Olanzapine-Associated Deaths

The FDA is investigating the unexplained deaths of 2 patients who received intramuscular injections of olanzapine pamoate (Zyprexa Relprevv). The patients died 3–4 days after receiving appropriate doses of the drug, and both patients were found to have very high olanzapine blood levels after death. High doses of olanzapine can cause delirium, cardiopulmonary arrest, cardiac arrhythmias, and reduced level of consciousness ranging from sedation to coma.

Under a risk evaluation and mitigation strategy (REMS), patients are required to receive the olanzapine pamoate injection at a certified facility, to be continuously monitored for ≥3 hours after an injection, and to be accompanied home from the facility. The label contains warnings about postinjection delirium sedation syndrome (PDSS), a serious condition in which the drug enters the blood too fast after an intramuscular injection, causing greatly elevated blood levels with marked sedation and/or delirium. However, it is not clear whether these 2 patients died from PDSS.


Antipsychotic Drugs Differ in Efficacy, Tolerability

Antipsychotics have substantial differences in side effects and modest but statistically significant differences in efficacy, according to a large meta-analysis of clinical trials.

Methods: The multiple-treatment meta-analysis* included controlled trials of monotherapy with orally administered haloperidol, chlorpromazine, and 13 different second-generation drugs. The analysis included published and unpublished studies, from between 1955 and September 2012, of acute treatment (usually 6 weeks) of schizophrenia or related disorders. It excluded relapse prevention studies and studies in patients with predominantly negative symptoms or refractory illness. The primary outcome measure was overall change from baseline in symptoms, measured
using the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS). Effect sizes were calculated as standardized mean differences. Secondary outcomes included drug discontinuation and the known antipsychotic side effects.

**Results:** The analysis included 212 studies conducted in >43,000 patients (mean age, 38 years; mean illness duration, 12 years). Two-thirds of the studies were carried out by pharmaceutical companies; all used appropriate methods. Nine studies included only first-episode patients.

All drugs were significantly more effective than placebo (see table), and clozapine was significantly more effective than the other drugs. A second rank of efficacy included amisulpride, olanzapine, and risperidone. Effect sizes* for between-drug differences, although statistically significant, were small, ranging from 0.11 to 0.55 (median, 0.24). All-cause discontinuation was used as a measure of drug acceptability. All drugs were significantly less likely to be discontinued than placebo, with the exception of zotepine. Amisulpride, olanzapine, clozapine, paliperidone, and risperidone had significantly lower all-cause discontinuation rates than several other drugs.

All drugs except haloperidol, ziprasidone, and lurasidone produced more weight gain than placebo. Olanzapine, followed by zotepine and clozapine, produced more weight gain than most other drugs. Clozapine had the lowest incidence of extrapyramidal side effects, followed by sertindole, olanzapine, and quetiapine. Rates of prolactin elevation were highest with risperidone and paliperidone, and QTc elevation risk was greatest with sertindole. Clozapine, zotepine, and chlorpromazine were the most sedating antipsychotics.

**Discussion:** The differences in efficacy between drugs were smaller than the differences for adverse effects. However, the efficacy differences of the drugs from placebo were only medium (effect sizes, 0.33–0.88; median 0.44), which suggests differences between drugs may be large enough to be clinically important. The most effective drugs had the lowest discontinuation rates, suggesting that patients may prioritize efficacy over tolerability.

As many of the second-generation antipsychotics have become available as generics, cost-effectiveness of the newer drugs is a matter of debate. This analysis suggests the new drugs do have some favorable properties, such as acceptable weight gain.

