Longer-Acting Aripiprazole Lauroxil Approved

The FDA has approved a 2-month dose of aripiprazole lauroxil extended-release injectable suspension (Aristada) for the treatment of schizophrenia. The agent will now be available at 441 mg, 662 mg, and 882 mg for once-monthly injection, 882 mg for injection once every 6 weeks, and at 1064 mg for injection once every 2 months. The new 2-month dose is expected to be available this month.


Prenatal Antidepressant Exposure and Autism

A systematic review and meta-analysis of epidemiologic studies found an association between antidepressant exposure before and during gestation and autism spectrum disorders. However, the analysis could not untangle the contribution of maternal depression to the outcome.

Methods: A comprehensive literature search was undertaken to identify cohort and case-control studies that examined the relationship between fetal antidepressant exposure and autism spectrum disorders. A total of 10 studies were identified: 3 cohort and 7 case-control. All were of high quality.

Results: The systematic review found inconsistent results among the studies. Of those that analyzed risk in the different trimesters, 4 of 9 found associations with first-trimester exposure and 2 of 8 demonstrated associations with second- and third-trimester exposure. The association between preconception antidepressant exposure and autism was consistently significant in the 5 studies that examined this exposure period. However, the meta-analysis showed statistically significant increases in autism risk with antidepressant exposure both pre-conception and during pregnancy. The analysis showed high heterogeneity among studies, and risk estimates were diminished after adjusting for past maternal depression. (See table, next page.)
**Discussion**: The prevention and/or control of depressive episodes during pregnancy is an important goal given the known adverse effects of uncontrolled depression on the offspring. Although the small number of published studies, high heterogeneity, and the possibility of publication bias limit the conclusions that can be drawn from this analysis, the evidence does not appear to be strong enough to warrant discontinuation of antidepressants during pregnancy in all cases. To minimize the risk, the authors suggest that medication be reserved for women with severe depression and psychological approaches be explored for women with milder symptoms.

**Study Rating**— 16 (89%): This study met most criteria for a systematic review/meta-analysis. However, the source of funding was not disclosed.

Mezzacappa A, Lasica P, Gianfagna F, Cazas O, et al: Risk for autism spectrum disorders according to period of prenatal antidepressant exposure: a systematic review and meta-analysis. *JAMA Pediatrics* 2017; doi 10.1001/jamapediatrics.2017.0124. From Bicetre University Hospital, Le Kremlin Bicêtre, France; and other institutions. Source of funding not stated. Two of 8 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.

*See Reference Guide.

**Mood Stabilizers and Stimulant-Emergent Mania**

Results of a registry-based study indicate that methylphenidate monotherapy is associated with emergent mania in adults with bipolar disorder and ADHD, but concomitant use of mood-stabilizing medication may protect against methylphenidate-emergent mania. This observation suggests that concomitant therapy of ADHD is safe and feasible in adults with bipolar disorder who are also receiving mood stabilizers.

**Methods**: The study was based on data from national registries in Sweden where methylphenidate is essentially the only stimulant used to treat comorbid ADHD in bipolar disorder. Patients were included in the analysis if they were given a prescription for methylphenidate in 2005–2013, received a diagnosis of bipolar disorder before receiving methylphenidate, and were ≥18 years of age before starting methylphenidate. The cohort was further divided into patients who were and were not receiving ongoing treatment with approved mood-stabilizing medications (i.e., lithium, valproate, aripiprazole, olanzapine, or quetiapine) with ≥2 dispensions in the 9 months preceding the initiation of methylphenidate. The analysis compared the onset of mania in the 6 months before and after starting methylphenidate, with each patient serving as his or her own control.

**Results**: A total of nearly 66,000 patients with bipolar disorder were identified in the registry, of whom about 5500 (8%) received a prescription for methylphenidate and approximately 2300 met the study’s inclusion criteria. Women made up two-thirds of the group. About 15% of the
study subjects were aged 18–24 years, nearly half were aged 25–39 years, and 38% were ≥40 years. About half were receiving mood stabilizers.

