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PSYCHIATRY DRUG ALERTS

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New CME Activities Have Been Released . . . Are You Enrolled?

Unauthorized Lithium Products

Health Canada has issued a warning regarding the safety of 3 products—*Lithium Plus*, *Serotonin Support*, and *Brain Support*—as they may contain lithium orotate. The products, which can pose serious health risks, are marketed by Cutting Edge Naturals.

MedEffect e-Notice: Unauthorized products "Lithium Plus, Serotonin Support, and Brain Support" may pose serious health risks. Available at http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/61608a-eng.php.

Cariprazine: Long-Term Safety and Tolerability

In a manufacturer-sponsored study of cariprazine in patients with schizophrenia, there were no new or unexpected adverse events and no loss of efficacy over 1 year of continuous treatment.

Methods: The present study—a 53-week extension of a 6-week, double-blind trial with 3 treatment arms (cariprazine, placebo, and risperidone)—was designed to test the long-term safety and tolerability of cariprazine; efficacy was a secondary concern. Open-label treatment was offered to participants who completed the acute treatment study with a final Clinical Global Impression–Severity (CGI–S)* score of ≤3 and a ≥20% reduction from baseline in the Positive and Negative Syndrome Scale (PANSS) total score. Of the 464 patients who completed the initial study, 93 participated in the extension study and were hospitalized for ≥1 week to begin open-label cariprazine, which was titrated to maximum of 4.5 mg/day. Most participants (57%) had received cariprazine in the initial study; 27% received risperidone, and 16% received placebo. Evaluations were conducted weekly for 6 weeks, and then biweekly for the rest of the study.

Results: A total of 46 patients (49%) completed 1 year of treatment. The most frequent reasons for discontinuation were withdrawal of consent (17%) and adverse events (11%). Adverse events that led to cariprazine discontinuation were completed suicide (n=1), worsening of schizophrenia (n=4), worsening of psychotic disorder (n=2), and headache, pneumonia, sedation, and insomnia (n=1 each).

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Although the majority of patients (83%) reported adverse effects, most were mild to moderate and occurred early in treatment. The most common adverse effects believed to be treatment-related were akathisia (13%), tremor (8%), and joint stiffness (<5%). No unanticipated adverse events emerged during long-term treatment. There were few clinically relevant changes in lipids, fasting glucose, prolactin, or electrocardiogram parameters. No patient had a QTc-interval increase of ≥60 ms or a post-baseline value of >500 ms. One third of patients had a potentially clinically significant (≥7%) increase in weight. Extrapyramidal symptoms were generally mild or moderate. Although efficacy was not tested formally, decreases from baseline in PANSS and CGI–S scores appeared to be maintained in patients who continued treatment.

Durgam S, Greenberg W, Li D, Lu K, et al: Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. *Psychopharmacology* 2017;234 (January):199–209. From Allergan, Jersey City, NJ; Gedeon Richter Plc, Budapest, Hungary; and Apostle Clinical Trials, Long Beach, CA. **Funded by Forest Research Institute Inc.; and Gedeon Richter Plc. Seven authors disclosed relationships with commercial sources; 1 author did not include disclosure of potential conflicts of interest.**

Common Drug Trade Names: **cariprazine—*Vraylar*; risperidone—*Risperdal***

***See Reference Guide.**

Antipsychotic Safety in COPD

According to a population-based study, antipsychotic drugs are associated with increased risk of acute respiratory failure (ARF) in patients with chronic obstructive pulmonary disease.

Methods: Data from the Taiwan Longitudinal Health Insurance Database were analyzed for patients with COPD between 2000 and 2011. Case patients were those admitted to the hospital or receiving emergency care for ARF. With each patient serving as his or her own control, use of antipsychotics was compared between the 14 days preceding ARF treatment and the 75–88 days before ARF. The 14-day exposure period is based on previous case reports, in which ARF usually developed within 10 days of taking an antipsychotic, and the 75–88 days represents the half-life of depot antipsychotics.