*Leucht S, Cipriani A, Spineli L, Mavridis D, et al: Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013; doi 10.1016/S0140-6736(13)60733-3. From the Technical University of Munich, Germany; and other institutions. This study was conducted without funding. Three study authors disclosed financial relationships with commercial sources; the remaining authors declared no conflicts of interest.*

**Drug Trade Names:** amisulpride—Solian; aripiprazole—Abilify; asenapine—Saphris; chlorpromazine—Thorazine; clozapine—Clozaril; haloperidol—Haldol; iloperidone—Fanapt; lurasidone—Latuda; olanzapine—Zyprexa; paliperidone—Invega; quetiapine—Seroquel; risperidone—Risperdal; sertindole—Serdolect; ziprasidone—Geodon; zotepine—Nipolept

*See Reference Guide.*
Nicotinic Agent for Adult ADHD

In a preliminary study, a nicotinic receptor agonist improved performance on a response inhibition task and reduced a range of symptoms in adults with ADHD. The finding supports the proposition that stimulation of nicotinic acetylcholine receptors improves executive function and may be a promising avenue for ADHD drug development.

**Methods:** AZD3480 (also termed TC-1734) is a novel partial nicotinic agonist that is highly selective for α4β2 nicotinic receptors. Based on previous pilot and preclinical studies, 2 dosages of the agonist, 5 mg/day and 50 mg/day, were selected for evaluation in a placebo-controlled crossover study. Participants were 24 adults recruited via advertisement or clinical referral who had at least moderately severe ADHD. They were required to be nonsmokers (i.e., smoked <100 cigarettes in their lifetime and had not smoked weekly in the previous 3 years) and to have ≥1.5 functional copies of the CYP2D6 gene, to exclude poor metabolizers of the agonist. After washout of any ADHD medication, each participant completed 3 treatment periods (2 weeks each), in randomized order, separated by drug-free washouts (3 weeks each). Response inhibition was measured with the Stop Signal Task (SST), cognitive function with the Clinical Drug Research battery, and ADHD symptoms with the investigator-rated Conners Adult ADHD Rating Scale (CAARS) and the Clinical Global Impression Severity (CGI-S) index.*

**Results:** Study participants ranged in age from 19 to 60 years (mean age, 44 years), 18 were male, and the mean CGI-S score was 5. After 2 weeks of treatment, the 50-mg/day dosage of AZD3480 was associated with a significant reduction from baseline in the stop signal reaction time measure of the SST (p=0.009), the primary cognitive outcome measure. Both placebo and the 5-mg/day dosage had virtually no effect; the effect size* for the 50-mg dose vs. placebo was 0.73 (p<0.03). The treatments had few effects on other cognitive measures.

The 50-mg/day dosage also resulted in significant improvement from baseline in the CAARS total score and on subscales measuring inattentive symptoms, hyperactive-impulsive symptoms, emotional lability/impulsivity, and memory problems (p<0.05 for all subscales). Twenty percent of participants were rated as improved (CGI-S score of 1 or 2) while using 50 mg/day AZD3480, compared with 9% with placebo (p=0.06). With response defined as a >5-point improvement in the CAARS total score, 11 of the 18 patients who were classified were considered responders to 50 mg/day AZD3480. Overall effects of the 5-mg/day dosage were intermediate, between the other treatments, and generally not different from placebo.

**Discussion:** The effect size of 50 mg/day AZD3480 in this study is larger than the average effect size of nonstimulants in adult ADHD and similar to average effect sizes for long-acting stimulants. AZD3480 had its largest clinical effect on inattention symptoms, consistent with the known role of the cholinergic system in regulating attention.

Potter A, Dunbar G, Mazzulla E, Hosford D, et al: AZD3480, a novel nicotinic receptor agonist, for the treatment of attention-deficit/hyperactivity disorder in adults. Biological Psychiatry 2013; doi 10.1016/j.biopsych.2013.06.002. From the University of Vermont, Burlington; Targacept Inc., Winston-Salem, NC; and Vanderbilt University, Nashville, TN. Funded by Targacept. Four of the 5 study authors disclosed financial relationships with commercial sources; the fifth author declared no conflicts of interest.

Centrally-Acting ACE Inhibitors and Cognitive Decline

In an observational study of patients attending a dementia clinic, centrally acting ACE-inhibitor therapy was associated with a reduced rate of cognitive decline over 6 months.

