New Atypical Antipsychotic Approved

The FDA has approved a new, once-daily atypical antipsychotic lurasidone (Latuda) for the treatment of schizophrenia in adults.¹ According to the manufacturer, the FDA reviewed data from >40 clinical trials involving >2500 patients. The approval was based on results of four 6-week placebo-controlled trials in which lurasidone produced significantly greater improvement than placebo on the Positive and Negative Syndrome Scale and the Brief Psychiatric Rating Scale.² None of the placebo-controlled trials had a duration of >6 weeks, and the effectiveness of lurasidone for longer-term use has not been established. Common adverse effects include akathisia, nausea, tremor, parkinsonism, and agitation. In short-term studies, lurasidone produced a mean weight gain of <2 lbs, and in longer-term open-label extension studies, patients lost an average of 1.5 lbs over 1 year. The recommended starting dosage is 40 mg once daily, and the maximum dosage is 80 mg/day. Lurasidone should be taken with food. As with all other atypical antipsychotics, the lurasidone label will carry a Boxed Warning on increased risk of death in elderly patients treated for dementia-related psychosis (an unapproved indication). Lurasidone is expected to be available in U.S. pharmacies in early 2011.


Adjunctive Sildenafil Improved Negative Symptoms

Adding sildenafil to risperidone resulted in significant negative-symptom improvement in patients with schizophrenia.¹

Background: Several studies have suggested that targeting phosphodiesterase 5 (PDE5) to increase cyclic guanosine monophosphate could correct deficits that result from NMDA receptor hypofunction in schizophrenia as well as improve negative symptoms.²³

Methods: Study subjects were 40 inpatients in their early thirties with chronic schizophrenia (36 males) who were experiencing prominent negative symptoms. Following a 1-week antipsychotic washout, all patients received 6 mg/day risperidone plus 75 mg/day double-blind sildenafil or matching placebo for 8 weeks. The primary outcome was change in Positive and Negative Syndrome Scale (PANSS) score.
Results: Total PANSS scores decreased significantly (p<0.001) with treatment in both groups: from a baseline mean of 113 in each group to 55 and 70 in the sildenafil and placebo groups, respectively, at 8 weeks. The significant advantage of sildenafil over placebo (p<0.001) was driven by greater change on the negative symptom subscale. The mean baseline negative symptom scores were 27 and 26, respectively. The reduction at 8 weeks in the sildenafil group was double that of the placebo group (12 vs 6 points; p<0.001). General psychopathology score change showed a similar but nonsignificant pattern (-28 points vs -20 points), and positive symptom changes did not differ between groups. Response did not appear to be affected by patient age, gender, or duration of illness.

There were no significant between-group differences in extrapyramidal symptoms or other adverse effects. The most commonly reported were those generally associated with risperidone (e.g., drowsiness; constipation; dizziness; headache; appetite changes; nervousness; and dry mouth). Tachycardia developed in 6 sildenafil-treated patients and in 2 placebo-treated patients (30% vs 10%), but the difference was not statistically significant.

Discussion: Negative symptoms of schizophrenia are more difficult to treat than positive symptoms. Results of this study, the first that has been adequately powered to evaluate efficacy, support adding sildenafil to antipsychotic treatment for control of negative symptoms.

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

1Akhondzadeh S, Ghayyoumi R, Rezaei F, Salehi B, et al: Sildenafil adjunctive therapy to risperidone in the treatment of the negative symptoms of schizophrenia: a double-blind randomized placebo-controlled trial. Psychopharmacology 2010; doi 10.1007/s00213-010-2044-z. From Tehran University of Medical Sciences, Iran; and other institutions. Funded by Tehran University of Medical Sciences. The authors disclosed no competing interests.


Drug Trade Names: risperidone—Risperdal; sildenafil—Viagra

*See Reference Guide.

