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Efficacy, Safety of Newer Antidepressants in Depression

The newer second-generation antidepressants levomilnacipran, vilazodone, and vortioxetine do not offer any advantage in efficacy or safety compared with other second-generation agents, according to a systematic review and network meta-analysis.

Methods: A comprehensive literature search identified antidepressant studies published since 2010, or unpublished, conducted in adult outpatients with major depressive disorder. The efficacy analysis included head-to-head randomized controlled comparisons between all available second-generation drugs representing all current drug classes, used in the recommended dosage range. Placebo-controlled trials were included in the network meta-analysis, and the analysis of harms also was planned to include non-randomized trials with a sample size of ≥100. The preferred efficacy outcome was response, defined as a ≥50% improvement from baseline in Hamilton Rating Scale for Depression (HAM-D) score.

Results: The analysis included 7 head-to-head trials involving 1 of the 3 newer antidepressants and 17 placebo- and active-controlled trials for the network meta-analysis. No additional non-randomized trials were identified for inclusion in the safety analysis.

Although there were no head-to-head comparisons involving levomilnacipran, it did not show superior efficacy to other second-generation antidepressants as a class. Vilazodone was directly compared with citalopram, showing no efficacy difference; vilazodone also had similar efficacy to the class of second-generation agents. In head-to-head comparisons, vortioxetine showed generally similar effects to duloxetine, paroxetine, and venlafaxine. The network meta-analysis showed that vortioxetine was associated with about one-third higher response rates than bupropion and fluoxetine, but this comparison was strongly determined by a single study with a high response rate for vortioxetine relative to placebo, and did not survive removal of that study from the analysis.

The safety analysis was based on limited evidence. Five trials compared safety and tolerability between 1 of the 3 newer antidepressants and an existing second-generation agent. The newer

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drugs had similar rates of overall adverse events and related discontinuation relative to other second-generation agents. There were some differences in rates of individual adverse events, but the quality of evidence for these differences was low.

Discussion: The present results suggest that levomilnacipran, vilazodone, and vortioxetine do not differ significantly in efficacy from each other or from older second-generation antidepressants. The choice of the initial antidepressant treatment for major depression should be based on patient preference after a thorough discussion of the advantages and disadvantages and the feasibility (e.g., costs, likely adherence) of different agents.

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

Wagner G, Schultes M-T, Titscher V, Teufer B, et al: Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: a systematic review and network meta-analysis. *Journal of Affective Disorders* 2017; doi 10.1016/j.jad.2017.11.056. From Danube University Krems, Austria; and other institutions. **Funded by the Drug Effectiveness Review Project of the Pacific Northwest Evidence-Based Practice Center. The authors did not include disclosure of potential conflicts of interest.**

Common Drug Trade Names*: bupropion—*Wellbutrin*; citalopram—*Celexa*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; levomilnacipran—*Fetzima*; paroxetine—*Paxil*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Trintellix

***See Reference Guide.**

Ketamine for Suicidal Ideation

In a randomized trial, ketamine infusion resulted in a rapid reduction in suicidal ideation in patients with major depressive disorder. The effects were moderate relative to IV midazolam, the control treatment.

Methods: Study participants were clinically- or self-referred individuals with a DSM-IV diagnosis of major depressive disorder, a score of ≥16 on the 17-item Hamilton Rating Scale for Depression (HAM-D), and clinically significant suicide risk as indicated by a score of ≥4 on the Scale for Suicidal Ideation (SSI). Study participants were voluntarily admitted to the inpatient research unit for the study and discharged when they were no longer deemed at risk. In the unit, participants were randomly assigned to receive a single 40-minute infusion of 0.5 mg/kg ketamine or 0.02 mg/kg midazolam, a short-acting benzodiazepine anesthetic chosen as the control treatment because it has a similar half-life to ketamine and no established antidepressant or antisuicidal effects. Following the 24-hour assessment, patients received optimized standard clinical pharmacotherapy for 6 months and underwent weekly research ratings for the first 6 weeks. The primary efficacy outcome measure was change in SSI score 24 hours post infusion. Patients who did not experience response to midazolam were offered an open-label infusion of ketamine, usually on the second study day.

Results: A total of 80 patients (mean age, 40 years; 60% women) received randomized treatment. At baseline, patients had been experiencing depression for a median of about 1 year and had a mean SSI score of 15; 39 had made a prior suicide attempt. About half of the patients were currently taking an antidepressant, and use of other psychotropic medications was high.