**Background:** Results of previous clinical trials of antihypertensives in dementia have been inconclusive. This study was conducted to assess the effect of centrally acting agents, which cross the blood-brain barrier and may have a greater effect than peripherally acting agents.
Methods: Data were collected on patients attending memory clinics at 2 university hospitals. Included patients had received a diagnosis of Alzheimer’s, vascular, or mixed dementia. Other types of dementia, which are not believed to be affected by antihypertensive medications, were excluded. The study also excluded patients with mild cognitive impairment and those with depression. Patients’ mental status was assessed using the Standardized Mini-Mental State Examination (SMMSE) and the Quick Mild Cognitive Impairment (Qmci) screen. The final sample included 85 patients taking a centrally acting ACE inhibitor (i.e., perindopril; ramipril; trandolapril; captopril; fosinopril; lisinopril) on admission and 276 who were not. Of the latter group, 30 received a new prescription for an ACE inhibitor at the clinic.

Results: Patients in the treated and untreated groups were of similar age (mean, 78 years) and gender (about half were men). About 80% were taking cholinesterase inhibitors, and one-quarter were taking memantine.

Median SMMSE scores decreased from baseline by 2 points in patients receiving a centrally acting ACE inhibitor and by 3 points in untreated patients, a difference that was not statistically significant. SMMSE scores increased by 1 point in the patients newly treated with a centrally acting ACE inhibitor (p=0.003 vs. those treated since baseline, and p=0.001 vs. the untreated). After adjustment for other factors, including blood pressure, there were significant differences (p=0.002) in endpoint SMMSE among all 3 groups.

Changes in the Qmci score showed a similar pattern, with a statistically significant difference only between those who had been receiving since baseline and those not receiving an ACE inhibitor at baseline (p=0.049).

Discussion: Research has shown blood-pressure control to be associated with a reduced rate of cognitive decline, regardless of the class of medication. ACE inhibitors and angiotensin receptor blockers appear to lower dementia risk independent of their blood-pressure lowering properties. The present study, one of few observational studies, showed a small reduction in the rate of decline that might translate to a clinically meaningful difference if sustained over years. However, it is also possible that ACE inhibitors interfere with the degradation of amyloid-beta, potentially accelerating cognitive decline in at least some patients. Because this study is observational, selection bias is possible and the results need to be replicated in studies with stronger designs.


Drug Trade Names: captopril—Capoten; fosinopril—Monopril; lisinopril—Prinivil, Zestril; memantine—Namenda; perindopril—Aceon; ramipril—Altace; trandolapril—Mavik

Adjunctive Antidepressants for Negative Symptoms

Depressive symptoms are common in schizophrenia and have considerable overlap with negative symptoms. The literature on antidepressant treatment of negative symptoms is scant and conflicting. In a randomized trial, adjunctive antidepressants did not improve negative symptoms of schizophrenia, and there was no difference in efficacy between an SSRI and an SNRI.

Methods: Study subjects were 51 patients with schizophrenia and predominantly negative symptoms, as reflected by a score of ≥4 on at least 1 item of the Positive and Negative Syndrome Scale (PANSS) negative symptom subscale. Patients had been receiving stable antipsychotic medication (see table, next page) for ≥2 weeks prior to randomization, and these were unchanged throughout the 4-week study. Following a baseline evaluation, participants were randomly assigned to receive adjunctive treatment with 20–40 mg citalopram b.i.d., 4–8 mg reboxetine b.i.d., or placebo. Neither mean patient age (range, 38–42 years) nor mean duration of illness (9–15 years) differed significantly among the treatment groups. The primary
outcome measures were the PANSS negative symptom subscale, with response defined as a ≥25% decrease in score, and the Clinical Global Impression Severity scale. The Hamilton Rating Scale for Depression (HAM-D) was a secondary outcome measure.

