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Lithium, Mood Stabilizers and Placental Complications

Results of a cohort study suggest that women taking lithium or mood-stabilizing anticonvulsants during the first half of pregnancy are at increased risk of preterm delivery and other placenta-mediated complications. However, risk appears to be associated with the underlying illness.

Methods: The study was based on nearly 1.5 million Medicaid-covered deliveries between 2000 and 2010. Exposed women were those who filled a prescription for lithium or an anticonvulsant (carbamazepine, lamotrigine, oxcarbazepine, topiramate, or valproate) in the first 20 weeks of pregnancy. The study outcomes were complications likely related to placental insufficiency: small for gestational age births, placental abruption, and a composite outcome that included these and also low birth weight at term and preterm delivery. The analysis was extensively adjusted using a propensity score that included indications for the prescription and other variables.

Results: During the first 20 weeks of pregnancy, 10,575 women (0.7%) were exposed to a single mood stabilizer, and 917 women (0.1%) were exposed to polytherapy. The indications for monotherapy were bipolar disorder (39%), migraine (32%), epilepsy (25%), and neuropathic pain (7%). Pregnancies with exposure had increased risk of ischemic placental disease: relative risk (RR),* 1.34 for monotherapy and 1.56 for polytherapy. However, after adjustment for treatment indication, risk was no longer elevated (adjusted RR, 0.97 for monotherapy and 1.16 for polytherapy). Risk was not elevated for any individual medication or for most individual complications. Only polytherapy was associated with risk of preeclampsia and possibly placental abruption, but confidence intervals for these estimates were wide. Women who continued filling prescriptions during the second half of pregnancy were at lower risk of complications than those who stopped taking the medications.

Sensitivity analysis stratified by indication for treatment found mood stabilizer monotherapy in women with bipolar disorder was not associated with increased risk of preeclampsia or small for gestational age births. However, risk for placental abruption was increased in these women.

Discussion: Previous studies linking anticonvulsant mood stabilizers and lithium with placenta-related complications may not have adequately accounted for the effects of underlying

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indications. The authors hypothesize that smoking, diabetes, other medication use, and lifestyle-associated factors may account for increased risk of placenta-mediated complications in exposed women. Conversely, women who continued taking medications throughout pregnancy may have been at lower risk due to behavioral factors associated with compliance with their medications. The authors caution that other evidence of these agents' possible teratogenicity, which was not assessed in the study, should be considered when making treatment decisions.

Cohen J, Huybrechts K, Patorno E, Desai R, et al: Anticonvulsant mood stabilizer and lithium use and risk of adverse pregnancy outcomes. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.18m12572. From Harvard TH Chan School of Public Health, Boston, MA; and other institutions. **Funded by the NIMH. Six of 7 authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

Common Drug Trade Names*: carbamazepine—*Tegretol*; lamotrigine—*Lamictal*; oxcarbazepine—*Trileptal*; topiramate—*Topamax*; valproate—*Depakene, Depakote

***See Reference Guide.**

Optimizing Antidepressant Dosage

According to the results of a systematic review and meta-analysis, the optimal balance between antidepressant efficacy and tolerability occurs at the low-to-medium end of the licensed dosing range for the most commonly prescribed agents.[1]

Methods: The meta-analysis focused on the most commonly prescribed antidepressants in the UK: 5 SSRIs (i.e., citalopram, escitalopram, fluoxetine, paroxetine, and sertraline), plus venlafaxine and mirtazapine. Acute treatment trials were included if they were randomized comparisons of oral monotherapy at multiple fixed dosages and/or drug versus placebo. Treatment groups within or outside the labeled dosage range were included. For SSRIs, doses were converted to fluoxetine equivalents. The study outcomes were response (≥50% reduction on an observer-rated depression scale), tolerability (dropouts due to adverse effects), and treatment acceptability (dropouts for all causes, which could include lack of efficacy as well as tolerability).

