PSYCHIATRY DRUG ALERTS

Volume XXXII / October 2018 / Number 10 www.alertpubs.com

Important Reminder . . . Delivery of *Psychiatry Drug Alerts* is now 100% electronic.

Transdermal Nicotine in Late-Life Depression

In a preliminary study, open-label nicotine patches resulted in a robust and rapid antidepressant response in nonsmokers with late-life depression. Transdermal nicotine also produced some cognitive benefits.

Background: Smoking rates are increased in individuals with depression, which may reflect self-medication. In a few small trials, transdermal nicotine was effective in midlife depression and it has been shown to have cognitive benefits. There is currently no approved medication that alleviates both mood and cognitive symptoms of late-life depression.

Methods: Study participants (n=15; 10 women) were aged ≥60 years and met DSM-IV-TR criteria for major depressive disorder, recurrent or single episode, with a baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥15. Participants were also required to have some degree of cognitive decline, with Montreal Cognitive Assessment scores of ≥24 and subjective decline, defined as endorsing ≥20% of items on the Cognitive Complaint Index. Participants were required to be nonsmokers for at least the past year and could be either antidepressant free or currently on stable antidepressant monotherapy.

All participants received treatment with open-label transdermal nicotine, escalated as tolerated to a target dosage of 21 mg/day. The primary efficacy outcome for mood was change from baseline to 12 weeks in MADRS score, and the primary cognitive outcome was change on the Conners Continuous Performance Test (CPT), a test of attention. Patients were also evaluated using standardized measures for: secondary symptoms of anhedonia, anxiety, apathy, fatigue, and rumination; self-referential negativity bias; subjective cognitive performance; as well as attention, executive function, episodic memory, working memory, and processing speed.

Results: Of the 15 patients who started the study, 14 completed all 12 weeks of patch use. The mean final daily dose was 15 mg. Most patients had early-onset depression, with an average onset age of 26 years, 5 were past smokers, and 6 were antidepressant free.

The mean MADRS score decreased by 18 points from a baseline of 28 (p=0.004). Statistically significant change from baseline was evident beginning at week 3. A total of 13 patients (87%)

PSYCHIATRY DRUG ALERTS (ISSN 0894-4873) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psych@alertpubs.com.

Online subscription $105 a year in the U.S.; $113.50 Canada; $123.50 elsewhere; $157 institutional. Individual issues are available for $10.00 each. Subscribers may enroll in the 12-month CME program for an additional $83.00 per year, or enroll in the comprehensive, annual Self-Assessment program for $270 (in the U.S.). M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

met response criteria (≥50% decrease in MADRS score), and 8 patients (53%) achieved remission (MADRS score ≤8). Changes in depression were not associated with nicotine dose, smoking history, or antidepressant use. Study participants also showed significant decreases in apathy and rumination.

Although there were no statistically significant changes in cognitive performance on the CPT, patients reported some improvement in subjective cognitive performance. Improvements in objectively measured working memory and immediate recall were significant (p=0.049). Measures of self-referential negativity bias were also significantly improved (p=0.046). Cognitive improvement was correlated with change in the MADRS, suggesting that cognitive effects may be dependent on the antidepressant effects of nicotine.

Discussion: Observations in the present study are consistent with results in younger patients. However, the results require replication, and future studies would benefit from measures of plasma nicotine levels to assess bioavailability.

Gandelman J, Kang H, Antal A, Albert K, et al: Transdermal nicotine for the treatment of mood and cognitive symptoms in nonsmokers with late-life depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.18m12137. From Vanderbilt University School of Medicine, Nashville, TN; and other institutions. **Funded by the NIH; and the National Center for Advancing Translational Sciences. The authors declared no competing interests.**

Psychiatric Adverse Effects of Oseltamivir

Prophylactic use of oseltamivir (*Tamiflu*) is associated with a small but statistically significant increase in psychiatric adverse events, according to an analysis of adverse-event data from clinical study reports.[1]