Fish Oil Does Not Prevent Postpartum Depression

High-dose fish oil supplementation during pregnancy did not reduce women’s risk of postpartum depression or improve neurocognitive development in their children.1

Methods: Women pregnant <21 weeks who were not already taking supplements containing fish oil were eligible for the study. Participants were randomly assigned to receive a daily supplement containing 800 mg docosahexaenoic acid (DHA) and 100 mg eicosapentaenoic acid (EPA) or control capsules containing a comparable amount of vegetable oils. Postpartum mood was assessed at 6 weeks and 6 months using the Edinburgh Postnatal Depression Scale (EPDS) self-report, with a cutoff score of 12 for formal depression screening. Women also were asked whether they had received a formal diagnosis of depression or were receiving antidepressant medication. Neurocognitive development was measured at 18 months in a randomly selected subsample of children using the Bayley Scales of Infant and Toddler Development, Third Edition. The intent-to-treat analysis of postpartum depression included 2320 women, and the infant development analysis included 694 children.

Results: Similar proportions of women in both treatment groups had EPDS scores suggestive of depression: 116 in the DHA group and 134 in the control group (9.7% vs 11.2%; p=0.09). Rates of postpartum depression were higher among women with previous or current depression at study entry, but rates did not differ between the treatment groups (21% vs 24%). DHA supplementation was not associated with a lower rate of clinically diagnosed depression or use of antidepressant medication.
Children’s mean cognitive scores were similar in both groups at 18 months. The group that received DHA had fewer very preterm births (<34 weeks’ gestation), but more post-term births requiring inductions or cesarean delivery. Fish oil did not differ from the vegetable oil control in rates of most maternal adverse events, very few (n=4) of which were serious.

**Discussion:** Recommendations suggest pregnant women consume 200 mg/day DHA to support fetal neurologic development. Increasing intake during pregnancy has been recommended on the basis of epidemiologic studies of postnatal depression, despite a lack of well-controlled clinical trials. The present study suggests that the high-dose supplementation should not be recommended to reduce postpartum depression or to improve neurocognitive function. However, omega-3 fatty acid status is critical for fetal development and women should consume the currently recommended daily amount.²

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

1Makrides M, Gibson R, McPhee A, Yelland L, et al: Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. *JAMA* 2010;304 (October 20): 1675–1683. From Women’s and Children’s Hospital, Adelaide, Australia; and other institutions. **Funded by the Australian National Health and Medical Research Council.** Several study authors disclosed financial relationships with commercial sources.

2Oken E, Belfort M: Fish, fish oil, and pregnancy [editorial]. *JAMA* 2010;304 (October 20):1717–1718. From Harvard Medical School, Boston; and Children’s Hospital Boston, Mass.

*See Reference Guide.

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**Ginkgo Biloba for Tardive Dyskinesia**

A standardized formulation of gingko biloba (EGb-761) significantly improved symptoms of tardive dyskinesia (TD) in a group of patients with schizophrenia.

**Background:** Although many medications have been investigated for TD, no consistently effective treatment has been established. A role for free radicals in the pathophysiology of TD has been suggested. Ginkgo biloba is a free radical scavenger, and because it is fat soluble and readily crosses the blood-brain barrier, it was investigated in a randomized controlled trial for treatment of TD.

**Methods:** Inpatient males (n=157; mean age, 45 years) with schizophrenia and confirmed TD who were treated at a Veterans Affairs psychiatric hospital were enrolled in the study. Following a 1-week placebo lead-in, participants were randomized to double-blind treatment with 80 mg ginkgo biloba t.i.d. (n=78) or placebo (n=79) for 12 weeks. Antipsychotic medication remained fixed throughout the trial. The large majority of patients received clozapine (n=128). Other medications, each administered to <8 patients, included risperidone; aripiprazole; olanzapine; quetiapine; chlorpromazine; haloperidol; and sulpiride. Anticholinergics were permitted provided no changes were made during the study period. Symptoms of TD were measured using the Abnormal Involuntary Movement Scale (AIMS). After 12 weeks, study medication was stopped. The ginkgo biloba group was then followed for an additional 6 months.

**Results:** Mean baseline AIMS scores were 7.0 in the active treatment group and 6.9 in the placebo group. After 12 weeks, the ginkgo biloba group showed significant improvement (p<0.0001), while the placebo group did not. Mean endpoint scores were 4.9 and 7.0 in the groups, respectively (p<0.0001). Improvement was strongest among patients with greater baseline severity.

