In a manufacturer-sponsored study, the investigational multimodal antidepressant compound Lu AA21004 (vortioxetine) was superior to placebo in elderly patients with major depressive disorder.\(^1\)

**Background:** The new antidepressant combines several modes of serotonergic activity: it is a 5-HT\(_3\) and 5-HT\(_7\) receptor antagonist, an agonist of 5-HT\(_{1A}\) and partial agonist of 5-HT\(_{1B}\), and an inhibitor of the 5-HT transporter. Previous Phase II trials have demonstrated its short-term antidepressant efficacy in adults aged 18–65 years.\(^2\)

**Methods:** The present study enrolled 452 patients, aged ≥65 years, with major depressive disorder and a current episode of ≥4 weeks' duration and at least 1 prior depressive episode before age 60 years. Patients were excluded if they had a Mini-Mental State Examination score of <24. Most patients (about 91%) had concurrent medical, psychiatric, or neurological disorders. Participants were randomly assigned to 8 weeks of treatment with 5 mg/day Lu AA21004, 60 mg/day duloxetine (Cymbalta), or placebo. The duloxetine arm was included to test the validity of the trial, and efficacy of Lu AA21004 and duloxetine was not compared directly. The primary efficacy measure was the 24-item Hamilton Rating Scale for Depression (HAM-D24).

**Results:** At baseline, patients had at least moderate depression with a mean HAM-D score of 30. At 8 weeks, Lu AA21004 was associated with a 14-point mean decline in the HAM-D24, 3.3 points greater than the decline in the placebo group (p=0.0011). Duloxetine was also superior to placebo (17-point HAM-D decline; p<0.0001), indicating that the trial was capable of discriminating between placebo and an active agent. Lu AA21004 was also statistically superior to placebo at week 6, but not at week 4. The new agent was also superior to placebo for the secondary efficacy measures: the Montgomery-Asberg Depression Rating Scale, the Hamilton Rating Scale for Anxiety, and the Clinical Global Impressions-Severity and
Improvement scores. HAM-D24 response (≥50% reduction) occurred in 53% of patients receiving Lu AA21004 and in 35% of the placebo group (p<0.01); remission (HAM-D17 of <7) was observed in 29% and 19% of patients, respectively (p<0.05). Response and remission rates with duloxetine were 63% and 35%, respectively (p<0.001 vs placebo).

An exploratory analysis of treatment effects on cognition was also conducted. Lu AA21004 had direct positive effects on some measures of cognition. Duloxetine also had positive effects on cognition, but these were largely driven by improvement in depression.

Rates of treatment withdrawal were comparable in the 3 groups, with approximately 87% of patients receiving study medication for ≥50 days. There were few clinically relevant adverse effects in any treatment group. Sexual dysfunction occurred in 6 patients in the duloxetine group but none in the Lu AA21004 or placebo groups.

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

1Katona C, Hansen T, Olsen C: A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *International Clinical Psychopharmacology* 2012; published online ahead of print; doi 10.1097/YIC.0b013e3283542457. From University College London, U.K.; and H. Lundbeck A/S, Valby, Denmark. Funded by H. Lundbeck A/S and Takeda Pharmaceutical Company. All study authors reported relationships with commercial sources, including Lundbeck A/S.


*See Reference Guide.

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**Polypharmacy and Mortality in Schizophrenia**

A population-based study of mortality in patients with schizophrenia found that benzodiazepine use was associated with substantially increased mortality. Neither antidepressants nor concomitant use of multiple antipsychotics was linked with increased risk of death.

**Methods:** Investigators analyzed data from a registry of all residents of Finland who were hospitalized for the first time with schizophrenia between 2000 and 2007 and who had not been given a prescription for an antipsychotic in the preceding 6 months. The study population consisted of 2588 patients (mean age, 38 years; 62% males). Follow-up began after hospital discharge, and the mean duration was 4.2 years. Medication use was assessed using purchase records from a national insurance database. Comparisons of mortality were adjusted for age, gender, duration of hospitalization, and current and past use of medications, including psychotropics and selected other categories.

**Results:** A total of 160 patients died during follow-up; all but 16 deaths occurred after discharge from the index hospitalization. Current antipsychotic polypharmacy was not associated with increased mortality compared with monotherapy. The death rate was elevated in patients who did not receive an antipsychotic, compared with those who did (hazard ratio [HR],* 2.09). Compared with no antipsychotic use, current use of ≥2 antipsychotics was associated with lower mortality (HR, 0.41). Mortality was also reduced in patients currently taking antidepressants (HR, 0.57), but it was increased in patients taking benzodiazepines (HR, 1.91).