Results: Nearly 12,000 cases of ARF were identified among >60,000 patients with COPD. After applying exclusion criteria, such as previous ARF, the analysis was limited to 5032 incident cases. More than three-fourths were men, and the average age was 73 years.

Among the patients with ARF, 593 (12%) had filled ≥1 antipsychotic prescription during the 14-day antipsychotic-exposure window, compared with 443 patients (9%) during the control period (adjusted odds ratio,* 1.66; p<0.001). Risks were increased by a similar amount whether the antipsychotic was a conventional agent or an atypical and whether it was given orally or by injection. Risks were increased even at the lowest antipsychotic dosages (≤25% of the defined daily dose), although they were highest in patients receiving the defined daily dose or more (adjusted odds ratio, 3.74; p=0.001).

Discussion: This study was prompted by 12 case reports of ARF in patients taking a variety of antipsychotics, and the results highlight a life-threatening adverse respiratory effect of antipsychotic treatment that is not usually considered clinically. According to the case reports, ARF may occur shortly after increasing the dose or after an overdose, and stopping the antipsychotic leads to resolution of symptoms within 48 hours. Antipsychotics may inhibit the respiratory pattern generator in the brainstem via their effects on serotonin, dopamine, and histamine. Other potential mechanisms include dystonia in the larynx due to dopamine blockade and serotonin-related collapse of upper airway muscles.

Wang M-T, Tsai C-L, Lin C, Yeh C-B, et al: Association between antipsychotic agents and risk of acute respiratory failure in patients with chronic obstructive pulmonary disease. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2016.3793. From the National Defense Medical Center, Taipei, Taiwan; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

***See Reference Guide.**

Dopamine Agonists and Impulse Control

Results of a pharmacoepidemiologic study support the increased risk of gambling and impulse control disorders in patients taking aripiprazole. However, these adverse events are rare in exposed patients.[1]

Methods: The study cohort consisted of patients, aged 15–60 years, included in a U.S. medical claims database in 2006–2014. Cases were patients with onset of pathologic gambling or impulse control disorder, according to ICD-9 classification. Each case was matched with 10 controls for age, gender, follow-up time, and calendar time, excluding those with bipolar disorder or alcohol or drug dependence. Exposure to aripiprazole was defined as ≥1 prescription during the year before disorder onset. Risk of the 2 outcomes was also assessed for pramipexole and ropinirole—2 positive controls that are also dopamine agonists associated with increased risk of gambling—and with ranitidine, a drug not associated with either disorder.

Results: In a cohort of >6 million patients, there were 355 incident cases of pathologic gambling and 4341 cases of impulse control disorder. Gambling had onset at a mean age of about 45 years and affected equal numbers of men and women. Impulse control disorder had onset at a mean age of 37 years, and two-thirds of affected individuals were men. Risk of both disorders was elevated in patients with recent exposure to aripiprazole (see table), although the absolute number of cases with aripiprazole exposure was small. Incidence was also elevated with pramipexole and ropinirole (relative risks,* 7.61 for gambling and 3.28 for impulse control disorder), but not with ranitidine.

Adjusted odds ratio for gambling disorder and impulse control disorder with aripiprazole

	Number of Cases		Adjusted Relative Risk
	Total	Exposed to Aripiprazole	
Gambling Disorder	355	5	5.23
Impulse Control Disorder	4341	97	7.71

Discussion: Aripiprazole, pramipexole, and ropinirole could increase the risk for gambling and impulse control disorders via their affinity for D_3 receptors. Although the actual number of cases appears to be small, the present results support the recent FDA warning for aripiprazole.[2]

[1]Etminan M, Sodhi M, Samii A, Procyshyn R, et al: Risk of gambling disorder and impulse control disorder with aripiprazole, pramipexole, and ropinirole. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000634. From the University of British Columbia, Canada; and other institutions. **Funded by the British Columbia Provincial Health Services Authority. Two study authors disclosed financial relationships with commercial sources; 2 additional authors declared no competing interests; and the remaining 2 authors did not include disclosure of potential conflicts of interest.**

[2]FDA MedWatch Alert: Aripiprazole (Abilify, Abilify Maintena, Aristada): Drug safety communication–FDA warns about new impulse-control problems. Available at http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm498823.htm. See *Psychiatry Drug Alerts* 2016;30 (May):33.

