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Cannabis for Negative Affect

Individuals who used cannabis to relieve negative affect reported substantial but temporary reductions in depression, anxiety, and stress, according to results of a study based on anonymous data from a medical-cannabis user app. Patients did not become habituated to the effects of repeated cannabis use, but repeated use did not lead to long-term reductions in these symptoms.

Methods: The investigators analyzed data from a free app, Strainprint, that records users' demographic data, medical conditions and symptoms, use of specific cannabis products, and symptoms immediately before and after consuming cannabis. The study was conducted in Canada, where all licensed cannabis products are analyzed for content of the 2 cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD). The sample was limited to persons who used medical cannabis to treat symptoms of depression, anxiety, or stress and to users of inhalation but not oral administration methods.

Results: The analysis was based on nearly 12,000 tracked inhalation sessions in 561 medical cannabis users who used the app to track changes in depression symptoms, 770 who tracked anxiety, and 726 who tracked changes in stress.

Participants reported that cannabis reduced depressive symptoms in 89% of tracked sessions, anxiety in 93.5% of sessions, and stress in 93% of sessions ($p < 0.001$ vs baseline for all 3 symptoms). Symptoms were increased in 2–3% of sessions. Women reported greater reductions in anxiety symptoms than men ($p < 0.001$), but there were no differences between genders in reduction of depression or stress. Effects of treatment were somewhat dependent on the cannabinoid content of products and on dosage. Products with high CBD and low THC content were associated with the largest perceived improvement in depression, and those with high content of both cannabinoids were associated with the greatest improvement in stress. Ten or more puffs of cannabis were reportedly more effective in relieving stress than a smaller number; 2 or more puffs were most effective for anxiety; and changes in depression were apparently not dose-related. Participants reported no changes in the perceived efficacy of cannabis as they continued its use. Baseline symptom ratings immediately before each inhalation session showed a significant increase in depression symptoms with time, but no change in anxiety or stress.

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Discussion: The results of this uncontrolled naturalistic study are consistent with the reported anxiolytic and stress-relieving effects of cannabis. However, some research suggests that long-term use of cannabis to relieve depression may increase susceptibility to the disorder by altering CBD receptor type 1 availability; yet other research indicates these changes can be reversed by abstaining from cannabis for about 2 days.

Cuttler C, Spradlin A, McLaughlin R: A naturalistic examination of the perceived effects of cannabis on negative affect. *Journal of Affective Disorders* 2018;235:198–205. From Washington State University, Pullman. **Funded by Washington State University. The authors declared no competing interests.**

Quetiapine and Risk of Congenital Malformations

Exposure to quetiapine (*Seroquel*) during pregnancy is associated with little, if any, excess risk of fetal malformations, according to a preliminary analysis of data from a registry of second-generation antipsychotic exposures in pregnancy.

Methods: The National Pregnancy Registry for Atypical Antipsychotics (NPRAA) was established at Massachusetts General Hospital in 2008 to collect data on the reproductive safety of all second-generation agents. Any pregnant woman with a history of psychiatric illness may enroll. Women are prospectively interviewed during pregnancy and 12 weeks after delivery. Obstetric records and first 6 months of pediatric medical records are also evaluated for women who give consent. To avoid biasing the results, pregnancies with a birth defect identified by prenatal testing at the time of enrollment are excluded from the analysis. The present analysis compared pregnancies with exposure to quetiapine during the first trimester with pregnancies without first-trimester exposure to a second-generation antipsychotic.

Results: Of 888 women enrolled in the registry, 357 with evaluable data were exposed to a second-generation antipsychotic during the first trimester, including 152 who received quetiapine. A total of 205 comparison women with evaluable data were not exposed to any second-generation antipsychotic. Exposed women had a higher prevalence of bipolar disorder than controls (68% vs 28%), the latter being more likely to suffer from depression or an anxiety disorder. Most of the women who used quetiapine during the first trimester continued to take it throughout pregnancy.

