PSYCHIATRY DRUG ALERTS

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Augmenting Clozapine in Resistant Schizophrenia

More than half of patients with resistant psychosis do not achieve response with clozapine treatment. According to the results of a comprehensive review, the agents with the best evidence for efficacy as clozapine augmentation are aripiprazole, fluoxetine, and valproate. Memantine may be effective for negative symptoms.

Methods: A comprehensive literature search identified all randomized controlled trials of clozapine augmentation published in any language with a target patient population of adults with ongoing psychotic symptoms unresponsive to an adequate trial of clozapine. The primary outcome was total psychotic symptoms. Secondary outcomes were positive symptoms, negative symptoms, and adverse drug reactions. The search identified 46 articles describing 25 different interventions. Studies ranged from 3 weeks to 12 months, and most were conducted in community settings. Augmentation agents were antipsychotics (19 studies), antidepressants (10 studies), mood stabilizers (5 studies), glutamatergic agents (7 studies), "other" pharmacotherapies (2 studies), and nonpharmacological strategies (3 studies).

Results: Ten different antipsychotic agents were evaluated in a total sample of 1131 patients: aripiprazole, risperidone, haloperidol, penfluridol, pimozide, sulpiride/amisulpride, sertindole, olanzapine, quetiapine, and ziprasidone. However, only 3 agents—aripiprazole, risperidone, sulpiride/amisulpride—were evaluated in >1 study. Among the antipsychotics, only aripiprazole was superior to placebo for total psychosis scores (standardized mean difference [SMD],* -0.57). It was not superior in terms of positive or negative symptoms. In addition, aripiprazole was the only agent with sufficient data to examine specific adverse drug reactions. It was associated with more restlessness and less sedation than placebo, but no differences in weight gain, abnormal electrocardiography, hyperprolactinemia, or other adverse effects. Risperidone and sulpiride/amisulpride were not superior to placebo, and single studies of other antipsychotics were negative or inconclusive.

Antidepressant analyses included fluoxetine, paroxetine, duloxetine, and mirtazapine in a total of 476 patients. Fluoxetine was found to be superior to placebo for total symptoms (SMD, -0.73),

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as well as for positive and negative symptoms; however, after removal of low-quality studies the effects on positive and negative symptoms were no longer significant. Studies of other antidepressants had negative results or were limited by small sample sizes or other quality issues.

The mood stabilizers valproate, lithium, topiramate, and lamotrigine were evaluated in 278 patients. Among these, valproate was effective for total symptoms (SMD, -2.36,) and positive symptoms (SMD, -1.54), but study quality was low. Topiramate appeared to be effective for positive and negative symptom clusters, and lithium appeared to have positive effects on total and positive symptom scores, but each agent was evaluated in only 1 study. Lamotrigine did not produce improvement in any symptom domain.

The glutamatergic agents memantine, glycine, and sarcosine were evaluated in 212 patients. Only memantine had positive effects and only in terms of negative symptoms (SMD, -0.56). Other agents with very limited supporting evidence include Gingko biloba for total and negative symptom scores and minocycline for negative symptoms. In single studies of nonpharmacologic interventions, ECT reduced total psychosis scores, but cognitive behavioral therapy and transcranial magnetic stimulation were not effective.

Siskind D, Lee M, Ravindran A, Zhang Q, et al: Augmentation strategies for clozapine refractory schizophrenia: a systematic review and meta-analysis. *Australian & New Zealand Journal of Psychiatry* 2018; doi 10.1177/0004867418772351. From Metro South Health, Brisbane, Australia; and other institutions. **This research was conducted without funding. The study authors declared no financial relationships with commercial sources.**

Common Drug Trade Names*: amisulpride (not available in the U.S.)—*Solian*; aripiprazole—*Abilify*; clozapine—*Clozaril*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; haloperidol—*Haldol*; lamotrigine—*Lamictal*; memantine—*Namenda*; mirtazapine—*Remeron*; olanzapine—*Zyprexa*; paroxetine—*Paxil*; penfluridol (not available in the U.S.)—*Semap*; pimozide—*Orap*; quetiapine—*Seroquel*; risperidone—*Risperdal*; sertindole (not available in the U.S.)—*Serdolect*; sulpiride (not available in the U.S.)—*Dogmatil*; topiramate—*Topamax*; valproate—*Depakene, Depakote*; ziprasidone—*Geodon

***See Reference Guide.**

Inhaled Loxapine for Acute Agitation

In a multicenter, randomized, controlled trial, inhaled loxapine had a more rapid onset of action than injected aripiprazole in patients with acute agitation associated with bipolar I disorder or schizophrenia.

