PSYCHIATRY DRUG ALERTS

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Clozapine Warning Strengthened

An existing label warning regarding clozapine (*Clozaril*)-associated constipation has been updated to reflect the possibility of progression to serious bowel complications including bowel obstruction, which can lead to hospitalization or death. Prescribers are encouraged to advise patients of the significant risk of constipation and life-threatening bowel issues and the need to stay hydrated to prevent constipation. In addition, bowel function should be evaluated before starting a patient on clozapine. Coprescribing other anticholinergic medicines that can cause GI hypomotility should be avoided, and patients should be monitored for symptoms of hypomotility (e.g., nausea, abdominal distension or pain, vomiting). Prophylactic laxative treatment should be considered for patients with a history of constipation or bowel obstruction.

FDA MedWatch Alert: Clozaril, Fazaclo ODT, Versacloz (clozapine): Drug safety communication—FDA strengthens warning that untreated constipation can lead to serious bowel problems. Available at www.fda.gov/safety/medical-product-safety-information/clozaril-fazaclo-odt-versacloz-clozapine-drug-safety-communication-fda-strengthens-warning-untreated.

Adjunctive Pimavanserin for Refractory Depression

In a randomized trial, adjunctive pimavanserin (*Nuplazid*) was effective in patients with depression and an inadequate response to SSRI or SNRI therapy. No new safety concerns were raised for the drug, which is currently approved to treat Parkinson's disease psychosis.

Methods: The trial enrolled adults with a unipolar major depressive episode of ≥1 year in duration and an inadequate response to medication. Nonresponse was determined based on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ). The minimum antidepressant trial for inclusion was 8 weeks, with the last 4 weeks at a stable dose. The study used a 2-stage sequential parallel comparison design, designed to minimize the risk of distortion by a large placebo response and reduce sample size and variability. Patients were initially randomized to receive adjunctive treatment with 34 mg/day pimavanserin or placebo in a 1:3 ratio. After 5 weeks, patients who did not meet response criteria (i.e., ≥50% decrease in Hamilton Rating Scale for Depression [HAM-D] score) with placebo were rerandomized to switch to pimavanserin or continue placebo for another 5 weeks. The primary study outcome was change from baseline to each 5-week endpoint on the 17-item HAM-D. The Sheehan Disability Scale measured function, the key secondary outcome.

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Results: A total of 207 patients (73% women) were enrolled in the study: 52 who were initially randomized to pimavanserin and 155 to placebo. Following 5 weeks of treatment, 58 patients were rerandomized, 29 each to pimavanserin and placebo. Thus 44 patients (85% of those initially randomized) completed 10 weeks of treatment with pimavanserin, 29 completed 10 weeks of placebo treatment, and 24 completed 5 weeks of each treatment.

Mean baseline HAM-D scores were 23 and 22 in the pimavanserin and placebo groups, respectively. At week 5 (i.e., stage 1 endpoint), adjunctive pimavanserin was significantly more effective than placebo with mean a decrease in HAM-D score of 11.5 vs 7.5 with placebo (p=0.003; effect size,* 0.63). Pimavanserin diverged statistically from placebo after 1 week of treatment. Pimavanserin was also significantly superior for rates of response and remission at week 5, with numbers needed to treat* of 3.6 and 8.1, respectively.

In the prespecified primary analysis combining stages 1 and 2, pimavanserin was associated with a significantly larger decrease in HAM-D score than placebo (mean difference, 1.7 points; p=0.039). Stage 2 results were less robust than those from stage 1 likely because placebo non-responders may have been a more refractory group. In the combined analysis, pimavanserin was also associated with a significantly larger improvement in the Sheehan Disability Scale score (p=0.004). The positive effects of pimavanserin were stronger in patients with more severe depression at baseline. Efficacy did not differ when added to SSRI or SNRI therapy.

The predominant adverse effects associated with pimavanserin were dry mouth, nausea, and headache. Treatment was not associated with glucose or lipid changes, extrapyramidal symptoms, impaired sexual function, or somnolence.