In the exposed pregnancies, there were 2 infants (1.3%) with major malformations: 1 with transposition of the great arteries and 1 with pulmonary stenosis due to dysplastic pulmonary valve. There were 3 major malformations (1.4%) in the control group. The unadjusted odds ratio* for major malformations in exposed infants was 0.90. Adjustment for potential confounding variables (e.g., demographic characteristics, psychiatric diagnoses, and use of concomitant medications and illicit substances) did not change the results of the analysis.

Discussion: Available reproductive safety data do not suggest second-generation antipsychotics as a class are major teratogens. However, risk estimates based on existing studies are imprecise due to small sample sizes. Quetiapine is among the most commonly prescribed atypical antipsychotics in publicly insured pregnant women and is used primarily for the management of bipolar disorder. The risk of malformations in the present study is consistent with a pooled risk estimate derived from controlled trials, indicating no increased risk. The sample size in the registry is relatively large in comparison to these studies, and the risk estimates will become more precise as NPRAA data accumulate.

Cohen L, Góez-Mogollón L, Sosinsky A, Savella G, et al: Risk of major malformations in infants following first-trimester exposure to quetiapine. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.18010098. From Massachusetts General Hospital, Boston; and other institutions. **Funded by Alkermes, Forest/Actavis, Otsuka, Sunovion, and Teva. Four of 8 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

*See Reference Guide.

Brexanolone for Postpartum Depression

Intravenous brexanolone had rapid antidepressant effects in women with postpartum depression, according to a combined analysis of 2 phase III clinical trials. Brexanolone is a proprietary formulation of allopregnanolone, an endogenous progesterone metabolite that modulates GABA_A receptors. Perinatal fluctuations in this hormone have been implicated in the pathophysiology of postpartum depression.

Methods: The 2 studies enrolled women, aged 18–45 years, who were ≤6 months postpartum and experiencing depression with onset in the peripartum period. A baseline score on the 17-item Hamilton Rating Scale for Depression (HAM-D) of ≥26 was required for 1 study, and scores of 20–25 were required for the second. Participating women had stopped lactating or temporarily suspended breastfeeding while receiving study medication. Concomitant psychotropic medication was permitted. Women were randomly assigned to receive a single, 60-hour infusion of 90 µg/kg brexanolone per hour, 60 µg/kg brexanolone per hour (in 1 study only), or placebo. Patients received treatment in a medically supervised setting for the 60 hours of infusion and remained for an additional 12 hours for assessments. The primary efficacy outcome of both studies was change from baseline to 60 hours (end of infusion) in HAM-D score, which was administered throughout treatment and again at days 7 and 30 of follow-up.

Results: A total of 138 women participated in the first study, and 108 in the second. Across the studies, 13% of women did not complete the protocol, most because they did not begin the infusion or were lost to follow-up.

In the first study, HAM-D total scores were significantly reduced with brexanolone relative to placebo at 24 hours and all subsequent time points, including the primary 60-hour time point. (See table.) In the second study, HAM-D scores were significantly lower with brexanolone than placebo from 48 hours until day 7. HAM-D remission (score ≤7) occurred at 60 hours in 51% of the 60-µg brexanolone group and 16% of the placebo group (odds ratio, * 6.0; p=0.0011); the remission rate for 90-µg brexanolone was not reported. In the second study, 61% of patients in the brexanolone group had remission at 60 hours, compared with 38% of the placebo group (odds ratio, 3.4; p=0.0033). Across both studies, dosages, and other efficacy endpoints, brexanolone was generally statistically superior to placebo at multiple time points, extending to 30 days. A total of 22% of women were receiving concomitant psychotropic medication; results were comparable in women who were and were not receiving other drugs.

Brexanolone infusion was generally well tolerated, with dizziness and somnolence the most common adverse events. Five patients experienced

Change from baseline to 60 hours in mean HAM-D scores				
	Mean Baseline Score	Mean change from baseline	Least squares mean* difference from placebo	Significance
Study 1				
placebo	28.6	-14	—	—
brexanolone 60 µg/hr	29.1	-19.5	-5.5	p=0.0013
brexanolone 90 µg/hr	28.4	-17.7	-3.7	p=0.0252
Study 2				
placebo	22.7	-12.1	—	—
brexanolone 60 µg/hr	22.6	-14.6	-2.5	p=0.016

excessive sedation due to brexanolone, which stopped shortly after the infusion was halted.

