criteria (i.e., ≥50% reduction in HAM-D score to a final score of <14 plus a CGI-I score of 1 or 2) with antidepressant monotherapy were randomly assigned to an additional 6 weeks' treatment with either brexpiprazole (titrated to 2 mg/day over 3 weeks) or placebo, in addition to the same SRI or SNRI antidepressant. The primary efficacy endpoint was change from baseline in the MADRS total score.

Results: Of 837 patients who entered single-blind treatment, 14.5% withdrew from the study and 38.5% experienced response to the antidepressant. The remaining 394 (mean age, 43 years; 74% women) received adjunctive brexpiprazole or placebo. Background antidepressants in these patients included 10 or 20 mg/day escitalopram (n=74); 40 or 60 mg/day duloxetine (n=69); 20 or 40 mg/day fluoxetine (n=68); 75–225 mg/day extended-release venlafaxine (n=66); 100–200 mg/day sertraline (n=60); and 37.5 or 50 mg/day controlled-release paroxetine (n=57). More than 90% of this group completed the double-blind treatment phase.

Mean MADRS total scores at baseline were 26 and 27 in the placebo and brexpiprazole groups, respectively. Brexpiprazole was associated with a significantly larger change from baseline in MADRS score than placebo (-10.4 vs -8.1 points; p=0.0074). Significant differences were evident beginning in the third week of treatment, when the drug was titrated to the therapeutic dose. A key secondary efficacy endpoint, change from baseline in the Sheehan Disability Scale score, favored brexpiprazole numerically but did not reach statistical significance. Among the other secondary endpoints, brexpiprazole was superior to placebo in patients with DSM-5 anxious distress (p=0.0099) and in those with <25% improvement during antidepressant monotherapy (p=0.026).

Adverse effects were similar to those observed in other brexpiprazole studies. The most common were akathisia and restlessness (8% each). Patients gained an average of 3.3 lbs with

brexpiprazole and 1.1 lb with placebo ($p<0.0001$). There were no clinically significant adverse effects on prolactin levels, sexual function, or suicidality.

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

Hobart M, Skuban A, Zhang P, Augustine C, et al: A randomized, placebo-controlled study of the efficacy and safety of fixed-dose brexpiprazole 2 mg/d as adjunctive treatment of adults with major depressive disorder. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m12058. From Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ; and H. Lundbeck A/S, Copenhagen, Denmark. **Funded by Otsuka and Lundbeck. All study authors disclosed financial relationships with Otsuka or H. Lundbeck.**

Common Drug Trade Names*: brexpiprazole—*Rexulti*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; paroxetine, controlled release—*Paxil CR*; sertraline—*Zoloft*; venlafaxine, extended release—*Effexor XR

***See Reference Guide.**

Prenatal Antidepressants and Child Motor Development

Maternal antidepressant use during pregnancy was associated with a small negative effect on motor development in children, according to a systematic review and meta-analysis.

Background: Many studies have evaluated the risk of structural abnormalities and immediate physiologic effects of antidepressant exposure in newborns, but there have been few studies of long-term neurodevelopmental outcomes. A causal association is biologically plausible because SSRI medications cross the placenta and the blood-brain barrier and may possibly alter serotonin signaling and the development of serotonin circuitry.

Methods: The analysis was based on English-language cohort or case-control studies using an accepted measure of motor performance in children or infants exposed to antidepressants in utero. Studies were excluded if they focused solely on the neonatal period. Few studies compared exposed children with those whose mothers had depression but did not receive antidepressants; therefore the meta-analysis was limited to 18 studies with a healthy control group of unexposed women. In the included studies, the Bayley Scales of Infant Development was the most commonly used assessment tool; several other rating scales were used, and a handful of studies were based on clinician or parent observation.

Results: The overall effect size* for impaired motor function in children exposed to antidepressants in utero was 0.22. Researchers in 7 of the 18 studies reported outcome with categorical data. The pooled effect size from these studies (0.40) was statistically significant, while the pooled effect size from researchers reporting numerical scores (0.08) was not. The study results were significantly heterogeneous, with most heterogeneity attributable to the type of data. There was no evidence of publication bias.