Discussion: Despite being limited by a small sample size and short duration of treatment, the present results suggest that adjunctive pimavanserin can produce rapid and clinically meaningful improvement in resistant depression. In addition, the agent does not appear to be associated with the safety or tolerability concerns, such as metabolic dysregulation, sexual dysfunction, extrapyramidal effects, that are associated with atypical antipsychotics

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

Fava M, Dirks B, Freeman M, et al: A phase 2, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin in patients with major depressive disorder and an inadequate response to therapy (CLARITY). *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.19m12928. From Massachusetts General Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by ACADIA Pharmaceuticals Inc., San Diego, CA. All study authors declared potentially relevant financial relationships.**

***See Reference Guide.**

Anticonvulsant Exposure Via Breast Feeding

According to the results of an observational study, plasma concentrations of anticonvulsants are generally low in breastfed infants compared with maternal concentrations. For most drugs, concentrations in the infants were below the assays' lower limits of quantification (LLoQ). These observations may explain why previous studies have found no adverse neurodevelopmental effects of these drugs in breastfeeding infants.

Methods: The present analysis was part of an ongoing multicenter study that enrolled >300 pregnant women with epilepsy. Carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproic acid, and zonisamide exposure was measured in blood samples obtained from breastfed infants and their mothers at the same visit, between 5 and 20 weeks after birth.

Results: Of the total study population, 146 infants were breastfed and had antiepileptic drugs measured during the exposure window. A total of 164 matching mother–infant concentration pairs were available for analysis, obtained at a median infant age of 13 weeks. Some infants had

>1 drug concentration measured because of maternal polytherapy (about 18% of the mothers). Infant drug concentrations did not differ between those exposed to mono- or polytherapy.

Drug concentrations were below the assays' LLoQ in 68 of the infants (42%). All concentrations were below the LLoQ in infants whose mothers were receiving carbamazepine, oxcarbazepine, topiramate, or valproic acid. Concentrations were below the LLoQ in 71% of those exposed to levetiracetam and 60% of those exposed to zonisamide. In contrast, most concentrations of lamotrigine were above the LLoQ; however, the LLoQ value for lamotrigine is lower than for other drugs, and the median proportion of infant to maternal lamotrigine levels was 29%.

Discussion: These results suggest that anticonvulsant exposure via breast milk is considerably lower than fetal exposure during pregnancy and is unlikely to confer any additional risks.

Birnbaum A, Meador K, Karanam A, et al: Antiepileptic dug exposure in infants of breastfeeding mothers with epilepsy. *JAMA Neurology* 2019; doi 10.1001/jamaneurol.2019.4443. From the University of Minnesota, Minneapolis; and other institutions. **Funded by the National Institute of Neurological Disorders and Stroke; and the National Institute of Child Health and Development.**

Common Drug Trade Names*: carbamazepine—*Tegretol*; lamotrigine—*Lamictal*; levetiracetam—*Keppra*; oxcarbazepine—*Trileptal*; topiramate—*Topamax*; valproic acid—*Depakene, Depakote*; zonisamide—*Zonegran

Lumateperone Efficacy in Schizophrenia

In a multicenter phase 3 trial, the newly-approved antipsychotic lumateperone (*Caplyta*) was superior to placebo at reducing symptoms of schizophrenia in patients experiencing an acute exacerbation of symptoms.[1] Despite a unique receptor-binding profile, it is not clear whether lumateperone is a game-changing antipsychotic or another "me too" agent.[2]

Methods: The study, conducted at 12 U.S.clinical sites, recruited patients, aged 18–60 years, with a DSM-5 diagnosis of schizophrenia who were experiencing an acute episode of psychosis (total Brief Psychiatric Rating Scale [BPRS] score of ≥40 and moderate severity of ≥2 positive symptoms). Participants were required to have achieved response with antipsychotic medication in a previous episode. Eligible patients were admitted for a 2–7 day screening period that was followed by 4 weeks of randomly assigned, double-blind treatment with 28 or 42 mg/day lumateperone or placebo. The primary study outcome was change from baseline on the Positive and Negative Syndrome Scale (PANSS). Change in the Clinical Global Impression–Severity (CGI–S) score was the key secondary outcome.

