

PSYCHIATRY DRUG ALERTS

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Benzodiazepines and Pneumonia Risk

Most commonly prescribed benzodiazepines are associated with a dose-related increased risk of pneumonia in patients with schizophrenia, according to a nationwide case-control study.

Methods: Data were collected from Taiwan's National Health Insurance Research Database for patients who were hospitalized with a first diagnosis of schizophrenia in 2000–2010. Case patients were those who were hospitalized with pneumonia after the baseline schizophrenia hospitalization. Each case patient was matched with up to 4 controls who had a hospitalization for schizophrenia but without any subsequent pneumonia hospitalization, based on gender, age, and the year of baseline psychiatric admission. Exposure to benzodiazepines was characterized as current (within 30 days of the pneumonia hospitalization) or past. Because patients with schizophrenia have been found to have higher rates of chronic lung disease and smoking, which could increase pneumonia risk, a separate sensitivity analysis including >63,000 patients with other psychiatric conditions was also conducted.

Results: The study group consisted of 2501 case patients and nearly 10,000 controls. Patients' average age at the baseline psychiatric hospital admission was 43 years. Current use of most benzodiazepines was associated with a higher incidence of pneumonia, compared with past or no use. After adjustment for potential confounders not included in the matching process (e.g., concomitant medications, psychiatric history, and physical illness comorbidity), relative risk (RR)* for pneumonia was significantly elevated with midazolam (RR, 6.6; $p<0.001$), diazepam (RR, 3.4; $p<0.001$), lorazepam (RR, 2.2; $p<0.001$), triazolam (RR, 1.8; $p=0.019$), clonazepam (RR, 1.7; $p<0.001$), and alprazolam (RR, 1.6; $p<0.001$).

For most of the benzodiazepines that were associated with increased risk of pneumonia, the risk increased with the duration of use and the cumulative defined daily dose. Pneumonia risk was highly correlated with GABA-A receptor binding affinity (correlation coefficients,* 0.92–0.96 for the 3 receptor subunits). Half-lives of the benzodiazepines were not associated with pneumonia risk, perhaps because the agents are dosed frequently for some indications, obscuring any potential relationship.

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Results of the sensitivity analysis confirmed the main findings, suggesting the association is not based on schizophrenia-specific factors. In this broader psychiatric population, RRs for pneumonia with the same agents ranged from 1.2 for alprazolam to 1.8 with diazepam ($p \leq 0.003$ for all).

Discussion: The mechanism by which benzodiazepines affect pneumonia risk are unclear. However, it may be related to benzodiazepine-receptor associated immunomodulation or to GABA-receptor associated sedation and muscle relaxation, which could lead to aspiration.

Cheng S-Y, Chen W-Y, Liu H-C, Yang T-W, et al: Benzodiazepines and risk of pneumonia in schizophrenia: a nationwide case-control study. *Psychopharmacology* 2018;235 (November):3329–3338. doi 10.1007/s00213-018-5039-9. From Taipei City Hospital, Taiwan; and other institutions. **Funded by the Taiwan Ministry of Science and Technology; and Taipei City Hospital. The authors declared no competing interests.**

Common Drug Trade Names: alprazolam—*Xanax*; clonazepam—*Klonopin*; diazepam—*Valium*; lorazepam—*Ativan*; midazolam—*Versed*; triazolam—*Halcion*

*See Reference Guide.

Antidepressant Effects of Testosterone

According to the results of a meta-analysis, testosterone treatment may produce dose-related reductions in depressive symptoms in men.¹ However, the effect is small and the evidence shows a high risk of bias.

Background: Results of previous research on testosterone for mood symptoms have been mixed, and most studies were limited to hypogonadal or middle-aged men. The present analysis was undertaken to evaluate the treatment in eugonadal versus hypogonadal men and those aged older versus younger than 60 years.