Methods: This randomized head-to-head comparison, funded by the manufacturer of loxapine, was conducted at 23 centers in 4 European countries. Participants, aged 18–65 years, had a diagnosis of schizophrenia or bipolar I disorder and presented with agitation during hospitalization or at an emergency department, with a score of ≥4 on the Clinical Global Impression–Severity (CGI-S) scale.* Randomized treatment consisted of either 10 mg inhaled loxapine or 9.75 mg/1.3 mL intramuscular (IM) aripiprazole, with the option of a second dose ≥2 hours after the first if needed. Patients could receive rescue medication if needed to treat agitation beginning 20 mins after the second dose of study medication. Baseline and post-treatment clinical assessment was carried out by a blinded rater at prespecified intervals up to 24 hours after the first dose. The primary efficacy outcome was time to response, defined as the first time point at which a CGI-S score of 1 or 2 was registered.

Results: Of 359 patients randomized to treatment, 297 had schizophrenia and 60 had bipolar I disorder. The mean patient age was 40 years, and 51% were men. The median time to onset of action was 50 min for inhaled loxapine and 60 min for IM aripiprazole (treatment difference, 10 mins; p=0.0005). The time to onset was shorter for loxapine in both patients with schizophrenia and those with bipolar disorder, although in the latter group, the difference was not statistically significant, probably owing to the small sample size. The treatments differed as early as the first assessment, 10 mins after the first dose, when response rates were 14% in the loxapine group and 4% in the aripiprazole group (p=0.0009). There continued to be more responders in the

loxapine group at every assessment time point up to 1 hour (70% vs 56%; p=0.0075). At 2 hours, response rates were 83–84% in the 2 groups. A second dose of randomized medication was required in 7% of patients in the loxapine group and 10% of those in the aripiprazole group. A single patient, in the loxapine group, required rescue medication for agitation at 2.5 hours. Patient satisfaction was greater with loxapine—with 54% very satisfied or extremely satisfied with their treatment—compared with 36% of aripiprazole-treated patients. Common adverse effects of loxapine included occasional altered taste, cough, and throat irritation.

Discussion: Although oral medication administration is often preferred, it may not have a sufficiently rapid onset of action in acutely agitated patients. IM antipsychotics generally provide faster symptomatic control than oral formulations, but administration via this route may distress the patient. In addition to the more rapid action than IM injection, inhaled loxapine may have other advantages that are relevant to treating agitation, including a non-coercive, noninvasive mode of administration and a sustained therapeutic effect.

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

San L, Estrada G, Oudovenko N, Montanes F, et al: PLACID study: a randomized trial comparing the efficacy and safety of inhaled loxapine versus intramuscular aripiprazole in acutely agitated patients with schizophrenia or bipolar disorder. *European Neuropsychopharmacology* 2018; doi 10.1016/j.euroneuro.2018.03.010. From Parc Sanitari Sant Joan de Deu, Barcelona, Spain; and other institutions. **Funded by Ferrer Internacional. All 8 study authors disclosed potentially relevant financial relationships.**

Common Drug Trade Names*:** **aripiprazole, intramuscular—*Abilify Maintena*; loxapine, inhaled—*Adasuve

***See Reference Guide.**

Vortioxetine Pharmacology and Interactions

According to a review of phase-I study data compiled by the manufacturer, vortioxetine can be administered without adjustments to the recommended dosage in most patient populations and there are few clinically significant potential drug interactions.