Results: A total of 450 patients (mean age 42 years; 77% men) were randomized (150 to each group), and 81% completed randomized treatment. There were 16 discontinuations due to withdrawn consent or lack of efficacy in the 42 mg/day lumateperone group, 18 in the lower-dose group, and 33 in the placebo group.

Mean baseline PANSS scores ranged from 141 to 148, with no significant between-group differences. Treatment with 42 mg/day lumateperone produced a significantly larger decrease in PANSS total score than placebo: 16 points vs 12 points (effect size,* 0.3; p=0.02). Improvement was evident as early as the first week of treatment with lumateperone. Significant differences from placebo were evident on the positive symptom, general psychopathology, and prosocial factor PANSS subscales (effect sizes, 0.24 to 0.33; p≤0.04 for all), but not the negative symptom subscale (effect size, 0.20; p=ns). The change in PANSS score with the 28 mg/day lumateperone dose did not differ significantly from that with placebo. Response (i.e., ≥30% improvement in PANSS total score) occurred in 36.5% of patients treated with 42 mg/day lumateperone, 36.2% of those receiving the 28-mg dose, and 25.5% of the placebo group. The number needed to treat* with 42 mg/day lumateperone for 1 additional PANSS response was 9.1. The 42-mg dose also produced significantly greater improvement than placebo in CGI–S scores (effect size, 0.4; p=0.003). Lumateperone efficacy was not affected by patient age, sex, or ethnicity.

The most frequent adverse effects of lumateperone were somnolence (12–17%), sedation (9–13%), fatigue (5–6%), and constipation (4–7%). There were no severe adverse effects clearly attributable to the drug. Extrapyramidal symptoms were rare. Patients receiving the higher dose gained an average of about 2 lbs, compared with 1.3 lbs in the 28-mg group and 1.5 lbs in the placebo group. Metabolic parameters did not differ from placebo.

Discussion: Lumateperone simultaneously modulates neurotransmission by serotonin, dopamine, and glutamate—key neurotransmitters involved in serious mental illness—and does not interact with off-target receptors that cause side effects with other drugs. The effect sizes for the agent in this study are similar to those previously found with the standard-of-care antipsychotics and other newly approved agents. However, the efficacy of lumateperone compared with some of the most effective antipsychotics (e.g., olanzapine, clozapine) is unknown, and it is not yet clear whether its activity profile is truly novel and clinically relevant, or if lumateperone is simply another moderately effective antipsychotic that is more metabolically friendly.

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

[1]Corell C, Davis R, Weingart M, et al: Efficacy and safety of lumateperone for treatment of schizophrenia: a randomized clinical trial. *JAMA Psychiatry* 2020; doi 10.1001/jamapsychiatry.2019.4379. From Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; and other institutions including Intra-Cellular Therapies Inc., New York, NY. **Funded by Intra-Cellular Therapies, Inc. Seven of 10 study authors disclosed potentially relevant financial relationships (including 6 with Intra-Cellular Therapies); the remaining authors declared no competing interests.**

[2]Kantrowitz J: The potential role of lumateperone—something borrowed? Something new? [Editorial] *JAMA Psychiatry* 2020; doi 10.1001/jamapsychiatry.2019.4265. From Columbia University Medical Center, New York, NY. **The author declared potentially relevant financial relationships.**

Common Drug Trade Names*:** **clozapine—*Clozaril*; lumateperone—*Caplyta*; olanzapine—*Zyprexa

***See Reference Guide.**

Pharmacotherapy for PTSD

Posttraumatic stress disorder is a potentially chronic and debilitating condition that affects about 6% of the U.S. population. Currently, only the SSRIs paroxetine and sertraline have FDA approval to treat PTSD. However polypharmacy and off-label prescribing are common.