In patients receiving methylphenidate monotherapy, the incidence of emergent mania increased significantly in the 3 months after starting the stimulant, compared with the 3 months before starting the drug (hazard ratio,* 6.67; p=0.002). Risk was further elevated in the subsequent 3 months (hazard ratio, 9.67; p<0.001). Among patients receiving a concomitant mood stabilizer, risk of emergent mania was reduced during the first 3 months of methylphenidate use (hazard ratio, 0.56; p=0.01) and returned to pre-methylphenidate levels afterward.

**Discussion:** Previous research on methylphenidate-emergent mania is limited. Bipolar disorder and ADHD are frequently comorbid, possibly reflecting shared genetic etiologies or in some cases, a specific subtype of early-onset bipolar disorder. The protective effect of mood-stabilizing drugs may be analogous to their effects in preventing antidepressant-emergent mania.


**Common Drug Trade Names:** aripiprazole—Abilify; methylphenidate—Ritalin; olanzapine—Zyprexa; quetiapine—Seroquel; valproate—Depakene, Depakote

*See Reference Guide.

### New Cholinesterase Inhibitor for Alzheimer's

A novel synthesized acetylcholinesterase (AChE) inhibitor, octohydroaminoacridine, improved cognitive function with few adverse effects in a phase-II study in patients with Alzheimer’s disease. The drug is more highly selective for centrally active acetylcholinesterase (the peripheral enzyme that may be related to the side effects of many members of this drug class) than other AChE inhibitors.

**Methods:** The study, conducted in China, enrolled patients, aged 50–85 years, with a diagnosis of mild-to-moderate probable Alzheimer’s disease, according to standardized criteria. Patients underwent brain imaging, and were excluded if they had evidence of other forms of dementia or a history of significant systemic or psychiatric conditions or traumatic brain injury. After a 4-week screening/washout period, they were randomly assigned to 16 weeks of double-blind treatment with 1 of 3 different octohydroaminoacridine dosage groups (3, 6, or 12 mg/day) or placebo. The primary efficacy outcome was change from baseline in the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog).

**Results:** A total of 284 patients were randomized, and 79–81% of each treatment group completed the study. Patients had an average age of about 72 years and mean baseline ADAS-Cog scores of 28–31.

After 16 weeks, changes in ADAS-Cog scores differed significantly among the groups (p<0.001 for each active treatment group vs placebo). The placebo group demonstrated a 1.4-point increase in ADAS-Cog score, while active treatment produced 2.1, 2.2, and 4.2-point decreases with low, middle, and high doses, respectively. Some secondary outcome measures also favored the active drug: the Clinician’s Interview-Based Impression of Change Plus (p=0.011) and activities of daily living scores, which were superior to placebo in the middle- and high-dosage groups (p<0.01). The Neuropsychiatric Inventory, which measures behavioral disturbances, showed no differences among groups.

Adverse events did not occur more frequently with octohydroaminoacridine than with placebo, and laboratory abnormalities were found more often in the placebo group. The rate of adverse
events with octohydroaminoacridine was not dose-dependent, unlike other cholinesterase inhibitors. The most common adverse events were gastrointestinal (GI) and cardiovascular in nature. These effects usually followed a dose increase and were mild and transient. There was no evidence that the drug compromised cardiovascular function in the study patients, many of whom had cardiovascular disease. Serious adverse events occurred in 2.9% of the placebo group, compared with 2.9% of the low-dose group and 4.6% of the middle-dose group; there were no serious adverse events in the high-dose group.

**Discussion:** AChE inhibitors are widely used to improve cognitive function in Alzheimer’s disease. However, the agents are associated with dose-dependent adverse effects, primarily in the GI tract. These results suggest that octohydroaminoacridine improves both cognitive function and behavior without dose-dependent adverse effects. The highest dose of the medication will be investigated in upcoming phase III trials.

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

Xiao S, Wang T, Ma X, Qin Y, et al: Efficacy and safety of a novel acetylcholinesterase inhibitor octohydroaminoacridine in mild-to-moderate Alzheimer’s disease: a phase II multicenter randomised controlled trial. *Age and Ageing* 2017; doi 10.1093/ageing/afx045. From Shanghai Jiao Tong University School of Medicine, China; and other institutions. Funded by Changchun Huayang High-Science and Technology Co, Ltd.; and other sources. The authors declared no competing financial interests.