At 24 hours post infusion, SSI scores decreased on average by 5 more points with ketamine than with midazolam (effect size,* 0.75; $p<0.001$). At the 24-hour assessment, response (i.e., ≥50% decrease in SSI score) was achieved by 55% of the ketamine group and 30% of the midazolam group (odds ratio,* 2.85; $p=0.024$; number needed to treat,* 4). The decrease in suicidal ideation was greater with ketamine than midazolam beginning with the first evaluation, 230 minutes (nearly 4 hours) post-infusion.

Patients who received open-label ketamine had a nearly 8-point average reduction in the SSI, comparable to those who had received double-blind ketamine. Mean HAM-D scores decreased

somewhat in both groups. Improvements in depression and suicidal ideation persisted during 6 weeks of follow-up.

Adverse effects of ketamine, mainly blood pressure increase and dissociative symptoms, were similar to those reported in other ketamine studies. There was no evidence of ketamine abuse at the 6-month follow-up. There were 3 suicide attempts after the study procedures were carried out, 2 completed suicides occurred after the end of the study, and 3 patients were hospitalized for increased suicidal ideation during follow-up.

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

Grunebaum M, Galfalvy H, Choo T-H, Keilp J, et al: Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17060647. From Columbia University Medical Center; and New York State Psychiatric Institute, New York. **Funded by the NIMH. Five of 12 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: ketamine—*Ketalar*; midazolam—*Versed

***See Reference Guide.**

Intranasal Esketamine for Depression

In a phase-II clinical trial, intranasal esketamine, an enantiomer with a higher NMDA affinity than racemic ketamine, produced rapid, dose-related reductions in depression when added to antidepressant medication.[1] Efficacy persisted after reduction in the dosing frequency and eventual discontinuation.

Methods: Study participants were adults with treatment-resistant depression, defined as an inadequate response to ≥2 agents, with ≥1 inadequate response in the current episode. Participants were required to have moderate-to-severe depression, as measured using the clinician-rated Inventory of Depressive Symptomatology. All patients continued the antidepressants they were taking at study entry. After screening, patients were randomly assigned to double-blind treatment with intranasal esketamine or placebo for 1 week (study phase 1). At the end of this phase, those in the placebo group who continued to have moderate-to-severe symptoms were re-randomized to placebo or esketamine treatment for another week (study phase 2). Subsequently, patients could enter an optional 60-day phase of open-label treatment with flexible-dose esketamine, followed by 8 weeks of post-treatment follow-up. Active treatment consisted of 2 weekly administrations of esketamine, mixed in a uniform solution and inhaled in 1, 2, or 3 sprays, resulting in doses of 28 mg, 56 mg, or 84 mg. Esketamine was given in decreasing dosing intervals during the open-label phase: twice weekly for the first 2 weeks, and then weekly for 3 weeks and every other week thereafter. The primary study endpoint was change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) score.

Results: A total of 67 patients (mean age, 45 years; 38 women) were randomized in study phase 1. Of the 33 patients initially assigned to placebo, 28 continued to experience moderate to severe depressive symptoms at the end of the first phase and were re-randomized at the start of phase 2. Of the 60 patients who completed the second phase, 57 entered open-label treatment, 51 entered the follow-up phase, and 41 completed this phase.

Efficacy was significantly greater with esketamine than placebo after 1 week, and the 2 higher doses were significantly more effective than placebo after 2 weeks. (See table, next page.) Efficacy was dose related and seemed to be better sustained between treatments with the 2 higher doses. MADRS scores continued to improve during the open-label phase, with an average decrease of 7.2 additional points from the open-label baseline. Improvement was maintained over the 8-week follow-up phase without additional esketamine. Adverse effects of esketamine were similar to those reported for ketamine and included transient dissociative symptoms and blood-pressure elevations.

Mean change in MADRS scores from baseline to end of phase 1 and phase 2				
	Placebo	Esketamine, twice-weekly dose		
		28 mg	56 mg	84 mg
Phase 1 baseline MADRS score	35	31.3	33.2	35
MADRS score after week 1	30.1	21.5	20.8	19.7
Significance vs placebo	—	p=0.05	p=0.006	p<0.001
Phase 2 baseline MADRS score±	29.3	31.3	34.9	30.4
MADRS score after week 2	24.8	23.7	26	19
Significance vs placebo	—	p=ns	p=0.08	p=0.03
±Includes re-randomized placebo-treated patients, making scores higher than period 1 endpoint				

Discussion: The unusual design of this study allowed for a smaller sample size than the traditional parallel-group design and also minimized interference from a placebo response. A phase-III trial is underway. According to an editorial,[2] the results are notable not only because of the rapid, lasting effects of esketamine, but also the intranasal route of administration. This route allows patient self-administration, leading to wider general use. Bioavailability is increased, and it is possible that there is a direct nose-to-brain neural link, bypassing the blood-brain barrier. However, variations in nasal cavity physiology and poor self-administration practices may present a challenge.