Common Drug Trade Names*: aripiprazole—*Abilify*; pramipexole—*Mirapex*; ranitidine—*Zantac*; ropinirole—*Requip

***See Reference Guide.**

Continuing Cholinesterase Inhibitors in Alzheimer's

Patients who do not experience response to cholinesterase inhibitors after 3 months may still benefit from more prolonged treatment, according to the results of a naturalistic longitudinal study. This observation contradicts some guidelines that recommend discontinuing these agents after 3 or 6 months in patients without an initial response

Methods: This retrospective longitudinal study included 628 patients who received treatment with a cholinesterase inhibitor at 2 memory clinics in Italy. Patients were aged ≥65 years, had a diagnosis of Alzheimer's disease according to standard criteria, and initially had mild-to-moderate dementia. Patients were evaluated after 3 months of treatment and then at 6-month intervals for up to 3 years, while still receiving treatment. After 3 months of treatment, those whose Mini-Mental State Examination (MMSE) scores were increased or unchanged were considered responders and those whose MMSE scores decreased were considered nonresponders. Based on population averages, the investigators defined disease progression as a loss of ≥2 points per year on the MMSE. Functional status was evaluated at every visit using the Katz Index of Independence in Activities of Daily Living (ADL) and the Lawton-Brody Instrumental Activities of Daily Living (IADL). Patients were classified as either young-old (≤75 years) or old-old (≥76 years). The 3 available cholinesterase inhibitors (i.e., donepezil, rivastigmine, galantamine) were evaluated as a class because they are believed to have equivalent efficacy.

Results: After 3 months of cholinesterase-inhibitor treatment, 56% of patients met response criteria. The responder group was predominantly female (67%) and younger than the nonresponders (mean ages, 74 and 78 years, respectively). Responders had significantly earlier age of onset of the disease ($p<0.0001$), a higher level of education ($p<0.001$), and lower baseline MMSE scores ($p=0.004$) but higher ADL ($p<0.0001$) and IADL scores ($p=0.017$). Outcomes did not differ among the 3 cholinesterase inhibitors.

The effect of initial response on the longitudinal disease course was assessed in 247 patients who had 6 follow-up evaluations over the 3 years. In these patients, MMSE scores remained lower in initial nonresponders than in responders, but the average course of decline was slower in nonresponders: 1.0 versus 1.6 points per year ($p<0.0001$). Initial response did not influence scores on the ADL or IADL evaluations of functional status.

The old-old patients had a slower annual rate of MMSE decline than the younger patients: 1.0 versus 1.32 points ($p=0.004$). They also had significantly slower rates of decline on the 2 measures of function. Old age was associated with a lower probability of progression of disease (odds ratio,* 0.948; $p=0.003$). Patients who initially had response to treatment had a higher likelihood of disease progression (odds ratio, 3.733; $p<0.0001$).

Discussion: There have been few other studies of the long-term effects of cholinesterase inhibitors in Alzheimer's disease. This study shows that, in terms of cognitive impairment, patients with a positive initial response have better long-term outcomes, but those without initial response also benefit via a slower rate of decline. In addition, functional impairment is the primary cause of nursing home placement in patients with dementia, and as suggested by these results, continuing treatment could also slow functional decline.