Vortioxetine is a multimodal antidepressant with 2 actions: agonist activity at multiple serotonin receptors and inhibition of the 5-HT transporter. It may owe its antidepressant effects to modulation of neurotransmission in multiple systems including serotonin, norepinephrine, dopamine, acetylcholine, histamine, glutamate, and GABA. The therapeutic dose range is 5–20 mg, taken once daily. Oral bioavailability is about 75%, and the peak plasma concentration of vortioxetine is reached within 7–11 hours post-dose. Administration with food has no important effect on drug absorption.

Vortioxetine is metabolized almost entirely by the liver through oxidation by cytochrome P450 (CYP) enzymes, predominantly CYP2D6. Six metabolites have been identified, but the parent compound is responsible for pharmacologic activity. Renal clearance accounts for less than 1% of total clearance. The elimination half-life has ranged from 59 to 69 hours in various studies. Vortioxetine pharmacokinetics are dose-proportional and linear within the range that has been studied—2.5–75 mg for single-doses or 2.5–60 mg for multiple doses. Steady-state levels are reached after about 2 weeks of daily dosing.

Vortioxetine pharmacokinetics have been investigated in populations classified by gender, age, race/ethnicity, body size, and existence of hepatic or renal impairment. Dosage adjustments are not needed for any of these categories. Variations in the CYP2D6 genotype can affect drug exposure, but these variations were not found to be clinically significant, and routinely genotyping patients before starting treatment is not recommended. Depending on the individual response, patients known to have the poor metabolizer genotype may require a dose adjustment.

A range of potential drug interactions have been investigated. Bupropion, a strong CYP2D6 inhibitor, can double vortioxetine peak serum concentrations and area under the plasma drug

concentration-time curve. It is recommended that the vortioxetine dose be reduced by half when given with bupropion or other strong inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine. Ketoconazole has modest, clinically insignificant effects on vortioxetine kinetics, and no effects were found for aspirin, ethanol, or omeprazole. Vortioxetine was not found to have clinically important effects on levels of other drugs that are metabolized by CYP2D6.

In pharmacodynamic studies, vortioxetine was found not to affect cardiac repolarization or to impair driving, cognitive function, or psychomotor skills. For the most part, it did not increase impairment induced by alcohol or diazepam. Like other serotonergic agents, its use can lead to serotonin syndrome, especially when combined with other drugs that affect that system.

Chen G, Hojer A-M, Areberg J, Nomikos G: Vortioxetine: clinical pharmacokinetics and drug interactions. *Clinical Pharmacokinetics* 2018;57 (June):673-686. From Takeda Development Center Americas, Inc., Deerfield, IL; and H. Lundbeck A/S, Copenhagen-Valby, Denmark. **Funded by Takeda Development Center Americas, Inc.; and H. Lundbeck A/S. All 4 study authors disclosed potentially relevant financial relationships.**

Common Drug Trade Names*: bupropion—*Wellbutrin*; fluoxetine—*Prozac*; ketoconazole—*Nizoral*; omeprazole—*Prilosec*; paroxetine—*Paxil*; vortioxetine—*Trintellix

Antipsychotics and Gestational Diabetes

In a cohort of women who received antipsychotic treatment before pregnancy, those who continued taking some antipsychotics during pregnancy had an elevated risk of gestational diabetes, compared with those who stopped. Olanzapine use was associated with the highest risk, which was dose-related.

Methods: This analysis was based on nationwide Medicaid claims data on pregnancies occurring in 2000–2010. Women without preexisting diabetes were included in the cohort if they were taking 1 of the 5 most frequently used antipsychotics—aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone—during the 3 months before their last menstrual period. Those receiving antipsychotic polypharmacy and those whose antipsychotic was changed during pregnancy were excluded. Risk of gestational diabetes was compared between women who continued to receive the same antipsychotic during the first 20 weeks of pregnancy and those who stopped. Analyses were conducted separately for each individual drug and for 3 groups classified according to the potential to induce weight gain and diabetes in nonpregnant patients. Aripiprazole and ziprasidone were classified as low-risk, quetiapine and risperidone were medium-risk, and olanzapine was high-risk. The analysis was adjusted for propensity scores* incorporating a large number of covariates.