Treatment response (≥30% decrease in AIMS score) was achieved by 40 of the 78 ginkgo-biloba patients and 4 of the 79 placebo patients (51% vs 5%; p<0.001). A total of 11 patients, 10 of whom received ginkgo biloba, no longer exhibited any TD symptoms at 12 weeks. Antipsychotic medication and dose, duration of illness, and use of anticholinergics did not affect TD response.
Improvements associated with ginkgo biloba were maintained at follow-up evaluation 6 months after treatment was discontinued. Although details were not given, adverse effects were considered "mild and brief" and there were no significant changes to laboratory parameters.

**Discussion:** These results suggest ginkgo biloba is safe and effective in the treatment of antipsychotic-associated TD. However, because of study limitations including the short duration of treatment, inclusion of only male patients, and the overwhelming use of clozapine, the results need to be replicated in longer-term studies and in other populations.

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


From Peking University, China; and other institutions. Funded by the National Basic Research Program of China; and the National Natural Science Foundation of China. The authors disclosed no competing interests.

**Drug Trade Names:**
- aripiprazole—Abilify
- chlorpromazine—Thorazine
- clozapine—Clozaril
- haloperidol—Haldol
- olanzapine—Zyprexa
- quetiapine—Seroquel
- risperidone—Risperdal
- sulpiride (not available in the U.S.)—Arminol, Dogmatil

*See Reference Guide.

### Quetiapine for Generalized Anxiety Disorder

In a manufacturer-sponsored study, maintenance therapy following response to extended-release quetiapine (Seroquel) was associated with continuing clinical response in patients with generalized anxiety disorder (GAD).

**Methods:** More than 1200 adults who met DSM-IV criteria for GAD were enrolled in the multicenter trial. Inclusion criteria were a Hamilton Rating Scale for Anxiety (HAM-A) score of ≥20 and a Clinical Global Impression Severity* (CGI-S) score of ≥4. All patients received open-label quetiapine during a 4- to 8-week run-in period and an additional 12-week stabilization phase. Response was defined as a HAM-A score of ≤12 points and a CGI-S score of ≤3. Those who experienced a stable response to quetiapine for 12 weeks (n=432) were then randomly assigned to continue the active drug or switch to placebo for up to 52 weeks. The study was discontinued when a predetermined number of anxiety events (≥46) was reached. The primary efficacy outcome was time from randomization to a first anxiety event.

**Results:** A large number of patients discontinued quetiapine before entering the randomization phase. Primary reasons were adverse events (n=235), unwillingness to continue in the study (n=147), and lack of response (n=29).

During randomized maintenance treatment, quetiapine was associated with significantly reduced likelihood of an anxiety event compared with placebo (hazard ratio* [HR], 0.19; p<0.001). An anxiety event occurred during maintenance in 10% of the quetiapine group and in 39% of the placebo group. Quetiapine was associated with fewer drug discontinuations than placebo (25% vs 55%), largely because of the lower relapse rate. Differences in secondary endpoints, such as HAM-A total scores, CGI-S scores, and quality-of-life measurements, all favored quetiapine. Drug dosages at the end of treatment were 50 mg/day in 25% of patients, 150 mg/day in 50%, and 300 mg/day in 25%.

Adverse events of quetiapine were similar to those previously observed. Sedation and somnolence resulted in drug discontinuation in 10% of patients, usually within the first week of open-label treatment. About 7% of patients experienced extrapyramidal symptoms; they were mild and usually did not lead to discontinuation. Patients experienced weight gain during the stabilization period, with 9% having a ≥7% weight increase.

**Discussion:** Response rates in GAD are variable with conventional agents, remission rates are low, and relapse is common. Although several atypical antipsychotics have been shown to be
helpful as augmentation of more well-established treatments such as antidepressants, this is the first study of any atypical antipsychotic as long-term maintenance monotherapy.

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


*See Reference Guide.

### Nalmefene for Pathological Gambling

In a multicenter, randomized controlled trial, the opioid receptor antagonist nalmefene (*Revex*) was not more effective than placebo in the primary analysis. However, when only patients who received full-dose medication for at least 1 week were included, 40 mg/day nalmefene had large, statistically significant effects on gambling urges.