Boccardi V, Baroni M, Smirne N, Clodomiro A, et al: Short-term response is not predictive of long-term response to acetylcholinesterase inhibitors in old age subjects with Alzheimer's disease: a "real world" study. *Journal of Alzheimer's Disease* 2016; doi 10.3233/JAD-160904. From the University of Perugia; and the Regional Neurogenetic Centre, Catanzaro, Italy. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names*: donepezil—*Aricept*; galantamine—*Razadyne*; rivastigmine—*Exelon

***See Reference Guide.**

Loperamide Abuse

The over-the-counter antidiarrheal opioid loperamide is being used increasingly to self-medicate for opioid withdrawal and, less frequently, to achieve opioid psychoactive effects, according to a brief review. Once a Schedule V drug, loperamide is now widely and legally available, with the indication of decreasing the frequency of diarrhea.

At the recommended doses, loperamide acts mainly on intestinal opioid receptors, but high doses result in entry into the central nervous system (CNS). Cardiotoxicity is its main risk. Loperamide has not been recognized as a drug of abuse and has been the subject of few reports in the literature. It is also not tracked by national surveys or surveillance programs.

At the recommended antidiarrheal dosage range of 2–16 mg/day, loperamide is actively pumped out of the CNS at the blood-brain barrier by the P-glycoprotein transporter protein. At higher doses, this system is saturated and loperamide enters the CNS. Loperamide is metabolized by the cytochrome P450 system. Bioavailability is only about 10–20%. The onset of action is about 1 hour after ingestion, and the half-life is between 7 and 19 hours.

Before 2013, there were no published reports of loperamide misuse. Reports of recreational use that described dosages in the range of 70–100 mg/day began appearing in social media in 2013. These were accompanied by drug and poison control agencies' reports of increases of 71% in presentations due to loperamide overdose. Social-media discussions suggest it is mainly used to treat opioid withdrawal symptoms. Prior use of opioids is a predisposing factor, and there are no reports or mentions of loperamide being a gateway drug. Some persons who use loperamide to treat withdrawal describe effects similar to buprenorphine, but without the cravings that result from discontinuation. Some recreational users describe a euphoric effect. There are no analgesic benefits.

High loperamide doses have been associated with cardiotoxicity: QT-interval prolongation and widening of the QRS interval. Because use is usually short term, there have been few reports of tolerance. Most users have been able to taper the drug successfully, with few or mild symptoms.

It can be difficult to detect misusers of loperamide. Overdose has been associated with drowsiness, vomiting, and abdominal pain. Patients who have taken a supratherapeutic dose may present with cardiac arrhythmias, and management should be aimed at reversing cardiotoxicity. Loperamide intoxication can be managed with naloxone. Identification of loperamide misuse should prompt a discussion of the underlying reason for use and possible treatment for opioid addiction.

Stanciu C, Gnanasegaram S: Loperamide, the "poor man's methadone": brief review. *Journal of Psychoactive Drugs* 2016; doi 10.1080/02791072.2016.1260188. From East Carolina University, Greenville, NC. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

Common Drug Trade Names*: buprenorphine—*Subutex*; loperamide—*Imodium A-D*; naloxone—*Narcan

Risks of Metformin in Psychiatric Patients

Metformin (*Glucophage*) is emerging as an important drug for treating the metabolic side effects of antipsychotic agents. Psychiatrists should be aware of the common and uncommon adverse effects of the drug.

GI adverse effects are fairly common with metformin treatment, affecting up to 25% of patients and causing up to 5% to discontinue treatment. These effects include nausea, vomiting, abdominal discomfort, flatulence, and diarrhea. GI disturbances can be minimized through gradual dose titration, taking the medication with meals, and use of slow-release formulations.

Lactic acidosis is rare, with a reported incidence of 3–10 cases per 100,000 patient-years, but metformin can cause dose-dependent increases in plasma lactate levels. These are generally not clinically significant unless metformin levels are substantially elevated as a result of kidney disease, when lactic acid generation is pathologically increased because of hypoxia due to respiratory or cardiac causes, or when clearance is reduced as in severe liver disease. However, metformin is often used safely even in patients with relative contraindications.

