Adjunctive treatment with the selective estrogen receptor modulator (SERM) raloxifene (Evista) reduced illness severity in women with refractory schizophrenia in a placebo-controlled trial.

**Background:** Estradiol has been shown to have many positive effects in the brain, including enhanced neurogenesis, antiinflammatory effects, and enhanced dopamine release. Estradiol therapy has been shown to improve schizophrenia in women but has undesirable systemic effects. Raloxifene has mixed estrogen receptor agonistic and antagonistic activity, depending on its location in the body.

**Methods:** Study participants were peri- or postmenopausal women, aged 40–70 years, with schizophrenia or schizoaffective disorder and a Positive and Negative Syndrome Scale (PANSS) total score of ≥60 while receiving stable doses of antipsychotic medication. The women were randomly assigned to receive 12 weeks of adjunctive treatment with either 120 mg/day raloxifene or placebo. The primary outcome was change from baseline in the PANSS total score. Clinical response, a secondary outcome, was defined as a ≥20% reduction in PANSS score.

**Results:** A total of 54 women (mean age, 53 years) were randomized and began treatment. Of these, 46 (85%) completed the 12-week study. Withdrawals were for various circumstantial reasons that did not include adverse effects.

Mean baseline PANSS total scores did not differ between treatment groups: 80 and 77 in the raloxifene and placebo groups, respectively. By week 12, the women taking raloxifene had a significantly larger reduction in the PANSS total score than the placebo group (10 points vs. 4 points; p=0.02), as well as a larger reduction in the PANSS general psychopathology subscale (5.5 vs. 2 points; p=0.02). There were no significant differences between groups in the PANSS positive or negative symptom subscale changes, or in Montgomery-Asberg Depression Rating Scale scores or a battery of cognitive function tests. Clinical response was observed in 11 of 26 women receiving raloxifene and in 4 of 30 receiving placebo.
(42% vs. 13%; p=0.01; hazard ratio,* 5.79). Sex hormone levels appeared unaffected by raloxifene, and there were no notable adverse effects of treatment.

**Discussion:** There have been previous reports of positive effects of raloxifene in women with schizophrenia, but this is the first large study in women with refractory illness. There is some suggestion that its effects are dose-specific (a high dose of raloxifene was used in this study), symptom-specific, and gender-specific; requiring additional investigation. Potential risks of treatment should be noted; thromboembolic events and fatal stroke have been observed in large, controlled trials in women with or at high risk of cardiovascular disease.

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

Kulkarni J, Gavrilidis E, Gwini S, Worsley R, et al: Effect of adjunctive raloxifene therapy on severity of refractory schizophrenia in women: a randomized clinical trial. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1383. From Monash University, Melbourne, Australia; and other institutions. Funded by the Australian National Health and Medical Research Council. Four study authors disclosed potentially relevant relationships with commercial sources; the remaining 6 authors declared no competing interests.

*See Reference Guide.

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**Raloxifene and Negative Symptoms**

Clinical trials of the effects of the selective estrogen receptor modulator (SERM) raloxifene (*Evista*) on negative symptoms in women with schizophrenia have had inconsistent results. Results of a post-hoc exploratory analysis from 1 of these studies suggests that genetic variants may partially explain the failure to replicate study results.

**Methods:** This pharmacogenetic study was conducted as a secondary aim of a raloxifene clinical trial in postmenopausal women with schizophrenia and prominent negative symptoms. Patients were continued on stable doses of their background antipsychotic medication and were randomly assigned to treatment with 60 mg/day raloxifene or placebo for 24 weeks. The primary outcome of the genetic analysis was change from baseline in the negative symptom subscale of the Positive and Negative Syndrome Scale. Positive symptoms and general psychopathology were explored as secondary outcomes. Genotyping was performed for 3 single-nucleotide polymorphisms (SNPs) located in the estrogen receptor 1 (ESR1) gene and for 1 additional SNP in the UDP-glucuronosyltransferase 1A8 (UGT1A8) gene, which is involved in the major metabolic pathway of raloxifene.

**Results:** A total of 65 women (mean age, 62 years) participated in the study. None of the ESR1 SNP variants was associated with a differential response of negative symptoms to raloxifene. However, women who had a specific UGT1A8 genotype were more likely than others to show improvement in negative symptoms when receiving treatment with raloxifene (p=0.04). These women were homozygous for the C allele in the rs1042597 SNP of UGT1A8. One of the ESR1 gene SNPs, rs2234693, was associated with a larger response of positive symptoms to raloxifene (p=0.04).

