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Esketamine Nasal Spray: Approval Recommended

The FDA Psychopharmacologic Drug Advisory Committee and Drug Safety and Risk Management Advisory Committee together agree that the risk–benefit profile of esketamine nasal spray (*Spravato*) is favorable in patients with treatment-resistant depression and have recommended approval of the agent. The recommendation is based on the results of 5 phase III studies and a long-term safety study. Data from these studies indicate that treatment with esketamine nasal spray in addition to a newly initiated oral antidepressant produced rapid, sustained, clinically meaningful improvement in treatment-resistant depression. Esketamine was well tolerated, with most adverse effects (e.g., dissociative symptoms, dizziness, increased blood pressure, sedation) occurring shortly after administration and resolving the same day.

The FDA is not bound by the committee's recommendation, but the agency does take its advice into consideration. If approved, esketamine nasal spray would represent the first newly approved mechanism of action in treatment-resistant depression in 3 decades.

FDA Advisory Committee recommends approval of Spravato™ (esketamine) Nasal Spray CIII for adults with treatment-resistant depression [press release] Titusville, NJ; Janssen: February 12, 2019. Available at www.prnewswire.com/news-releases/fda-advisory-committee-recommends-approval-of-spravato-esketamine-nasal-spray-ciii-for-adults-with-treatment-resistant-depression-300794493.html.

SRIs and Newborn Pulmonary Hypertension

Exposure to SSRIs or SNRIs during pregnancy is associated with a 2-fold increase in risk of persistent pulmonary hypertension of the newborn (PPHN), according to the results of a meta-analysis. This uncommon condition, associated with increased resistance in the pulmonary blood vessels, has variable presentations and is associated with an increased risk of death. Sertraline may be the safest option among these antidepressants for pregnant women.

Methods: A comprehensive literature search identified all published case–control and cohort studies assessing the association of prenatal SSRI or SNRI exposure with PPHN. Meta-analysis was conducted to compare the risk of PPHN in the 11 identified studies—3 case-control and 8 cohort—conducted from the mid-1990s onward. Because few studies evaluated SNRIs, a network meta-analysis* assessed risk differences only among individual SSRIs.

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Results: The studies included a total of nearly 157,000 exposed pregnancies. PPHN was detected in 452 exposed newborns (2.9 per 1000 live births). After adjustment for a range of factors (e.g., maternal diabetes, obesity, and asthma; gestational age at delivery; mode of delivery), SSRI or SNRI exposure was associated with a >2-fold increase in risk for PPHN (adjusted odds ratio,* 2.42). However, the absolute risk is small and the number needed to harm* is 1000. In an analysis limited to exposure in the 20th gestational week or after, SSRIs and SNRIs remained associated with a 2-fold increase in risk of PPHN. The association persisted in an analysis limited to late preterm and term deliveries. Comparisons of sertraline, citalopram, fluoxetine, escitalopram, and paroxetine found sertraline to be associated with the lowest risk of PPHN and, in pairwise comparisons, associated with significantly lower risk than fluoxetine (odds ratio, 0.34).

Discussion: Serotonergic agents are thought to cause PPHN via increased serotonin in the fetal circulatory bed, leading to vasoconstriction and increased pulmonary vascular resistance. These results suggest that this is a class effect of SSRIs. Sertraline may be safer because it crosses the placenta in a lower percentage than other SSRIs. It also has fewer drug interactions than other SSRIs and SNRIs.

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

Masarwa R, Bar-Oz B, Gorelik E, Reif S, et al: Prenatal exposure to selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors and risk for persistent pulmonary hypertension of the newborn: a systematic review, meta-analysis, and network meta-analysis. *American Journal of Obstetrics and Gynecology* 2019; doi 10.1016/j.ajog.2018.08.030. From Hebrew University of Jerusalem and Hadassah-Hebrew University Medical Centers, Jerusalem, Israel. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names*: citalopram—*Celexa*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; paroxetine—*Paxil*; sertraline—*Zoloft

Olanzapine Weight Gain in Anorexia

In a placebo-controlled trial, olanzapine (*Zyprexa*) produced modest weight gain in adults with anorexia nervosa. However, it had no effect on psychological features of the disorder.

