PSYCHIATRY DRUG ALERTS

Volume XXXII / July 2018 / Number 7 www.alertpubs.com

Change Coming . . . See back page for details.

New Aripiprazole Formulation

The FDA has approved a new injectable aripiprazole formulation (*Aristada Initio*) to be used in combination with a single 30-mg dose of oral aripiprazole (*Abilify*) to initiate treatment for schizophrenia, along with any available dose of long-acting injectable aripiprazole lauroxil (*Aristada*) on day one. Previously, the standard initiation regimen for *Aristada* included 21 consecutive days of oral aripiprazole treatment starting concurrently with the first *Aristada* dose. The new *Aristada Initio* regimen produces relevant aripiprazole levels within 4 days of initiation. The first dose of *Aristada* can be administered on the same day as *Aristada Initio* or within the subsequent 10 days.

Although both *Aristada* and *Aristada Initio* contain aripiprazole lauroxil, they are not interchangeable because of differing pharmacokinetic profiles. *Aristada Initio* uses a proprietary NanoCrystal® technology designed to provide an extended-release formulation using a smaller particle size that enables faster dissolution and leads to more rapid achievement of relevant levels of aripiprazole.

FDA approves Aristada Initio™ for the initiation of Aristada® for schizophrenia [press release]. Dublin, Ireland; Alkermes: July 2, 2018. Available at http://phx.corporate-ir.net/phoenix.zhtml?c=92211&p=irol-corporateNewsArticle&ID=2356744.

Psychotropic Drugs and Breastfeeding

Use of psychotropic drugs, primarily antidepressants and benzodiazepines, during breastfeeding was not associated with long-term adverse effects in infants followed for up to 33 months. Exposed children had normal growth and met normal developmental milestones.

Methods: Study subjects were mothers who called in to a hospital's drug-consultation center for advice about the safety of psychotropic medications during breastfeeding. A comparison group consisted of women who called the consultation center to inquire about receiving short-term antibiotic monotherapy during breastfeeding, which is generally considered safe. Women taking psychotropic drugs were given information about their particular medication but were

PSYCHIATRY DRUG ALERTS (ISSN 0894-4873) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psych@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. Postmaster: Send address changes to Psychiatry Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405.

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not discouraged or encouraged to use any specific medication or given advice on less-risky alternatives. Women were administered a structured questionnaire during their initial call. In a follow-up telephone call several months to 5 years after the first call, women were asked about the specifics of drug exposure during pregnancy and lactation, adverse reactions in the infant, growth as recorded on well-baby forms, and developmental milestones.

Results: After excluding those who decided not to breastfeed, took no medication, or took multiple medications, the study enrolled 280 women taking psychotropic medication. These women were contacted for follow-up a median of 32 months after the initial call, when their infants were a median of 20 months old (range, 11–33 months). The 152 women in the antibiotic group were followed a median of 35 months after the initial call, when their babies were a median of 36 months old (range, 20–48 months).

Most of the women in the exposed group were receiving treatment for depression (60%) or anxiety (34%). The most common medications were SSRIs (69%), followed by benzodiazepines (13%) and other types of antidepressants; 13 women were taking antipsychotics. All were receiving doses within the recommended range.

Rates of maternal pregnancy complications did not differ between groups, overall. However, there were 15 cases of fetal distress in the exposed group, compared with none in the comparison group (p=0.002), but no other differences in neonatal complications.

At follow-up, children in the 2 groups did not differ in height, weight, head circumference, or weight/length ratio percentile. Adverse reactions were reported in 14 exposed infants: transient sleepiness in 8, poor weight gain in 4, and shivering in 2. Diarrhea was reported in 7 unexposed children and no psychotropic-exposed children. Some developmental milestones—e.g., smiling and lifting the head—occurred a few days to weeks later on average in exposed children than controls (p≤0.001), but all were within the normal developmental range.

Women taking psychotropic drugs stopped breastfeeding earlier than controls (24 vs 36 weeks; p<0.001) and were less likely to breastfeed exclusively (35% vs 61%; p<0.001). To eliminate these effects, a further analysis was conducted in 120 pairs of propensity score-matched* women. The results were similar to the larger cohort.

Discussion: Existing information on the effects of psychotropic drugs during breastfeeding is limited to case reports, drug-specific studies, or observation of small samples. The present study suggests the drugs do not result in growth retardation or important developmental delays. Sleepiness, which usually had onset soon after birth and resolved quickly, may reflect the previously reported phenomenon of poor neonatal adaptation.