**Discussion:** Because estrogens are known to improve psychotic symptoms, raloxifene and other SERMs are under investigation as potential treatments. Results of previous studies suggest they may improve positive and negative symptoms, general psychopathology, and cognition. Other studies have shown no effects on negative symptoms. It is possible that genetic variants in UGT1A8 may influence the bioavailability of raloxifene, leading to the inconsistent results.

**Pherine Nasal Spray for Social Anxiety**

A nasal spray containing a novel substance that targets chemosensory neurons was effective for as-needed treatment of social anxiety symptoms in a pilot study. The active ingredient is a pherine, an odorless synthetic molecule that induces rapid activation of specific brain areas, distinct from olfactory targets that can modulate autonomic and behavioral responses.

**Background:** FDA-approved medications for social anxiety disorder (i.e., paroxetine, sertraline, and venlafaxine) require sustained treatment and have limited benefits for many patients. The events/social encounters that cause distress for patients with social anxiety disorder are predictable; making an effective, rapidly-acting treatment that could be taken as needed before such an event a particularly attractive option.

**Methods:** The study was conducted in adults who met DSM-IV criteria for social anxiety disorder, generalized type, with symptoms of at least moderate severity. Subjects had no other significant psychiatric conditions and were not taking psychotropic medications. During a 2-week baseline period, study participants were encouraged to enter into distressing social and performance situations as much as possible and to record their anticipatory and peak symptoms using the Subjective Units of Distress Scale (SUDS). Those who had ≥6 occasions of significant distress during the baseline period then began 4 weeks of double-blind crossover treatment using the study investigational drug PH94B, or a placebo. They were instructed to use the medication ≤4 times daily, 15 minutes before an anticipated stressful situation but after they began to experience anticipatory anxiety. The primary study outcome was change from baseline in mean peak scores on the SUDS, which range from 0 to 100.

**Results:** A total of 22 patients participated in the study. Patients (50% women) had a mean age of 40 years and social anxiety onset at a mean age of 10 years. Participants administered a mean of 19 doses of active PH94B and 21 doses of placebo per 2-week period. No patient used more than 4 doses per day. Distressing situations recorded in the diaries ranged widely, and included job interviews, business presentations, and driving classes.

Mean peak SUDS scores were between 65 and 70 at baseline and they decreased by 16 points in patients receiving the active nasal spray, compared with 8 points in the placebo group (p=0.006; effect size,* 0.66). In patients switched from PH94B to placebo, mean peak SUDS scores worsened after the switch but did not return to baseline levels. Those who received placebo first showed a modest initial improvement, which increased when they were switched to active medication. Average baseline scores on the Liebowitz Social Anxiety Scale (LSAS) indicated patients were severely ill. In the first 2 weeks of treatment, patients who received PH94B had a larger (although nonsignificant) improvement in LSAS score than the placebo group (p=0.07), but the effect size was large (0.81). For the sample as a whole, differences between treatments in the LSAS were small, possibly because of a carryover effect of active medication in those who received it before placebo. It is

### Common Adverse Effects of Treatment

<table>
<thead>
<tr>
<th>Common Adverse Effects of Treatment</th>
<th>PH94B</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Ear, nose, throat symptoms</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Tachycardia</td>
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<td>1</td>
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<tr>
<td>Lightheadedness</td>
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<td>Irritability</td>
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<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>1</td>
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also possible that the significant positive effects of the medication on avoidance, which are reflected on the LSAS avoidance subscale, could have led patients to participation in more and more challenging situations. After the first 2 weeks, 7 of the patients receiving PH94B and 1 of those receiving placebo rated themselves as treatment responders. Clinical Global Impression–Severity ratings show a similar pattern, with between-group differences limited to the first 2 study weeks. Adverse effects were reported by 9 patients (see table on previous page); all were mild or moderate. Of the 22 patients, 21 completed the full 2 weeks of each treatment.

Discussion: While these results are positive, they cannot be considered definitive and will need to be replicated in larger studies.

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


From the Medical Research Network, LLC, New York, NY; and other companies including Pherin Pharmaceuticals, Los Altos, CA. Funded by Pherin Pharmaceuticals. All 6 study authors disclosed financial relationships with commercial sources.