Methods: The study was conducted at 5 U.S. tertiary-level outpatient anorexia treatment centers. Study participants, aged 18–65 years, received a diagnosis of DSM-IV anorexia nervosa, and had a body mass index (BMI) of 14–18.5. They were required to be free of other antipsychotic medication for ≥4 weeks before randomization but could be receiving other psychotropic medications or psychotherapy. Patients with acute suicidality, current substance abuse or dependence, schizophrenia, schizophreniform disorder, or bipolar disorder were excluded. Participants received 16 weeks of double-blind randomized treatment with either olanzapine, increased to a maximum of 10 mg/day over the first 4 study weeks, or placebo. Patients had brief weekly psychiatrist visits that were designed to enhance adherence. Weight was the study's primary physical outcome measure. The primary psychological outcome measure was the obsessionality component of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

Results: A total of 152 patients (96% women) were enrolled in the trial. The average age was 28–30 years, and the mean baseline BMI was 16.7. A comorbid anxiety disorder was present in 40% of patients, and 33% had a comorbid mood disorder. Concomitant psychotropic use included antidepressants in 30% of patients and sedative-hypnotics in 15%.

There were no significant differences in study completion or medication compliance between the treatment groups. At the midpoint assessment, 65% of patients were continuing to take their study medication; at trial end, 55% remained adherent.

Olanzapine was associated with a significantly higher rate of weight gain than placebo, but the absolute difference was small: a mean monthly gain of 0.3 BMI points, versus 0.1 for placebo

(effect size,* 0.63; p=0.026). This difference is equivalent to about 1 lb per month for a woman of medium height. Study treatment had no effect on Y-BOCS total or subscale scores. Patients receiving olanzapine had a 3-fold greater likelihood of being rated much or very much improved on the Clinical Global Impression (CGI) Improvement scale, but this was not statistically significant. The groups did not differ in changes in the CGI–Severity score, in measures of depression or anxiety, or in most concerns measured by the Eating Disorder Examination, with the exception of shape concerns, which were greater in the olanzapine group. Olanzapine was not associated with higher rates of metabolic abnormalities.

Discussion: Although modest, the weight gains observed with olanzapine were notable given the difficulty of inducing weight gain in adults with anorexia. The lack of significant between-group differences in symptom severity and global improvement suggest that olanzapine alone is not a sufficient treatment for anorexia and it should be combined with other therapy.

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

Attia E, Steinglass J, Walsh T, Wang Y, et al: Olanzapine versus placebo in adult outpatients with anorexia nervosa: a randomized clinical trial. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.18101125. From Columbia University, New York, NY; and other institutions. **Funded by NIMH; and other sources. Five of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Psychotropic/Antiretroviral Interactions: Anxiolytics, Mood Stabilizers

Anxiety is present in >10% of patients with HIV, and severe anxiety is predictive of non-adherence to antiretroviral therapy (ART). In addition, the prevalence of bipolar disorder is nearly 4-times higher in adults with HIV (8%) than in the general population, and patients with bipolar disorder are more likely to engage in behaviors that increase their risk of acquiring HIV. As a result, coprescription of anxiolytics and/or mood stabilizers with ART is likely to occur.

Many antiretrovirals are metabolized by the hepatic cytochrome P450 (CYP450) system (see the printable ART cytochrome P450 properties table at www.alertpubs.com/sdaonlinecontent for details), as are most of the anxiolytics and mood stabilizers. While data on ART/anxiolytic interactions are sparse, interactions between ART regimens and most mood stabilizers are well documented. (See tables.) When concomitant anxiolytic and ART are required, benzodiazepines that are not dependent on CYP metabolism (e.g, lorazepam, oxazepam) are recommended. When coprescribing a mood stabilizer and ART, lithium may be the best option because its lack of CYP effects makes it unlikely to cause hepatically-mediated interactions.

Interactions of ART Therapies with Anxiolytics	
Buspirone	Caution is required when used with agents that inhibit CYP3A4 (e.g., ritonavir, cobicistat). Dosing adjustments may be required, but specific recommendations are not available.
Midazolam	HIV treatment guidelines recommend against concomitant administration with ritonavir, cobicistat, and efavirenz because these agents inhibit midazolam metabolism, markedly increasing exposure.
Diazepam	Guidelines recommend against concomitant administration with ritonavir or cobicistat, as coadministration slows diazepam metabolism and prolongs its effects. The NNRTIs efavirenz and nevirapine induce CYP activity, possibly decreasing diazepam exposure and necessitating dose adjustments. Etravirine has CYP induction activity, but also inhibits CYP2C19—a pathway of diazepam metabolism. Concurrent use should be undertaken cautiously.
Alprazolam	Data regarding the effects of CYP 3A4 inhibitors (e.g., ritonavir, cobicistat) on alprazolam are conflicting but suggest lengthened alprazolam half-life and increased exposure. If coadministration is required, alprazolam should be initiated at a low dose and titrated carefully. HIV treatment guidelines recommend monitoring for alprazolam efficacy and potentially increasing alprazolam doses with concomitant use of efavirenz, etravirine, or nevirapine.