Risk of suicide was decreased markedly with antidepressant use (HR, 0.15), was increased with benzodiazepine use (HR, 3.83), and was not elevated in patients taking multiple antipsychotics. The rate of nonsuicidal deaths was elevated with benzodiazepine use, but not to a statistically significant degree. Of the 26 deaths in patients receiving benzodiazepines, 7 were from suicide and 5 from other accidental or violent causes.

**Discussion:** Current schizophrenia treatment guidelines do not recommend antipsychotic polypharmacy and offer no conclusions about use of antidepressants and benzodiazepines.
Results of the present study suggest overall treatment effectiveness can be investigated using mortality as an endpoint because both efficacy and tolerability have effects on mortality. A handful of previous studies using less accurate methods have reached conclusions similar to the present one.

The investigators speculate that the marked increase in suicide risk associated with benzodiazepine use may result from patients using the agents at faster rates than prescribed. In these cases, deaths are likely to occur when the medication runs out before expected and withdrawal occurs. Long-term benzodiazepine use, in violation of treatment guidelines, was fairly common in the Finnish patients and may be even more common in other developed countries, such as the U.S., where these drugs may contribute substantially to violent and accidental deaths in patients with schizophrenia.

Tiihonen J, Suokas J, Suvisaari J, Haukka J, et al: Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Archives of General Psychiatry 2012; 69 (May):476–483. From the University of Eastern Finland, Kuopio; and other institutions. Funded by the Finnish Ministry of Social Affairs and Health; and by Janssen-Cilag. All study authors disclosed financial relationships with commercial sources including Janssen-Cilag.

*See Reference Guide.

**Continuation Treatment with St. John's Wort**

In the continuation phase of a randomized trial in patients with major depressive disorder, St. John’s wort, sertraline (Zoloft), and placebo had similar efficacy. The investigators concluded that each of the treatments had antidepressant effects and that the robust placebo response, common to some acute-phase antidepressant trials, is noteworthy in a continuation study.

**Methods:** In the acute-treatment phase of this study, >400 patients completed a 1-week placebo run-in. Those who still met criteria for major depression (n=340) were randomly assigned to flexible-dose St. John’s wort (90–1500 mg/day), sertraline (50–100 mg/day), or placebo. A total of 124 patients responded (i.e., ≥50% decrease in the Hamilton Rating Scale for Depression [HAM-D] score) to the 8 weeks of acute treatment and went on to 18 weeks of additional treatment: 35 with St. John’s wort, 49 with sertraline, and 40 with placebo.

**Results:** In the 82 patients who completed the continuation phase (63%, 69%, and 68% of the sertraline, St. John’s wort, and placebo groups, respectively), average HAM-D scores did not differ among the groups: 5.7 with placebo, 7.1 with sertraline, and 6.6 with St. John’s wort. Results of an intent-to-treat analysis were similar. Remission, defined as a HAM-D score of ≤7, occurred in 58% of the sertraline group, 63% of the St. John’s wort group, and 74% of the placebo group. Relapse rates ranged from 8% to 16% and did not differ among groups. No secondary outcome measure differed among the groups.

**Discussion:** The acute trial phase may be considered as "failed" due to the lack of separation between placebo and the active comparator. Previous studies of St. John’s wort have shown efficacy in mild-to-moderate depression, but with small effect sizes; other studies have not shown superiority to placebo. It is interesting that the placebo effect was pronounced even in this study, which excluded responders to the placebo run-in. The failure of active treatment to separate from placebo may reflect the robust placebo effect and limited efficacy of biological treatments in mild-to-moderate depression. It may be important to note that, while neither active treatment significantly outperformed placebo, the efficacy of St. John’s wort and sertraline were equivalent.

Sarris J, Fava M, Schweitzer I, Mischoulon D: St. John’s wort (Hypericum perforatum) versus sertraline and placebo in major depressive disorder: continuation data from a 26-week RCT. Psychopharmacology 2012; doi 10.1007/s-0023-1306348. From the University of Melbourne, Australia; and other institutions. The clinical trial was funded by the NIMH; and the National Center for Complementary and Alternative Medicine. The present analysis was funded by the Massachusetts General Hospital Depression Clinical and Research Program; and other institutions. The authors declared no direct conflicts of interest.
Antidepressants and Cardiac Arrest Risk

Results of a population-based study suggest a link between antidepressant use and out-of-hospital cardiac arrest. The excess risk appears to be driven primarily by citalopram and nortriptyline.