**Methods:** Adults with pathological gambling were recruited via newspaper advertisement. After screening at 1 of 25 participating centers, patients with a score of ≥21 on the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS) entered a placebo lead-in phase. Those whose PG-YBOCS score was ≥15 after 1 week (n=233) were randomized to 20 or 40 mg/day oral nalmefene or placebo for 10 weeks. Response (≥35% decrease in PG-YBOCS score) was the primary outcome.

**Results:** In the intent-to-treat analysis that included 43 patients who discontinued study medication, neither nalmefene dose was more effective than placebo. Response occurred in 47% of patients assigned to 20 mg/day nalmefene, 56% of those assigned to 40 mg/day nalmefene, and 60% of those who received placebo. However, in a post-hoc analysis that included only patients who received their assigned dose for at least 1 week (n=187), total PG-YBOCS improvements were significantly larger with 40 mg/day nalmefene than with placebo (-9.1 points vs -6.8 points; effect size*, 1.96; p<0.05). Urges to gamble also decreased significantly more in the 40-mg nalmefene group (effect size, 2.1; p<0.05). Adverse effects were not detailed, but they were described as "consistent with prior studies," and no unexpected events occurred.

**Discussion:** The dropout rate in this study was high but consistent with other studies of pathological gambling. The authors suggest nalmefene’s effects may be dose-dependent. Because the benefit was found only in the post-hoc analysis of patients who reached their assigned dose, the results must be replicated in intent-to-treat analyses.

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

Grant J, Odlaug B, Potenza M, Hollander E, et al: Nalmefene in the treatment of pathological gambling: multicentre, double-blind, placebo-controlled study. *British Journal of Psychiatry* 2010;197:330–331. From the University of Minnesota School of Medicine, Minneapolis; and other institutions. Funded by Somaxon Pharmaceuticals. Several study authors disclosed commercial relationships with pharmaceutical-industry sources.

*See Reference Guide.

### Reboxetine Evidence Reportedly Incomplete

According to a meta-analysis of published and unpublished trials, reboxetine is not more effective than placebo and is less effective than SSRIs in acute treatment of major depression.1 In addition, the investigators found evidence of a large publication bias.

**Background:** Although reboxetine is available in several European countries, where it has a small market share among antidepressants, approval was denied in the U.S. A 2009 network meta-analysis that assessed 12 new-generation antidepressants ranked reboxetine last in terms
of efficacy. The new meta-analysis suggests evaluation of published data overestimated the benefits of reboxetine relative to placebo and SSRIs and underestimated the harms relative to placebo.

**Methods:** Initially the study authors identified 7 published and 3 unpublished trials comparing acute reboxetine treatment with a placebo or SSRI comparator in adults with major depressive disorder. The manufacturer subsequently released additional data from partially published or unpublished studies. The final analysis was based on 13 trials conducted in 4098 patients. Data on 74% of the patients were previously unpublished. Efficacy outcomes, measured with the Hamilton Rating Scale for Depression (HAM-D), were response (≥50% reduction in score) or remission (final score of ≤10).

**Results:** When all published and unpublished data were included, response and remission rates did not differ between reboxetine and placebo. Reboxetine was less effective than SSRIs in producing response (odds ratio,* 0.80) and remission (odds ratio, 0.80). Reboxetine was associated with about twice the rate of adverse events and event-related withdrawals as placebo.

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


**Drug Trade Names:** reboxetine (not available in the U.S.)—Edronax, Vestra

### Acamprosate Augmentation for Anxiety

Results of a small open-label study suggest acamprosate (Campral) augmentation may be effective in the treatment of resistant anxiety.

**Background:** SSRIs are commonly used to treat anxiety disorders, but as many as half of patients do not experience complete symptom resolution. A glutamate and gamma-aminobutyric acid (GABA) imbalance is believed to have a role in the pathophysiology of anxiety. Because acamprosate is effective in other disorders thought to be related to these systems (e.g., alcoholism), it was investigated in a small group of patients with treatment-resistant anxiety disorders.

**Methods:** Patients, aged 18–65 years, with generalized anxiety disorder, panic disorder, posttraumatic stress disorder, or social anxiety disorder were eligible for the study. A total of 13 patients (mean age, 41 years; 11 females) with residual symptoms of at least moderate severity, despite a ≥6 week trial of serotoninergic antidepressant therapy at an adequate dose, were enrolled. In addition to their primary anxiety medication, participants received open-label treatment with 1998 mg/day acamprosate in 3 divided doses for 8 weeks. Those with comorbid psychiatric conditions or a history of substance abuse were excluded. The primary outcome measure was the Hamilton Rating Scale for Anxiety (HAM-A), with response defined as a ≥50% decrease in score and remission as a final score of ≤7.