Common Drug Trade Names: paroxetine—Paxil; sertraline—Zoloft; venlafaxine—Effexor

*See Reference Guide.

Early Lurasidone Dose Escalation in Schizophrenia

In a manufacturer-sponsored controlled trial, patients with a weak response to 80 mg/day lurasidone (Latuda) after 2 weeks demonstrated greater improvement after prompt dose escalation than patients continuing at the initial dose.

Background: Early nonresponse to antipsychotics is a robust predictor of poor short-term outcomes in patients with schizophrenia. Strategies to overcome poor response include augmentation, switching, and dose escalation. The present study was undertaken to evaluate early lurasidone dose escalation to the upper limit of the recommended range.

Methods: Study participants were 412 patients with schizophrenia of ≥6 months’ duration who were experiencing a symptom exacerbation. Participants were required to have a Positive and Negative Syndrome Scale (PANSS) total score of ≥80; at least moderate scores for ≥2 PANSS items—delusions, conceptual disorganization, hallucinations, or thought disturbances; and a Clinical Global Impression–Severity (CGI–S) rating of at least “moderately ill.” Patients were initially randomized to 3 treatment groups in a 1:2:1 ratio: 20 mg/day lurasidone, 80 mg/day lurasidone, and placebo. After 2 weeks, patients assigned to 80 mg lurasidone were classified as either early responders (≥20 decrease from baseline in the PANSS total score) or nonresponders (<20% PANSS improvement). Nonresponders were then re-randomized to either continue at the 80-mg dose or to have an increase to 160 mg/day. The primary efficacy endpoint was change from baseline to week 6 in PANSS total score. The CGI–S score was the key secondary endpoint.

Results: After 2 weeks of treatment with 80 mg/day lurasidone, 98 patients (50%) were classified as early nonresponders and underwent re-randomization. Among this group, the average decrease in PANSS total scores from baseline to 6 weeks was significantly greater for those who had dose escalation compared with those who continued on the 80-mg dose (17 vs. 9 points; p<0.05; effect size,* 0.52). CGI–S scores decreased by 1 point with dose escalation and by 0.6 in the comparison group (p=ns; effect size, 0.4). Overall response occurred in 74% of early nonresponders receiving dose escalation and in 60% of those continuing on the original dose (p=ns; number needed to treat,* 7).
Early nonresponders who underwent dose escalation reported a higher incidence of anxiety; abdominal discomfort; akathisia; insomnia; and somnolence compared with those who continued on the 80-mg dose. However, between-group differences in adverse effects were small and not significant. Dropout rates were similar in the early nonresponder groups (16–18%) regardless of re-randomized lurasidone dose.

**Discussion:** The effects of lurasidone dose escalation in this study were consistent with previous observations of a dose-response effect and with the drug’s known mechanisms of action. Serum drug concentrations are correlated with dopamine D₂ receptor occupancy, and doses greater than 80 mg/day may be required to reach threshold levels of D₂ receptor occupancy in some patients. A substantial percentage of patients considered nonresponders at week 2 went on to achieve response without dose escalation. Consequently, the increased probability of response with dose escalation must be weighed against the moderate increase in adverse effects associated with the dose increase.

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


*See Reference Guide.

**Adjunctive Liraglutide and Alzheimer's Progression**

In patients with Alzheimer’s disease, treatment with the GLP-1 analog liraglutide (*Victoza*) prevented the predicted decline of brain glucose metabolism, a marker for disease progression. Treatment did not affect cognition or amyloid deposition.

**Background:** Liraglutide is a GLP-1 receptor agonist used to treat type 2 diabetes. Common pathophysiological mechanisms for type 2 diabetes and Alzheimer’s disease include deficient insulin and GLP-1 signaling and beta-cell toxicity. GLP-1 receptor agonists cross the blood-brain barrier and have been reported to be neuroprotective of several neurodegenerative disorders in animal models.

**Methods:** Study subjects were 38 patients with Alzheimer’s disease, recruited from dementia clinics. Patients were required to be aged 50–80 years, able to give informed consent, and have mini-mental state examination scores of 18–21. Those with diabetes were excluded. In addition to existing medications (including cholinesterase inhibitors), participants were randomly assigned to treatment with liraglutide (maintenance dose, 1.8 mg injected daily) or placebo for 26 weeks. Outcomes included beta-amyloid deposition and glucose metabolic rate, measured by PET scan, and cognitive function, measured using the Brief Cognitive Status Exam from the Wechsler Memory Scale.