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

[1]Daly E, Singh J, Fedgchin M, Cooper K, et al: Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy: a randomized clinical trial. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3739. From Janssen Research and Development, LLC, Titusville, NJ; and other institutions. **Funded by Janssen. Eight of 11 study authors disclosed financial relationships with commercial sources, including Janssen; the remaining authors declared no competing interests.**

[2]Quintana D, Steen N, Andreassen O: The promise of intranasal esketamine as a novel and effective antidepressant [editorial]. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3738. From the University of Oslo, Norway. **All 3 authors declared financial relationships with commercial sources.**

Common Drug Trade Names*: esketamine (not available in the U.S.)—*Ketanest*; ketamine—*Ketalar

***See Reference Guide.**

Samidorphan for Olanzapine-Induced Weight Gain

In a proof-of-concept study in healthy volunteers with no psychiatric disorder, adding the opioid antagonist samidorphan to olanzapine treatment had a modest effect in reducing weight gain associated with olanzapine (*Zyprexa*).

Methods: This multicenter U.S. study enrolled healthy, non-overweight men, aged 18–40 years. Study subjects were required to have stable weight for ≥3 months prior to enrollment. Participants were randomized into 4 treatment groups: 10 mg/day olanzapine plus placebo, 5 mg/day samidorphan plus placebo, both drugs, or double placebos. The primary study outcome was change in body weight after 3 weeks of study medication.

Results: A total of 106 men were randomized, and 91 (86%) completed the study. Men in both olanzapine groups gained weight, but the increase was significantly less in those who also received samidorphan: 6.8 lbs versus 4.8 lbs (p=0.02). Participants receiving samidorphan alone or placebo gained <0.25 lbs and 1.8 lbs, respectively. Following drug discontinuation, average weight of the 2 olanzapine groups began to return to previous levels. The olanzapine-only group was the only treatment group to show a statistically significant (relative to placebo) decrease from baseline in the fasting glucose-to-insulin ratio and increase in triglycerides and total cholesterol. LDL and HDL cholesterol did not differ among the 4 groups. Adverse effects observed in the trial were generally those associated with olanzapine. Samidorphan treatment

was associated with transient nausea, which is consistent with opioid antagonist treatment. However, the incidence was lower in those who received samidorphan plus olanzapine, possibly due to the antiemetic effects of olanzapine.

Discussion: While olanzapine is considered one of the most effective treatments of schizophrenia, weight gain and adverse metabolic effects limit its clinical use. Concomitant samidorphan appears to improve olanzapine tolerability, but the study is limited by the small sample of only men with no psychiatric disease. A combined formulation of samidorphan–olanzapine (ALKS-3831) is now being evaluated in phase-III clinical trials in patients with schizophrenia.

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

Silverman B, Martin W, Memisoglu A, DiPetrillo L, et al: A randomized, double-blind, placebo-controlled proof-of-concept study to evaluate samidorphan in the prevention of olanzapine-induced weight gain in healthy volunteers. *Schizophrenia Research* 2017; doi 10.1016/j.schres.2017.10.014. From Alkermes, Inc., Waltham, MA; and other institutions. **Funded by Alkermes. All study authors disclosed financial relationships with commercial sources including Alkermes.**

***See Reference Guide.**

Prenatal Safety of Methylphenidate

According to the results of a study conducted by the International Pregnancy Safety Study Consortium, methylphenidate exposure during pregnancy is associated with a small increase in risk of congenital cardiac malformations, while amphetamine exposure is not.[1]

Methods: The study was conducted in 2 populations in tandem. The primary analysis included pregnant women enrolled in Medicaid during 2000–2013. Results of this analysis were validated in a cohort of all women enrolled in the national health registries of 5 Scandinavian countries during a similar time span. A pregnancy was considered exposed if a woman filled a prescription for a stimulant—methylphenidate or amphetamine/dextroamphetamine—during the first 90 days of pregnancy, the period of embryogenesis. Pregnancy was considered unexposed if no ADHD medication prescription was filled in the 3 months before conception to the end of the first trimester. Pregnancies were excluded from the analysis if there was a fetal chromosomal abnormality or exposure to a known teratogen. Outcomes were analyzed separately for all malformations and for cardiovascular malformations. The analyses were adjusted for a broad range of known or possible risk factors, and sensitivity analyses were carried out using a propensity score* based on 200 potential confounding factors. The primary U.S. methylphenidate analysis was repeated in the Nordic cohort, but the amphetamine analysis was not because there were too few exposed pregnancies.