<table>
<thead>
<tr>
<th>Background Antipsychotic Use by Randomized Group</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Citalopram</td>
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<tr>
<td>Reboxetine</td>
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<tr>
<td>Placebo</td>
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</table>

Results: At study entry, mean PANSS negative symptom scores were 25 in the citalopram group, 26 in the reboxetine group, and 27 in the placebo group. These improved by a modest 4–8 points over the 4 weeks in all groups. However, the effects of citalopram and reboxetine did not differ from each other or from placebo. Mean CGI ratings improved by about one-half of a point in each antidepressant group and by 1 point in the placebo group. Both citalopram and reboxetine were well tolerated; there were no serious adverse effects reported. However, agitation occurred significantly more often in the citalopram groups (p<0.001 compared with reboxetine and placebo).

A separate analysis was conducted in 30 patients with minor depression (i.e., HAM-D of >13 points). Antidepressant response did not differ significantly between the groups and occurred in 9 of 11 patients treated with citalopram, in 6 of 12 with reboxetine, and in 3 of 7 with placebo.

Hinkelmann K, Yassouridis A, Kellner M, Jahn H, et al: No effects of antidepressants on negative symptoms in schizophrenia. *Journal of Clinical Psychopharmacology* 2013:33 (October):1–5. From the University of Hamburg, Germany; and other institutions. *Funded by the Stanley Medical Research Institute*. Five of the 6 study authors disclosed financial relationships with commercial sources; the remaining author declared no conflicts of interest.

Drug Trade Names: amisulpride (not available in U.S.)—Solian, Sulamid; aripiprazole—Abilify; citalopram—Celexa; clozapine—Clozaril; olanzapine—Zyprexa; quetiapine—Seroquel; reboxetine (not available in U.S.)—Vestra; risperidone—Risperdal

Prazosin for Combat-Related PTSD

The antihypertensive alpha-adrenergic antagonist prazosin (*Minipress, and others*) reduced trauma-related nightmares and overall posttraumatic stress disorder symptoms in a controlled trial of active-duty soldiers with combat-related PTSD.

Methods: Study subjects were 57 men and 10 women receiving treatment at an Army medical facility in the U.S. All had experienced combat-related trauma while serving in Iraq or Afghanistan. Participants met DSM-IV criteria for PTSD, had ≥1 life-threatening combat experience, and continued to have combat-related nightmares ≥2 nights per week. Participants received double-blind, randomly assigned prazosin or placebo for 15 weeks. After dose titration, study medication was administered twice daily because of the short duration of action of prazosin. In the active treatment group, prazosin was titrated to a maximum dosage of 5 mg midmorning and 20 mg at bedtime in men. Because women are more sensitive to the drug’s beneficial and adverse effects, the maximum doses were 2 and 10 mg. Primary outcome measures were the nightmare item of the Clinician-Administered PTSD Scale (CAPS), the Pittsburgh Sleep Quality Index, and the Clinical Global Impression (CGI) scale change item.

Results: Of the 67 participants, 5 in the prazosin group and 6 in the placebo group withdrew from the study before the first outcome evaluation at 7 weeks: 2 patients opted to receive open-label prazosin; 2 patients in the prazosin group withdrew because of an adverse event; and 7 patients withdrew for reasons unrelated to medication. A total of 26 patients met criteria for major depression, and 10 patients in the prazosin group and 14 in the placebo group were receiving maintenance therapy with an antidepressant (mainly SSRIs) that had been stable for ≥4 weeks before enrollment and remained unchanged during the study. Forty-six patients—23 in
each group—completed the study. Prazosin was significantly superior to placebo for all 3 primary outcomes, as well as for general PTSD symptoms. (See table.) CGI response (marked or moderate improvement) occurred in 64% of patients receiving prazosin, compared with 27% of the placebo group (odds ratio,* 4.8; p<0.001).

Improvement in the total CAPS score was greater with prazosin than placebo, whether the CAPS nightmare item was included or excluded. Differences in improvement of reexperiencing, avoidance, and depression favored prazosin but were not statistically significant. In the patients taking an SSRI, the positive effects of prazosin on CAPS scores were substantially smaller than those in patients not receiving an SSRI and they did not differ from placebo.