Kronenfeld N, ziv Baran T, Berlin M, Karra N, et al: Chronic use of psychotropic medications in breastfeeding women: is it safe? *PLOS One* 2018; doi 10.1371/journal.pone.0197196. From the Hebrew University of Jerusalem, Israel; and other institutions. **This study was conducted without specific funding. The authors declared no competing interests.**

***See Reference Guide.**

Antipsychotics and Kidney Disease

According to the results of a population-based case-control study, second-generation antipsychotics may be associated with increased risk of chronic kidney disease (CKD).

Methods: A cohort of >13,600 patients hospitalized for psychiatric disorders in 2000–2013 and discharged with a diagnosis of schizophrenia were identified in a Taiwanese nationwide claims database. Within the cohort, case patients (n=3411) were those who subsequently received a diagnosis of CKD. Each case patient was matched for gender and the age and year of schizophrenia diagnosis with 3 controls free of CKD. The analysis compared CKD incidence in 4

separate groups of patients receiving: first-generation antipsychotics as a class, second-generation antipsychotics as a class and individually, combined first-and second-generation drug combinations, and no antipsychotic therapy.

Results: Patients had a mean age of 41 years and supplied an average of nearly 8 years of follow-up data after discharge. Rates of several relevant comorbidities, such as diabetes, cardiovascular disease, lipid abnormalities, and obesity, were significantly higher in the patients with CKD, but analyses were adjusted for these factors. A large majority of patients (87%) were receiving combined treatment with both first- and second-generation antipsychotics; 12% received only a first-generation agent; and <1% each received only a second-generation agent or no medication.

Using patients who received first-generation agents alone as the reference group, adjusted odds ratios* (OR) for CKD were 0.53 for those receiving no antipsychotic medication, 1.06 for those receiving only a second-generation agent, and 1.28 for those receiving both first- and second-generation agents. The only difference that reached statistical significance was for those receiving both types of antipsychotic (p= 0.0009). When analyzed by cumulative exposure, CKD risk was significantly increased in patients taking second-generation antipsychotics (alone or in combination) for durations of 90–180 days and >1000 days. Risks were also significantly elevated for several individual second-generation antipsychotics, although associations did not follow a consistent pattern of relationship to days of exposure and were not corrected for multiple comparisons. The analysis did not reveal a dose-dependent relationship of second-generation antipsychotics to CKD.

Discussion: Because the study data were drawn from a claims database, variables such as lifestyle factors, family history, and other factors that could affect outcomes and medication choice could not be examined. However, the results do support further investigation of the association between second-generation agents and kidney disease.

Wang H-Y, Huang C, Feng I, Tsuang H-C: Second-generation antipsychotic medications and risk of chronic kidney disease in schizophrenia: population-based nested case-control study. *BMJ Open* 2018; doi 10.1136/bmjopen-2017–019868. From Chi Mei Medical Center, Yung Kang, Taiwan; and other institutions. **Funded by Chi Mei Medical Center. The authors declared no competing interests.**

***See Reference Guide.**

Adjunctive Thyroid Hormones in Rapid Cycling

In a randomized 3-group trial, adjunctive levothyroxine favorably altered mood cycles in patients with rapid cycling bipolar disorder refractory to lithium.

Methods: Study participants, aged 18–65 years, were receiving treatment at a single university-based bipolar disorders clinic and met criteria for rapid cycling, with ≥4 mood episodes in the 12 months before study entry. All were taking lithium and continued to do so throughout the study, with dosages adjusted to maintain therapeutic serum levels. All patients were clinically euthyroid at study entry. Following pre-treatment evaluation lasting through at least 1 full mood cycle or ≥1 month for patients with the most rapid cycling, patients were randomly assigned to receive: levothyroxine, at doses that maintained the free thyroxine (T_4) index in a target range or achieved thyroid stimulating hormone suppression; triiodothyronine (T_3) at doses that maintained T_3 resin uptake in a target range; or placebo. All groups received placebo tablets as well. Thyroid status was measured approximately every week starting 1 month after the achievement of desired thyroid hormone levels (or a plausible interval for placebo) and continuing for ≥3 months. Outcomes were measured weekly by raters unaware of treatment assignment, using the Hamilton Rating Scale for Depression and Young Mania Rating Scale. Patients' mood switches were tracked, and the amount of time patients spent in each of 4 mood

states (euthymic, manic/hypomanic, depressed, mixed) was estimated using each individual's personal symptom threshold, which was established during pretreatment evaluation. Patients were followed for a minimum of 3 months (range, 4–11 months).