**Results:** Participants had a mean age of about 65 years. By chance, the treatment groups were somewhat unbalanced; members of the group receiving liraglutide were older on average, were more likely to be female, and had a significantly longer mean duration of Alzheimer’s disease—30 vs. 15 months (p<0.05). Four patients did not complete liraglutide treatment, but only 1 for a drug-related reason: nausea and anorexia. The patients who received liraglutide lost >10 pounds on average during the first 3 months, after which their weight stabilized. Fasting plasma glucose levels were lower during the study in the group receiving liraglutide.

Measures of amyloid deposits in different brain regions showed increases during the study, to a similar extent in both groups. In the placebo group, measures of glucose metabolism had
statistically significant decreases over the course of treatment in the precuneus (p=0.009); the parietal, temporal, and occipital lobes (p=0.04, 0.046, and 0.009, respectively); and the cerebellum (p=0.04). There were small, nonsignificant increases in glucose metabolism in the liraglutide group. Cognitive outcomes did not differ between the 2 groups.

Discussion: Current treatments for Alzheimer’s disease target neurotransmission without addressing neurodegeneration or neuronal metabolism. Liraglutide potentially affects neurodegeneration, neuronal performance, and neuroinflammation, suggesting it could reduce intracerebral amyloid deposition and improve glucose metabolism in the CNS of patients with Alzheimer’s disease, which would then improve cognition. In the present study, liraglutide prevented the decline of brain glucose consumption but had no effect on amyloid accumulation or cognition, possibly because the study lacked the statistical power to show positive effects of liraglutide on these outcomes.

Gejl M, Gjedde A, Egefjord L, Møller A, et al: In Alzheimer’s disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. Frontiers in Aging Neuroscience 2016; doi 10.3389/fnagi.2016.00108. From Aarhus University, Denmark; and other institutions. Funded by Novo Nordisk Scandinavia; and Aarhus University. Three study authors declared financial relationships with commercial sources; the remaining 10 authors declared no competing interests.

Canadian Depression Guidelines: Pharmacotherapy

The Canadian Network for Mood and Anxiety Treatments (CANMAT) has updated its guidelines for the use of pharmacotherapy, psychological therapies, neurostimulation, and complementary and alternative treatment of unipolar major depression in adults. The pharmacotherapy update is based on meta-analyses and systematic reviews published between 2009 and 2015 and includes information on recently introduced drugs, meta-analyses of the relative efficacy of antidepressants, adjunctive versus switching strategies, and management of the new DSM-5 entity persistent depressive disorder.

Most second-generation antidepressants are recommended as first-line treatments for depression of at least moderate severity, including SSRIs; SNRIs; agomelatine; bupropion; and mirtazapine. Antidepressants are not recommended as first-line treatment for mild depression unless the patient has not had a response with nonpharmacologic interventions, there is a history of response to an antidepressant, or the patient prefers a drug to the alternatives. A number of comparative meta-analyses have shown little difference in efficacy among agents, although some appear to have modest superiority: escitalopram, mirtazapine, sertraline, and venlafaxine. However, studies only show a 5–6% differential in efficacy among all antidepressants. There is no evidence to support any particular agent in older patients, those with anxiety, or those with a longer duration of illness; nor does evidence provide any medication selection guidance in patients with different depressive subtypes.

Several new antidepressants have been introduced since the CANMAT 2009 guideline was released. Levomilnacipran, an SNRI, has greater selectivity for noradrenaline compared with other agents in its class. Vilazodone is a multimodal agent that must be taken with food and titrated according to a fixed schedule in order to avoid GI side effects. Both levomilnacipran and vilazodone are endorsed as second-line therapies. Vortioxetine, another multimodal antidepressant, may have additional beneficial effects on cognition and is included as a first-line treatment option.

The guideline recommends that prior to prescribing, assessment should be made of suicidality, bipolarity, and depression symptom specifiers or dimensions; for treatment preferences; and for antidepressant medication history including each drug’s dose, duration, response, and side effects. Once given an antidepressant prescription, patients should be reassessed for
tolerability, safety, and early efficacy within 2 weeks. Pharmacogenetic testing for drug selection or routine therapeutic drug monitoring is not recommended. If an initial course of treatment is not successful, the decision between adding an adjunctive medication and switching should be individualized based on clinical factors. There is little evidence supporting selection of a specific adjunctive agent to target specific residual symptoms.