Vitamin B_{12} deficiency may also be associated with metformin treatment because the drug can impair B_{12} absorption. Research has shown the odds of B_{12} deficiency are nearly doubled in patients treated with metformin compared with control treatments (incidence, 11% vs 6%). Clinical effects of reduced B_{12} absorption and outright deficiency are slow to develop. Symptoms may include peripheral neuropathy, anemia, and psychiatric disorders such as depression and reversible dementia. Given the inaccuracy and expense of monitoring serum B_{12} levels, alternative approaches are recommended. An oral supplement can prevent deficiency, but could further complicate already-complex drug regimens and may be ineffective in patients with diabetes. A simpler solution might be annual intramuscular B_{12} injections for patients taking metformin.

Andrade C: Use of metformin for cardiometabolic risks in psychiatric practice: need-to-know safety issues. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.16f11263. From the National Institute of Mental Health and Neurosciences, Bangalore, India. See related story in *Psychiatry Drug Alerts* 2016;30 (December):89–90.

Clozapine and Pneumonia

Among patients hospitalized at a large urban medical center, those taking clozapine were more likely to be admitted for pneumonia than those receiving risperidone and those in the general patient population not taking an antipsychotic.

Methods: Records were reviewed for all adults, aged >18 years, admitted to a tertiary care hospital in Minnesota from July 2010 to July 2012. A total of 155 patients were admitted while receiving clozapine. These patients were matched with the same number of patients taking risperidone on admission and a control group of patients not taking any antipsychotic medication. Patients taking a second medication in addition to risperidone were excluded. None of the patients taking clozapine were receiving other antipsychotics.

Results: Despite attempts at matching, the general admitted population was younger on average than the 2 groups taking an antipsychotic (48 years vs 57 years), and men were more heavily represented in the clozapine and general-population groups than in the risperidone group. Patients in the clozapine group were significantly more likely than others to have a history of chronic obstructive pulmonary disease or gastroesophageal reflux disease.

Overall there were 94 incident cases of pneumonia: 54 in the clozapine group, 22 in the risperidone group, and 18 in the no-antipsychotic group. The rate was significantly higher in the clozapine group than in the risperidone and general population groups. (See table.) Risperidone was not associated with increased pneumonia hospitalizations, compared with the untreated group. Aspiration pneumonia and healthcare-associated pneumonia occurred more frequently with clozapine than in the general population, and community-acquired pneumonia and unspecified pneumonia were more frequent in the clozapine group than in the risperidone group. There was no significant dose-response relationship with pneumonia for either of the antipsychotics. Older age was associated with increased risk of pneumonia only in the risperidone group.

Prevalence of pneumonia in hospitalized patients, according to antipsychotic use

	Prevalence of Pneumonia	Adjusted Odds Ratio*; p Value	
		Vs No Antipsychotic	Vs Risperidone
Clozapine	35%	4.07; p<0.0001	3.23; p<0.0001
Risperidone	14%	1.26; p=NS	—
No Antipsychotic	12%	—	—

Discussion: Known adverse effects of clozapine include agranulocytosis, sialorrhea, and impairment of swallowing with esophageal dilatation and hypermotility. These effects may place patients at risk for pneumonia. Extra caution appears to be warranted when prescribing clozapine for patients with increased risk of pneumonia or who are immunocompromised. Patients taking clozapine who have recurrent pneumonia should be evaluated for management of drug-related adverse effects such as sialorrhea and sedation; other antipsychotic treatment options might be considered.

Stoecker Z, George W, O'Brien J, Jancik J, et al: Clozapine usage increases the incidence of pneumonia compared with risperidone and the general population: a retrospective comparison of clozapine, risperidone, and the general population in a single hospital over 25 months. *International Clinical Psychopharmacology* 2017; doi 10.1097/YIC.0000000000000162. From Hennepin County Medical Center, Minneapolis; and Regions Hospital, St Paul, MN. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names*: clozapine—*Clozaril*; risperidone—*Risperdal