Background: Following the reports of 2 suicides in adolescents who received treatment with oseltamivir, as well as >100 reports of neuropsychiatric adverse effects with the drug, the FDA issued an alert in 2006 warning that patients should be carefully monitored for abnormal behavior during treatment.[2] Analyses of neuropsychiatric adverse effects conducted since then, including several Cochrane Reviews based on published trials, have been inconclusive. Clinical study reports—produced by manufacturers seeking regulatory approval of drugs and containing individual patient-level data on adverse events with a high level of detail, including duration and severity—have recently been made available to researchers by the European Medicines Agency and by some manufacturers. To further clarify the risk of neuropsychiatric effects with prophylactic oseltamivir use, the present study evaluated adverse events in clinical study reports.

Methods: The present analysis was based on clinical study reports from 4 placebo-controlled trials of oseltamivir. The analysis was limited to prophylactic trials to avoid counting any psychiatric symptoms related to existing influenza. Data on clinical adverse events classified under the psychiatric system organ class, representing a change from baseline that occurred after study treatment began, were collected from the reports irrespective of whether study investigators believed it was related to oseltamivir treatment. The primary outcome of the analysis was the proportion of days patients suffered from psychiatric adverse events. This method allowed grouping of multiple adverse events, regardless of their nature—e.g., days suffering from depression and from anxiety by a single patient could be combined. In a secondary analysis, adverse events were weighted based on severity.

Results: The main analysis was based on combined data from 1 trial conducted in adults (n=1559) and 2 trials in elderly nursing-home residents (n=920), all of whom received oseltamivir or placebo for 6 weeks. An additional short-term trial was conducted in adults and adolescents (n=955) who received treatment for 7 days. Psychiatric adverse events were not reported in the journal publications from any of the trials.

A total of 35 psychiatric adverse events (10 of depression) occurred with oseltamivir and 15 with placebo. Excluding the 7-day trial, which reported very few events, the proportion of days patients suffered from a psychiatric adverse event was significantly greater with oseltamivir than placebo (odds ratio,* 4.12). There was little difference between oseltamivir and placebo for less severe adverse events, but severe events occurred on more days with oseltamivir (odds ratio, 34.5). However, the absolute difference between oseltamivir and placebo was small: For every 290 days of treatment, there was 1 additional day of suffering from a psychiatric adverse event of any level of severity.

Discussion: The increasing chance of more severe adverse events with oseltamivir suggests a causal relationship. Although the relative effect of oseltamivir is very high for severe events, the absolute increase is small in the context of all patients included in the trials.

[1]Jones M, Tett S, Del Mar C: Psychiatric adverse events in oseltamivir prophylaxis trials: novel comparative analysis using data obtained from clinical study reports. *Pharmacoepidemiology and Drug Safety* 2018; doi 10.1002/pds.4651. From the University of Queensland, Brisbane; and Bond University, Gold Coast, Australia. **This research was conducted without specific funding. All 3 authors disclosed potentially relevant financial relationships.**

[2]Maxwell S: Tamiflu and neuropsychiatric disturbance in adolescents: the case is not proved but caution is advisable. *British Medical Journal* 2007;334 (June 16):1232–1233.

***See Reference Guide.**

Minocycline in Schizophrenia

The antibiotic minocycline (*Minocin*) has antiinflammatory and neuroprotective actions that have attracted attention as potential treatments for several psychiatric disorders, including schizophrenia. Several case reports, open-label studies, and small controlled trials have suggested the agent is beneficial, particularly for negative symptoms. However, in the largest randomized controlled trial to date, adjunctive minocycline, given for 1 year, did not produce added improvement in symptoms, functional status, or inflammatory markers in patients with recent-onset psychosis.