*See Reference Guide.

**Low Antidepressant Adherence in All Drug Classes**

Antidepressant adherence and persistence are low, regardless of the drugs’ therapeutic class, according to a retrospective analysis of U.S. prescription claims data. The study, reportedly the largest to date and covering the largest number of medications, showed that a majority of patients discontinue antidepressant therapy before the clinically recommended 6–9 months.

**Methods:** The study was based on a database comprising commercially insured, Medicare, and Medicaid claims for antidepressant medication coverage in 2003–2013. Patients were required to have an ICD-9 diagnosis of a depression spectrum disorder. The index prescription was defined as the first pharmacy claim for an antidepressant within 60 days of the depression diagnosis. Patients were excluded for certain other mental disorders, pregnancy (because of its possible effects on drug discontinuation), and/or an initial prescription of ≥2 antidepressants. Medication adherence was estimated as the proportion of days covered (PDC), a widely used method consistent with other studies. PDC was calculated as the total proportion of days the medication was available over the follow-up period, and patients were classified as nonadherent if the PDC was <80%. Persistence was calculated as the days of treatment until a 30-day gap in therapy. The investigators calculated adherence and persistence at 3, 6, 9, and 12 months, according to established standards for the length of effective acute, continuation, and maintenance phases. Adherence and persistence were calculated separately as continued use of the initially prescribed medication, another drug from the same class, and any antidepressant therapy.

**Results:** Among an estimated 200 million patients covered by the database, >6.6 million had a qualifying depression diagnosis. After applying the exclusion criteria, the analysis was based on nearly 528,000 patients who received a new prescription for an antidepressant. SSRIs accounted for 74% of prescriptions. Sertraline was the most commonly prescribed SSRI (19% of the cohort), and extended-release bupropion the most common non-SSRI (5%). The analysis did not include any patients taking vortioxetine or levomilnacipran, which were too recently introduced.
Overall, about one-third of patients showed continued medication adherence and persistence at 6 months. When the analysis was stratified by medication class, SNRIs had the highest adherence and persistence at all time frames (e.g., 37% and 37%, respectively, at 6 months), and TCAs the lowest (16% and 17%, respectively, at 6 months; see table). Adherence and persistence with MAOIs did not differ statistically from SSRIs. Results were similar in comparisons at 3, 9, and 12 months.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Odds Ratio*</th>
<th>Significance, compared with SSRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRIs</td>
<td>1.23</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>MAOIs</td>
<td>Similar to SSRIs</td>
<td>p=ns</td>
</tr>
<tr>
<td>TCAs</td>
<td>0.45</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>0.77</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

**Discussion:** Acute-phase treatment of depression encompasses the first 6–12 weeks of therapy, and continuation phase treatment is recommended for at least an additional 4–9 months. Adherence and persistence appear to differ by therapeutic class.

Keyloun K, Hansen R, Hepp Z, Gillard P, et al: Adherence and persistence across antidepressant therapeutic classes: a retrospective claims analysis among insured US patients with major depressive disorder (MDD). CNS Drugs 2017;31 (May):421–432. From Allergan, Irvine, CA; and other institutions. Funded by the University of Washington; and Allergan. Four of the 6 study authors disclosed financial relationships with commercial sources, including Allergan; the remaining 2 authors declared no competing interests.

Common Drug Trade Names: bupropion—Wellbutrin; levomilnacipran—Fetzima; sertraline—Zoloft; vortioxetine—Trintellix

See Reference Guide.

**Antipsychotic Cotreatment Strategies**

According to a qualitative review of meta-analyses of pharmacologic cotreatment strategies for schizophrenia, existing meta-analyses appear to support the efficacy of multiple cotreatment strategies. However, these analyses are generally based on low-quality studies, with small sample sizes, high heterogeneity, and a high risk of publication bias.

**Methods:** The analysis included published meta-analyses of pharmacologic treatments added to antipsychotic medications, compared with antipsychotic monotherapy or placebo, in patients with schizophrenia. Older meta-analyses were excluded if there was a more recent update. The primary outcome was effect size* of the difference between treatment and control on a measure of total psychopathology—i.e., either the Positive and Negative Syndrome Scale or the Brief Psychiatric Rating Scale. Quality of the meta-analyses was assessed using a standardized scale. The authors developed an additional scale, called AMSTAR-Plus, to rate the content quality of each of the clinical trials on which each meta-analysis was based.