**Background:** Reports of prolonged QT interval and torsades de pointes with citalopram have led to an FDA warning and to concerns about the cardiac safety of other antidepressants. Previous studies have examined the relationship between antidepressant classes and cardiac events, but none have evaluated individual agents. A large cohort study, using national data, was undertaken to further clarify the risks.

**Methods:** All patients who experienced an out-of-hospital cardiac arrest in Denmark between 2001 and 2007 were identified. Antidepressant use was evaluated in relation to cardiac arrest in >19,000 patients (mean age, 71 years). Each patient also served as his or her own control, with antidepressant exposure in the 30 days before the event compared with 2 more remote periods: 60–90 and 90–120 days before the event.

**Results:** A total of 2913 of the patients (15%) who had experienced cardiac arrest were receiving an antidepressant at the time. Of these, 58% received an SSRI only, 10% received a TCA only, and 19% received the SNRI venlafaxine or “other” antidepressants (e.g., mianserin, mirtazapine). Thirteen percent were treated with antidepressants from more than 1 class. Patients receiving an SSRI or a TCA had significantly fewer psychiatric hospitalizations and were less likely to receive concomitant antipsychotics; no other significant differences in comorbid diagnoses or concomitant medications were found at baseline.

Treatment with any antidepressant was associated with increased risk of out-of-hospital cardiac arrest (odds ratio [OR],* 1.23). When individual drug classes were examined, similar risk estimates were obtained for SSRIs and TCAs. Risk was not increased with venlafaxine or "other" antidepressants or with use of multiple antidepressants. When individual drugs were analyzed, risk was significantly increased with citalopram (OR, 1.29) and with nortriptyline (OR, 5.14).

**Discussion:** Inherent to its observational design, this study is limited by the lack of information on the indication for antidepressant therapy, the degree of severity, and other patient-specific factors that could influence outcomes. In addition, depression may be associated with cardiac events, and the study could not distinguish between the risks of starting medication and those associated with the disease itself. Nevertheless, the results do suggest that citalopram and nortriptyline may increase risk of cardiac arrest. Because the sample sizes were small for many of the other agents evaluated, their lack of association with cardiac arrest does not necessarily indicate that they are safer.

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**Clozapine-Associated Bowel Obstruction: Reminder**

Constipation is a relatively common (>5%) adverse effect of antipsychotic medications. A dynamical ileus, a nonmechanical obstruction of the bowel due to paralysis of the bowel wall, is a rare but serious adverse effect that has been associated with clozapine therapy. Anticholinergic effects are believed to underlie most cases of adynamical ileus, nearly 30% of which are fatal.
A 65-year-old male with schizophrenia had been receiving 30 mg/day olanzapine and was admitted for psychotic decompensation. Trials of other antipsychotics had been unsuccessful, and clozapine was initiated and titrated to 100 mg/day while the olanzapine was tapered for discontinuation. Docusate sodium was also started to prevent constipation. A CT scan, 9 days after starting clozapine (with olanzapine tapered to dosage of 10 mg/day), uncovered bowel obstruction, and other medical complications developed. Clozapine was stopped, and olanzapine was restarted. Several weeks later, the patient died from suspected complications of ileus.

This patient had no known risk factors for ileus (e.g., recent surgery, malignancy), but the combination of olanzapine and clozapine, both of which have anticholinergic effects, may have contributed to its development. Patients should be carefully monitored for this complication, particularly during cross-tapering of anticholinergic medications.


Drug Trade Names: clozapine—Clozaril; docusate sodium—Colace, and others; olanzapine—Zyprexa

Statin Use Reduced Depressive Symptoms in Heart Disease

According to the results of a prospective cohort study, use of statins may be associated with a reduced risk of depression in patients with stable coronary heart disease.1

Methods: The study, designed specifically to investigate the effect of statins on depression, was conducted in a naturalistic sample of patients with evidence of ≥1 of the following: coronary stenosis, exercise-induced ischemia, or a history of revascularization or myocardial infarction (MI). Use of statins was not randomized. Depressive symptoms were measured annually for 6 years using the self-report Patient Health Questionnaire, whose 9 items correspond with the DSM-IV criteria for major depression. Scores of ≥10 (out of a maximum of 27) were the cutoff for clinical depression.