***See Reference Guide.**

Aripiprazole vs Paliperidone: Multidimensional Comparison

According to a secondary analysis of a manufacturer-sponsored, randomized, head-to-head comparison, long-acting injected aripiprazole may be superior to injected paliperidone palmitate across some dimensions of functional outcome.[1]

Background: The Quality of Life with Abilify Maintena trial found once-monthly injectable aripiprazole to be superior to once-monthly paliperidone at improving health-related quality of life.[2] The present analysis examined the effects of treatment on additional measures of clinical effectiveness, quality of life, functioning, tolerability, and readiness to work

Methods: Participants, aged 18–60 years (n=268), with a diagnosis of schizophrenia were enrolled from 71 sites in 10 countries in Europe and North America. Patients were receiving stable treatment with an oral antipsychotic for ≥3 months and had been recommended for injectable treatment by a study investigator because of inadequate response, poor tolerance, or poor adherence. At study entry, patients were mildly-to-markedly ill and were randomly assigned to aripiprazole or paliperidone. Over the first 3 study weeks, patients were switched to the oral formulation of study medication while their previous antipsychotic was tapered. Following the switch, patients received monthly injections with 400 mg aripiprazole or flexibly-dosed paliperidone for 28 weeks. Blinded raters administered the Quality of Life Scale (QLS), and raters not who were not blinded to treatment assignment administered the Clinical Global Impression–Improvement (CGI-I) and Severity (CGI-S) scales and the newly developed Work Readiness Questionnaire (WoRQ). Patient-rated measures were the Subjective Well-Being Under Neuroleptic Treatment–short version (SWN-S) and the Tolerability and Quality of Life questionnaire (TooL).

Results: Of the 295 patients enrolled, 268 (68% of the aripiprazole groups and 57% of the paliperidone group) completed 28 weeks of treatment and were included in the analysis. For all individual items on the observer-rated QLS scale, improvements were numerically larger in patients who received aripiprazole than those in the paliperidone group, but the difference was statistically significant ($p<0.05$) for only 3 of the 21 items on the scale: social initiative, sense of purpose, and aimless inactivity.

More patients were rated by nonblinded evaluators as responders in the aripiprazole group, with a ≥1-point decrease in CGI–S scale score (63% vs 44%; adjusted odds ratio,* 2.26; $p=0.01$) or by ratings of "much improved" or better on the CGI–I scale (52% vs 29%; adjusted odds ratio, 2.51; $p=0.0032$). As measured by the WoRQ scale, a larger percentage of patients shifted from not ready to ready to work in the aripiprazole group than in the paliperidone group (26% vs 12%; $p=0.004$).

Patient ratings showed slightly better outcomes with aripiprazole than paliperidone. At baseline, both groups had a positive opinion of their current medication. Both groups showed improvement from baseline on the SWN-S total score when switched to injectable medication, and improvement did not differ statistically between groups. Improvements numerically favored aripiprazole on the SWN-S subscales of mental functioning, physical functioning, and self-control. Mean ratings on the TooL showed minimal impact of pre-study medication on quality of life. Scores improved in both groups after 28 weeks on randomized injectable medication, with no significant differences between aripiprazole and paliperidone.

[1]Potkin S, Loze J-Y, Forray C, Baker R, et al: Multidimensional assessment of functional outcomes in schizophrenia: results from QUALIFY, a head-to-head trial of aripiprazole once-monthly and paliperidone palmitate. *International Journal of Neuropsychopharmacology* 2016; doi 10.1093/ijnp.pyw093. From the University of California, Irvine; and other institutions including Otsuka Pharmaceutical Europe, Wexham, UK and Lundbeck LLC, Paramus, NJ. **Funded by Lundbeck; and Otsuka. All study authors disclosed financial relationships with commercial sources including Otsuka and/or Lundbeck.**

[2]Naber D, et al: Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. *Schizophrenia Research* 2015;168:498–504. See *Psychiatry Drug Alerts* 2015;28 (September):66–67.