Meltzer-Brody S, Colquhoun H, Riesenbergr R, Epperson C, et al: Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet* 2018; doi 10.1016/S0140-6736(18)31551-4. From the University of North Carolina School of Medicine, Chapel Hill; and other institutions including Sage Therapeutics, Cambridge, MA. **Funded by Sage Therapeutics. Of 12 study authors, 11 declared relevant financial relationships; the remaining author declared no competing interests.** See related stories in *Psychiatry Drug Alerts* 2017;31 (May):36–37 and 2017;31 (July):51–52.

*See Reference Guide.

Prazosin for Alcohol Use Disorder

In a placebo-controlled trial of patients with alcohol dependence, prazosin (*Minipress*) was associated with reductions in drinking, but not with abstinence. This finding suggests prazosin may be most useful in reducing heavy drinking as part of a harm-reduction approach.

Methods: The study enrolled individuals with a DSM-IV diagnosis of alcohol dependence and a goal of abstaining from alcohol. Minimum required baseline alcohol consumption was ≥ 14 drinks per week for women and ≥ 21 drinks per week for men. The trial excluded subjects with PTSD to isolate the effects of prazosin, which has been shown to reduce PTSD symptoms, on alcohol use. Patients were randomly assigned to receive 12 weeks of double-blind treatment with either prazosin or placebo. Prazosin was titrated over 2 weeks to a target dosage of 4 mg in the morning, 4 mg in the afternoon, and 8 mg at bedtime. In addition to study medication, all patients received weekly brief medication-management counseling and were encouraged to attend self-help meetings. Primary study outcomes were the number of drinks per week, number of drinking days per week, and number of heavy drinking days per week. Patients reported their alcohol consumption, cravings, and medication adherence in a daily telephone call with automated prompts.

Results: Of 92 patients (19 women) enrolled, 8 in the prazosin group and 4 in the placebo group dropped out during the 2 weeks of titration and were not included in the efficacy analysis. Of 80 patients who completed titration, 35 in each group received the target drug dose; 26 prazosin-treated patients and 30 receiving placebo completed all 12 weeks of treatment.

Over the 90 days before randomization, participants consumed an average of 9 drinks per day. In the final week of treatment, average drinks per day were about 2 in both the prazosin and placebo groups. The number of drinks per week, drinking days per week, and heavy drinking days per week were reduced in both treatment groups. However, the effects of prazosin were significantly greater in terms of number of drinks per week and heavy drinking days. (See table.) The groups did not differ in changes in alcohol craving over time. The primary adverse effects of prazosin were drowsiness and edema.

Effects of Treatment on Drinking Outcomes					
	Prazosin		Placebo		Significance of between-group difference in improvement
	Week 3	Week 12	Week 3	Week 12	
Drinks per week	21.3	13.3	14.6	13.1	p=0.03
Drinking days per week	3.2	2.8	2.8	2.3	p=ns
Heavy drinking days per week	1.8	1	1.5	1.2	p=0.01

Discussion: The present results indicate prazosin may be useful in reducing heavy drinking associated with negative consequences, rather than by promoting full abstinence. Similar moderate effects have been observed with other drugs for alcohol use disorder, including FDA-approved medications; the authors suggest that combining drugs with different mechanisms may be a useful approach.

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

Simpson T, Saxon A, Stappenbeck C, Malte C, et al: Double-blind randomized clinical trial of prazosin for alcohol use disorder. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.17080913. From the VA Puget Sound Health Care System, Seattle, WA; and other institutions. **Funded by the National Institute on Alcohol Abuse and Alcoholism. Two of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Bleeding Risk with Antidepressants

Serotonergic antidepressants are associated with increased risk of bleeding, especially early in the course of treatment, according to a nonsystematic literature review. Clinicians should be aware of options when prescribing for high-risk patients, including antidepressants with low potential to induce bleeding and strategies for preventing gastrointestinal (GI) bleeding.

