Eszopiclone Warning

A study found that patients taking the recommended 3-mg dose of the sleep aid eszopiclone (Lunesta) at bedtime continued to have impaired driving skills, memory, and coordination for as long as 11 hours after ingestion. Patients were often unaware they remained impaired. As a result, the FDA has recommended decreasing the starting dosage of eszopiclone to 1 mg at bedtime. The change should result in lower blood levels the next day. The agency continues to evaluate the risk of impaired alertness with other sleep aids, including over-the-counter agents.

Eszopiclone containing sleep aids: drug safety communication – can cause next-day impairment. Available at www.fda.gov/drugs/drugsafety/ucm397260.htm.

Melatonin for Olanzapine Metabolic Effects

In a small placebo-controlled trial, adding melatonin to olanzapine (Zyprexa) therapy attenuated weight gain in patients with schizophrenia.

**Background:** Melatonin is a multifunctional hormone that regulates sleep, energy metabolism, and fat distribution. It was shown to decrease visceral fat and abdominal obesity in several different animal models. Its sleep-enhancing effects, but not its metabolic effects, have been previously studied in patients with schizophrenia.

**Methods:** The study enrolled 48 inpatients, aged 18–65 years, who were experiencing first-episode schizophrenia and were candidates for olanzapine treatment. Participants received olanzapine plus double-blind, randomly assigned melatonin or placebo for 8 weeks. In all patients, olanzapine was started at 5 mg/day and titrated to a maximum dosage of 25 mg/day. A 3-mg melatonin or placebo tablet was administered every evening at 9:00 PM. Participants remained hospitalized for at least the first few weeks of treatment, and compliance was directly observed. After discharge, compliance was assessed by pill count. Weight, biochemical measurements, and psychiatric symptoms were assessed at baseline and after 4 and 8 weeks of treatment. Change from baseline in body weight was the primary study outcome.
Results: Of the 48 randomized patients, 36 had ≥1 post-baseline assessment and were included in the analysis. At the 8-week evaluation, patients in the melatonin group had gained significantly less weight than those in the placebo group (3.3% vs. 8.5%; \( p = 0.023 \)). Patients in the melatonin group also had a significantly smaller increase in body mass index than the placebo group (mean difference, 1 point; \( p = 0.024 \)) and a smaller increase in waist circumference (mean difference, 2.83 cm; \( p = 0.041 \)). Fewer patients in the melatonin group gained >7% of their initial weight: 9 vs. 4 (50% vs. 22%; \( p = 0.083 \)). Melatonin was associated with a near-significant decrease in triglycerides, but not with any effect on insulin levels, fasting blood glucose, insulin resistance, or cholesterol. An unexpected finding was a difference between treatment groups in psychotic symptoms: Patients in the melatonin group had significantly lower Positive and Negative Syndrome Scale (PANSS) total scores than those in the placebo group (\( p = 0.006 \)).

Discussion: Melatonin may counteract metabolic disturbances in schizophrenia by restoring normal sleep rhythms, enhancing energy expenditure, or interacting with the hormone leptin. The unexpected effect on psychotic symptoms suggests that the disturbances in melatonin secretion that have been reported in schizophrenia may be associated with the primary symptoms of the disorder.

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


Emerging Treatments for Negative Symptoms

Negative symptoms are an area of great unmet need in the treatment of schizophrenia. There is no common understanding of the neurobiology of these symptoms that would help in the development of new drug therapies. Several drugs that target glutamatergic and cholinergic systems are in advanced stages of development, but these and agents with other mechanisms show limited promise, according to a literature review.

Key brain regions involved in motivation may function abnormally in patients with negative symptoms: the prefrontal cortex, anterior cingulate, and striatum. In contrast to the excess of dopamine associated with positive psychotic symptoms, these regions involved in the reward circuitry may respond subnormally to changes in dopamine input or may receive too little of it. GABA and glutamate are important in regulating neural loops that connect these areas and also affect the modulation of dopamine release. Specifically, hypofunction of NMDA receptor transmission may be responsible for functional alteration in these key brain regions.

Drugs that enhance NMDA receptor activation are supported by preliminary evidence. These agents include glycine-site agonists such as glycine, D-serine, D-cycloserine, D-alanine, and sarcosine. Another approach is to increase synaptic D-serine levels by inhibiting its enzymatic degradation with an agent such as sodium benzoate. A third approach is to target the glycine binding site of the NMDA receptor. Bitopertin, a glycine reuptake inhibitor that increases the availability of synaptic glycine, a coagonist (with glutamate) of the NMDA receptor, is in phase III clinical trials, although results have been mixed. (See next story.)