Results: The study cohort comprised >10,000 women who received aripiprazole (n=1924), ziprasidone (n=673), quetiapine (n=4533), risperidone (n=1824), or olanzapine (n=1425) before pregnancy. The proportion continuing on the same drug after becoming pregnant ranged from 19% (risperidone) to 34% (quetiapine). The absolute risk of gestational diabetes ranged from 4.2% to 12% among continuers and from 3.8% to 4.7% among discontinuers. After adjustment, risk for gestational diabetes was elevated for olanzapine (relative risk,* 1.61) and quetiapine (relative risk, 1.28), but not for the other agents. In a dose-response analysis, risk increased

Risk of gestational diabetes during pregnancy		
Risk Group‡	**Incidence**	**Adjusted Relative Risk**
Low-risk		
Continuers	4.6%	0.91
Discontinuers	4.3%	
Medium-risk		
Continuers	7.0%	1.37
Discontinuers	4.1%	
High-risk		
Continuers	12.0%	1.61
Discontinuers	4.7%	

‡Low-risk: aripiprazole, ziprasidone. Medium-risk: quetiapine and risperidone. High-risk: olanzapine.

with an increasing cumulative dose of olanzapine, reaching a plateau at 700 mg, but dose did not affect risk with the other agents. Stratification by diagnostic class (i.e., psychiatric vs nonpsychiatric indication for treatment) did not alter the results.

Discussion: Women who received olanzapine before pregnancy had a lower prevalence of diabetes risk factors than other groups, which suggests that despite selective prescribing, women who received olanzapine continued to have the highest risk of gestational diabetes, relative to discontinuers. Continued weight gain is the most plausible explanation for the increased risk with olanzapine. Reasons for discontinuation of treatment, which could be associated with illness severity or indication for treatment, were not available in the study data. However, the authors note that illness severity is not likely to explain the observed associations, as increased risk for gestational diabetes with found only with select antipsychotics.

Park Y, Hernandez-Diaz S, Bateman B, Cohen J, et al: Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.17040393. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by the NIMH. Seven of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*; ziprasidone—*Geodon

***See Reference Guide.**

Aripiprazole and Worsening Psychosis

According to a meta-analysis of randomized trials, switching to aripiprazole was not associated with increased risk of psychotic worsening compared with other antipsychotics. However, a switch to aripiprazole was associated with study discontinuation due to lack of efficacy.

Background: Numerous case reports have described worsening of psychotic symptoms following initiation of aripiprazole, often after simply adding aripiprazole to an existing regimen. Psychotic worsening is presumed to be caused by the drug's partial agonist activity at dopamine D_2 receptors, particularly after receptor up-regulation as a consequence of long-term exposure to other antipsychotics.

Methods: The meta-analysis was based on published randomized, parallel-group clinical trials conducted in patients with schizophrenia-spectrum disorders. The studies compared switching to aripiprazole versus switching to another antipsychotic (excluding those that share the partial D_2 agonist profile of aripiprazole) or that compared adding aripiprazole versus placebo as augmentation of another antipsychotic. Studies were excluded if ≥70% of patients were antipsychotic-naive or antipsychotic-free. Psychotic worsening, the primary outcome of the meta-analysis, could be reported as either lack of efficacy or an adverse event; all studies identified for the analysis reported this as an adverse event. Separate analyses were conducted for switching and augmentation studies.

Results: A total of 22 studies were identified—13 of switching and 9 of augmentation—with a total of nearly 5800 participants. All studies used an oral formulation of aripiprazole, with the mean daily dose ≥10 mg. The studies investigating a switch to aripiprazole found no significant difference between the groups in the number of patients experiencing worsening of psychotic symptoms as an adverse event, a serious adverse event, or an adverse event leading to study discontinuation. (See table, next page.) There were also no between-group differences in emergence of anxiety or agitation. For the studies of aripiprazole augmentation, no difference was found in the incidence of psychotic worsening reported as an adverse event or as a serious adverse event.