Discussion: The present analysis suggests that any effects antidepressants have on offspring motor development are small. In addition, the effects could be accounted for in a number of ways (e.g., effects of maternal depression itself) that do not directly implicate antidepressants. In addition, developmental scores in the exposed children generally fell within the normal developmental range, and abnormalities were not discernible on clinical examination. Thus the clinical significance of these findings remains unclear and they do not warrant changing antidepressant prescribing guidelines during pregnancy. However, monitoring of exposed children may be prudent.

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

Grove K, Lewis A, Galbally M: Prenatal antidepressant exposure and child motor development: a meta-analysis. *Pediatrics* 2018; doi 10.1542/peds.2018–0356. From Graylands Hospital, Mount Claremont, Australia; and other institutions. **This research was conducted without external funding. The authors declared no competing interests.**

***See Reference Guide.**

Antidepressant Increase for Resistant Disease

According to a meta-analysis of randomized controlled trials, increasing the dose of an SSRI is not effective in patients with unipolar major depression and initial treatment failure.

Background: Rates of antidepressant nonresponse have been shown to be as high as 30–40%. Current guidelines recommend switching antidepressants, augmenting with a second-generation antipsychotic or lithium, or increasing the initial antidepressant dose. Surveys show that nearly half of clinicians prefer to increase the dose in cases of nonresponse. Studies of this strategy have had mixed results or have been inconclusive.

Methods: A comprehensive literature search was undertaken to identify all randomized trials comparing a dose increase with unchanged medication continuation in patients with study-defined antidepressant treatment failure following ≥3 weeks of initial treatment. The primary outcome of the meta-analysis was efficacy of a dose increase compared with unchanged continuation, with efficacy described as a standardized mean difference* in rating scale scores.

Results: The search identified 9 studies with a total of 1273 patients. All of the studies reported on an SSRI, and 1 study also reported on maprotiline (*Ludiomil*). Initial treatment phases ranged from 3 to 9 weeks, and the double-blind phase ranged from 3 to 10 weeks.

The difference in outcome between dosage increase and unchanged continuation was not statistically significant (standardized mean difference, 0.053) but favored dose increase. Several of the studies had sample sizes too small to detect a medium-sized effect. Removing individual studies did not affect the outcome, indicating that no study strongly influenced the analysis. Secondary outcomes—response, remission, and dropout rates—did not favor either strategy.

Discussion: The study authors suggest that a possible explanation for their observations is that a dosage increase may not lead to increased serotonin transporter occupancy. Although the present conclusions apply only to SSRIs, some studies of antidepressant switches have also had negative results and the authors recommend other, empirically supported second-line treatments such as augmentation with lithium or a second-generation antipsychotic.

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

Rink L, Braun C, Bschor T, Henssler J, et al: Dose increase versus unchanged continuation of antidepressants after initial antidepressant treatment failure in patients with major depressive disorder: a systematic review and meta-analysis of randomized, double-blind trials. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17r11693. From the University of Cologne Medical School, Germany; and other institutions. **This analysis was conducted without funding. The authors declared no competing interests.**

***See Reference Guide.**

Vortioxetine for Physical Symptoms of Depression

According to a meta-analysis of short-term, manufacturer-sponsored, placebo-controlled trials, vortioxetine (*Trintellix*) is associated with improvement in the somatic symptoms of depression.

Methods: Of 17 short-term (6–8 week) trials that were conducted as part of the vortioxetine clinical development program, 5 were selected for the meta-analysis based on the use of both the Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) to measure physical symptoms. The meta-analysis combined data from the 5 studies, and then conducted separate analyses for each of the physical symptoms rated with the HAM-D or the HAM-A and for the 2 therapeutic doses of vortioxetine, 5 and 10 mg/day. Study participants were adults, aged 18–75 years, with a major depressive episode of ≥3 months' duration. Patients with significant anxiety (i.e., a baseline HAM-A score of ≥20) were analyzed as a subgroup.

Results: Nearly 2100 patients were randomized and received vortioxetine or placebo. The outcome analysis was based on 1729 patients who completed the individual study's treatment protocol. Baseline symptom ratings indicated that patients had, on average, moderate-to-severe depression and a significant level of anxiety. Vortioxetine was associated with statistically significant improvement in most HAM-D somatic items, although in some cases, improvement was limited to the higher dose. (See table.) Several HAM-A somatic items also improved with vortioxetine. In the subset of patients with a high level of anxiety, who made up nearly half of the study population, significant effects were seen for both vortioxetine doses on HAM-D early and middle insomnia, general somatic symptoms, somatic anxiety symptoms, and genital symptoms.