Results: Of >1.8 million U.S. pregnancies ending in a live birth, only about 2000 (0.11%) were exposed to methylphenidate and about 5500 (0.31%) to amphetamine. In the U.S. cohort, the fully adjusted model found no association for either category of malformation with amphetamine exposure. In contrast, for methylphenidate-exposed pregnancies, the fully adjusted relative risks* were 1.11 for any malformation and 1.28 for cardiac malformations. Propensity score adjustment had a negligible effect on these results. When specific cardiac malformations were examined, methylphenidate was associated with increased occurrence of conotruncal defects (relative risk, 3.44), but this finding was based on a small number of cases. The observations were generally confirmed in the Nordic cohort. In pooled data from the 2 cohorts, the relative risks for any malformation and a cardiac malformation with methylphenidate were 1.07 and 1.28, respectively.

Discussion: Methylphenidate was associated with a 28% increased risk of cardiac malformations; this increase corresponds to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy. ADHD

medication use is increasing in women of childbearing age, in whom a substantial portion of pregnancies are unplanned, as well as in pregnant women.[2] Although the absolute risk with methylphenidate is small, it should be considered for women who are or could become pregnant.

[1]Huybrechts K, Broms G, Christensen L, Einarsdottir K, et al: Association between methylphenidate and amphetamine use in pregnancy and risk of congenital malformations: a cohort study from the International Pregnancy Safety Study Consortium. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3644. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

[2]Cooper W: Shedding light on the risks of methylphenidate and amphetamine in pregnancy [editorial]. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3882. From Vanderbilt University School of Medicine, Nashville, TN. **The author declared no competing interests.**

Common Drug Trade Names*: amphetamine/dextroamphetamine—*Adderall, Dexedrine*; methylphenidate—*Concerta, Ritalin

***See Reference Guide.**

Cardiovascular Safety of Valbenazine

According to a pooled analysis of the manufacturer's registration trials, valbenazine (*Ingrezza*), introduced in mid-2017 for treatment of tardive dyskinesia in adults, confers minimal cardiac risk. The drug's labeling contains a single cardiovascular warning, of possible QT prolongation; although there are no explicit contraindications, it is recommended to avoid valbenazine in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. The present examination of the clinical-trial data has revealed no additional cardiovascular concerns.

Methods: The analysis was based on pooled data from 6-week phase II/III clinical trials (n=3) and a single extension study lasting up to 42 additional weeks. Study participants were patients, aged 18–85 years, with clinically stable schizophrenia, schizoaffective disorder, or mood disorder, and tardive dyskinesia of at least moderate severity. Among the studies' exclusion criteria were a history of long QT syndrome or cardiac tachyarrhythmia; QTcF (Fridericia correction) of >450 ms for men and >470 ms for women; or any clinically significant cardiac abnormality. Patients requiring concomitant medications known to prolong the QT interval were enrolled based on a medical review.

Results: The pooled safety population of the 3 trials comprised 400 patients: 178 who received placebo, 110 who received 40 or 50 mg/day valbenazine (referred to as the 40-mg/day group), and 112 who took 75 or 80 mg/day (referred to as the 80-mg/day group). At study entry, 53% of participants had a diagnosis of hypertension, and nearly 12% had a specific cardiac disorder, most commonly coronary artery disease or a prior myocardial infarction. Nearly 75% of patients were taking a concomitant medication with known potential to increase the QT interval.

The incidence of treatment-emergent cardiovascular adverse events was low and similar with valbenazine and placebo. During the 6-week double-blind trials, 5 cardiac events occurred in 1 patient each: chest pain and bradycardia with 40 mg/day valbenazine, blood pressure increase and a sudden death that may have been cardiac in nature with 80 mg/day valbenazine, and a fatal myocardial infarction in the placebo group. In the acute and extension studies, orthostatic hypotension and dizziness/falls, potentially related to hypotension, occurred in 24 valbenazine-treated patients and in 4 placebo-treated patients. None resulted in treatment discontinuation. There were no statistically significant differences in changes in vital signs between valbenazine and placebo except for a small mean increase in orthostatic diastolic blood pressure with 40 mg valbenazine.

Mean changes from baseline in ECG parameters were small and not considered clinically significant. During the double-blind trials, QTcF intervals >450 were recorded in 11 members of the placebo group, 11 receiving low-dose valbenazine, and 5 receiving the higher dose. During

the extension study, 5 patients taking valbenazine had a QTcF >480 ms, 1 had a QTcF >500 ms, and 6 had an increase of ≥60 ms.