Antidepressants. The American Psychiatric Association and the Veterans Affairs/Department of Defense recommend SSRIs as first-line pharmacotherapy for PTSD. Improvements with the agents appear to occur across all PTSD symptom clusters and effect sizes are similar to those seen in depression. The SNRI venlafaxine also appears to be effective, although it may have weaker effects on hyperarousal. Atypical antidepressants (e.g., mirtazapine, trazodone, nefazodone) are commonly prescribed, possibly because of their sedative effects, and effect sizes seem to be comparable to the SSRIs.

Alpha-adrenergic antagonists. Some research supports medium-to-large effects of prazosin on nightmares and overall PTSD symptoms, and at least 1 international guideline includes it as a first-line pharmacotherapy option. However, positive findings were not replicated in a large study of clinically stable patients with PTSD.

Atypical antipsychotics. Risperidone has been extensively studied in patients with PTSD, with some studies showing potential efficacy as monotherapy or as an adjunct to antidepressants. However, a recent large controlled trial found no benefit of augmenting antidepressants with risperidone. A single controlled trial found that compared with placebo, quetiapine monotherapy significantly improved PTSD symptoms.

Other drug classes. Benzodiazepines are often prescribed off-label for patients with PTSD, likely in an effort to control hyperarousal symptoms. However, research has found no measurable

positive effects. Some detrimental effects, such as symptom worsening, and increased risk of substance abuse, have been reported. The mood stabilizers lamotrigine and tiagabine have been evaluated in patients with PTSD, but there is no convincing evidence for their use. In contrast, a single study suggests potential efficacy for topiramate.

Regardless of the class, clinical effectiveness of pharmacotherapy for PTSD appears to be modest at best. Efficacy of trauma-focused psychotherapies appears to be similar to pharmacotherapy, but their widespread use is limited by patient resistance and other obstacles. In the few available studies, combining pharmacotherapy and psychotherapy did not appear to be more effective than either treatment modality alone. Ongoing research has demonstrated preliminary efficacy for ketamine as well as MDMA-augmented psychotherapy.

Akiki T, Abdallah C: Are there effective psychopharmacological treatments for PTSD? *Journal of Clinical Psychiatry* 2019; doi10.4088/JCP.18ac12473. From the U.S. Department of Veterans Affairs National Center for PTSD, West Haven, CT; and Yale University School of Medicine, New Haven, CT. **Funded by the US Department of Veterans Affairs. One study author disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

Common Drug Trade Names*: ketamine—*Ketalar*; lamotrigine—*Lamictal*; mirtazapine—*Remeron*; nefazodone—*Serzone*; paroxetine—*Paxil*; prazosin—*Minipress*; quetiapine—*Seroquel*; risperidone—*Risperdal*; sertraline—*Zoloft*; tiagabine—*Gabitril*; topiramate—*Topamax*; trazodone—*Desyrel*; venlafaxine—*Effexor

Antipsychotics: Dose Response

Dose-response relationships in drug development are often estimated from animal studies, and trials of higher or lower doses in humans are often not conducted. As a result, the licensed dosages of antipsychotic drugs may not represent their full range of efficacy, according to a meta-analysis of dose-response relationships of 20 different antipsychotic drugs. For some of the drugs, efficacy plateaus were not detected within the licensed range, which suggests higher doses might be tested in further trials.

Methods: A comprehensive literature search identified fixed-dose, placebo-controlled trials that compared the efficacy of ≥2 doses of antipsychotic medications in adult patients with acute exacerbations of schizophrenia or schizoaffective disorder. Outcome measures of the analysis were change from baseline in the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS), and, in patients with predominant negative symptoms, the Scale for the Assessment of Negative Symptoms (SANS). Dose-response curves were generated to estimate 50% effective (minimum) and 95% effective (maximum) doses—doses that produce 50% and 95% of the maximum symptom reduction on the PANSS or BPRS (ED50 and ED95). Separate analyses of 4 different patient subgroups—first-episode patients, patients with predominant negative symptoms, the elderly, and patients with treatment-resistant illness—were also planned, but small numbers of patients prevented most of these comparisons.