Results: A total of 32 patients (22 women) were included in the analysis. Of these, 7 had a history of hypothyroidism and were receiving thyroid hormone therapy at study entry: 4 in the levothyroxine group, 1 in the T_3 group, and 2 receiving placebo. Patients reached stabilization on thyroid hormones within a mean of 7 months (T_3) or 11 months (levothyroxine and placebo). Adverse effects were minimal, except for 1 patient who withdrew prematurely because of tachycardia.

Compared with pre-treatment, patients who received levothyroxine spent significantly less time in a depressed state (-18%; p=0.022) or in a mixed state (-13%; p=0.031) and more time euthymic (33%; p=0.022). Changes in the T_3 group followed a similar pattern but were smaller and not statistically significant. There was no change in the percentage of time spent in any mood state in placebo-treated patients. Between-group comparisons showed that favorable mood changes in patients who received levothyroxine were significantly superior to placebo for time spent euthymic and time spent in a mixed state (p=0.033 and p=0.045, respectively). Patterns for the T_3 group were similar but did not reach significance compared with placebo.

Discussion: Previous studies of levothyroxine in bipolar disorder have focused mainly on treating depression rather than on mitigating the course of rapid cycling. Therefore the finding in the present study of a reduction in time spent in mixed states is an important one. Results of the present study suggest that T3 may also be beneficial, although a larger sample size may be required to confirm this suggestion. The study was limited by its smaller-than-expected sample size, which did not allow investigators to analyze the results by gender or thyroid disease history. Gender differences in thyroid axis function are a well-known influence on response to pharmacologic treatments, and previous controlled studies suggest high-dose levothyroxine particularly benefits women with bipolar depression.

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

Walshaw P, Gyulai L, Bauer M, Bauer M, et al: Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder: a double-blind placebo-controlled trial of levothyroxine (L-T4) and triiodothyronine (T3). *Bipolar Disorders* 2018; doi 10.1111/bdi.12657. From the University of California Los Angeles; and other institutions. **Funded by the NIMH. Two of 7 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Anticholinergics and Dementia Risk

Exposure to anticholinergic antidepressant, antiparkinsonian, and urological drugs was associated with an increase in the incidence of dementia in a population-based study. Increased risk for several other anticholinergic categories could not be ruled out.

Methods: The study was based on data from the U.K.'s Clinical Practice Research Datalink, which contains primary-care records for >11 million patients. Case patients were aged ≥65 years and had received a diagnosis of dementia between 2006 and 2015. Each was matched with up to 7 control patients based on gender, age, and other factors. An anticholinergic drug exposure period was defined as a prescription lasting ≥1 year and ending ≥4 years before the date of dementia diagnosis. Anticholinergic drugs were classified according to the 3-point Anticholinergic Cognitive Burden (ACB) scale, based on serum anticholinergic activity, blood-brain penetration, and known associations with delirium. Drugs with serum anticholinergic activity or affinity for muscarinic receptors, but without known clinically

relevant negative cognitive effects are assigned an ACB score of 1 (possibly anticholinergic). Drugs with established and clinically relevant anticholinergic effects are assigned a score of 2, and drugs that meet those criteria and also have reported associations with delirium are assigned a score of 3. Drugs were further classified according to indication, and exposures were quantified by the defined daily dose, based on average maintenance doses. The analysis was adjusted for covariates suspected to be linked to dementia incidence and many other factors.

Results: The study population consisted of nearly 41,000 patients with dementia and >280,000 controls. Patients had a median age of 83 years at the index date (diagnosis of dementia). The median drug exposure period was >7 years.

During the anticholinergic drug exposure period, 35% of cases and 30% of controls were given a prescription for a drug with an ACB score of 3. The most frequently prescribed ACB-3 drugs were amitriptyline (29%), dosulepin or dothiepin (16%), paroxetine (8%), oxybutynin (7%), and tolterodine (7%). Use of drugs with an ACB score of 2 was rare, and use of drugs with an ACB score of 1 was near-universal. After adjustment, each ACB category was associated with a significant increase in risk for dementia. (See table.) A dose-response relationship was evident for drugs with an ACB score of 2 or 3. When drugs were analyzed by indication, significant risk of dementia was associated with ACB-3 anticholinergics prescribed as antidepressants, antiparkinsonian agents, and urologic treatments. Associations were also positive for ACB-2 antiparkinsonian drugs and for ACB-1 antidepressants. Anticholinergic antidepressants were consistently associated with dementia across the board, and these associations persisted after controlling for the presence and severity of depression. Gastrointestinal drugs had a negative association with dementia.