Discussion: Although patients with significant cardiac abnormalities were excluded from the studies, the population was otherwise generally representative of a real-world population. More information on the cardiovascular effects of the drug should become available with post-marketing surveillance data and ongoing studies.

Thai-Cuarto D, O'Brien C, Jimenez R, Liang G, et al: Cardiovascular profile of valbenazine: analysis of pooled data from three randomized, double-blind, placebo-controlled trials. *Drug Safety* 2017; doi 10.1007/s40264-017-0623-1. From Neurocrine Biosciences, Inc., San Diego, CA. **Funded by Neurocrine Biosciences. All 5 study authors disclosed financial relationships with commercial sources including Neurocrine Biosciences.** See related stories in *Psychiatry Drug Alerts* 2017;31 (April):25–26 and 2017;31 (December):89–90.

Estrogen for Perimenopausal Depression

In a randomized trial, transdermal estradiol plus progesterone reduced depressive symptoms during the early stage of the menopause transition.[1]

Background: Research suggests that estrogen, with or without progesterone, could minimize estradiol fluctuation and/or withdrawal and may be effective treatment for perimenopausal depression. The present study was undertaken to determine whether estrogen treatment could prevent depressive symptoms in euthymic women during the perimenopausal or early postmenopausal periods.

Methods: Study participants were self-referred women, aged 45–60 years, who were early premenopausal or postmenopausal according to the Stages of Reproductive Aging Workshop Criteria. All women were euthymic at study entry, but one-third had a history of major depression. Active treatment consisted of 0.1 mg 17β-estradiol patches for 12 months, with 200 mg/day oral micronized progesterone taken for 12 consecutive days every 2–3 months. Women were evaluated at the end of months 1 and 2, and then at 2-month intervals until the 12th month. The primary study outcome was the development of depressive symptoms, defined as a score of ≥16 on the Center for Epidemiologic Studies–Depression scale (CES-D).

Results: A total of 172 women (mean age, 51 years) entered the trial, of whom the majority (57.5%) were in late perimenopause at study entry. During randomized treatment, 43 women (25%) had a CES-D score of ≥16 on at least 1 occasion. Women who received placebo were more likely than those who received hormone therapy to experience a score above the threshold (odds ratio,* 2.5; p=0.03). Placebo-treated women also had more follow-up evaluations with CES-D scores above the threshold than women receiving active treatment (p=0.002) and had higher mean CES-D scores (p=0.03) across the 12 months of the study.

Subgroup analysis showed that the benefits of hormone therapy were confined to women in the early perimenopause stage (p<0.001) but did not extend to those in late perimenopause or early postmenopause. Benefits were also more apparent in women who had a recent history of multiple stressful life events. Effects of hormone therapy were not modified by a history of depression or physical or sexual abuse, baseline estradiol levels, or annoyance from vasomotor symptoms at baseline. The only evident adverse effect of treatment was vaginal bleeding, as expected from the progesterone regimen.

Editorial.[2] While the present study results suggest a potential role for gonadal steroids in the regulation of mood, they must be considered preliminary in light of important limitations and do not support a change in recommendations for women in the menopausal transition. Based on the study's measure of depression, it is not possible to determine whether hormone therapy can prevent syndromal depression because the CES-D has limited sensitivity and specificity in identifying a depressive episode. In addition, the estradiol dosage used in the

study is substantially higher than recommended and the progestin dosage is lower than recommended to prevent adverse endometrial effects of exogenous estrogen. Hormone therapy is currently approved for the treatment of hot flashes and vaginal dryness. The median duration of the menopausal transition is 4 years, and risks of long-term hormone therapy—e.g., venous thromboembolic disease, cardiovascular disease, and breast cancer—should be considered before prolonged off-label use for preventing depressive symptoms or other chronic disease.

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

[1]Gordon J, Rubinow D, Eisenlohr-Moul T, Xia K, et al: Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: a randomized clinical trial. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2017;3998. From the University of Regina, Canada; and other institutions. **Funded by the NIH; and the Fonds de la Recherche du Quebec-Sante. The authors declared no competing interests.**

[2]Joffe H, Hickey M: Should hormone therapy be used to prevent depressive symptoms during the menopause transition? [editorial]. *JAMA Psychiatry* 2018; doi 10.1001/jamapsy.1007.3945. From Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and the University of Melbourne, Australia. **Funded by the National Institute on Aging and the Australian National Medical Health and Medical Research Council. One author disclosed relationships with commercial sources.**

***See Reference Guide.**

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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.

Number Needed to Treat: 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 is 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.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias, making it possible to obtain average treatment effects.

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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