SRI-related bleeding is believed to be the result of inhibition of the serotonin transporter on platelets, leading to reduced platelet aggregation. SRIs also increase gastric acidity, which can predispose to GI bleeding. SRIs with high serotonin transporter binding affinity may place patients at higher bleeding risk than agents with intermediate or low affinity. (See table.) Cytochrome P450-mediated drug interactions further contribute to bleeding risk with SSRIs, particularly duloxetine, fluoxetine, fluvoxamine, and paroxetine.

A literature search identified 9 meta-analyses of SRI-related bleeding and 1 meta-analysis of bleeding risk with bupropion and mirtazapine. SRIs have been associated with GI bleeding,

intracranial hemorrhage, postpartum hemorrhage, and perioperative bleeding. Most of the studies have focused on GI bleeding, which makes it difficult to assess the risk at other sites. In 1 meta-analysis encompassing nearly 1.5 million patients, SSRIs increased bleeding risk by 41% (odds ratio,* 1.41; $p < 0.001$). Risk was especially high for GI bleeding (odds ratio, 1.55) and lower for intracranial hemorrhage (odds ratio, 1.16). However, in another analysis, SSRIs were associated with elevated risk of brain hemorrhage (odds ratio, 1.61). Women who take antidepressants during pregnancy have an increased risk of postpartum hemorrhage (odds ratio, 1.32; $p < 0.001$). It has been difficult to estimate risk of perioperative bleeding because of the use of other medications that affect coagulation. Concomitant medications can add to the risk of bleeding in patients taking SRIs. Increased risk has been documented in patients taking NSAIDs, antiplatelet therapy, and anticoagulants.

Serotonin transporter binding affinity		
High	Intermediate	Low
Clomipramine	Amitriptyline	Bupropion
Duloxetine	Citalopram	Doxepin
Fluoxetine	Escitalopram	Mirtazapine
Paroxetine	Imipramine	Nortriptyline
Sertraline	Venlafaxine	Phenelzine
Vilazodone		Tranlycypromine
Vortioxetine		Trazodone

Some evidence suggests that acid-suppressing agents decrease risk of GI bleeding in patients taking SRIs with NSAIDs. Proton pump inhibitors have not been investigated directly, but subgroup analyses in some studies suggest they may reduce bleeding risk. However, depression is a potential adverse effect of proton pump inhibitor use in the elderly.

Clinicians should consider preventive strategies for GI bleeding in high-risk patients and the elderly. Agents with low serotonin transporter binding affinity or bupropion, which has a mechanism independent of serotonin, may be prudent choices in patients with bleeding risk.

Bixby A, VandenBerg A, Bostwick J: Clinical Management of bleeding risk with antidepressants. *Annals of Pharmacotherapy* 2018; doi 10.1177/1060028018794005. From Michigan Medicine and the University of Michigan College of Pharmacy, Ann Arbor. **This review was not funded. The authors declared no competing interests.**

Common Drug Trade Names: amitriptyline—*Elavil*; bupropion—*Wellbutrin*; citalopram—*Celexa*; clomipramine—*Anafranil*; doxepin—*Silenor*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; imipramine—*Tofranil*; mirtazapine—*Remeron*; nortriptyline—*Pamelor*; paroxetine—*Paxil*; phenelzine—*Nardil*; sertraline—*Zoloft*; tranlycypromine—*Parnate*; trazodone—*Oleptro*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Trintellix*

*See Reference Guide.

Lurasidone and Sexual Function in Mixed Depression

A secondary analysis of data from a clinical trial suggests lurasidone (*Latuda*) is not associated with sexual dysfunction in patients with major depressive disorder and subthreshold hypomanic features.¹

Background: Impaired sexual function is common in patients with major depressive disorder and treatment initiation, particularly with SSRIs and/or atypical antipsychotics, which can exacerbate dysfunction. Lurasidone has a receptor binding profile that suggests low risk for sexual side effects and shares some similarities (e.g., 5-HT_{2A} antagonism and partial agonist effects on 5-HT_{1A}) with medications used to treat sexual dysfunction.