Results: The analysis included 77 studies with nearly 20,000 participants (61% women) with a mean age of 43 years. The studies included 201 treatment groups that received study medication for a median of 8 weeks. For SSRIs, dose-related efficacy increased to a peak between 20–40 mg fluoxetine equivalents and then showed a flat to decreasing trend at higher doses. (See table.) The rate of dropouts due to adverse effects increased with the dose in a linear fashion. The relationship to dropouts for any reason indicates optimal acceptability is also in the range of 20–40 fluoxetine equivalents. Mirtazapine showed a similar pattern, with peak response rates at 30 mg/day and optimal acceptability at the lower end of the dosing range. For venlafaxine, response rates continued to increase up to the highest dose evaluated, 375 mg, while dropout rates also increased throughout the dosing range.

Relative risks* for dose-outcome relationships with SSRIs

Fluoxetine equivalent dose	Response	Adverse event dropout	Dropout for any reason
10 mg	1.12	1.18	0.93
20 mg	1.24	1.40	0.88
30 mg	1.29	1.65	0.87
40 mg	1.27	1.94	0.91
60 mg	1.18	2.69	1.04
80 mg	1.09	3.73	1.20

Discussion: Clinical guidelines provide conflicting recommendations on antidepressant dosing, some stating that dose-dependent efficacy does not occur within the therapeutic range of SSRIs.

However, imaging studies indicate that about 80% serotonin transporter occupancy occurs at minimum therapeutic doses of SSRIs and venlafaxine, and further dose increases do not increase this proportion; nor does occupancy above 80% confer increased efficacy. For venlafaxine, noradrenaline reuptake blockade may be apparent only at higher doses. Mirtazapine mechanisms of action are not well understood.

Editorial.[2] According to calculations, efficacy plateaus occurred at about 30–40 mg citalopram, 10–15 mg escitalopram, 20–30 mg fluoxetine, 20–30 mg of paroxetine, 75–100 mg sertraline, 30 mg mirtazapine, and 375 mg venlafaxine. However, it should be noted that the study conclusions are based on fixed-dose trials, which may underestimate the efficacy of aggressive dosing used judiciously. Dose escalation could yield some additional benefit for selected patients, although the dose-escalation literature generally supports the low-to-medium range. The best strategy may be to aim initial dosing for the upper boundaries of these ranges.

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

[1]Furukawa T, Cipriani A, Cowen P, Leucht S, et al: Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: a systematic review and dose-response meta-analysis. *Lancet Psychiatry* 2019;6 (July):601–609. doi 10.1016/S2215-0366(19)30217-2. From Kyoto University, Japan; and other institutions. **Funded by the Japan Society for the Promotion of Science; and other sources. Three of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Hieronymous F: Which antidepressant doses are optimal? [editorial] *Lancet Psychiatry* 2019;6 (July):552–554. doi 10.1016/S2215-0366(19)30221-4. From the University of Gothenburg, Sweden. **The author disclosed potentially relevant financial relationships.**

Common Drug Trade Names*: citalopram—*Celexa*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; mirtazapine—*Remeron*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor

***See Reference Guide.**

Inflammation and Clozapine Activity

Because inflammation increases total clozapine (*Clozaril*) plasma concentrations, current clinical guidelines call for halving the dose of clozapine in patients with inflammation. However, a laboratory spiking experiment and a cross-sectional study suggest that inflammation may decrease levels of unbound clozapine, the pharmacologically active fraction. Thus, lowering the dose could increase risk of psychiatric deterioration.

A marked increase in total clozapine plasma concentrations into toxic ranges has been reported in patients with inflammation. This rise is unexplained, but a possible mechanism is an increase in the acute phase protein alpha-1-acid glycoprotein (AGP), which binds clozapine, leading to drug accumulation in plasma. These increases are generally not accompanied by toxic adverse effects.

A laboratory spiking experiment was undertaken using blood samples from 3 randomly selected patients receiving clozapine treatment. The anonymized samples were spiked with stock solutions of AGP at 2 different concentrations simulating concentrations that could be seen clinically. In all 3 patients, the unbound fraction of clozapine decreased after adding AGP, by an average of 28% (range, 22–31%; p=0.032) at the lower concentration and by 43% (range, 34–51%, p=0.048) at the higher concentration.