**Results:** The review included 29 meta-analyses that evaluated 42 different medication combinations. The meta-analyses were based on a mean of 8 different studies with an average of 50 patients per study. The augmentation agents included other antipsychotics, antidepressants, mood stabilizers, hormones, antioxidants, stimulants, and many others.

A total of 14 of 32 agents combined with antipsychotics were found to be significantly superior to controls (i.e., monotherapy or placebo) in improving total psychopathology. None of the 5 treatment combinations that included clozapine (Clozaril) outperformed controls. The mean quality score of the meta-analyses was high, averaging 9 out of a possible score of 11. However, the quality of the underlying studies was low (mean AMSTAR-Plus score, 2.8 out of a possible 9) and showed a small but significant inverse correlation with effect size (p=0.02). Only 1
meta-analysis had an AMSTAR-Plus score of >4. A large majority of the meta-analyses did not have a pooled sample size >500, none had a sample size of >1000, and none of the positive results were confirmed by a trial with >200 participants.

**Discussion:** Based on low confidence in treatment recommendations that are supported by meta-analytic evidence from poor-quality studies, the present authors concluded that there are no grounds for recommending any pharmacological combination for schizophrenia. Switching to clozapine remains the only option with support in the literature.

Correll C, Rubio J, Inczedy-Farkas G, Birnbaum M, et al: Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.0624. From the Zucker Hillside Hospital, Glen Oaks, NY; and other institutions. Funded by Zucker Hillside Hospital; and the NIMH. Two study authors disclosed relationships with commercial sources; the remaining 4 authors disclosed no competing interests.

*See Reference Guide.

## Psychiatric Medications and Osteoporotic Fractures

According to the results of a population-based cohort study, use of psychotropic medication is associated with an increased risk of fracture, independently of other risk factors. FRAX scores, which are widely used to estimate risk of osteoporotic fractures, may underestimate risk in persons with psychiatric disorders and in those taking psychotropic medications.

**Background:** The FRAX tool (available online at www.sheffield.ac.uk/FRAX/tool.jsp) is based on easily assessed fracture risk factors such as age, weight, and history of fracture, but it has not yet incorporated information on mental illness and psychotropic drug use, among several potentially important risk factors. Given the high prevalence of osteoporosis and mental-health disorders, improved recognition and management of fractures in psychiatric patients is needed.

**Methods:** Data for the study cohort were extracted from the Manitoba Bone Density Program database, which covers all residents of Manitoba, Canada, who received a dual-energy x-ray absorptiometry (DXA) bone density scan after 1990. The study cohort was limited to patients aged ≥40 years who received a scan between 1996 and March 2013: >62,000 women and nearly 6500 men. Patient data, collected from linked databases, included the FRAX score, comorbid medical illnesses, psychiatric illnesses (depression, anxiety disorders, and schizophrenia), and psychotropic medications used for at least half of the year prior to the DXA scan. Medication classes included were SSRIs, tricyclics, other antidepressants, lithium, other mood stabilizers, antipsychotics, and benzodiazepines. The primary study outcomes—hip fracture and major osteoporotic fracture, which included fractures of the hip, vertebra, humerus, or forearm—were analyzed separately, and patients whose fractures were associated with high-level trauma were excluded.

**Results:** Nearly 13,000 of the study cohort’s members (19%) had a mental-health diagnosis, most commonly depression, and nearly 12,000 of these patients (17% of the cohort) were receiving psychotropic medication. During a mean of nearly 7 years of observation, 8.4% of the population sustained an incident major osteoporotic fracture and 2.3% had a hip fracture. Rates of both types of fracture were increased in patients with psychiatric disorders and in those taking psychotropic medication.