**Results:** Of the 13 patients enrolled, 5 withdrew from the study before completing 2 study visits (1 because of nausea and the others for scheduling issues or unknown reasons), leaving 8 patients in the efficacy analysis. The mean HAM-A score at baseline in these patients was 20. After 8 weeks of acamprosate augmentation, the mean HAM-A score had decreased significantly to 8.9 (p<0.001). Five patients (62%) met response and remission criteria. Acamprosate was well tolerated. Nausea, GI upset, and increased dream activity each affected 1 patient.
Discussion: Because of the small sample size, high drop-out rate, and open-label design, these results must be considered preliminary. However, based on the magnitude of improvement and high response rate, additional study appears to be warranted.

Schwartz T, Siddiqui U, Raza S, Costello A: Acamprosate calcium as augmentation therapy for anxiety disorders. *Annals of Pharmacotherapy* 2010; doi 10.1345/aph.1P353. From SUNY Upstate Medical University, Syracuse, N.Y. Funded by Forest Pharmaceuticals, manufacturer of *Campral*. The authors report no conflicts of interest.

**Adjunctive Levetiracetam Did Not Improve Bipolar Depression**

Levetiracetam has been shown to affect brain regions widely implicated in mood disorders, and it has been suggested to be useful in bipolar mania. A small controlled trial found it no more effective than placebo in bipolar depression.

**Methods:** Adults with bipolar I or II depression, who had been unable to tolerate or whose symptoms were resistant to previous treatment, were included in the study if they were aged 18–65 years and had a Hamilton Rating Scale for Depression (HAM-D) score of ≥17. Patients with comorbid illnesses were not excluded provided bipolar disorder was the primary diagnosis. Participants (n=35) received adjunctive randomized, double-blind levetiracetam, flexibly dosed in the range of 500 to 3000 mg/day (mean, 1132 mg), or placebo for 6 weeks. Background medications included mood stabilizers, antidepressants, antipsychotics, and anxiolytics; 8 patients had discontinued their previous mood stabilizing regimens and received levetiracetam monotherapy.

**Results:** Levetiracetam produced numerically smaller mean HAM-D improvements than placebo (p=ns), as well as secondary measures of depression including the Montgomery Asberg Depression Rating Scale. Rates of response, defined as a ≥50% decrease in HAM-D score, were similar in both groups (22 and 23%, respectively). No patient treated with adjunctive levetiracetam achieved remission. Anxiety and manic symptom ratings also did not differ between the groups.

**Discussion:** Although the study had several important limitations, according to the authors, they would not likely have inflated placebo response. Because levetiracetam showed no indication of greater efficacy than placebo, it may not have a place in the treatment of resistant bipolar depression.

**Study Rating*—17 (100%):** Although the results are negative, this study met all criteria for a randomized controlled trial.

Saricicek A, Maloney K, Muralidharan A, Ruf B, et al: Levetiracetam in the management of bipolar depression: a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry* 2010; doi 10.4088/JCP.09m0569gre. From Yale University, New Haven; and Bristol-Myers Squibb, Walingford, Conn. Funded by the Stanley Medical Research Institute; and other sources. Two of the study authors disclosed commercial relationships with pharmaceutical industry sources.

**Reference Guide**

**Clinical Global Impression Severity (CGI-S) Scale:** A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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

**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 2 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.

**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.

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**In Memory of Our Founding Editor**

Our founding editor, Michael J. Powers, passed away on October 21, 2010, following a courageous battle with leukemia. Michael started the Drug Alert publications in 1974, with the mission of providing readers with the most up-to-date, clinically relevant information in an easy-to-read format. His keen sense of integrity, his work ethic, and his expectation of excellence were, and will always be, an inspiration to all of us at M.J. Powers & Co. Michael was a wonderful mentor and taught us well; we will forge ahead with his mission always in mind.

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**STATEMENT OF OWNERSHIP, MANAGEMENT, AND CIRCULATION**


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