AGP and unbound clozapine levels were also compared in 26 remnant samples of blood that had been obtained during therapeutic drug monitoring of patients receiving clozapine. The fraction of unbound clozapine was 25% lower in the 6 patients with elevated AGP concentrations than in the 20 with normal AGP levels (p=0.03). Higher total plasma concentrations of clozapine were observed in patients with elevated AGP, but the difference did not reach statistical significance, possibly due to small sample size. It is also possible that clinicians, guided by therapeutic drug monitoring, had already lowered the clozapine dosage in these patients.

These results are preliminary, and because the samples were anonymized potential confounding factors such as smoking, caffeine intake, concurrent medications, and clozapine dose could not be evaluated. However, further investigation with in-depth longitudinal clinical and pharmacologic studies that include clinical assessments appear to be warranted.

Man W, Wilting I, Heerdink E, Hugenholtz G, et al: Unbound fraction of clozapine significantly decreases with elevated plasma concentrations of the inflammatory acute-phase protein alpha-1-acid glycoprotein. *Clinical Pharmacokinetics* 2019,58:1069–1075. doi 10.1007/s40262-019-00744-6. From the University Medical Center Utrecht, the Netherlands; and other institutions. **This research was not funded. The authors declared no competing interests.**

Statins for Depression

According to the results of a meta-analysis of controlled trials, adjunctive use of statins improves depression in patients with major depressive disorder. The agents do not appear to worsen mental health outcomes in patients without clinical depression.

Background: Evidence has suggested a possible relationship between inflammation and depression. Because they have strong antiinflammatory properties, statins have been evaluated as potential depression treatments, but results have been mixed. Some studies have suggested statins are effective adjuncts to SSRIs in patients with clinical depression, while other studies suggest the agents may worsen depressive symptoms and psychological well being in patients without clinical depression.

Methods: A comprehensive literature search identified all randomized controlled trials evaluating the effects of a statin vs placebo on depressive symptoms in adults. Studies were included in the meta-analysis regardless of whether the patient population had clinically diagnosed depression. The primary outcome was the standardized mean difference* in score on a validated depression rating scale between patients who received a statin or placebo. Subgroup analyses were conducted in patients with and without unipolar major depression at study entry.

Results: A total of 10 studies (2517 patients) were included in the analysis. Of these, 3 studies were restricted to patients with clinically diagnosed major depression who received a statin (i.e., lovastatin, simvastatin, or atorvastatin) as an adjunct to SSRI therapy. The remaining studies evaluated statin therapy either in healthy patients or in those with hypercholesterolemia or other medical conditions.

Overall, statins were significantly more effective than placebo at reducing depression rating scale scores (standardized mean difference [SMD], 0.3; p=0.005). The 3 studies of patients with clinical depression found significantly greater reductions in Hamilton Rating Scale for Depression scores in the statin group, compared with the placebo group (SMD, 0.796; p=0.0001). In the nondepressed population, patients who received statins had numerically lower depression rating scores than the placebo group (SMD, 0.153), but the difference was not statistically significant.

Discussion: These results support the use of statins as adjuncts to SSRI therapy in patients with major depressive disorder. The lack of significant improvement in statin-treated patients without clinical depression may be associated with a "floor effect" (i.e., for patients with few symptoms there is little room for statistical improvement), but it should be noted that in contrast to other research, this study found no evidence that statins induce or worsen depressive symptoms.

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

Yatham M, Yatham K, Ravindran A, Sullivan F: Do statins have an effect on depressive symptoms? A systematic review and meta-analysis. *Journal of Affective Disorders* 2019; doi 10.1016/j.jad.2019.07.002. From the University of Manchester, U.K.; and other institutions. **This study was conducted without external funding. One of 4 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*:** **atorvastatin—*Lipitor*; lovastatin—*Altoprev*; simvastatin—*Zocor

***See Reference Guide.**

Medical Marijuana in Psychiatry

According to an evidence-based review, psychiatrists are likely to encounter patients seeking a prescription for or who are already using medical marijuana, which has been legalized in 33 states, the District of Columbia, Guam, and Puerto Rico. More than 2500 strains of the plant along with a multitude of marijuana-infused products such as edibles, waxes, and oils are available. However, the strength of evidence supporting marijuana use for psychiatric indications is very low, and concern remains about purity, tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations, and adverse effects.