Methods: The BeneMin study enrolled >200 patients from centers in the U.K. Participants were experiencing a first episode of schizophrenia, schizophreniform disorder, or schizoaffective psychosis; were within 5 years of symptom onset; and were receiving stable antipsychotic medication. Study treatment consisted of 300 mg/day minocycline or placebo added to background antipsychotic medication. The primary study outcome was overall severity of negative symptoms, measured using the Positive and Negative Syndrome Scale (PANSS) at months 2, 6, 9, and 12. Imaging and inflammatory markers were also evaluated to explore the potential neuroprotective and antiinflammatory mechanisms of treatment.

Results: A total of 207 patients were randomly assigned to active treatment or placebo. Before completing 1 year of treatment, 38% of patients had withdrawn from the study. Dropout rates were similar in the minocycline and placebo groups.

Mean scores for positive, negative, and depression symptoms improved in both the minocycline and placebo groups. At no point was there a statistically significant difference between the minocycline and placebo groups in PANSS negative symptoms. Treatment did not influence measures of function or cognitive performance and had no effect on the biomarker outcomes of medial prefrontal gray matter volume, circulating IL-6, and functional MRI tests of the dorsolateral prefrontal cortex. Adverse events were similar in the minocycline and placebo groups. There were 15 hospital admissions in the minocycline group and 10 in the placebo group, all for worsening of psychosis, primarily due to discontinuing antipsychotic medication.

Discussion: These results differ from several earlier studies with smaller sample sizes. The present study is the largest to date, and the lack of symptomatic or functional improvement,

taken with the lack of evidence supporting persistent neurodegeneration or systemic inflammation that minocycline could target, suggest that additional studies may not be warranted.

Deakin B, Suckling J, Barnes T, Byrne K, et al: The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomised, double-blind, placebo-controlled trial. *Lancet Psychiatry* 2018; doi 10.1016/S2215-0366(18)30345-6. From the University of Manchester, U.K; and other institutions. **Funded by the Medical Research Council; and other sources. Eight of 23 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Single-Dose IV Ketamine: Optimal Dosage

Most placebo-controlled clinical trials of IV ketamine for depression have used a uniform single dose of 0.5 mg/kg infused over 40 minutes. According to a dose-ranging trial, the antidepressant efficacy of ketamine is dose related, with significantly greater efficacy of 0.5 mg/kg and 1.0 mg/kg relative to lower doses and to placebo.

Methods: The trial enrolled 99 adults (aged 18–70 years; 49 women) with treatment-resistant depression, defined as an inadequate response to ≥2 medications in the current episode. Patients with a primary Axis I disorder other than MDD, substance use disorder (abuse or dependence), with the exception of nicotine, and those with a history of bipolar disorder, schizophrenia, schizoaffective disorder, or psychotic symptoms were excluded. Patients were randomly assigned to double-blind ketamine doses of 0.1, 0.2, 0.5, and 1.0 mg/kg or to an active placebo (0.045 mg/kg midazolam [*Versed*]). The purpose of the active placebo was to reduce the risk of unblinding due to absence of adverse events. Patients also received optimized, stable doses of their current antidepressant. The primary efficacy outcome was change from baseline on the 6-item Hamilton Rating Scale for Depression (HAM-D-6), which was administered at baseline and on days 1, 3, and 5, and at weeks 1, 2, and 4.

Results: The study retention rate was high, with 95% of participants completing the day 3 evaluation and 87% evaluated 4 weeks post treatment. Patients had experienced inadequate response to an average of 2–3 prior antidepressants and had mean baseline scores of 12–13 on the HAM-D-6.

In a combined analysis of all ketamine doses versus placebo, active treatment was associated with a significantly greater 3.25-point reduction than placebo in HAM-D-6 score on day 1 (p=0.01; effect size,* 0.86). At day 3, active treatment remained marginally superior but was no longer significant (p=0.11; effect size, 0.44). When individual ketamine doses were compared with placebo, only the 0.5 and 1.0 mg/kg doses were statistically superior, and only on day 1. (See table.)