Odds ratios* for dementia by ACB score

ACB score	Incidence of dementia		Adjusted odds ratio†
	% of cases	% of controls	
0	10.5%	12.8%	1.00 (reference)
1	89.4%	87.1%	1.11
2	3.5%	2.8%	1.10
3	35.5%	30.4%	1.16
ACB-3 drug class			
Antidepressant	21.6%	17.9%	1.13
Antiparkinsonian	0.7%	0.3%	1.45
Urologic	8.0%	5.9%	1.23

†Odds ratios are adjusted for covariates present at start of the drug exposure period

Exposure times were also classified in 3 different periods: 4–10, 10–15, and 15–20 years before the index date. Associations for drug classes with an ACB score of 3 were consistent across all of these timespans, with no decrease when used 15–20 years in the past. In contrast, associations of dementia with drugs with an ACB-1 or 2 rating were more apparent closer to the index date.

Discussion: The study included a 4-year diagnostic lag designed to reduce the chances that the anticholinergic drugs were prescribed for early or prodromal symptoms of dementia. The present findings suggest that the relationship of anticholinergic drugs to dementia is specific to the drugs, not the underlying conditions that they treat; however, a link to underlying disorders other than dementia cannot be ruled out. The observed class-specific effects may be related to differential ability of drugs to cross the blood-brain barrier.

Richardson K, Fox C, Maidment I, Steel N, et al: Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018; doi 10.1136/bmj.k1315. From the University of East Anglia, Norwich, U.K.; and other institutions. **Funded by the Alzheimer's Society. Four of 16 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: amitriptyline (not available in the U.S.)—*Elavil*; dosulepin/dothiepin (not available in the U.S.)—*Prothiaden*; oxybutynin—*Ditropan*; paroxetine—*Paxil*; tolterodine—*Detrol

***See Reference Guide.**

Roluperidone: Secondary Benefits in Schizophrenia

Results of a manufacturer-sponsored clinical trial of roluperidone (MIN-101), an investigational drug for negative symptoms of schizophrenia, suggest possible secondary benefits on cognitive performance.[1] The drug also appears to have the potential to improve negative symptoms and cognitive deficits, addressing 2 important unmet needs in schizophrenia treatment.

Background: Roluperidone has specific affinities for the sigma-2, 5-HT_{2a} and α_1-adrenergic receptors and weak activity at other receptors. It lacks the anticholinergic and antihistaminergic activity associated with other medications that can worsen cognitive function in patients with schizophrenia.

Methods: This report describes a post-hoc analysis from a trial whose primary aim was to evaluate roluperidone for negative symptoms of schizophrenia.[2] (See *Psychiatry Drug Alerts* August 2017 for study details.) Participants had clinically evident negative symptoms over the 3 months before enrollment and scores of ≥20 for negative symptoms on the Positive and Negative Syndrome Scale (PANSS). All psychotropic drugs were discontinued before the trial; concomitant antipsychotics were not permitted. Patients, aged 18–60 years, were randomly assigned to 2 different daily doses of roluperidone (32 mg or 64 mg) or placebo and received treatment for 12 weeks. Cognitive performance was assessed at weeks 4 and 12 with the Brief Assessment of Cognition in Schizophrenia (BACS), which measures 6 domains of cognitive function.

Results: A total of 244 patients participated in the study, which met its primary endpoint of improving negative symptoms with both roluperidone doses; 234 of those patients completed the cognitive assessment at baseline and were included in the present analysis. Overall, about 40% of patients showed a potentially clinically meaningful improvement in BACS composite score. At week 12, patients who received 32 mg/day roluperidone (n=78) showed significant improvement relative to placebo on the BACS composite score and the token motor and verbal fluency subscales ($p \leq 0.05$ for all). In patients who received the 64-mg dose (n=83), improvement was significant only for motor speed (p=0.05) and approached significance for verbal fluency (p=0.06). No group showed significant gains in executive function. Although the higher dose generally produced smaller, nonsignificant cognitive improvements than the lower dose, among patients who received the 64-mg dose, improvement in PANSS negative symptoms was significantly correlated with improvement in the BACS cognitive composite at 12 weeks (correlation coefficient [r],* -0.408; p=0.002). No significant correlations were seen in the 32-mg dose group.