Significant Differences from Placebo in Somatic Symptom Categories		
Vortioxetine Dosage	**HAM-D Symptoms**	**HAM-A Symptoms**
5 mg/day	Middle insomnia (p=0.006) Late insomnia (p=0.002) General somatic (p=0.013)	Somatic muscular (p=0.021) Genitourinary (p=0.02)
10 mg/day	Early insomnia (p<0.001) Middle insomnia (p<0.001) Late insomnia (p=0.038) Somatic anxiety (p<0.001) General somatic (p<0.001) Genital (p<0.001)	Genitourinary (p<0.001) Autonomic (p=0.025)

HAM-D gastrointestinal symptoms and weight loss were unaffected by vortioxetine treatment. Nonsignificant differences were observed for HAM-A somatic sensory, cardiovascular, respiratory, and gastrointestinal items.

Discussion: The presence of physical symptoms in depression predicts a more chronic course of disease, and residual physical symptoms may increase the risk of recurrence. Vortioxetine has multimodal interacting mechanisms of action that may affect somatic symptoms. Both serotonin and norepinephrine are probably involved in physical symptoms of depression and in pain. In addition, nonclinical studies indicate vortioxetine modulates multiple neurotransmitter symptoms involved in centrally mediated pain.

Study Rating*—16 (89%): This study met most criteria for a meta-analysis; however, while the authors disclosed that data was collected from studies funded by H. Lundbeck A/S, Valby, and Takeda Pharmaceuticals Inc., the funding source for the present analysis was not declared.

Christensen M, Florea I, Lindsten A, Baldwin D: Efficacy of vortioxetine on the physical symptoms of major depressive disorder. *Journal of Psychopharmacology* 2018; doi 10.1177/0269881118788826. From H. Lundbeck A/S, Denmark; and other institutions. **Source of funding not stated. All study authors declared potentially relevant financial relationships.**

***See Reference Guide.**

Depression as Medication Adverse Effect

Use of medications that have depression as a potential adverse effect is common and increasing, according to a longitudinal series of surveys of American adults. Use of ≥3 of these medications was associated with simultaneous depression.

Methods: The authors analyzed 5 waves of data from the U.S. National Health and Nutrition Examination Survey, an in-person audit of a representative sample of community-dwelling adults, which is conducted in 2-year cycles. The final sample included >26,000 persons interviewed between 2005 and 2014. Participants showed interviewers containers for all prescription medications taken in the past 30 days. Information about the relationship of drugs to depression and suicidal thoughts or behavior was obtained from Micromedex, an online database

that lists FDA-labeled adverse events. Depression was assessed using the Patient Health Questionnaire 9 (PHQ-9).

Results: Use of any medication with depression as a side effect increased from an estimated 35% of the population in 2005–2006 to 38% in 2013–2014. Concurrent use of ≥3 of these medications increased from 7% to 9.5%, and use of medications with suicidal symptoms as a potential adverse effect increased from 17% to 23.5%. Overall, antidepressants with depression as a labeled adverse effect were the most widely used medication class, and use increased significantly between the study waves, from 11% to 15% of surveyed patients (p=0.001). Use of gastrointestinal agents (in particular, proton pump inhibitors and histamine H_2 antagonists), anxiolytics and sedative/hypnotics, and anticonvulsants also increased significantly (p≤0.01 for all). Use of depression-related antihypertensives, analgesics and muscle relaxants, hormonal contraceptives, and hormone replacement therapy was frequent but did not increase over the 10 study years.

The estimated prevalence of depression increased from 4.7% in patients taking no medications with depression as a labeled adverse effect to 6.9% in those taking 1 medication (p=0.002), 9.5% for those taking 2 (p<0.001), and 15.3% for those taking ≥3 medications (p<0.001). A similar trend was seen for patients taking increasing numbers of medications with suicidal symptoms as potential adverse effects. Most of the combinations associated with depression involved the beta-blockers atenolol or metoprolol, the narcotic hydrocodone, or the anticonvulsant gabapentin. Use of multiple medications without depression as an adverse effect was not associated with depression risk, compared with no medication use. The associations persisted in analyses that excluded users of psychotropic drugs, suggesting the association was not dependent upon the underlying psychiatric diagnosis.