Neither aripiprazole switching nor augmentation was associated with an increased rate of all-cause study discontinuation. However, switching to aripiprazole was associated with a significantly increased likelihood of discontinuation for lack of efficacy. This difference was particularly robust in the 3 studies that compared switching to aripiprazole with continuing or switching to olanzapine (risk ratio,* 20.12; p=0.003).

Outcome of switching to or adding aripiprazole			
Outcome	**Studies**	**Patients**	**Risk Ratio***
Psychotic worsening			
Switching	7	3458	1.17
Adding	3	383	0.61
Discontinuation for lack of efficacy			
Switching	13	4858	1.46
Adding	8	881	2.08

Discussion: While the present results do not support an association between aripiprazole and worsening psychosis, the authors caution that industry sponsorship can have an effect on adverse-event reporting and two-thirds of the included studies had pharmaceutical industry funding. In practice, these observations suggest clinicians should closely monitor for worsening psychotic symptoms in patients switched to aripiprazole from another antipsychotic. The evidence on augmentation is insufficient to draw conclusions.

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

Takeuchi H, Fathi A, Thiyanavadivel S, Agid O, et al: Can aripiprazole worsen psychosis in schizophrenia? A meta-analysis of double-blind, randomized, controlled trials. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17r11489. From the Centre for Addiction and Mental Health, Toronto, Canada; and other institutions. **Funded by the Canadian Institutes for Health Research; and other sources. Three of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: **aripiprazole—*Abilify*; olanzapine—*Zyprexa***

***See Reference Guide.**

Preventing Rehospitalization in Bipolar Disorder

In a nationwide cohort study, lithium was associated with the lowest rate of rehospitalization due to mental or physical illness of all drug treatments for bipolar disorder.[1] The study also showed that long-acting injectable (LAI) medications resulted in better outcomes than their oral counterparts.

Methods: The cohort study included >18,000 patients (mean age, 47 years; 47% men) hospitalized for bipolar disorder in Finland between 1987 and 2012. The analysis had 3 outcomes: rehospitalization for any mental disorder (a proxy for treatment failure), hospitalization for all causes including somatic reasons (a proxy for overall drug effectiveness versus tolerability), and hospitalization for cardiovascular diseases (a proxy for cardiovascular tolerability). The incidence of each of these outcomes was compared within each patient during periods of exposure and nonexposure to specific medications and medication categories. Risk estimates were adjusted for demographic factors and concomitant psychotropic use.

Results: During an average follow-up of >7 years, 54% of patients were rehospitalized for psychiatric reasons. As a therapeutic group, mood stabilizers were associated with the lowest risk of psychiatric hospitalization, although the benefit was modest. Among individual drugs, lithium was associated with a largest reduction in risk of psychiatric rehospitalization (hazard ratio,* 0.67; p<0.001). Several other drugs were associated with large risk reductions, but these associations did not survive statistical correction for multiple comparisons or sensitivity analyses, in part due to small sample sizes. These agents included risperidone LAI, followed by gabapentin and perphenazine LAI. As a group, LAI formulations were associated with fewer hospitalizations than their oral counterparts (hazard ratio, 0.70; p=0.005), although few LAI

formulations were prescribed. The most commonly prescribed antipsychotic, quetiapine, was only modestly effective at reducing psychiatric hospitalization (hazard ratio, 0.92; p=0.02).

Only lithium was associated with a significantly lowered rate of all-cause hospitalization (hazard ratio, 0.71; p<0.001) after sensitivity analysis. Again, LAI antipsychotics were superior to oral formulations for all-cause hospitalization, and quetiapine was only modestly effective. Mood stabilizers, and particularly valproic acid and carbamazepine, were associated with increased risk of cardiovascular hospitalization. Benzodiazepines were associated with the highest rates of all 3 hospitalization outcomes.