In 2013, the American Psychiatric Association determined that no scientific evidence supported the use of medical marijuana for any psychiatric indication, and that there is evidence of a strong association between cannabis use and onset and/or worsening of psychiatric disorders, particularly in adolescents. Despite this guidance, medical marijuana has been approved in many states for psychiatric indications including anxiety, autism, agitation in Alzheimer's disease, PTSD, and Tourette's disorder. Interest in CBD-only products is growing, but results of their use in psychiatry are inconsistent.

Clinically significant drug interactions are possible when patients use products containing THC or CBD, which are both substrates for CYP450 isoenzymes, and psychotropic medications including antidepressants and antipsychotics. In addition, acute adverse effects of marijuana use include increased anxiety, panic attacks, psychosis, impaired decision making, and increased impulsivity and risk-taking behavior. Moreover, acute attention, verbal learning, working memory, and information processing are negatively affected. Chronic marijuana use can lead to tolerance, dependence, withdrawal, and cognitive and motivational deficits. Pulmonary and cardiac complications are also possible, and a syndrome of cyclic vomiting and compulsive bathing (cannabinoid hyperemesis syndrome) has been described.

Medical marijuana and THC are schedule 1 substances, and carry potential liability issues for prescribers. Documentation of discussions regarding risk/benefit assessment, acute and long-term adverse effects, drug interactions, and other potential treatments are particularly important for physicians prescribing medical marijuana.

Radhakrishnan R, Ranganathan M, D'Souza D: Medical marijuana: what physicians need to know. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.18ac12537. From Yale University School of Medicine, New Haven, CT. **Funded by the Dana Foundation; and other sources. The authors declared no competing interests.**

Nabiximols for Cannabis Dependence

In a placebo controlled trial, nabiximols, a cannabis agonist delivered via nasal spray, was modestly effective in treating cannabis dependence. The preparation combines the 2 active ingredients of cannabis: cannabidiol (CBD) and tetrahydrocannabinol (THC).

Methods: Study participants were treatment-seeking adults treated at 4 specialist outpatient addiction clinics in Australia who met ICD-10 criteria for cannabis dependence. Participants were randomly assigned to double-blind treatment with nabiximols which contains nearly equal amounts of CBD and THC, or placebo to be administered in multiple sprays 4 times/day. Both the nabiximols and placebo groups were offered 6 structured, CBT-based, individual counseling sessions. The primary study outcome was the number of self-reported total days of illicit cannabis use over the 12 study weeks. Secondary outcomes such as withdrawal and craving were assessed using standardized questionnaires every 4 weeks.

Results: A total of 128 patients (mean age, 35 years; 98 men) were randomized and began study treatment. At baseline they reported using cannabis an average of 26 of the previous 28 days.

About 50% of patients completed the treatment protocol, with no difference between the groups. Patients in both groups attended an average of about 2.5 CBT sessions.

In an intent-to-treat analysis,* patients who received nabiximols reported using illicit cannabis an average of 35 days over the study period, compared with 53 days in the placebo group, a significant difference of 18 days after adjusting for baseline cannabis use (p=0.02). In patients who completed the study protocol, the difference was slightly larger: 20.3 days (p=0.02). More patients in the nabiximols group than placebo reduced their illicit cannabis use by ≥50% from baseline to week 12: 54% vs 29% (p=0.03). Other secondary outcomes, including completing ≥4 weeks of abstinence and reductions in cannabis-related problems, withdrawal, and cravings, did not differ between the 2 treatment groups.