Methods: The meta-analysis was based on 27 randomized, placebo-controlled trials conducted in 1890 men. Studies were included if they appeared in English-language peer-reviewed journals and reported on mood before and after the intervention, using a validated or original measurement scale for depressive symptoms. Of these, 4 of the trials reported the effects of testosterone monotherapy, and the remaining studies were conducted in patients who could be receiving other antidepressant treatments.

Results: One study was excluded from the analysis because it reported an extreme value for treatment effect. The remaining 26 studies had a combined effect size* (Hedges g) of 0.21 ($p < 0.001$) for the standardized difference in depression scores between testosterone and placebo. This translates to a 2.2-point reduction in Beck Depression Inventory (BDI) score. This effect exceeds the efficacy threshold of 2.0 points proposed by the National Institute for Health and Care Excellence (NICE) for treatment-resistant depression, but not the 3.0-point threshold for treatment-responsive depression. Patients who received testosterone had about a 2-fold increased odds of a response, defined as a $\geq 50\%$ symptom reduction from baseline (odds ratio,* 2.30; $p = 0.004$).

Analysis of possible moderators found treatment success was associated with testosterone dose. Rates of response were higher with 1.0 g/week than with 0.3 or 0.1 g/week ($p = 0.02$). Response rates were not affected by patient age, whether patients were hypo- or eugonadal, baseline depression symptom severity, HIV status, treatment duration, or mode of hormone administration. Attrition from treatment was comparable with testosterone and placebo.

Discussion: Few of the included trials had a low risk of bias. However, according to the authors, the risk of bias and "questionable research practices" were not likely to have materially affected the outcome of the meta-analysis. Even in the most conservative bias scenario, testosterone had a clinically significant effect at doses > 0.5 g/week when the analysis was limited to studies with

low variability in baseline symptoms. There remains a need for sufficiently powered long-term studies of testosterone safety.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis. However, the source of funding was not disclosed.

Editorial.² Heterogeneity of the trials is an important flaw of this meta-analysis. In addition, few of the studies were conducted in men with a standardized diagnosis of depression, which prevents reaching a strong conclusion about the efficacy of testosterone for inducing remission. It is not known whether improvements of the magnitude shown in the meta-analysis are clinically meaningful; and the long-term safety of testosterone treatment for depression has not been demonstrated. However, a large U.S. multicenter, double-blind, placebo-controlled trial of topical testosterone in hypogonadal men at increased risk for cardiovascular disease is currently being conducted. A substudy of the trial will examine the effects of testosterone therapy on depression remission in middle-aged and older hypogonadal men with late-onset depressive disorders. Unless those results replicate the findings of the present analysis, the editorialists recommend that clinicians continue to follow the guidelines of the Endocrine Society, which do not support using testosterone, particularly in supraphysiologic doses, to treat depressive disorder in men.

¹Walther A, Breidenstein J, Miller R: Association of testosterone treatment with alleviation of depressive symptoms in men: a systematic review and meta-analysis. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.2734. From the Technische Universität Dresden, Germany; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

²Bhasin S, Seidman S: Testosterone treatment of depressive disorders in men: too much smoke, not enough high-quality evidence [editorial]. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.2661. From Harvard Medical School, Brigham and Women's Hospital, Boston, MA; and other institutions. **One author disclosed potentially relevant financial relationships.**

*See Reference Guide.

Psychotropic/Antiretroviral Interactions: Antidepressants

Most categories of psychotropic drug can interact with antiretroviral therapy (ART) agents prescribed to treat HIV. Because HIV is highly comorbid with mood, anxiety, and cognitive disorders, clinicians are likely to encounter patients on complex regimens that include both ART and psychotropics. The 2 drug types may also have compounding adverse effects, according to an extensive literature review.

Editor's Note. This is the first report in a 5-part series on psychotropic/antiretroviral interactions. We will cover interactions with antidepressants in this issue, and then stimulants, antipsychotics, mood stabilizers, and medications for opioid and alcohol use disorders over the next 4 issues.

A comprehensive search was undertaken to identify relevant materials published through December 2017, including research articles, drug package inserts, and, where clinical data were lacking, in-vitro data. Examined in the review were all ART interactions with antidepressants, stimulants, antipsychotics, mood stabilizers, and treatments for opioid or alcohol use disorders.