Methods: The analysis was based on a multicenter, placebo-controlled, 6-week clinical trial of flexibly dosed 20–60 mg/day lurasidone.² Participants met DSM-IV criteria for major depressive disorder and had 2 or 3 manic or hypomanic symptoms. (The maximum was set at 3 to reduce the likelihood of including patients with undiagnosed bipolar disorder.) Sexual function, a safety outcome of the study, was measured with the 14-item Changes in Sexual Functioning Questionnaire (CSFQ-14), which has separate versions for men and women. The CSFQ-14 has 5 subscales that assess pleasure, desire/frequency, desire/interest, arousal/excitement, and orgasm/completion. The questionnaire is scored from 14 to 70, with higher scores indicating better function and thresholds for sexual dysfunction of ≤ 47 in men and ≤ 41 in women. An improvement of 3 points is considered to be clinically meaningful.

Results: The study met its primary efficacy outcome, demonstrating superior antidepressant efficacy to placebo. The safety analysis included a total of 206 patients who had a CSFQ-14 assessment at baseline and received ≥ 1 dose of study medication. A high proportion of patients—84.5% of women and 81% of men—initially met CSFQ-14 criteria for sexual dysfunction. Baseline severity of sexual dysfunction was not correlated with depression severity.

At 6 weeks, the mean CSFQ-14 score improved by 5.1 points in patients receiving lurasidone, compared with 3.1 points in the placebo group ($p=0.046$). Men and women had similar improvements in sexual function relative to placebo (effect sizes,* 0.22 in women and 0.33 in men). Lurasidone was associated with numerically greater improvement than placebo on all 5 CSFQ-14 subscales in men and on 4 in women (with no treatment effect seen in desire/frequency in women). Effects on sexual function were not dose-related and did not vary by patient age or the presence or absence of sexual dysfunction at baseline. Mediation analysis showed that improvements in sexual function were largely due to improvement in depression. There were no adverse events related to sexual function in the lurasidone group. Relative to placebo, lurasidone was associated with a mean 2.5 ng/mL increase in prolactin in women and a negligible decrease in men.

Discussion: In addition to having a low risk for inducing sexual dysfunction, these study results suggest that treatment with lurasidone may improve existing dysfunction in patients with mixed depression, but the change is likely due to reductions in depressive symptoms.

¹Clayton A, Tsai J, Mao Y, Pikalov A, et al: Effect of lurasidone on sexual function in major depressive disorder patients with subthreshold hypomanic symptoms (mixed features): results from a placebo-controlled trial. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.18m12132. From the University of Virginia, Charlottesville; and Sunovion Pharmaceuticals, Inc., Marlborough, MA, and Fort Lee, NJ. **Funded by Sunovion. All 5 study authors disclosed potentially relevant financial relationships; 4 of the 5 were employed by Sunovion.**

²Suppes T, et al: Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo-controlled study. *American Journal of Psychiatry* 2016;173(4):400–407.

*See Reference Guide.

Tianeptine for Geriatric Depression

Tianeptine, an antidepressant with a unique mechanism of action, was effective in a controlled trial in elderly patients with recurrent depression.¹ Unlike most other antidepressants, tianeptine, which is not marketed in the U.S., is not metabolized by the hepatic cytochrome P450 system and has little liability for drug interactions.

Background: There have been few controlled trials of antidepressants in the elderly; instead, treatment guidelines are largely based on expert opinion. The efficacy of second-generation antidepressants in older individuals is modest. In addition, tolerability is often problematic in older patients. Tianeptine has a distinctive mechanism of antidepressant action: It modulates monoaminergic neurotransmission; counteracts the effects of stress on glutamatergic neurotransmission and limbic neuroplasticity; decreases stress-related hypothalamic-pituitary-adrenal axis overactivity; and has antiinflammatory properties.