The 2 study groups had similar, low rates of adverse events, only headache affected >5% of patients. Of 70 patients who completed a questionnaire about aberrant medication behaviors, 21 reported these behaviors during the study, mainly giving away or selling medication or unauthorized dose escalation. Rates of aberrant behavior were similar in the nabiximols and placebo groups. Treatment satisfaction was high and also did not differ between groups.

Discussion: Although these results suggest it is effective, cannabinoid agonist treatment is not likely to be relevant to all individuals seeking treatment for cannabis dependence. Nearly three-fourths of the 409 individuals who were interested in treatment did not complete the study screening process, and 12-week treatment retention rates were modest. Nevertheless, cannabinoid agonist treatment remains promising and may have a role in a stepped care approach, particularly in patients not adequately treated with counseling alone.

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

Lintzeris N, Bhardwaj A, Mills L, Dunlop A, et al: Nabiximols for the treatment of cannabis dependence: a randomized clinical trial. *JAMA Internal Medicine* 2019; doi 10.1001/jamainternmed.2019.1993. From South East Sydney Local Health District, Australia; and other institutions. **Funded by the University of Sydney. Two of 18 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Anticholinergics and Dementia

A large case-control study found strong anticholinergic drugs are associated with increased risk of dementia. Types of anticholinergic drugs associated with the greatest risk include antidepressants, antiparkinsonian drugs, antipsychotics, antiepileptics, and bladder antimuscarinics. Anticholinergic antihistamines and GI antispasmodics were not associated with increased risk.

Methods: The study population comprised all patients aged ≥55 years registered in a British primary case database between 2004 and 2016 and with ≥10 years of available medication data. Case patients were those who had onset of dementia during the study period. Each case was matched with up to 5 controls by age, sex, and other characteristics. To reduce bias due to anticholinergic prescription in early dementia, exposure was defined as the cumulative dose of anticholinergics during 1–11 years before the diagnosis in cases or the same index date in controls. In addition, patients with diagnostic codes for subtypes of dementia associated with Huntington disease, Parkinson disease, Creutzfeldt-Jakob disease, or HIV were also excluded to reduce indication bias. The analysis included 56 drugs grouped by their main indication into 11 categories. Cumulative drug exposure was summed into 5 categories of total standardized daily doses.

Results: Out of a base cohort of more than 3.6 million patients, dementia developed during follow-up in >128,000. After applying the study's strict exclusion criteria, the analysis included nearly 59,000 case patients and 226,000 matched controls. About 60% received a diagnosis of Alzheimer's or mixed dementia, 36% of vascular dementia, and 4% of other types.

For anticholinergics as a whole, dementia risk increased incrementally from the lowest level of cumulative exposure, 1–90 standard daily doses, (odds ratio,* 1.06) to the highest, equivalent to 3 years of daily use of a single strong anticholinergic medication at the minimum effective dose recommended for older people, (odds ratio, 1.49). Of the 11 categories of anticholinergic medication 5 were significantly associated with increased risk of dementia at the highest level of cumulative exposure. (See table.) Anticholinergic drug types that were not associated with increased dementia risk were antihistamines, antivertigo and antiemetic drugs, muscle relaxants, GI antispasmodics, antiarrhythmics, and antimuscarinic bronchodilators.

Odds Ratios for Dementia in Patients with the Highest Cumulative Anticholinergic Drug Exposure 1–11 Years Before Onset.

Anticholinergic category	Adjusted odds ratio
Antipsychotics (n=1812)	1.70
Bladder antimuscarinics (n=6864)	1.65
Antiparkinson agents (n=292)	1.52
Antiepileptics (n=1411)	1.39
Antidepressants (n=15,938)	1.29

The association of anticholinergics with dementia was stronger in patients who received the dementia diagnosis before age 80 years, compared with those diagnosed at older ages. Associations were also stronger for vascular dementia than for Alzheimer's.