The nicotinic acetylcholine receptor agonists galantamine and donepezil have shown mixed results in early-phase clinical trials. However, both had greater effects on negative symptoms than cognition. Another agent in this category, TC-5619, had promising, but mixed, effects on cognition and negative symptoms in a proof-of-concept study.
Glutamatergic transmission can also be targeted by modifying metabotropic glutamate receptors, specifically receptor subtype 2. Research on this drug category is in very early stages.

Several other drugs and drug categories are either in preliminary studies or have shown mixed or weak evidence of efficacy: psychostimulants; antiinflammatory drugs; selective serotonin-3 receptor antagonists; lamotrigine; the NMDA receptor antagonist memantine; the neurosteroid pregnenolone; and sildenafil. Folate supplementation has shown promising effects, but only in a subgroup of patients.

Chue P, Lalonde J: Addressing the unmet needs of patients with persistent negative symptoms of schizophrenia: emerging pharmacological treatment options. *Neuropsychiatric Disease and Treatment* 2014;10:777–789. From the University of Alberta, Canada; and Roche SAS, Boulogne-Billancourt, France. **Funded by F. Hoffmann-LaRoche, Ltd.** Both study authors disclosed financial relationships with commercial sources.

**Drug Trade Names:** donepezil—Aricept; galantamine—Razadyne; lamotrigine—Lamictal; memantine—Namenda; sildenafil—Viagra

## Bitopertin for Negative Symptoms of Schizophrenia

In a manufacturer-sponsored, multicenter, phase II clinical trial, the glycine reuptake inhibitor bitopertin showed promise in improving negative symptoms.1

**Methods:** The proof-of-concept study, conducted at 66 sites in 9 countries, enrolled patients receiving stable antipsychotic medication who had prominent negative symptoms and few positive symptoms, and no confounding depression or extrapyramidal symptoms. After a 4-week run-in to document clinical stability, patients were randomly assigned to 8 weeks of double-blind bitopertin at 10, 30, or 60 mg/day or placebo. The primary efficacy outcome was change from baseline in a composite score of negative and global symptoms on the Positive and Negative Syndrome Scale (PANSS).

**Results:** A total of 323 patients completed the run-in and were randomized to study treatment; 231 completed the study according to protocol. (See table for baseline characteristics.) The majority of patients who withdrew before completing the protocol did so for non-safety-related reasons. However, discontinuation for adverse events occurred more frequently in the 2 higher dose bitopertin groups.

### Baseline Characteristics of the Per-Protocol Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=61)</th>
<th>10 mg/day Bitopertin (n=60)</th>
<th>30 mg/day Bitopertin (n=57)</th>
<th>60 mg/day Bitopertin (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years)</td>
<td>39</td>
<td>41</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>56</td>
<td>68</td>
<td>53</td>
<td>62</td>
</tr>
<tr>
<td>Previous Hospitalizations (mean number)</td>
<td>4.3</td>
<td>4.3</td>
<td>2.8</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Primary Antipsychotic (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>26</td>
<td>32</td>
<td>27</td>
<td>28</td>
</tr>
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<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>11</td>
<td>17</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Risperidone</td>
<td>30</td>
<td>27</td>
<td>41</td>
<td>34</td>
</tr>
<tr>
<td>Risperidone LA</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>
Baseline PANSS Negative Symptom Factor scores averaged 26–27 points. In the per-protocol population, these scores were significantly reduced by 25% in both the 10-mg and 30-mg bitopertin groups, compared with nonsignificant declines of 19% with placebo and 20% with the 60-mg dose. Effect sizes* were 0.37 and 0.40 for 10 and 30 mg bitopertin, respectively. The proportion of patients who met response criteria (i.e., ≥20% decrease in PANSS Negative Symptom Factor score) was significantly higher with 10 mg bitopertin than with placebo (65% vs. 43%; p=0.01). Response rates with the 30-mg and 60-mg doses (60% and 43%) did not differ from placebo. Other secondary outcomes, including the Clinical Global Impression scores and measures of function, all favored the 2 lower bitopertin doses and especially the 10-mg dose. An intent-to-treat analysis had similar results that reached trend-level significance.