Discussion: The positive effects of roluperidone shown on the token motor and verbal fluency tests suggest that it may improve the ability to process information, complete simple tasks, and express knowledge. It is not clear whether the drug would have the same results when used as add-on therapy.

[1]Keefe R, Harvey P, Khan A, Saoud J, et al: Cognitive effects of MIN-101 in patients with schizophrenia and negative symptoms: results from a randomized controlled trial. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11753. From Duke University Medical Center, Durham, NC; and other institutions. **Funded by Minerva Neurosciences, Inc., Waltham, MA. All 7 study authors disclosed potentially relevant financial relationships.**

[2]Davidson M, et al: Efficacy and safety of MIN-101: a 12-week randomized, double-blind, placebo-controlled trial of a new drug in development for the treatment of negative symptoms in schizophrenia. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17010122. See *Psychiatry Drug Alerts* 2017;314 (August):60–61.

***See Reference Guide.**

VMAT-2 Inhibitors for Tardive Dyskinesia

Robust evidence supports the efficacy of deutetrabenazine and valbenazine for treating tardive dyskinesia, according to a systematic review and meta-analysis. Both of these drugs received FDA approval for this indication in 2017. A third member of the vesicular monoamine

transporter-2 (VMAT-2) inhibitor drug class, tetrabenazine (approved for treatment of Huntington's disease), has no high-quality evidence of safety or efficacy in tardive dyskinesia and should therefore be considered a third-line, off-label treatment.

Background: VMAT-2 inhibitors work by reducing transport of dopamine from the cytoplasm into presynaptic vesicles, leading to less dopamine release into the synaptic cleft and less stimulation of neurons in the nigrostriatal pathway, thought to be involved in involuntary movements.

Methods: Literature databases, clinical-trials registries, and conference proceedings were systematically reviewed for studies of VMAT-2 inhibitors. All types of studies were eligible for inclusion in the review, but the meta-analysis was limited to double-blind, randomized, placebo-controlled trials that reported results using the Abnormal Involuntary Movement Scale (AIMS).

Results: The systematic review included information from 8 double-blind controlled trials, 2 single-blind controlled studies, 7 open-label studies, and 3 retrospective studies or case series. Tetrabenazine, the first VMAT-2 inhibitor to be introduced, was investigated in 12 studies, including 2 randomized trials conducted in the 1970s. The studies had small sample sizes, flawed measurement of outcomes, and other design issues, and could not be included in the meta-analysis.

Deutetrabenazine and valbenazine were evaluated in 6 randomized trials. Meta-analysis of these trials found the 2 drugs as a class reduced AIMS scores significantly more than placebo (standardized mean difference,* -0.46; $p<0.001$). The 2 drugs' effect sizes were similar. The 2 VMAT-2 inhibitors were associated with a higher likelihood than placebo of a ≥50% reduction in the AIMS score (risk ratio,* 2.66; $p<0.001$), with a number needed to treat* of 5. Similar results were seen for response according to Clinical Global Impression criteria, although when the agents were analyzed individually, superiority to placebo was statistically significant for valbenazine but not deutetrabenazine.

A second meta-analytic comparison was also performed for adverse effects of the 2 newer drugs. Neither the VMAT-2 inhibitors as a class nor either of the drugs individually was associated with an increased risk of adverse events relative to placebo. The drugs did not increase risk of depression, suicidal ideation, sedation, or somnolence.

Discussion: At present, deutetrabenazine and valbenazine have not been directly compared in a head-to-head trial, and the choice between them is based on individual medication properties. Due to its short half-life of about 5 hours, tetrabenazine has large variations in drug levels that have off-target effects such as sedation, acute motor syndromes, and possibly depression and suicidality. The 2 newer VMAT-2 inhibitors appear to lack these effects. Deutetrabenazine has a half-life of 9–10 hours, requiring twice-daily dosing, while valbenazine's half-life of 20 hours allows once-daily dosing.

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

Solmi M, Pigato G, Kane J, Correll C: Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. *Drug Design, Development and Therapy* 2018;12:1215-1238. From the University of Padua, Italy; and other institutions. **Source of funding not stated. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining 2 authors declared no competing interests.**

Common Drug Trade Names*: deutetrabenazine—*Austedo*; tetrabenazine—*Xenazine*; valbenazine—*Ingrezza

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Correlation Coefficient (r): A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1. An r value near 1 indicates a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r-value indicates a negative relationship.

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 the treatment.

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.

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.

Risk Ratio: 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.

Standardized Mean Difference: The difference between 2 normalized means—i.e., the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

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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