Interactions of ART Therapies with Mood Stabilizers	
Carbamazepine	Carbamazepine is a CYP3A4 substrate and inducer in addition to a CYP1A2 inducer, which increases the likelihood of pharmacokinetic interactions. Interactions between carbamazepine and strong CYP3A4 inhibitors (e.g., ritonavir) are well documented and can cause toxic plasma levels, that may manifest as blood dyscrasias, ocular abnormalities, cardiovascular instability, neurologic deficits, or severe dermatologic reactions (e.g., Stevens Johnson Syndrome). Hematologic monitoring should be increased when carbamazepine is combined with antiretroviral agents known to disrupt hematologic parameters, and dose adjustments should be made as indicated. Carbamazepine is contraindicated in patients receiving antiretroviral agents that are CYP3A4 substrates (e.g., indinavir, dolutegravir), as concomitant use would result in suboptimal antiretroviral plasma levels. Coadministration with efavirenz is contraindicated, as plasma levels of both medications are decreased with concomitant use. As a CYP3A4 inducer, carbamazepine has also been associated with accelerated nevirapine clearance, which may increase the risk of nevirapine resistance.
Valproic Acid	Valproic acid coadministered with zidovudine has been shown to elevate plasma and cerebral spinal fluid levels of zidovudine, likely due to valproic acid-induced inhibition of zidovudine glucuronidation. Patients may require a decreased zidovudine dose if valproic acid is also prescribed. However, recommendations are not uniform. Data on coadministration of valproic acid with efavirenz, ritonavir, saquinavir, stavudine, atazanavir, and nevirapine are conflicting, with some guidelines recommending dosage adjustments while others do not. Close monitoring and valproic acid dose titrations as indicated are advisable.
Lamotrigine	Both the half-life and overall exposure to lamotrigine are reduced when coadministered with ritonavir combinations. Decreased lamotrigine exposure in patients with bipolar disorder could result in subtherapeutic concentrations and exacerbations of bipolar depression or mania/hypomania. Patients receiving the agents concomitantly may require a 50% increase in lamotrigine dose to maintain therapeutic serum concentrations.
Lithium	Although pharmacokinetic interactions are unlikely, lithium can become toxic in cases of dehydration and impaired renal function. Multiple antiretrovirals are associated with nausea, vomiting, and diarrhea, which could increase risk of dehydration and resulting lithium toxicity. Additionally, there is a theoretical concern with combining lithium, which has been linked to atrioventricular block and bradyarrhythmia, with cardiotoxic antiretrovirals. Long-term lithium may independently impair renal function, and several of the NRTIs (e.g., tenofovir, zidovudine) carry recommendations for dose reductions in patients with renal impairment.

In addition to pharmacokinetic interactions, there is the potential for ART regimens to augment expected adverse events of anxiolytics and mood stabilizers. In particular, benzodiazepines pose a concern for excessive sedation, and mood stabilizers for hypotension, constipation, nausea, vomiting, dizziness, and somnolence. Coadministration of ART can have additive effects. Efforts should be made to alleviate these symptoms, and selection of anxiolytics, mood stabilizers, or antiretrovirals that are less likely to compound these effects should be considered.

Editor's Note. This is the fourth report in a 5-part series on psychotropic/antiretroviral interactions. We previously covered interactions with antidepressants, stimulants, and antipsychotics. (See November 2018 through January 2019 issues.) The final report on medications for opioid and alcohol use disorders will appear in the next issue.