Methods: Study participants were aged ≥ 65 years and experiencing a moderate-to-severe episode of recurrent unipolar major depression. Patients whose depression had not responded to ≥ 2 prior antidepressants (from different classes) were excluded from the trial. Participants were randomly assigned to 8 weeks of double-blind treatment with 25–50 mg/day tianeptine, 10 mg/day escitalopram as an active control, or placebo. The primary study outcome was change from baseline on the 17-item Hamilton Rating Scale for Depression (HAM-D).

Results: A total of 311 patients were enrolled in the study, and 309 were included in the efficacy and safety analyses. Patients had a mean age of 70 years, and more than one-third had severe depression. About 11% withdrew from study treatment, including 4% of patients in the tianeptine group and 6% of those in the escitalopram and placebo groups who withdrew because of adverse events.

Both tianeptine and escitalopram were associated with a larger mean decrease in depressive symptoms than placebo. (See table). The response rates were also larger with both active treatments than with placebo, although the difference for tianeptine was not statistically significant ($p=0.06$ for tianeptine; $p=0.002$ for escitalopram). Clinical Global Impression Severity and Improvement ratings also showed a statistically significant treatment effect for both active agents ($p<0.001$ for both). With both active medications, patients reported significantly greater improvement in social and family life (measured with the Sheehan Disability Scale), but work and total scores did not differ statistically from placebo.

Select Outcomes of Tianeptine, Escitalopram, and Placebo at 8 Weeks			
HAM-D Total Score	Tianeptine (n=105)	Escitalopram (n=106)	Placebo (n=98)
Baseline	26.7	26.7	26.6
Endpoint	13.3	13.1	17.1
Significance vs Placebo	$p<0.001$	$p<0.001$	—
HAM-D Response ($\geq 50\%$ decrease)	47%	55%	34%

Rates of medication-related adverse events, mostly mild, were 23% for tianeptine, 41% for escitalopram, and 21% for placebo. The most common adverse events were similar in all 3 groups: headache, nausea, flatulence, fatigue, and dizziness. Adverse events led to treatment discontinuation in 4 patients in the tianeptine group, 6 in the escitalopram group, and 6 in the placebo group.

Editor's Note: Tianeptine is marketed in some European, Asian, and Latin American countries for treatment of depression and anxiety.² Although it is not approved in the U.S., it can be obtained online as a dietary supplement or research chemical. The drug acts upon opioid receptors in the brain, and there are indications that people are using it as an alternative to narcotics. At a standard dose, tianeptine does not produce a "high", but excessively high doses (e.g., up to a gram/day) can lead to euphoria and a high, and repeated use can lead to addiction and opiate withdrawal.³

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

¹Emsley R, Ahokas A, Suarez A, Marinescu D, et al: Efficacy of tianeptine 25–50 mg in elderly patients with recurrent major depressive disorder: an 8-week placebo- and escitalopram-controlled study. *Journal of Clinical Psychiatry* 2018; doi: 10.4088/JCP.17m11741. From the University of Stellenbosch, South Africa; and other institutions. **Funded by Servier, Suresnes, France. Five of 15 study authors disclosed financial relationships with commercial sources, including Servier; the remaining authors declared no competing interests.**

²Opioid addicts turning to unapproved antidepressant. WebMD: available at <https://www.webmd.com/mental-health/addiction/news/20180802/opioid-addicts-turning-to-unapproved-antidepressant#1>.

³Ehrenfeld T: The Controversy Over the Antidepressant Tianeptine. Healthline: available at <https://www.healthline.com/health-news/controversy-over-antidepressant-tianeptine#1>.

Common Drug Trade Names: escitalopram—*Lexapro*; tianeptine (not available in the U.S.)—*Coaxil, Stablon*

*See Reference Guide.

Reference Guide

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.

Least Squares Mean: An average estimated from a linear model. In contrast to an arithmetic mean, which is a simple average of the values, least squares means are adjusted for other terms in the model and are less sensitive to missing data.

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.

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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