Results: The analysis was based on 965 patients who had ≥2 annual measurements of depressive symptoms. At baseline, 65% were receiving statins. Users of statins were older, more likely to be male, and less likely to smoke than non-users. Statin use was more common among patients with a history of MI, stroke, diabetes, hypertension, and heart failure and in those using other cardiovascular drugs. Treated patients also had better exercise capacity, and lower non-HDL cholesterol and C-reactive protein values. Fewer statin-treated patients had a history of depression at baseline (27% vs 34%; p=0.02).

Statin use was associated with reduced depression both before and after adjusting for multiple variables. At baseline, patients who were taking statins had lower depressive symptom scores (p<0.01) and were less likely to meet the cutoff for clinical depression (17% vs 24%, p=0.02). During follow-up, patients who initially took statins continued to have fewer depressive symptoms (p=0.02 after adjustment). Of the patients taking a statin, 28% experienced an episode of clinical depression at least once during follow-up, compared with 40% of nonusers (adjusted odds ratio,* 0.67; p<0.02). Among the 776 patients who were free of depression at baseline, statin use was associated with a 40% reduction in depression risk (18% vs 28%; adjusted odds ratio, 0.62; p=0.026).

Discussion: The observed reduction in depression risk is consistent with the only other prospective cohort study evaluating the effect of statins on depression.2 Results of other studies have varied, possibly owing to different designs, less precise methods of measuring
depression, and smaller sample sizes. The results of the present study are consistent with the hypothesis that statins’ effects on cerebrovascular processes may protect against the development of vascular depression.

1 Otte C, Zhao S, Whooley MA: Statin use and risk of depression in patients with coronary heart disease: longitudinal data from the Heart and Soul Study. Journal of Clinical Psychiatry 2012;73 (May):610-615. From Charite University Medical Center, Berlin, Germany, and other institutions. Funded by the U.S. Department of Veterans Affairs and other sources. One study author disclosed financial relationships with commercial sources.


*See Reference Guide.

### Antipsychotics for Schizophrenia Relapse Prevention

The results of an updated meta-analysis suggest that, in patients with schizophrenia, maintenance antipsychotic therapy reduces relapse risk for up to 2 years.\(^1\) The effects appear to be particularly robust in patients recovering from a first episode and in those who have achieved remission.

**Background:** Naturalistic studies have shown that up to 80% of patients with schizophrenia experience a relapse within 5 years of successful treatment. Although the efficacy of maintenance pharmacotherapy has been documented, questions remain about optimal treatment durations and which patients should receive maintenance therapy.

**Methods:** Investigators identified randomized clinical trials of antipsychotic drugs for relapse prevention published in the Cochrane Schizophrenia Group’s registry through 2008 or indexed in PubMed, Embase, and ClinicalTrials.gov through mid-2011. The analysis included all randomized, placebo-controlled trials of continuation vs withdrawal of antipsychotic medications in patients who had stabilized during treatment.

**Results:** The investigators identified 65 randomized trials with 6493 participants. The average duration of follow-up was 26 weeks. Thirty-one studies included only inpatients, and 27 only outpatients; the remaining studies had either mixed populations or the setting was unclear. Mean illness duration was about 14 years, and mean length of stability before randomization was 36 weeks. Antipsychotics were tapered gradually in 11 studies and withdrawn abruptly in the rest. The trials’ definitions of relapse varied.

Relapse rates were lower in patients given antipsychotic drugs than in those given placebo. When the analysis was limited to reports that included both relapse and readmission as endpoints, 25% of patients who received active drug therapy relapsed, compared with 69% of patients who received placebo (relative risk,\(^*\) 0.35). Readmission rates were 10% and 25%, respectively (relative risk, 0.39). The difference in these outcomes was evident at all follow-up times, up to the maximum study length of 171 weeks.

The main cause of dropout was relapse because study protocols required that relapsed patients leave the study. Participants in drug groups dropped out because of inefficacy less often than those in placebo groups (16% vs 41%). Both groups had comparable rates of dropout for adverse events (5% and 4%, respectively). Fewer patients given active treatment than controls behaved aggressively (2% vs 12%). In the 3 studies that evaluated quality of life, quality was significantly better in patients who received active medication. Deaths were rare, and there were no differences in mortality between groups. Patients who received drug treatment had more adverse events, including dystonia, akathisia, movement disorders, sedation, and weight gain.