Goodlet K, Zmarlicka M, Peckham A: Drug-drug interactions and clinical considerations with co-administration of antiretrovirals and psychotropic drugs. *CNS Spectrums* 2018; doi 10.1017/S109285291800113X. From Midwestern University College of Pharmacy, Glendale, AZ; and other institutions. **Source of funding not stated. Two of 3 study authors disclosed potentially relevant relationships; the remaining author declared no competing interests.**

Common Drug Trade Names*: alprazolam—*Xanax*; atazanavir—*Reyataz*; buspirone—*Buspar*; carbamazepine—*Carbatrol, Tegretol*; cobicistat—*Tybost*; diazepam—*Valium*; dolutegravir—*Tivicay*; efavirenz—*Sustiva*; etravirine—*Intelence*; indinavir—*Crixivan*; lamotrigine—*Lamictal*; lopinavir–ritonavir—*Kaletra*; lorazepam—*Ativan*; midazolam—*Versed*; nevirapine—*Viramune*; oxazepam—*Serax*; ritonavir—*Norvir*; saquinavir—*Invirase*; stavudine—*Zerit*; tenofovir—*Viread*; valproic acid—*Depakene, Depakote*; zidovudine—*Retrovir

Medication for Cannabis Withdrawal

In a small placebo-controlled trial, the investigational drug PF-04457845 reduced withdrawal symptoms and cannabis use in men seeking treatment for cannabis dependence.

Background: Cannabis use disorder is associated with long-term adaptive changes to the endocannabinoid system, and substitution therapy with THC (δ-9-tetrahydrocannabinol), which creates a state of controlled dependence, has little effect on relapse prevention. An alternate approach to treatment is to potentiate endocannabinoid function by increasing concentrations of primary endocannabinoids. The investigational agent PF-04457845 inhibits fatty acid amide hydroxylase (FAAH), an enzyme that degrades the endocannabinoid anandamide. Drugs in this class offer a novel approach to treating cannabis use disorder by increasing levels of the endocannabinoid as cannabis itself is withdrawn.

Methods: The study enrolled self-referred men, aged 18–55 years, with varying levels of desire to discontinue cannabis use. Participants met DSM-IV criteria for cannabis dependence and had made ≥1 prior attempt to quit that was accompanied by withdrawal symptoms. Participants were admitted to an inpatient unit for 5–8 days to achieve abstinence. From the first day, they received randomly assigned 4 mg/day PF-04457845 or placebo. They were directly observed taking the medication while hospitalized and discharged with the remaining supply, with a smartphone app to monitor adherence. The study had multiple primary outcomes: cannabis withdrawal symptoms during the first 4 days of abstinence, measured using the Marijuana Withdrawal Checklist (MWC); and self-reported cannabis use and urinary THC metabolite (THC-COOH) concentrations at 4 weeks, when treatment ended.

Results: By design, two-thirds of the 70 participants were assigned to active medication and one-third to placebo. A total of 8 patients dropped out of treatment with PF-04457845, and 4 dropped out from the placebo group. Medication adherence was 95% during the inpatient portion of the study and an estimated 88% after patients were discharged.

On the first 2 days of abstinence, scores on the MWC were significantly lower in the active treatment group than the placebo group ($p \leq 0.048$). Afterward, the 2 groups had similar symptom scores through the remaining inpatient days.

At baseline, the men were smoking an average of 3 joints per day. After 4 weeks, mean daily consumption was 0.4 in the PF-04457845 group and 1.27 in the placebo group ($p=0.0003$). Urine concentrations of THC-COOH were higher in the placebo group than the group receiving PF-04457845. Exploratory analyses also found PF-04457845 reduced self-reported depression, anxiety, and irritability and improved sleep. Adverse events were mild and did not differ between the active medication and placebo.

Discussion: BIA 10-2474, another FAAH inhibitor, was withdrawn from development because of serious adverse events, including 1 death, in a clinical trial. The FDA had determined this to be a unique toxicity that does not extend to other drugs in this class. However, the positive effects and apparent safety of PF-04457845 suggest further study of endocannabinoid modulation via FAAH inhibition for the treatment of cannabis use disorder may be warranted.

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

D'Souza D, Cortes-Briones J, Creatura G, Bluez G, et al: Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial. *Lancet Psychiatry* 2019; doi 10.1016/S2215-0366(18)30427-9. From the VA Connecticut Healthcare System, West Haven; and other institutions. **Funded by the U.S. δ-9-tetrahydrocannabinol National Institute on Drug Abuse. Five of 17 study authors declared potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Potential for Repurposing Nonpsychiatric Drugs

Several classes of medication for common physical illnesses were associated with reduced rates of psychiatric hospitalization and self-harm in patients with serious mental illness. The 3 drug categories studied—HMG-CoA reductase inhibitors (statins), L-type calcium channel (LTCC) antagonists, and biguanides—each have a theoretical basis for effectiveness. The drugs are ideal candidates for repurposing as mental-illness treatments because they are globally licensed, commonly used, inexpensive, and relatively safe.