Adverse events were dose-related. The safety profile of the 10-mg dose was similar to placebo. The most frequent adverse events, each affecting ≥5% of patients, were somnolence, dizziness, and headache. There were no drug-related effects on weight, glucose, lipids, or ECG parameters, including the QTc interval. The mean estimated occupancy of the glycine transporter type 1 receptor was 47% in the 10-mg bitopertin group, 67% with 30 mg, and 77% with 60 mg. This finding suggests moderate receptor occupancy was associated with the strongest clinical effect.

Editorial. Bitopertin was developed based on the glutamatergic model of schizophrenia and appears to be the first suitable drug to provide a good test for this hypothesis. As a phase II exploratory study, the present results were encouraging; however, the manufacturer recently announced that 2 of 3 subsequent phase III studies have had negative results. The negative studies need to be examined to determine whether patient heterogeneity or design factors led to the failure to replicate these promising results.

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


Drug Trade Names: aripiprazole—Abilify; olanzapine—Zyprexa; paliperidone—Invega; quetiapine—Seroquel; risperidone—Risperdal; risperidone LA—Risperdal Consta

*See Reference Guide.

Efficacy of Medications for Alcohol Use Disorders

According to results of a meta-analysis, acamprosate and naltrexone are effective in treatment of alcohol use disorders when added to psychosocial interventions. In addition, nalmefene and topiramate have at least suggestive evidence of efficacy.¹

Methods: The systematic review and meta-analysis was based on all studies of pharmacotherapy for DSM-III or IV alcohol use disorders published since 1970, plus unpublished studies from various sources. The literature search included all medications FDA-approved for alcohol use disorders, as well as 23 off-label medications. Study subjects were adult outpatients who received treatment for ≥12 weeks. In most studies, medication was prescribed as an adjunct to psychosocial interventions. Outcomes included measures of alcohol consumption; injuries; quality of life; mortality; and adverse effects.

Results: A total of 123 studies were included in the review, and 95 in the meta-analysis. These included 44 placebo-controlled trials of naltrexone, 22 of acamprosate, and 4 of disulfiram. There were few placebo-controlled trials of off-label agents including SSRIs and other antidepressants, first- and second-generation antipsychotics, and mood-stabilizing anticonvulsants.
Both naltrexone and acamprosate were associated with improvement in measures of alcohol consumption. To prevent 1 abstinent person from returning to any drinking, the numbers needed to treat (NNT)* were 12 for acamprosate and 20 for oral naltrexone. (These NNTs reflect the added effects of medication beyond those of psychosocial interventions and placebo.) Naltrexone and acamprosate showed equivalent efficacy in head-to-head comparisons. Disulfiram did not have a positive effect on any outcome. For most medications used off-label, there was insufficient evidence to determine effectiveness in reducing alcohol consumption. However, nalmefene and topiramate were associated with lower consumption. Valproic acid, investigated in 2 small studies including 1 in patients with bipolar disorder, also appeared to be effective.

There were too few studies of health outcomes to assess the effects of treatment on these outcomes. Evidence on adverse effects was also insufficient. There was no evidence of differential treatment effects on subgroups such as smokers versus nonsmokers, age and gender groups, or ethnic minorities.

Editorial. This analysis highlights treatment options in an area where care is suboptimal.2 Patients with alcohol use disorders receive poorer care than those with any other chronic conditions; and medications are particularly underutilized. Because treatment of alcohol use disorder is now considered an essential benefit under health care reform, many more patients will require access to these treatments.

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


2Bradley K, Kivlahan D: Bringing patient-centered care to patients with alcohol use disorders [editorial]. JAMA 2014;311 (May 14):1861–1862. From Group Health Research Institute, Seattle, WA; and other institutions. One author disclosed financial relationships with commercial sources.

Drug Trade Names: acamprosate—Campral; disulfiram—Antabuse; nalmefene (not available in the U.S.)—Selincro; naltrexone (oral)—ReVia; topiramate—Topamax; valproic acid—Depakene, Depakote

*See Reference Guide.

Overview of Vortioxetine

Vortioxetine was recently approved by the FDA for the treatment of major depressive disorder. The agent has a novel mechanism of action but apparently no clear advantages over other available treatments, according to a review of published literature.

Vortioxetine is a multimodal agent with the same major mechanism of action as most SSRIIs— inhibition of the 5-HT transporter protein. It also has a mix of agonistic and antagonistic effects at different 5-HT receptor subclasses. The result of treatment is increased levels of serotonin, norepinephrine, dopamine, acetylcholine, and histamine.