Relapse rates did not differ in patients who underwent abrupt vs gradual withdrawal of antipsychotics. Depot formulations of haloperidol and fluphenazine were associated with...
lower relapse rates than other drugs, and as a class, depot drugs were associated with lower relapse rates than oral drugs. The effects of first- and second-generation antipsychotics did not differ.

**Editorial:** This study presents robust evidence that maintenance therapy prevents relapse but leaves some questions unanswered. It remains unknown whether patients prefer drugs to placebo; whether the effects apply to negative symptoms and cognitive alteration as well as they do to positive symptoms, the usual definition of relapse; and what are the effects of maintenance treatment beyond 26 weeks, particularly on antipsychotic-related morbidity and mortality. Also, the comparable results after rapid and gradual drug withdrawal do not support the "supersensitivity psychosis" hypothesis in which it is proposed that increased dopamine receptor sensitivity after antipsychotic treatment may result in rapid relapse.

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

1. Leucht S, Tardy M, Komossa K, Heres S, et al: Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012; published online ahead of print; doi 10.1016/S0140-6736(12)60239-6. From the Technische Universität München, Munich, Germany; and other institutions. *Funded by the German Ministry for Education and Research*; and other sources. Several of the study authors disclosed financial relationships with commercial sources.

2. van Os J, Howes O: Antipsychotic drugs for prevention of relapse [editorial]. *Lancet* 2012; published online ahead of print; doi 10.1016/S0140-6736(12)60239-6. From Maastricht University, Netherlands; and King's College, London, U.K. The authors disclosed financial relationships with commercial sources.

**Antidepressants and Acute Glaucoma**

In a large, population-based study in older patients, antidepressants were associated with increased risk of acute angle-closure glaucoma.

**Methods:** Using linked administrative databases from the Institute for Clinical Evaluative Sciences in Toronto, Canada, investigators identified all adults, aged ≥65 years, who were treated for acute angle-closure glaucoma between 1998 and 2010. Acute angle-closure glaucoma was identified from records of its definitive treatment with peripheral laser iridotomy. Because this type of glaucoma is believed to be an effect of transient exposure, 3 risk periods were compared for antidepressant exposure: 30 days before glaucoma (the hazard window) and 2 earlier control periods. Patients with long-term antidepressant exposure (>6 months in the preceding year) were excluded.

**Results:** A total of 6470 patients were included in the analysis. The mean patient age was 74 years, and most (66%) were female. Concomitant medication use was common; 41% of patients were taking ≥1 other drug with anticholinergic properties, and 18% were taking other medications that could precipitate acute angle-closure glaucoma.

A total of 365 patients (5.6%) had received an antidepressant for <6 months in the year preceding glaucoma surgery; 56% received an anticholinergic antidepressant, 21% a serotonergic-noradrenergic antidepressant, and 22% a serotonergic-only agent. Antidepressant use was more likely to occur in the 30 days before glaucoma than earlier (odds ratio,* 1.62; p=0.005). Risks did not appear to vary significantly by antidepressant class. However, female gender, age ≤75 years, and concomitant use of nonantidepressant drugs with anticholinergic activity did appear to increase risk.

**Discussion:** Acute angle-closure glaucoma occurs when pupil dilation occludes the eye’s outflow system, leading to increased intraocular pressure and, potentially, to irreversible ocular damage. Advanced age is a risk factor. Although the iris contains adrenergic and cholinergic synapses, studies have shown that dopaminergic and serotonergic effects may
also influence iris tone and pupil diameter. The investigators recommend monitoring older patients with a recent antidepressant prescription for visual disturbances and eye pain.


*See Reference Guide.

**Counterfeit Adderall**

Adderall is currently on the FDA shortage list because of ingredient supply issues, and consumers may be looking for alternative supply sources. A counterfeit version of Teva Pharmaceutical Industries’ 30-mg Adderall tablets is currently being sold on the internet. Rather than mixed amphetamine salts, the tablets contain the pain relievers acetaminophen and tramadol (Ultram). The counterfeit tablets are white and have no markings. The authentic tablets are orange/peach with "dp" embossed on one side and "30" on the other. In addition, the package labels for the counterfeit products contain misspellings (e.g., "asparttne" rather than "aspartate"). The counterfeit products are considered ineffective, unsafe, and potentially harmful and should not be taken.


**Reference Guide**

**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 one group has half the risk of the other group.

**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.

**Relative Risk:** The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.