Results: A total of 68 studies of 20 second generation drugs or haloperidol were included in the analysis. For the predefined analysis of patient subgroups, sufficient data were available only for patients with predominant negative symptoms. See table (next page) for detailed results of the dose-response analyses.

For most of the drugs, the dose-response curve plateaued within the tested range or showed a downturn at higher doses. However, for clozapine (in resistant illness), iloperidone, lurasidone, injectable and oral olanzapine, paliperidone, and ziprasidone the curve did not plateau, suggesting the potential for further efficacy increases at higher doses. In addition, increasing efficacy at higher doses was suggested for oral olanzapine in patients with predominantly positive symptoms, but not those with predominantly negative symptoms. For aripiprazole and risperidone the dose-response curve was bell-shaped, possibly suggesting doses within the licensed range are higher than the maximum effective doses.

Minimum and Maximum Effective Doses for Available Antipsychotics			
Agent	**# of Studies**	**ED50**	**ED95**
Aripiprazole Oral	5	4.8 mg/day	11.5 mg/day
Aripiprazole LAI	1	217.19 every 4 weeks	463 mg every 4 weeks
Asenapine	6	2.82 mg/day	11 mg/day
Brexpiprazole	4	0.73 mg/day	3.4 mg/day
Cariprazine	4	1.65 mg/day	7.6 mg/day
Clozapine	1	—	567 mg/day
Haloperidol	1	2.96 mg/day	6.3 mg/day
Iloperidone	4	5.75 mg/day	20.1 mg/day
Lurasidone	6	43.88 mg/day	147 mg/day
Olanzapine Oral	3	6 mg/day (positive symptoms) 2.9 mg/day (negative symptoms)	15.1 mg/day (positive symptoms 6.5 mg/day (negative symptoms)
Olanzapine LAI	1	127mg every 2 weeks	277 mg every 2 weeks
Paliperidone Oral	5	3.86 mg/day	13.4 mg/day
Paliperidone LAI	4	34.23 every 4 weeks	120 mg every 4 weeks
Quetiapine	4	207.41 mg/day (IR, ER combined)	297 mg/day IR; 739 mg/day ER
Risperidone Oral	3	2.82 mg/day	6.3 mg/day
Risperidone LAI	1	17.57 every 2 weeks	37 mg every 2 weeks
Ziprasidone	4	68.47 mg/day	186 mg/day

Discussion: It is important to note that the analysis did not take the drugs' adverse effects into consideration. Adverse effects in animal studies might limit attempts to trial higher doses in humans. In addition, the present data provide guidance based on "average" patients with chronic illness, and may not be applicable to special populations such as the elderly and those with resistant disease.

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

Leucht S, Crippa A, Siafis S, et al: Dose-response meta-analysis of antipsychotic drugs for acute schizophrenia. *American Journal of Psychiatry in Advance* 2019; doi 10.1176/appi.ajp.2019.19010034. From the Technical University of Munich School of Medicine, Germany; and other institutions. **Source of funding not stated. Two of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify, Abilify Maintena, Aristada*; asenapine—*Saphris*; brexpiprazole—*Rexulti*; cariprazine—*Vraylar*; clozapine—*Clozaril*; haloperidol—*Haldol*; iloperidone—*Fanapt*; lurasidone—*Latuda*; olanzapine—*Zyprexa, Zyprexa Relprevv*; paliperidone—I*nvega, Invega Sustenna*; quetiapine—*Seroquel*; risperidone—*Risperdal, Risperdal Consta*; ziprasidone—*Geodon

***See Reference Guide.**

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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 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). Checklists are posted at alertpubs.com.

Off-Label Drug Use Statement: Some drugs discussed for specific indications in ***Psychiatry Drug Alerts*** articles may not be approved for labeling and advertising for those indications by the United States FDA.