Many antiretrovirals are metabolized by the hepatic cytochrome P450 (CYP450) system, which can lead to pharmacokinetic interactions whose effects range from trivial to life threatening. Integrase strand transfer inhibitors (INSTIs) are a newer drug class, gaining prominence in part because of their favorable adverse-effect profile and, in some cases, a decreased potential for drug/drug interactions. All currently available protease inhibitors are metabolized by and inhibit CYP3A4, the most common enzyme pathway for hepatically metabolized drugs. Hepatic effects of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) vary widely. These agents can induce and/or inhibit CYP enzymes. The other major drug categories,

nucleoside reverse transcriptase inhibitors (NRTIs) and entry inhibitors, appear to have little potential for hepatic enzyme-related interactions. (See the printable ART cytochrome P450 properties table at www.alertpubs.com/sdaonlinecontent for details.)

The majority of newer antidepressants are also extensively metabolized by the CYP450 system and have the potential to interact with ART agents. (See table.) Antidepressant effectiveness and tolerability in the context of ART varies among individual patients, and no 1 drug or class can be broadly recommended. Individual patient risk factors and potential drug interactions should be considered when selecting an antidepressant.

Antidepressant/Antiretroviral Interactions		
Antidepressant	Interaction Potential	Recommendations
Citalopram, Escitalopram	Minimal	May be a preferable antidepressant for patients with HIV, specifically those receiving protease inhibitors.
Fluoxetine	Limited	Serotonin toxicity has been reported with fluoxetine and concomitant ART. Titrating dose to clinical response and monitoring for loss of antidepressant efficacy are recommended.
Paroxetine	Limited	
Sertraline	Limited	
Fluvoxamine	Clinically significant	Increased adverse effects are possible; an alternate antidepressant should be considered.
Vortioxetine, Vilazodone	Unlikely	No empirical evidence to support or refute safety.
Venlafaxine, Desvenlafaxine	Unknown	Theoretical potential for reduced antiretroviral concentrations; an alternate antidepressant should be considered.
Duloxetine	Theoretical	Potential duloxetine concentration elevation with 2D6-inhibiting ART; an alternate antidepressant should be considered.
Milnacipran, Levomilnacipran	Unlikely	No empirical evidence to support or refute safety.
Trazodone	Clinically significant	Potential for clinically significant increase in trazodone adverse effects; an alternate antidepressant should be considered.
Mirtazapine	Not well described	Use lowest effective mirtazapine dose when coadministered with potent CYP1A2, 3A4, or 2D6 inhibitors or inducers.
Bupropion	Clinically significant	Bupropion dose increase may be necessary if administered with 2B6 inducers.
TCAs	Unknown	Caution and close monitoring recommended when coadministered with 3A4 or 2D6 inhibitors.
MAOIs	Unlikely	Despite a seemingly benign interaction potential with ART, MAOIs are not preferred due to limitations of the class (e.g., narrow therapeutic index, dietary precautions).
St John's wort	Clinically significant	Contraindicated in patients taking protease inhibitors, NNRTIs, or several INSTIs.

Goodlet K, Zmarlicka M, Peckham A: Drug-drug interactions and clinical considerations with co-administration of antiretrovirals and psychotropic drugs. *CNS Spectrums* 2018; doi 10.1017/S109285291800113X. From Midwestern University College of Pharmacy, Glendale, AZ; and other institutions. **Source of funding not stated. Two of 3 study authors disclosed potentially relevant relationships; the remaining author declared no competing interests.**

Common Drug Trade Names: bupropion—*Wellbutrin*; citalopram—*Celexa*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; levomilnacipran—*Fetzima*; milnacipran—*Savella*; mirtazapine—*Remeron*; paroxetine—*Paxil*; sertraline—*Zoloft*; trazodone—*Oleptro*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Trintellix*

Injectable Olanzapine: Age Effects

A patient's age appears to have little effect on drug exposure with the long-acting injectable (LAI) formulation of olanzapine, in contrast to oral olanzapine, according to the results of an observational study.¹ According to the authors, these results suggest that modifying the dose of LAI olanzapine in older patients may not be necessary.