Antidepressant effects of ketamine versus placebo: change from baseline in HAM-D-6

	Difference from placebo	Adjusted significance†	Effect size
0.5 mg/kg	-4.79	p<0.01	1.21
1.0 mg/kg	-3.76	p=0.04	0.95

†Adjusted for multiple comparisons

Secondary study outcomes included a number of alternative measures of depression. There were medium-to-large, but statistically nonsignificant, effects of ketamine on all secondary outcomes at all but the 0.1-mg/kg ketamine dose. Effects tended to be larger on day 1 than day 3. Rates of response (≥50% improvement in the HAM-D-6) to ketamine were highest on day 1 and statistically superior to placebo on that day only. On day 1, response rates were 31% for 0.1 mg/kg ketamine, 21% for 0.2 mg/kg, 59% for 0.5 mg/kg, 53% for 1.0 mg/kg, and 11% for

midazolam. HAM-D-6 scores tended to remain lower with ketamine than placebo throughout the 30-day observation period.

Adverse effects of ketamine consisted of dissociation and transient blood-pressure alterations. Dissociation was more common at the 2 higher doses of ketamine than at lower doses.

Discussion: These observations suggest ketamine may have antidepressant effects throughout its dose range, although with greater effect at higher doses. It remains to be determined whether increasing the dose in patients who respond poorly to the standard 0.5-mg/kg dose is helpful and tolerated, or whether the dose can be reduced in those who cannot tolerate 0.5 mg/kg.

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

Fava M, Freeman M, Flynn M, Judge H, et al: Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Molecular Psychiatry* 2018; doi 10.1038/s41380-018-0256-5. From Massachusetts General Hospital, Boston; and other institutions. **Funded by the NIMH. Of 18 study authors, 14 disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Repeated Oral Ketamine for Resistant Depression

In a preliminary, placebo-controlled trial, repeated oral administration of ketamine was effective in patients with resistant depression. Oral at-home administration has been well described in patients with chronic pain and may be a promising alternative to IV ketamine in depression.

Methods: Study participants were adults, aged ≤75 years, with a diagnosis of major depressive disorder, a score of ≥19 on the Montgomery-Asberg Depression Rating Scale (MADRS), and inadequate response to ≥2 antidepressants. Patients with a psychotic disorder or psychotic symptoms, bipolar disorder, alcohol or substance misuse, unstable medical illness ,or any contraindication to ketamine were excluded. In addition to stable background antidepressant therapy, patients received double-blind, randomized treatment with either 1 mg/kg oral ketamine in solution or a liquid placebo. Both were administered orally, by syringe, 3 times/week for 3 weeks. Study medication was first administered in the clinic under observation. Patients were given subsequent doses, no more than 2 at a time, to take at home. The primary study outcome was change from baseline to day 21 in MADRS score. A follow-up evaluation was completed on day 28.

Results: A total of 40 patients (mean age, 38 years; 15 women) participated in the study, and 33 completed treatment. Two patients stopped ketamine and 1 stopped placebo due to lack of an effect; 1 stopped ketamine because of drowsiness; and 2 in the placebo group were withdrawn due to onset of suicidal ideation.

Baseline MADRS scores were 33 and 30 in the ketamine and placebo groups, respectively. Ketamine was associated with a significant decrease in the MADRS at all post-baseline time points. At day 21, ketamine was associated with significantly greater improvement in mean MADRS score than placebo and with higher rates of response (i.e., MADRS decrease of >50%) and remission (MADRS score of ≤10). (See table). The numbers needed to treat* with ketamine

Effects of repeated oral ketamine or placebo in treatment-resistant depression

Outcome	Ketamine (n=22)	Placebo (n=18)	Significance
MADRS: Mean Score Reduction	12.75	2.49	p<0.001
Achieved Response	7 (32%)	1 (5.6%)	p<0.05
Achieved Remission	6 (27.3%)	0	p<0.05

for response and remission were 3.8 and 3.7, respectively. At the 28-day follow-up evaluation, treatment effects were maintained and no rebound effects were evident.

Oral ketamine was well tolerated. Six patients experienced transient increases in blood pressure during ketamine treatment. Other transient adverse effects of ketamine included euphoria (n=4), dizziness (n=4), and drowsiness (n=2).