Background: Statins (e.g., atorvastatin, simvastatin) are believed to act via antiinflammatory or neuroprotective effects or by increasing absorption of antipsychotics. LTCC antagonists (e.g., nifedipine, verapamil) may affect calcium-dependent signaling, which is disordered in schizophrenia and bipolar disorder. The biguanide metformin is hypothesized to improve cognitive and mood symptoms by mitigating metabolic disturbances.

Methods: The study was based on Swedish national medical registry data. Patients were adults with a diagnosis of bipolar disorder, schizophrenia, or nonaffective psychosis, or who were given a prescription for an antipsychotic or mood stabilizer. Exposure was defined as treatment between 2005 and 2016 with medications from the 3 classes of interest—statins, LTCC antagonists, or the biguanide metformin. The primary outcomes of psychiatric hospitalization and self-harm with suicidal or undetermined intent were compared within patients during periods of exposure and nonexposure. Because statins may increase uptake of antipsychotics by the CNS, the possible interaction between the drug classes was also evaluated, and an exposure to thiazide diuretics (e.g., hydrochlorothiazide) was included as a control.

Results: Of >142,000 patients with a diagnosis of interest, nearly 58,000 patients had received a statin, LTCC antagonist, or metformin. HMG-CoA reductase inhibitors were associated with a reduced rate of psychiatric hospitalization in all 3 diagnostic groups and with statistically significantly fewer episodes of self-harm in patients with bipolar disorder or schizophrenia. (See table.) There was no evidence of an interaction between these drugs and antipsychotics. LTCC antagonists were associated with lower rates of both outcomes in all diagnostic groups. Metformin was associated with fewer psychiatric hospitalizations across the diagnostic groups and with fewer self-harm episodes in patients with bipolar disorder or schizophrenia. Thiazides were not associated with improved outcomes. Neither statins nor LTCC antagonists were associated with reduced nonpsychiatric hospitalization.

Adjusted hazard ratios* for psychiatric hospitalization and self-harm in patients with serious mental illness during periods of drug exposure vs nonexposure

	Psychiatric hospitalization	Self-harm
Statins (n=24,614)		
Bipolar disorder	0.86†	0.76†
Schizophrenia	0.75†	0.58†
Nonaffective psychosis	0.80†	0.86
LTC Antagonists (n=18,591)		
Bipolar disorder	0.92†	0.81††
Schizophrenia	0.80†	0.30†
Nonaffective psychosis	0.89††	0.56†
Metformin (n=1,772)		
Bipolar disorder	0.80†	0.73†
Schizophrenia	0.73†	0.64†
Nonaffective psychosis	0.85†	0.91

†p<0.001 ††p≤0.01

Discussion: Hypercholesterolemia, hypertension, diabetes, and prediabetes are common but often undertreated in patients with serious mental illness. Mental illness is part of risk calculations underlying clinical guidelines for prescribing these agents. The lack of effect of the study drugs on nonpsychiatric hospitalization along with the finding that thiazide diuretics had no effect on outcomes suggest the improvements were not driven by physical changes. The repurposing of

these drugs for psychiatric indications appears to warrant further investigation. Although the comparison of exposed and unexposed periods within individual patients reduces potential confounders, to be included in the analysis, patients had to be prescribed a study drug and to experience ≥1 outcome suggesting both poor physical and mental health. Therefore, these results may not generalize to healthier populations.

Hayes J, Lundin A, Wicks S, Lewis G, et al: Association of hydroxymethyl glutaryl coenzyme A reductase inhibitors, L-type calcium channel antagonists, and biguanides with rates of psychiatric hospitalization and self-harm in individuals with serious mental illness. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2018.3907. From the University College London, U.K.; and other institutions. **Funded by the Wellcome Trust; and other sources. One 7 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: atorvastatin—*Lipitor*; metformin—*Glucophage*; nifedipine—*Procardia*; simvastatin—*Zocor*; verapamil—*Calan

***See Reference Guide.**

Relapse Prevention with Cariprazine

According to a post-hoc analysis of previously reported data,[1] nearly two-thirds of patients receiving cariprazine (*Vraylar*) for schizophrenia sustained remission for ≥6 months.[2] Cariprazine was also associated with longer periods of sustained remission than placebo.