Vortioxetine was investigated in 10 short-term (6–8 week), randomized, placebo-controlled clinical trials in patients with major depressive disorder. The effects of doses ranging from 1 to 20 mg/day on the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS) were evaluated. Six of the 10 trials found at least 1 dose of vortioxetine to be superior to placebo. Rates of response (>50% symptom reduction) ranged from 34% to 72%, and remission rates from 21% to 49%, and they do not appear to be dose related. Many secondary outcomes were also evaluated, including measures of anxiety and disability, but vortioxetine was not consistently effective for these outcomes.

In an international relapse-prevention study, randomized vortioxetine was superior to placebo, with relapse rates of 13% versus 26% (p=0.0013) at 64 weeks in patients whose depression had
remitted with acute vortioxetine treatment. In several 52-week open-label extension trials, the proportion of patients whose depression responded or remitted increased with time. Withdrawal rates for adverse events ranged from 5% to 10%, and relapse rates in patients who were in remission at baseline were <10%.

Vortioxetine is available in doses ranging from 5 to 20 mg. It has a long plasma half-life of 57–66 hours and can be taken once a day. It is metabolized primarily by CYP2D6. The maximum recommended dosage of vortioxetine is 20 mg/day, or 10 mg/day in patients who are poor CYP2D6 metabolizers. The dose should be reduced by 50% if vortioxetine is given with drugs that inhibit CYP2D6, such as bupropion, fluoxetine, and paroxetine. Because of the risk of serotonin syndrome, vortioxetine is contraindicated in patients taking MAOIs and should be used cautiously with other serotonergic drugs.

Vortioxetine was associated with sexual dysfunction in the clinical trials, but rates decreased with extended use. It does not cause weight gain and is not associated with any laboratory abnormalities. It carries the usual FDA warning about suicidality. The efficacy of vortioxetine in comparison with other antidepressants or in treatment-resistant disease has not been evaluated. Its on-patent status will limit its affordability.

Benzodiazepines and Functional Decline

In a cohort of community-dwelling older adults, use of benzodiazepines was associated with declines in function and more frequent pain over 8.5 years of follow-up. Mobility was also reduced to a greater degree in benzodiazepine users, but only those living in rural areas.

Methods: In 1999–2001, 1000 study participants, aged ≥65 years, were enrolled in the longitudinal University of Alabama at Birmingham Study of Aging. Participants were selected randomly from Medicare beneficiaries, balanced by gender, rural or urban residence, and black or white ethnicity. All were living in their homes and had sufficient cognitive function to be interviewed. Medication use was ascertained at baseline. Mobility was measured using the Life Space Assessment, which asks about physical movement over the previous 4 weeks. Participants were also questioned about 5 basic activities of daily living (ADLs; e.g., dressing and eating), 6 instrumental ADLs (IADLs; e.g., shopping and using the telephone), and the frequency of pain.

Results: At study entry, participants had a mean age of 75 years, and about 10% of the sample was taking benzodiazepines. At baseline, rates of benzodiazepine use were higher in older patients, in women, in those with anxiety or depressive symptoms, and in those with lower initial levels of mobility and function. A total of 941 cohort members participated in ≥1 follow-up interview; nearly 400 died during follow-up.

Over the 8.5 years of follow-up, benzodiazepine use was significantly associated with a reduced sphere of mobility, but only in rural residents. In the entire sample, benzodiazepine use was also associated with decline in ADL and IADL performance and increases in pain frequency and pain interference with usual activities. These associations were present regardless of adjustment for demographic variables and factors such as income difficulty, cognitive function, Charlson Comorbidity Index count, smoking, and drinking alcohol. The associations with ADL and IADL, but not pain, tended to lose statistical significance when analyzed in a model that included measurements of depression and anxiety.
Discussion: Although benzodiazepine use does appear to affect mobility and functional decline, mental health symptoms that may have led to benzodiazepine prescription may also contribute to functional decline. The study results suggest benzodiazepines may have a continuous cumulative effect on physical movements and coordination as well as central pain processing over time.

Study Rating*—14 (100%): This study met all criteria for an observational study.


*See Reference Guide.

SSRI/PPI Interactions

Coadministration of proton pump inhibitors and SSRIs can result in clinically significant elevations of SSRI blood levels, according to results of a laboratory study.