Discussion: Causality cannot be attributed with this type of study. However, if the association is causal, about 10% of dementia diagnoses could be attributed to anticholinergic drugs. This proportion is comparable to other known modifiable risk factors for dementia, such as smoking, diabetes, or physical inactivity. Although the analysis accounted for a wide range of potential confounding factors including the possibility of treatment for prodromal symptoms, some possibility for residual confounding and indication bias may remain. The stronger association with vascular dementia is a novel finding that raises questions about how anticholinergic drugs might influence the development of dementia.

Coupland C, Hill T, Dening T, Morriss R, et al: Anticholinergic drug exposure and the risk of dementia: a nested case-control study. *JAMA Internal Medicine* 2019; doi 10.1001/jamainternmed.2019.0677. From the University of Nottingham, U.K. **Funded by the National Institute for Health Research; and other sources. Two of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Nabilone for Alzheimer's-Related Agitation

In a controlled trial, the synthetic oral THC analogue nabilone (*Casamet*) was moderately effective at reducing agitation in patients with moderate-to-severe Alzheimer's disease.

Methods: Study participants (n=38) met DSM-5 criteria for major neurocognitive disorder due to Alzheimer's Disease, had Mini-Mental State Examination (MMSE) scores of ≤24, and exhibited clinically significant agitation. Those taking cholinesterase inhibitors or psychotropics were required to have been receiving stable doses for ≥1–3 months. Patients received nabilone flexibly dosed to a target of 2 mg/day and placebo for 6 weeks each in randomized order, with a 2-week placebo washout between treatments. The primary study outcome measure was the Cohen Mansfield Agitation Inventory (CMAI), a 29-item scale that measures agitation, including physically aggressive and nonaggressive behaviors as well as verbally aggressive behaviors.

Results: Of the 38 patients who began randomized treatment (mean age, 87 years; 77% men), 2 died during the study and 9 were withdrawn early because of a serious adverse event. Five of these events occurred during nabilone treatment and 4 during placebo. After titration, participants received a mean nabilone dose of 1.6 mg/day.

Mean CMAI total scores decreased from 68 at study entry to 56 following 6 weeks of nabilone treatment, compared with 66 after 6 weeks of placebo (effect size,* 0.52; p=0.003). Nabilone was

also associated with greater improvement in many of the study's secondary measures, including the Neuropsychiatric Inventory (NPI) Nursing Home version total score (p=0.004) and caregiver distress subscale (p=0.041) and the sMMSE, an adapted version of the MMSE (p=0.026). Clinical Global Impressions rating indicated 47% of patients demonstrated at least minimal improvement with nabilone, compared with 23% with placebo. Sedation was the most common adverse event during nabilone treatment (17 patients, vs 6 with placebo). Sedation usually improved when the nabilone dose was reduced. Nabilone and placebo did not differ in the frequency of treatment-limiting sedation or in falls.

Discussion: The mean improvement in CMAI scores with nabilone versus placebo was larger than that reported in previous trials of atypical antipsychotics or antidepressants. Improvements in neuropsychiatric symptoms and caregiver burden were also larger than those reported with atypicals and most antidepressants. In contrast to other agents, nabilone was not associated with cognitive worsening. These observations suggest that cannabinoids, with their distinct pharmacological profile, may offer an alternative to atypical antipsychotics as a second-line treatment for agitation. Additional trials of nabilone appear to be warranted.

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

Herrmann N, Ruthirakuhan M, Gallagher D, Verhoeff N, et al: Randomized placebo-controlled trial of nabilone for agitation in Alzheimer's disease. *American Journal of Geriatric Psychiatry* 2019; doi: 10.1016/j.ajgp.2019.05.002. From Sunnybrook Health Sciences Centre, Toronto, Canada; and other institutions. **Funded by the Alzheimer's Drug Discovery Foundation; and other sources. Five of 7 study authors disclosed potentially relevant financial relationships; the remaining 2 authors declared no competing interests.**

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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.

Intent-to-Treat Analysis (ITT): An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone who begins treatment is included regardless of treatment completion. ITT analyses are done to avoid the effects of crossover, drop-out, and other factors that could alter the results or inflate the magnitude of effects.

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.

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.