Two patients in the placebo group had serious adverse events: suicidal ideation and a suicide attempt. Other adverse events were mild and comparable between prazosin and placebo. There were no significant differences in blood pressure measures between the groups throughout the study.

**Discussion:** SSRI s, the only drugs that are FDA-approved for treating PTSD, have not been shown to be effective in military veterans. Combat-related PTSD is usually associated with a high number and long duration of traumatic stressors and the unavoidable reexposure. Prazosin in single doses was previously shown to be effective in improving sleep disturbance and nightmares in veterans. The agent does not produce sedation, sexual dysfunction, or the adverse metabolic effects associated with some psychoactive drugs. Its efficacy in PTSD suggests that increased responsiveness to norepinephrine at the CNS alpha-1 adrenoreceptor contributes to the disorder. Prazosin has been used safely in desert soldiers, but it is important that patients using it maintain adequate hydration.

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

Raskind M, Peterson K, Williams T, Hoff D, et al: A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. *American Journal of Psychiatry* 2013; doi 10.1176/appi.ajp.2013.12081133. From VISN 20 Northwest Network Mental Illness Research, Education, and Clinical Center, Seattle, WA; and other institutions. Funded by the Department of Veterans Affairs; and the NIH. Three study authors disclosed financial relationships with commercial sources; the remaining 18 authors declared no conflicts of interest.

*See Reference Guide.

### Adjunctive Antipsychotics for Depression

As adjunctive treatment for depression, aripiprazole is associated with lower costs and fewer hospitalizations than either olanzapine or quetiapine, according to an analysis of claims data.

**Methods:** The retrospective analysis utilized a research database covering more than 23 million adult members of commercial health plans across the U.S. Study subjects filled a prescription for aripiprazole, olanzapine, or quetiapine between 2004 and 2010, had a primary diagnosis of major depressive disorder, and had been taking an antidepressant for ≥60 days prior to initiation of the antipsychotic, with a ≥14-day overlap of the 2 drugs. Medical claims data for 1 year following the initial antipsychotic prescription were analyzed.

**Results:** A total of 10,292 patients met study criteria. Quetiapine was used by 5410 patients (53%), aripiprazole by 3849 (37%), and olanzapine by 1033 (10%). Patients received adjunctive

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prazosin (n=32)</th>
<th>Placebo (n=35)</th>
<th>Between-Group Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS Nightmare Score</td>
<td>6.0</td>
<td>6.6</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index</td>
<td>14.1</td>
<td>14.5</td>
<td>p=0.003</td>
</tr>
<tr>
<td>CAPS Total Score</td>
<td>77.3</td>
<td>85.7</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>
antipsychotics for an average of 5–7 months. The prevalence of concomitant diabetes and hyperlipidemia did not differ between the groups.

During the year following the initiation of therapy, mean total medical care costs for outpatient visits, hospitalizations, and emergency department services totaled $10,664 for aripiprazole, $14,583 for quetiapine, and $16,556 for olanzapine (p<0.001). After adjustment for other relevant factors, medical costs in patients who received olanzapine or quetiapine were about 25% higher than for aripiprazole. Mental health-related medical costs showed a similar pattern, with a 33% excess for olanzapine and a 23% excess for quetiapine.

Rates of mental health-related hospitalization were about 2 times higher for olanzapine and quetiapine than for aripiprazole (adjusted odds ratio,* 1.81 for olanzapine, 1.78 for quetiapine; p<0.001 for both comparisons). Rates of hospitalization for any reason followed the same pattern as mental health-related hospitalization.

Of note, use of doses below the recommended therapeutic range differed significantly (p<0.001) between groups. The majority of patients (61%) in the aripiprazole group received doses in the recommended range, compared with 35% and 19% of the olanzapine and quetiapine groups, respectively. When the analysis was limited to patients who received doses in the therapeutic range, the cost difference between aripiprazole and olanzapine was no longer statistically significant.