Methods: The study, conducted over an 11-year period, included samples sent for the analysis of levels of citalopram, escitalopram, and sertraline. The investigators identified samples in which any of these antidepressants was coadministered with omeprazole, esomeprazole, lansoprazole, or pantoprazole in a patient aged >16 years (n=813). SSRI serum concentration-to-dose ratios (C/D ratios) in these samples were compared with those of 4500 samples from patients taking an SSRI but not a PPI. The analysis was adjusted for patient age and gender.

Results: All 4 PPIs increased the level of at least 1 of the SSRIs to some degree. The effect was larger for omeprazole and esomeprazole than for lansoprazole and pantoprazole. Escitalopram was affected to a greater extent than the other SSRIs. (See table.) Patient age was found to significantly affect the interaction between PPI use and SSRI levels. Younger patients, aged 20–60 years, showed the weakest effect of comedication. The effect was more pronounced in those aged >60 years and strongest in those aged >80 years. PPI-related SSRI elevations were 5–20% less in men than in women, an effect not seen consistently in other studies.

Discussion: These study results suggest that escitalopram dosages should be reduced in patients taking omeprazole or esomeprazole because the elevated levels could increase risk for QTc prolongation.

Gjestad C, Westin A, Skogvoll E, Spigset O: Effect of proton pump inhibitors on the serum concentrations of the selective serotonin reuptake inhibitors citalopram, escitalopram and sertraline. *Therapeutic Drug Monitoring 2014; doi 10.1097 /FTD.0000000000000101. From St. Olav University Hospital, Trondheim, Norway; and other institutions. Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.

Drug Trade Names: citalopram—Celexa; escitalopram—Lexapro; esomeprazole—Nexium; lansoprazole—Prevacid; omeprazole—Prilosec; pantoprazole—Protonix; sertraline—Zoloft

Antipsychotics, Prolactin, and Breast Cancer

FDA-approved antipsychotic drugs are labeled with warnings about their use in patients with established breast cancer. These warnings are based mainly on studies in transgenic mouse models, which clearly show an important role for prolactin pathways in the genesis and progression of mammary cancer. Data on risks in humans are limited, particularly for first-generation antipsychotics that have not been scrutinized as closely as newer drugs. The Nurses' Health Study showed that women with high-normal prolactin levels have an increased risk of
breast cancer, more rapid disease progression, and a lower survival rate. Drug database studies have not demonstrated a relationship between antipsychotics and breast cancer risk, and no clear association has been shown in clinical studies.

Clinicians must weigh the potential risks of treatment against the known benefits. The duration of antipsychotic treatment, the mental illness diagnosis and severity, potential medication effects on serum prolactin, and breast cancer staging should all be considered in the decision-making process. Women with intraductal breast cancers should be assumed to have an elevated risk of prolactin-related disease progression if they are receiving an antipsychotic.

For women with breast cancer who are receiving antipsychotic therapy, serum prolactin levels should be monitored, and switching to another class of drugs or adding dopamine agonists considered. If antipsychotics are necessary, treatment with drugs less likely to increase prolactin (see table) should be considered.

Prolactin is secreted mainly by the pituitary gland, but also in a variety of other tissues. Inhibition of prolactin release is controlled by dopamine; thus antipsychotic drugs that block dopamine D2 receptors result in increased prolactin levels. In addition, the metabolic side effects of antipsychotics, such as insulin resistance, dyslipidemia, and obesity, may contribute to breast cancer risk.

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Estimated Prolactin Increase</th>
<th>Recommendation for Use in Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>45 to &gt;100 ng/mL</td>
<td>Avoid</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>45 to &gt;100 ng/mL</td>
<td>Avoid</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>28–50 ng/mL</td>
<td>Avoid</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>23–34 ng/mL</td>
<td>Caution</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>20–32 ng/mL</td>
<td>Caution</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>≥5 x Upper Limit of Normal</td>
<td>Caution</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Minimal</td>
<td>Preferred</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Minimal</td>
<td>Preferred</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Minimal</td>
<td>Preferred</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Minimal</td>
<td>Preferred</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>May lower prolactin levels</td>
<td>Preferred</td>
</tr>
</tbody>
</table>

| Drug Trade Names: | aripiprazole—Abilify; asenapine—Saphris; clozapine—Clozaril; haloperidol—Haldol; iloperidone—Fanapt; lurasidone—Latuda; olanzapine—Zyprexa; paliperidone—Invega; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon |

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

**Number Needed to Treat (NNT):** 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.

**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.