Background: It has been shown that dose-adjusted exposure with oral olanzapine increases with age,² suggesting that lowered doses may be required for older patients. However, the effects of increasing age on LAI administration have not been described.

Methods: Data for the analysis were collected retrospectively from therapeutic drug monitoring information routinely collected at a hospital in Norway over a 12-year period. The analysis included olanzapine trough serum samples drawn 10–30 hours after an oral dose or 10–30 days after LAI injection. Absolute olanzapine concentrations, as well as concentration/dose ratios were compared between patients aged 18–49 years and those aged ≥50 years. In addition, because elderly is often defined as age ≥65 years, the comparison was repeated with 65 years as the cutoff.

Results: After excluding serum measurements from patients with compliance issues and those taking concomitant oral and LAI olanzapine, CYP inducers (i.e., carbamazepine, phenytoin, phenobarbital), or CYP inhibitors (e.g., valproic acid, fluvoxamine), >21,000 measurements from 8288 patients were included. Average daily doses of oral olanzapine were higher in patients aged <50 years than in older patients (14.2 vs 11.7 mg/day; $p < 0.001$). Younger patients also received higher doses of LAI olanzapine on average (20.8 vs 18 mg/day; $p < 0.001$). For oral olanzapine, there was a clear age-related increase in the concentration/dose ratio of olanzapine in patients aged ≥50 years. Concentration/dose ratios did not differ between younger and older patients receiving LAI olanzapine. Results were similar when smokers and nonsmokers were analyzed separately and when the analysis was repeated using the standard geriatric cutoff of 65 years. The concentration/dose ratio was about 25% higher in women than in men for both oral and LAI formulations ($p < 0.001$ for both).

Discussion: LAI antipsychotics are underused in many settings, and their use in the elderly has received little study. LAI formulations have higher bioavailability, requiring lower doses, and thus reducing the potential variability caused by oral dosing.

¹Tveito M, Smith R, Molden E, Haslemo T, et al: Age impacts olanzapine exposure differently during use of oral versus long-acting injectable formulations: an observational study including 8,288 patients. *Journal of Clinical Psychopharmacology* 2018;38 (December):570–576. doi 10.1097/JCP.0000000000000961. From the University of Oslo, Norway; and other institutions. **Funded by the South-Eastern Norway Regional Health Authority. Two of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

²Castberg I, et al: Effects of age and gender on the serum levels of clozapine, olanzapine, risperidone, and quetiapine. *Acta Psychiatrica Scandinavica* 2017;136:455–464.

Common Drug Trade Names: carbamazepine—*Epitol, Tegretol*; fluvoxamine—*Luvox*; olanzapine, LAI—*Zyprexa Relprevv*; olanzapine, oral—*Zyprexa*; phenytoin—*Dilantin*; valproic acid—*Depakene, Depakote*

Perimenopausal Depression: Treatment Guidelines

Although perimenopause has been recognized as a window of vulnerability for the development of both depressive symptoms and major depressive episodes, clinical recommendations are lacking. The North American Menopause Society and the National Network of Depression Centers' Women and Mood Disorders Task Group convened an expert panel to review the literature on depressive symptoms and disorders in midlife women and to develop guidelines addressing epidemiology, clinical presentation, antidepressant treatment, hormone therapy, and other therapies for affected women.

According to the panel, midlife depression in women commonly presents with the classic depressive symptoms, combined with menopausal complaints such as vasomotor symptoms, sleep and sexual disturbances, weight and energy changes, and concentration problems. Often the situation is further complicated by bereavement and other losses and stressors such as career shifts or caring for an aging parent. Contrary to previous beliefs, grown children leaving the home (the "empty nest") is believed to have positive rather than negative effects on mood.