Discussion: Oral administration of ketamine has rarely been reported for depression but is well recognized as an at-home treatment to manage chronic pain. The dosage used in this study was extrapolated from IV dosage, based on the known low oral bioavailability of ketamine. Among the questions still to be resolved are the optimal dosage and treatment duration, safety of long-term use, and the risk of misuse.

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

Domany Y, Bleich-Cohen M, Tarrasch R, Meidan R, et al: Repeated oral ketamine for out-patient treatment of resistant depression: randomised, double-blind, placebo-controlled, proof-of-concept study. *British Journal of Psychiatry* 2018; doi 10.1192/bjp. 2018.196. From Tel Aviv University, Israel; and other institutions. **Funded by the Tel Aviv Medical Center Brain Grant; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Residual Suicidal Ideation After CBT vs Medication

Individuals whose depression responds to antidepressant drugs or cognitive behavioral therapy have similar profiles of residual symptoms, according to a randomized comparison study. Those whose symptoms do not fully respond to medication still have significant reductions in suicidal thoughts.

Methods: The study was conducted to investigate the possibility that medications and CBT, which have different mechanisms of antidepressant action, may also have different trajectories of response for specific symptoms. Participants, treatment-naive adults with nonpsychotic major depressive disorder, were randomly assigned to 12 weeks of 30–60 mg/day duloxetine, 10–20 mg/day escitalopram, or CBT (16 1-hour individual sessions). Response was defined as a ≥50% reduction in the 17-item Hamilton Rating Scale for Depression (HAM-D) score, and remission as a final score of ≤7. Nonremitters were offered an additional 12 weeks of combined CBT and medication. For the present analysis, residual symptom profiles were assessed after the initial monotherapy phase using the Montgomery-Asberg Depression Rating Scale (MADRS), which rates 10 symptoms on a 6-point scale. Symptoms were considered persistent if they were scored as ≥2 at week 12.

Results: Of 315 patients who entered the study, 250 completed the first phase and were included in the analysis. A total of 166 patients were considered treatment responders: 123 (69%) of those who received medication and 43 (59%) of those who received CBT. Among responders, the 2 treatments did not differ in the mean number of residual symptoms at week 12: 2.02 for the CBT group and 2.22 for the combined medications group. Among patients who did not meet response criteria, the mean number of residual symptoms was 6.93 for CBT and 6.35 for medication.

In the group of patients who achieved response, the MADRS item with the most significant improvement was suicidal thoughts, which decreased by a mean of >95% in both treatment groups. However, among nonresponders, suicidal thoughts were less frequent in the medication group than the CBT group (0 of 54 patients vs 8 of 30 patients; p=0.001). CBT nonresponders showed a 15% decrease in suicidal thoughts, and medication nonresponders a 70% reduction. Patients in the CBT group were significantly more likely than those who received medication to experience a ≥2-point increase in scores for suicidal thoughts (p=0.007), with new onset in

3 CBT patients and worsening in 1. The frequencies of several other residual symptoms differed between treatment groups, but these differences did not survive statistical correction for multiple comparisons. A total of 69 nonresponders went on to receive combined treatment in the second study phase. After this phase, residual symptoms did not differ between patients who had medication added to CBT or vice versa.

Because suicidal ideation emerged as the most significant symptom in the overall analysis, the item was examined for its effect on outcomes. Suicidal ideation was present in significantly more patients who discontinued treatment (35% vs 23%; p=0.038), with a similar influence for both types of treatment. Equal proportions of patients with and without baseline suicidal ideation experienced response to their assigned treatment.

Discussion: These observations suggest that antidepressant medication may specifically reduce thoughts of suicide, even in the absence of overall improvement. In treatment responders, it appears that once the mechanisms of recovery from depression are engaged, the final symptom profile does not differ meaningfully between treatments. Even when treatments are ineffective overall, patients may experience limited benefits.