Background: Cariprazine has demonstrated acute and relapse-prevention effects in schizophrenia. Sustained remission, the long-term alleviation of symptoms to levels that do not significantly influence behavior, is associated with improved outcomes, including social functioning. The present analysis was conducted to determine the effects of cariprazine treatment on sustained remission using the Remission in Schizophrenia Working Group (RSWG) criteria, which are based on 3 dimensions of schizophrenia psychopathology—psychoticism, disorganization, and negative symptoms—and require scores of 3 (mild) or better on each of 8 individual items of the Positive and Negative Syndrome Scale (PANSS), sustained for ≥6 consecutive months. (See table.) Unlike relative improvement scores often used in clinical trials, this definition uses an absolute threshold of symptom severity that facilitates comparisons across the course of disease and between studies.

RSWG consensus definition of sustained remission: Ratings of mild or better on the following symptoms for ≥6 consecutive months	
Delusions	Mannerisms/posturing
Unusual thought content	Blunted affect
Hallucinatory behavior	Social withdrawal
Conceptual disorganization	Lack of spontaneity

Methods: The multinational relapse-prevention trial was conducted in patients with a duration of schizophrenia of ≥1 year and a current episode of <4 weeks' duration. First-episode patients and those with psychiatric or medical comorbidity were excluded. Patients were initially stabilized with 20 weeks of open-label cariprazine, flexibly dosed in the range of 3–9 mg/day. Those who met the study's criteria for stabilization (e.g., PANSS score ≤60, PANSS score decrease of ≥20%, global severity rating of moderately ill or better) were randomly assigned to receive continued cariprazine at the same dose or be switched to placebo. The outcome of sustained remission was based on the 8 RSWG symptom criteria. Patients were followed for 26–72 weeks of randomized treatment.

Results: Of the 765 patients who began treatment, 264 completed the open-label study phase and 200 stable patients (mean age, 38 years; 66% men) began randomized treatment. Nearly 85% of these patients met criteria for symptomatic remission at the start of the double-blind phase. Sustained remission for ≥6 months was achieved by 61% of patients in the cariprazine group and 35% of placebo-treated patients (odds ratio,* 2.85; p=0.001; number needed to treat,* 4). When the analysis was restricted to patients already meeting sustained remission at double-blind baseline, 47% in the cariprazine group, compared with 29% of those in the

placebo group, continued to meet criteria after 6 months (odds ratio, 2.1; number needed to treat, 6).

Time to loss of sustained remission was longer for patients receiving cariprazine than for those receiving placebo (hazard ratio,* 0.51; p=0.002). The time to loss of remission by 25% of patients was 58 days for cariprazine and 43 days for placebo. Although the time to loss of remission by 50% of patients could not be calculated in the cariprazine group, it was estimated to be >240 days, more than twice as long as the placebo group (126 days).

Discussion: An important limitation of this trial is that only patients who were stable on cariprazine and could tolerate it were included in the long open-label treatment period. A naturalistic study of sustained remission in a more representative patient sample, including those with significant comorbidities, appears to be warranted.

[1]Durgam S, et al: Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *Schizophrenia Research* 2016;176 (2–3):264–271.

[2]Correll C, Potkin S, Zhong Y, Harsanyi J, et al: Long-term remission with cariprazine treatment in patients with schizophrenia: a post hoc analysis of a randomized, double-blind, placebo-controlled, relapse prevention trial. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.18m12495. From the Zucker Hillside Hospital, Glen Oaks NY; and other institutions. **Funded by Allergan Plc; and Gedeon Richter Plc. All 6 study authors disclosed financial relationships with commercial sources including Allergan or Gedeon Richter.**

***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.

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.

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.

Network Meta-Analysis: An analytic method that extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common. For example, if in a clinical trial comparing treatment A with treatment B, option A is determined to be superior, and a separate trial in similar patients found option B superior to a third agent, option C, a network meta-analysis of these two trials would allow a researcher to conclude that treatment option A is more effective than option C, even though the two options have never been directly compared.

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.

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.

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.