Antidepressants, cognitive behavioral therapy, and other proven psychotherapies should remain first-line treatments for depression during menopause. Women with a history of successful drug therapy for depression should receive the previously effective agent. Desvenlafaxine, the only agent that has been investigated specifically in perimenopausal women, has shown efficacy in short-term trials. Small open-label studies have shown SSRIs (e.g., citalopram, escitalopram, fluoxetine, sertraline, vortioxetine), SNRIs (e.g., desvenlafaxine, duloxetine, venlafaxine), and mirtazapine improved mood in perimenopausal women and also had positive effects on vasomotor symptoms, sleep, and other menopausal symptoms. Bupropion is often prescribed because it produces less weight gain, sexual dysfunction, and sleepiness than other agents.

Some evidence suggests concomitant estrogen can improve response to antidepressant drugs, but it is not FDA approved to treat depression. Hormonal contraceptives may improve mood in women approaching menopause. This and other evidence suggests there may be a window of opportunity with estrogen that does not extend into the postmenopausal period. The available evidence is insufficient to recommend herbal or other alternative remedies for treatment of perimenopausal depression.

Maki P, Kornstein S, Joffe H, Bromberger J, et al: Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause: The Journal of the North American Menopause Society* 2018; doi 10.1097/GME.0000000000001174. From the University of Illinois at Chicago; and other institutions. **These guidelines were created without funding. Five of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: bupropion—*Wellbutrin*; citalopram—*Celexa*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; mirtazapine—*Remeron*; sertraline—*Zoloft*; venlafaxine—*Effexor*; vortioxetine—*Trintellix*

Lacosamide in Bipolar Disorder

The third-generation anticonvulsant lacosamide (*Vimpat*), currently approved for treatment of partial-onset seizures, was at least as effective as other antiepileptic drugs at improving a spectrum of outcomes in patients with bipolar disorder. This nonrandomized study, which compared patients receiving lacosamide with control patients receiving other anticonvulsants, also found the agent to have better tolerability than other anticonvulsants.

Background: Lacosamide has little-to-no interaction with cytochrome P-450 enzymes and a low potential for drug interactions. It has shown incidental antidepressant and anxiolytic effects in patients with epilepsy.

Methods: The study retrospectively compared patients with bipolar disorder treated consecutively with lacosamide (n=102) or with other antiepileptic drugs (n=123). Eligible subjects had received lacosamide, had DSM-5 bipolar I or II disorder, and had been recently hospitalized with an acute mood episode. They had received treatment with 50–300 mg/day lacosamide for 30 days; they could also have received antipsychotics but not lithium. Outcome measures included the Brief Psychiatric Rating Scale (BPRS), the Young Mania Rating Scale (YMRS), the Hamilton Rating Scales for Depression (HAM-D) and Anxiety (HAM-A), the Clinical Global Impression–Severity (CGI-S) scale, and the Global Assessment of Functioning (GAF).

Results: Patients who received lacosamide were significantly younger than control patients and had significantly less substance use comorbidity. The groups did not differ with regard to the

number of prior mood episodes or duration of illness. Clinical measures showed no baseline differences between the groups on any symptom or functional rating scale.

Both patient groups showed striking improvements in all outcomes measured from baseline to nearly all time points beginning on day 7, with large effect sizes* at day 30. (See table.) Patients who received lacosamide showed significantly greater improvement in mania and overall illness severity than patients who received other anticonvulsants, who had significantly larger improvements in general psychopathology.

Depression ratings did not differ between the groups. Drug dosages were not correlated, or only poorly correlated, with clinical effects. Improvement occurred regardless of the type of episode or the type of bipolar disorder.

Previous observations have suggested that lacosamide may be associated with psychosis and sexual dysfunction, and there is a single known report of increased suicidal ideation. In the present study, no patient had onset of suicidal ideation, psychosis, or sexual dysfunction.

Lacosamide adverse effects—headache, dizziness, nausea, confusion, and cognitive symptoms—were few, mild, and transient. Cognitive adverse effects occurred significantly less often with lacosamide than with the other drugs (1% vs 20%; $p < 0.0001$).