Discussion: According to the authors, these results suggest lithium should remain the first-line treatment for bipolar disorder. LAI antipsychotics might provide a safe and effective alternative for patients who cannot take lithium. The results for quetiapine contrast those of a recent meta-analysis suggesting the agent is among the most effective at preventing mood episodes.[2] Although hospitalization is a clinically relevant outcome in bipolar disorder, not all patients who relapse experience full episodes or suicidality thus requiring hospitalization. The present findings do not necessarily apply to alleviating other symptoms, such as subthreshold depressive symptoms, that do not require hospitalization. In addition, because mania is a more common reason for hospitalization than depression in patients with bipolar disorder, the present results may favor drugs with more antimanic than antidepressant efficacy, as well as those with antisuicidal efficacy, as suicidal patients are hospitalized more often.

[1]Lahteenvuo M, Tanskanen A, Taipale H, Hoti F, et al: Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. *JAMA Psychiatry* 2018;75 (April):347–355. From the University of Eastern Finland; and other institutions. **Funded by the Finnish Ministry of Social Affairs and Health. All study authors disclosed potentially relevant financial relationships.**

[2]Leucht S, Davis J: Enthusiasm and skepticism about using national registers to analyze psychotropic drug outcomes [editorial]. *JAMA Psychiatry* 2018;75 (April):314–315. From the Technische Universitat Munchen, Munich, Germany; and other institutions. **One study author disclosed potentially relevant financial relationships; the other author declared no competing interests.**

Common Drug Trade Names*: carbamazepine—*Tegretol*; gabapentin—*Neurontin*; perphenazine—*Trilafon*; quetiapine—*Seroquel*; risperidone LAI—*Risperdal Consta*; valproate—*Depakene, Depakote

***See Reference Guide.**

Sustained-Release Amantadine for Dyskinesia

In a pooled analysis of 2 randomized controlled trials of patients taking levodopa for Parkinson's disease, sustained-release amantadine (*Gocovri*) was associated with significant reductions in both dyskinesia and total daily "off" time.

Methods: The 196 study participants were receiving a stable levodopa regimen to which placebo or sustained-release amantadine was added and increased to 274 mg/day (equivalent to 340 mg immediate-release amantadine). The primary efficacy measure was the Unified Dyskinesia Rating Scale (UDysRS), which includes patient ratings of "on" dyskinesia, "off" dystonia, and their effects on daily living, as well as more detailed clinician ratings of dyskinesia.

Results: At baseline, patients reported a mean of 2.8 hours of "off" time per day, 4.9 hours per day of "on" time with troublesome dyskinesia, and about 8.5 hours of "on" time without dyskinesia. Compared with placebo, sustained-release amantadine was associated with significantly greater improvement in dyskinesia (p<0.0001) at all study time points. By week 12, scores on the UDysRS decreased by 41% in the active treatment group, compared with 14% in the placebo group (p<0.0001). The magnitude of improvement was similar on the patient- and clinician-rated sections of the UDysRS. Patients receiving sustained-release amantadine reported increases in "on" time without troublesome dyskinesia. According to clinician global illness ratings, 57 patients in the active treatment group and 15 in the placebo group showed moderate-to-marked improvement. The benefits of amantadine were not significantly affected by baseline dyskinesia

severity. Hallucinations were the most troubling adverse effect of amantadine. One patient experienced suicidal ideation thought to be related to the study drug. Dizziness, dry mouth, peripheral edema, constipation, falls, and orthostatic hypotension were also common with sustained-release amantadine, affecting 13–16% of treated patients. Amantadine did not worsen the underlying Parkinson's disease or impair the motor activities of daily living.

Elmer L, Juncos J, Singer C, Truong D, et al: Pooled analyses of Phase III studies of ADS-5102 (amantadine) extended-release capsules for dyskinesia in Parkinson's disease. *CNS Drugs* 2018;32 (April):387–398. From the University of Toledo College of Medicine, OH; and other institutions. **Funded by Adamas Pharmaceuticals, Inc. Seven of 9 study authors disclosed potentially relevant financial relationships; the remaining 2 authors declared no competing interests.**

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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.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other 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.

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.

Risk Ratio: 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.

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 are posted at www.alertpubs.com.

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