The DSM-5 has added a new diagnosis, persistent depressive disorder, which subsumes the DSM-IV categories of dysthymic disorder and chronic major depressive disorder. A single meta-analysis supported the efficacy of most of the drugs in depression lasting ≥2 years. However, some experts have argued that this disorder requires a chronic disease management approach, with greater relative emphasis on improving function and quality of life and greater use of psychotherapy and nondrug treatments.

Kennedy S, Lam R, McIntyre R, Tourjm an S, et al: Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3: pharmacological treatments. Canadian Journal of Psychiatry 2016; doi 10.1177.0706743716659417. From the University of Toronto, Canada; and other institutions. Funded with internal CANMAT funds. Twelve study authors declared financial relationships with commercial sources; 2 authors declared financial relationships with noncommercial sources; and 4 authors declared no competing interests.

Common Drug Trade Names: agomelatine (not available in U.S.)—Valdoxan; bupropion—Wellbutrin; escitalopram—Lexapro; levomilnacipran—Fetzima; mirtazapine—Remeron; sertraline—Zoloft; venlafaxine—Effexor; vilazodone—Viibrid; vortioxetine—Trintellix

Antipsychotics and Birth Defects

According to results of a large population-based study, with the possible exception of risperidone, use of antipsychotic medications early in pregnancy is not associated with increased risk of congenital malformations.¹

Methods: Data were analyzed from >1.3 million pregnant women who gave birth in 2000–2010 and who were covered by Medicaid. Women exposed to known teratogens or with evidence of chromosomal abnormalities were excluded. Exposure to an antipsychotic was based on filling a prescription during the first 90 days of pregnancy, the relevant period for organogenesis. The overall incidence of congenital malformations and that of 13 specific malformation groups were analyzed, with separate comparisons for first- and second-generation antipsychotics. Following propensity score* stratification, congenital malformations were compared among the offspring of the 733 first-generation antipsychotic-exposed women, 9258 second-generation antipsychotic-exposed women, and unexposed women. Final comparisons were adjusted for a broad range of potential confounders including age, race, smoking, multiple gestation, indication for antipsychotic use, comorbid conditions, concomitant medication use, and general markers of the burden of illness.

Results: The most frequently used second-generation antipsychotic was quetiapine (n=4221), followed by aripiprazole (n=1756), risperidone (n=1566), olanzapine (n=1394), and then ziprasidone (n=697). Overall, rates of congenital malformations were higher among exposed infants than those who were not exposed—38 per 1000 with first-generation antipsychotics and 45 per 1000 with second-generation antipsychotics, compared with 33 per 1000 with no exposure. However, after adjustment for multiple confounding factors, neither relative risk (RR)* for overall malformations nor cardiac malformations were increased with first-generation antipsychotics and 45 per 1000 with second-generation antipsychotics, compared with 33 per 1000 with no exposure. However, after adjustment for multiple confounding factors, neither relative risk (RR)* for overall malformations nor cardiac malformations were increased with first-generation agents (RRs, 0.9 and 0.75, respectively) or with second-generation antipsychotics (RRs, 1.05 and 1.06, respectively). Among individual agents, only risperidone showed significantly increased risk for both overall and cardiac malformations (RR, 1.26 for both).

Discussion: These results support prescribing antipsychotic medication in pregnant women as it is justified by the need to minimize the overall impact of the disease, which is greater
than that of the drug.2 The risperidone association could be due to chance or unmeasured confounding factors and it should not yet be viewed not as causal, but rather as a potential safety signal requiring further investigation. It is also possible that prolactin elevation or its treatment might be a link.

1Huybrechts K, Hernandez-Diaz S, Patomo E, Desai R, et al: Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1520. From Brigham and Women's Hospital Boston, MA; and other institutions. **Funded by the NIMH; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 8 authors declared no competing interests.**

2Wisner K, Jeyong H, Chambers C: Use of antipsychotics during pregnancy: pregnant women get sick—sick women get pregnant [editorial]. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1538. From Northwestern University Feinberg School of Medicine, Chicago, IL; and other institutions. **Two authors disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

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

*See Reference Guide.*

### Reference Guide

**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**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.

**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 is the treatment.

**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. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

**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 are posted at [www.alertpubs.com](http://www.alertpubs.com).