Discussion: The antidepressant efficacy of different atypical antipsychotics has not been previously compared directly. The few previous studies that compared costs, with shorter follow-up durations than the present study, reached similar conclusions. The present results suggest that in clinical practice, atypical antipsychotics are often used at doses below those recommended by the product labeling.


Funded by Bristol-Myers Squibb, Inc., and Otsuka Pharmaceutical Co., Ltd. Five study authors disclosed financial relationships with either Bristol-Myers Squibb or Otsuka Pharmaceutical.

Drug Trade Names: aripiprazole—Abilify; olanzapine—Zyprexa; quetiapine—Seroquel

*See Reference Guide.

**Atypical Antipsychotics in Mixed Episodes**

Second-generation antipsychotics are effective in treating acute manic/mixed episodes of bipolar disorder, according to a meta-analysis.

**Background:** Few guidelines for bipolar disorder specifically discuss the treatment of mixed episodes. Published research is sparse, and most studies that do exist are post-hoc analyses of populations with both manic and mixed symptoms.

**Methods:** Published and unpublished, English-language, randomized, placebo-controlled trials of atypical antipsychotics in manic or mixed episodes of bipolar disorder conducted after 1990 were identified by literature search. Each trial used an oral atypical antipsychotic as monotherapy or in combination with mood stabilizing medications. Outcomes were measured with the Young Mania Rating Scale (YMRS) or the mania rating scale (MRS) from the Schedule for Affective Disorders and Schizophrenia. Effect size was measured using the standardized mean difference (SMD)* from placebo.

**Results:** The analysis was based on 9 trials—6 of monotherapy and 3 of adjunctive therapy—with a total of 1289 patients. The studies were 3 or 6 weeks in duration and included 6 different atypical antipsychotics: aripiprazole; asenapine; olanzapine; paliperidone; risperidone, and ziprasidone. Seven of the 9 studies reported data for pure manic and mixed episodes separately.
In all of the trials combined, atypical antipsychotics were associated with a significant reduction in mania scores relative to placebo (SMD, 0.41; p<0.0001). There was no significant heterogeneity among studies, suggesting all drugs were equally effective. The agents were effective as monotherapy (SMD, 0.35; p<0.00001) and as adjunctive therapy with mood stabilizers (SMD, 0.55; p<0.00001). The atypicals were equally effective in pure mania and mixed states, with effect sizes* of 0.56 and 0.44, respectively.

Two of the trials also reported the effects of atypicals on depressive symptoms occurring as part of mixed episodes. In these trials, asenapine and olanzapine were associated with significant improvement in depression (SMD, 0.30; p<0.001).

**Discussion:** The finding that atypical antipsychotics are apparently equally effective in mania and mixed states is clinically important in light of changes to the DSM. Mixed states are no longer a category in DSM-5; instead, mixed features are a course specifier for both manic and depressive episodes.

**Study Rating**—16 (89%): This study met most criteria for a systematic review/meta-analysis, but individual study quality was not assessed.

Muralidharan K, Ali M, Silveira L, Bond D, et al: Efficacy of second-generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials. *Journal of Affective Disorders* 2013; doi 10.1016/j.jad.2013.04.032. From the University of British Columbia, Vancouver, Canada; and other institutions. **This study was conducted without funding. Several study authors disclosed financial relationships with commercial sources.**

**Drug Trade Names:** aripiprazole—A bilify; asenapine—Saphris; olanzapine—Zyprexa; paliperidone—Invega; risperidone—Risperdal; ziprasidone—Geodon

*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.

**Multiple Treatment Meta-Analysis (MTMA):** Also known as network meta-analysis, MTMA can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common. For example, if in a clinical trial comparing treatment A with treatment B, option A is determined to be superior, and a separate trial in similar patients found option B superior to a third agent, option C, a network meta-analysis of these 2 trials would allow a researcher to conclude that treatment option A is more effective than option C, even though the 2 options have never been directly compared.

**Odds Ratio:** A comparison of the probability of an event in two 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.

**Standardized Mean Difference:** The difference between two normalized means - i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

**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 have been posted at www.alertpubs.com.