Discussion: These preliminary results suggest that lacosamide may have some advantages over other antiepileptics in patients with bipolar disorder. Although the mechanism by which lacosamide exerts these effects is unclear, it appears to be achieved at dosages lower than those used to treat epilepsy. Additional study of lacosamide in bipolar disorder appears to be warranted.

Cuomo I, Piacentino D, Kotzalidis G, Lionetto L, et al: Lacosamide in bipolar disorder: a 30-day comparison to a retrospective control group treated with other antiepileptics. *Psychiatry and Clinical Neurosciences* 2018; doi 10.1111/pcn.12784. From the Clinica Von Siebenthal Neuropsychiatric Hospital, Rome, Italy; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

Effect sizes for change from baseline to day 30		
	Lacosamide	Other Anticonvulsants
BPRS	1.59	2.30
YMRS	1.58	1.16
HAM-D	1.52	1.90
HAM-A	1.59	1.51
CGI-S	3.83	1.54
GAF	2.51	2.01

Gabapentin Abuse

A 51-year-old man with a history of substance-induced mood disorder, as well as opioid, cocaine, and alcohol use disorders, presented to the emergency department following an intentional gabapentin overdose with suicidal intent. Following medical stabilization with supportive care, the patient was transferred to a psychiatric unit. His regular medication regimen included sertraline, divalproex, trazodone, and gabapentin. Review of his medication use suggested a pattern of gabapentin abuse characterized by overuse and requests for the medication from different physicians on varying pretexts. On questioning, the patient admitted that for ≥ 9 months he had been crushing and insufflating 3–4 600-mg gabapentin tablets at 2-hour intervals in bingeing episodes. He described the "high" he achieved as characterized by increased focus, energy, and productivity, followed by a calm/relaxation similar to opioid intoxication. Abrupt discontinuation resulted in withdrawal symptoms. The patient denied misuse of his other psychotropic medications, and a urine screen for illicit drugs was negative.

Gabapentin is widely used off-label as adjunct treatment for several psychiatric disorders including bipolar disorder, anxiety, PTSD, and depression. It has also shown potential for treatment of withdrawal and craving in alcohol, benzodiazepine, opioid, and cocaine dependence. The drug is well tolerated, has few interactions with other drugs, and is relatively inexpensive.

Because it is presumed to have no abuse potential, it is currently not scheduled as a controlled substance. However, there have been other reports of gabapentin abuse and misuse, mainly among patients with a history of substance abuse and psychiatric comorbidity. The pharmacologic properties that underlie gabapentin's abuse potential are unknown. Increasing rates of diversion, comparable to those with oxycontin, have also been documented. Although the present patient denied "cutting" heroine or buprenorphine with gabapentin, there have been reports of gabapentin being used illicitly in combination with opioids and to potentiate the effects of buprenorphine–naloxone. Gabapentin misuse by patients with opioid use disorder is especially concerning, given the recent increases in opioid-related mortality and evidence linking gabapentin use with increased risk of accidental opioid-related overdose deaths. Prescribers should be aware of the potential for gabapentin abuse in at-risk populations and should closely monitor these patients.

Khalid Z, Hennen M-A, Aldana-Bernier L: Gabapentin abuse by nasal insufflation: a case report [letter]. *Journal of Clinical Psychopharmacology* 2018 doi 10.1097/JCP.0000000000000983. From Rutgers New Jersey Medical School, Newark; and VA New Jersey Healthcare System, East Orange. **The authors declared no competing interests.**

Common Drug Trade Names: buprenorphine–naloxone—*Suboxone*; divalproex—*Depakene, Depakote*; gabapentin—*Neurontin, Gralise*; sertraline—*Zoloft*; trazodone—*Desyrel, Oleptro*

Reference Guide

Correlation Coefficient (r): A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1. An r value near 1 indicates a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r-value indicates a negative relationship.

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.

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.

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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