Dunlop B, Polychroniou P, Rakofsky J, Nemeroff C, et al: Suicidal ideation and other persisting symptoms after CBT or antidepressant medication treatment for major depressive disorder. *Psychological Medicine* 2018; doi 10.1017/S0033291718002568. **From Emory University School of Medicine, Atlanta, GA; and other institutions. Funded by the NIH. Four of 6 study authors disclosed potentially relevant financial relationships.**

Common Drug Trade Names*: duloxetine—*Cymbalta*; escitalopram—*Lexapro

Pimavanserin Safety

Patients with Parkinson's disease psychosis, for which pimavanserin (*Nuplazid*) is the only approved antipsychotic, are known to have a higher-than-normal mortality rate due to their older age, advanced Parkinson's disease, and other medical conditions. Following an extensive postmarketing review of deaths and serious adverse events, the FDA has concluded that the benefits of pimavanserin treatment for patients with hallucinations and delusions of Parkinson's disease psychosis continue to outweigh the risks. Although no new or unexpected safety risks were identified, some potentially concerning prescribing patterns emerged, such as the concomitant use of pimavanserin, which carries a boxed warning regarding QT prolongation and serious arrhythmia, and additional antipsychotics or other drugs that can also cause QT prolongation.

FDA News Release: FDA analysis finds no new or unexpected safety risks associated with Nuplazid (pimavanserin), a medication to treat the hallucinations and delusions of Parkinson's disease psychosis. Available at https://www.fda.gov/Drugs/DrugSafety/ucm621160.htm.

Fluvoxamine for Social Anxiety Disorder

According to the results of a meta-analysis, fluvoxamine (*Luvox*) is an effective, well-tolerated treatment for social anxiety disorder in adults.

Methods: The analysis was based on a literature search for randomized, placebo-controlled trials of fluvoxamine in patients, aged ≥18 years, with a diagnosis of social anxiety disorder according to DSM-III or later criteria. Trials were required to last ≥10 weeks. Primary efficacy outcome measures were the Liebowitz Social Anxiety Scale (LSAS) and the Clinical Global Impression (CGI)–Severity scale.* Secondary efficacy measures were response (i.e., CGI–Improvement ratings of much or very much improved) and change from baseline in the Sheehan Disability Scale (SDS). Tolerability was assessed using the rate of treatment discontinuation due to adverse effects.

Results: The search identified 5 studies with a combined sample size of 1001 subjects (range, 92–300). Fluvoxamine was flexibly-dosed, up to 300 mg/day, in all 5 studies. Change from

baseline in LSAS score in the 4 studies from which data could be pooled favored fluvoxamine over placebo with a 12-point between-group difference ($p<0.001$). CGI-Severity ratings, available from 3 studies, also favored fluvoxamine ($p<0.001$). The odds ratios* for response with fluvoxamine treatment versus placebo were 1.71 for the CGI-based measure and 2.11 for the SDS.

Discontinuation due to adverse events occurred significantly more often with fluvoxamine than placebo (90 vs 15 events; odds ratio, 5.99), but the number of serious adverse events did not differ between the treatment groups (4 and 3, respectively). The most frequent adverse effects of fluvoxamine were nausea, somnolence, insomnia, and abnormal ejaculation. Compared with placebo, fluvoxamine was not associated with an increased incidence of headache or with abnormal weight gain.

Discussion: SSRIs are often recommended as first-line pharmacotherapy for social anxiety disorder in adults; however, there has been little published analysis of the efficacy of fluvoxamine. The present results suggest it is effective and has acceptable tolerability in these patients.

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

Liu X, Li X, Zhang C, Sun M, et al: Efficacy and tolerability of fluvoxamine in adults with social anxiety disorder: a meta-analysis. *Systematic Review and Meta-Analysis* 2018; doi 10.1097/MD.0000000000011547. From Jilin University, Changchun, China. **The study was conducted with no external funding. The authors declared no competing interests.**

***See Reference Guide.**

Reference Guide

Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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 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.

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.