Discussion: The study population reported using >200 different drugs with depression or suicidal symptoms as a labeled adverse effect. Some of these drugs, including proton pump inhibitors and emergency contraceptives, are also available over the counter, and product labeling does not always include full information about adverse effects. Furthermore, commonly used screening instruments for depression do not include evaluation of prescribed medications that have depression as a potential adverse effect.

Qato D, Ozenberger K, Olfson M: Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. *JAMA* 2018:319 (June 12):2289–2298. From the University of Illinois College of Pharmacy, Chicago; and other institutions. **Funded by the Robert Wood Johnson Foundation; and other sources. Two of 3 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

Common Drug Trade Names*: atenolol—*Tenormin*; gabapentin—*Neurontin*; hydrocodone—*Hysingla, Zohydro*; metoprolol—*Lopressor

Escitalopram and Cardiac Outcomes

In a placebo-controlled trial, patients who received treatment with escitalopram (*Lexapro*) for depression following acute coronary syndrome (ACS) had a reduced incidence of cardiovascular events in the subsequent 8 years.

Methods: This study was a planned secondary analysis of an escitalopram efficacy trial in patients with ACS. Potential patients were hospitalized for ACS at a central hospital in South Korea, treated by study cardiologists, and screened for depression within 2 weeks of admission. After further diagnostic evaluation by a study psychiatrist, patients who met criteria for minor or major depressive disorder were offered random assignment to escitalopram or placebo for 24 weeks of double-blind treatment. Previously published primary study results indicated that escitalopram was significantly superior to placebo for the principal outcome of depression remission. The focus of the present analysis is major adverse cardiac events (MACE), a composite of cardiovascular death, all-cause mortality, myocardial infarction (MI), and percutaneous coronary intervention.

Results: More than 4800 patients with ACS were screened for depression, 1152 underwent depression screening, 446 received a diagnosis of depression, and 300 were included in the randomized trial. Participants were followed for a mean of 8 years (range, 5–11 years). During follow-up, MACE occurred in 41% of the escitalopram group, compared with 54% of the placebo group (hazard ratio [HR],* 0.69; p=0.03). This difference was entirely accounted for by MIs (HR, 0.54; p=0.04). The treatment groups did not differ in rates of all-cause mortality, cardiac death, or percutaneous procedures. After adjustment for age, gender, and cardiac factors (e.g., hypertension, smoking, history of ACS, left ventricular ejection fraction), regardless of treatment group, patients in whom depression remitted had significantly lower hazards of MACE (HR, 0.52; p=0.001), all-cause mortality (HR, 0.46; p=0.01), and percutaneous procedures (HR, 0.48; p=0.05) compared with those without remission.

Discussion: These observations conflict with 2 previous, large trials of antidepressant treatment in patients with ACS, which found antidepressant treatment did not improve depression or long-term cardiac outcomes.[3,4] Escitalopram may modify the course of ACS through reduction of depressive symptoms or via positive effects on levels of brain-derived neurotrophic factor and proinflammatory cytokines and normalization of autonomic and platelet dysfunction.

[1]Kim J-M, Stewart R, Lee Y-S, Lee H-J, et al: Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: a randomized clinical trial. *JAMA* 2018:320 (July 24–31):350–357. From Chonnam National University Medical School, Republic of Korea; and other institutions. **Funded by the National Research Foundation of Korea; and other sources. One of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Kim J, et al: Escitalopram treatment for depressive disorder following acute coronary syndrome: a 24-week double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry* 2015;76:62–68.

[3]vanMelle J, et al: MIND-IT Investigators: effects of antidepressant treatment following myocardial infarction. *British Journal of Psychiatry* 2007;190:460–466.

[4]Glassman H, et al: Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: seven-year follow-up of SADHART participants. *Archives of General Psychiatry* 2009;66:1022–1029.

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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 1 group has half the risk of the other group.

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

Standardized Mean Difference: The difference between 2 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 to 0.2 is considered a negligible effect, 0.2 to 0.5 a small effect, 0.5 to 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.