In a statistical model that analyzed disorders and medications separately, after adjusting for the FRAX score, all 3 mental disorders and all medication categories except tricyclics were significantly associated with risk of osteoporotic fracture; associations were weaker for hip fractures. In a model that combined the effects of disorders and medications and was then adjusted for FRAX score, none of the 3 mental disorders was significantly associated with fracture risk, but significant associations remained for some medications. (See table, next page.)
In this population, standard FRAX scoring underestimated the 10-year risk of major osteoporotic fracture by 63% in patients taking mood stabilizers, by 60% in those taking antipsychotics, by 36% in SSRI users, and by 29% in patients with depression. Hip fracture risk was underestimated by 171% in patients taking antipsychotics, 98% in patients with schizophrenia and those taking mood stabilizers, and by about 50% in patients with depression.

**Discussion:** The study authors noted several limitations that should be considered when interpreting these findings. Because the sample comprised only those referred for DXA testing, the results may not generalize to younger patients who are not considered to be at risk for osteoporosis. In addition, while the mechanism of the association may be due to the bone-mediated effects of psychotropic medications, falls, which are also associated with psychotropic use, could affect fracture risk, but they were not assessed in the study.

**Bolton J, Morin S, Majumdar S, Sareen J, et al:** Association of mental disorders and related medication use with risk for major osteoporotic fractures. *JAMA Psychiatry* 2017;74 (June):641–648. From the University of Manitoba, Canada; and other institutions. **Source of funding not stated. Two of 10 study authors disclosed financial relationships with commercial sources.**

*See Reference Guide.*

### Clozapine Augmentation with Antiepileptic Drugs

According to a meta-analysis, augmenting clozapine treatment with antiepileptic drugs is not well supported by clinical trial evidence. However, adding valproate sodium may be effective in patients with resistant schizophrenia.

**Methods:** A comprehensive search of multiple English- and Chinese-language databases was conducted to identify randomized controlled trials of clozapine augmentation with antiepileptic drugs, compared with clozapine alone or with placebo, in patients with treatment-resistant schizophrenia. The primary outcome measure of the analysis was change from baseline in Positive and Negative Syndrome Scale total score or Brief Psychiatric Rating Scale score.

**Results:** Despite searching using specific drug names and examining reference lists of published articles, only 4 augmenting drugs were identified—lamotrigine, topiramate, valproate sodium, and magnesium valproate (not available in the U.S.)—in 22 studies, with a total of 1227 patients, who received treatment for a mean of 12 weeks. Methodologic quality and risk of bias were mixed. Due to the limited number of studies of each drug, publication bias could not be assessed.

Based on 19 studies with data that could be pooled, there was an overall positive effect of augmentation, as well as statistically significant efficacy for 2 of the individual drugs. Both topiramate and sodium valproate were consistently associated with significantly greater clinical improvement than clozapine alone. However, topiramate was the least well tolerated of the drugs, with a significantly higher rate of discontinuation than clozapine monotherapy (relative risk,* 1.99; p=0.01; number needed to harm,* 7). Outcomes of treatment with lamotrigine were heterogeneous, and after excluding 2 studies with extreme results, the effect was not statistically significant. Magnesium valproate did not produce significant benefits.
Discussion: The authors note that many of the studies did not measure serum clozapine levels to rule out pharmacokinetic interactions. The literature, although limited, suggests that topiramate and lamotrigine have no relevant pharmacokinetic effects on clozapine metabolism. The complex effects of valproate may include increasing serum clozapine concentrations. Also, all of the valproate studies were conducted in China where clozapine is prescribed in relatively low doses because Chinese patients have on average a lower clozapine metabolic capacity than Westerners. The results need to be replicated in non-Chinese populations.

Zheng W, Xiang Y-T, Yang X-H, Xiang Y-Q, et al: Clozapine augmentation with antiepileptic drugs for treatment-resistant schizophrenia: a meta-analysis of randomized controlled trials. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16r10782. From Affiliated Brain Hospital of Guangzhou Medical University, China; and other institutions. Funded by the University of Macau, China. The authors declared no competing interests.

Common Drug Trade Names: clozapine—Clozaril; lamotrigine—Lamictal; topiramate—Topamax; valproate sodium—Depakene, Depakote

*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 Harm: A measure of how many patients need to be exposed to a risk factor to cause harm in 1 patient that would not otherwise have been harmed. Lower NNH indicates more attributable risk.

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.

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.

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