Common Drug Trade Names*: aripiprazole, injectable—*Abilify Maintena*; paliperidone palmitate, injectable—*Invega Sustenna

***See Reference Guide.**

Reference Guide

Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

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.

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SSRIs/Warfarin and Bleeding

Concomitant use of SSRIs increases risk of bleeding in patients taking warfarin because of the combination of anticoagulant action of warfarin and SSRIs' antiplatelet effects. Results of a cohort study suggest that bleeding risk is not further increased with use of fluoxetine or fluvoxamine, SSRIs that inhibit the enzyme that metabolizes warfarin.

Background: Because cardiovascular and cerebrovascular diseases often co-occur with depression, it is common for patients to receive anticoagulant and antidepressant therapy concomitantly. Numerous studies have found increased rates of bleeding associated with concomitant use of warfarin and SSRIs, assumed to be related to cytochrome (CYP) P450 metabolism. In addition to increased bleeding risk, there is also a presumed protective effect in terms of thromboembolic and ischemic events. However, the differential effects of SSRIs with and without strong CYP2C9 activity have not previously been investigated.

Methods: The study cohort was selected from 5 U.S. claims databases covering 1994–2013 and included all patients who started warfarin and then received an SSRI prescription during warfarin treatment. Patients were followed for ≤180 days from the beginning of concomitant treatment. Outcomes were compared between patients receiving 1 of the 2 antidepressants with high CYP2C9 activity (i.e., fluoxetine and fluvoxamine) and those receiving any other SSRI. The outcomes of interest were hospitalization for composite bleeding events (upper gastrointestinal [GI] bleeding, lower GI bleeding, hemorrhagic stroke, major urogenital bleeding, and other major bleeding), hospitalization for composite ischemic or thromboembolic events (acute myocardial infarction [MI], ischemic stroke, systemic embolism, transient ischemic attack, or venous thromboembolism), and all-cause mortality.

Results: The cohort comprised >52,000 patients (mean age, 54 years; 28% men) who received an SSRI while taking warfarin. The large majority of patients received an SSRI that was not a potent CYP2C9 inhibitor; 15% of patients received fluoxetine and <1% received fluvoxamine. For the major outcome comparisons, patients in the 2 SSRI groups were matched according to a

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propensity score* for receiving fluoxetine or fluvoxamine, resulting in a final cohort of 8000 patients receiving these SSRIs and nearly 42,000 receiving other SSRIs.

Average follow-up was 52 days of concomitant treatment. During this time, there was no significant increase in risk of any of the composite study outcomes between patients taking fluoxetine/fluvoxamine versus those taking other SSRIs. (See table). Among individual outcomes, there was a numerically higher risk of upper GI bleeding in patients receiving these SSRIs, but the difference was not statistically significant. Event rates did not differ between groups in various subgroup analyses or in sensitivity analyses limited to follow-up times of continuous warfarin use before SSRI prescription (7,14, 28, or 56 days), intended to rule out the effects during warfarin stabilization.

Hazard ratio comparing SSRIs that are potent CYP2C9 inhibitors with other SSRIs		
Outcome	**Number of Events in Total Cohort**	**Adjusted Hazard Ratio***
Bleeding events	822	1.14
Ischemic or thromboembolic events	1169	1.03
Mortality	766	0.90

Discussion: Results of the present study indicate that rates of bleeding and ischemic or thromboembolic outcomes are similar regardless of the CYP2C9 inhibiting activity of the SSRI.

Dong Y-H, Bykov K, Choudhry N, Donneyong M, et al: Clinical outcomes of concomitant use of warfarin and selective serotonin reuptake inhibitors: a multidatabase observational cohort study. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000658. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by the Agency for Healthcare Research and Quality; and other sources. Three study authors declared financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

Common Drug Trade Names*: fluoxetine—*Prozac*; fluvoxamine—*Luvox*; warfarin—*Coumadin

***See Reference Guide.**

Vilazodone in Generalized Anxiety Disorder

In a multicenter, manufacturer-sponsored, placebo-controlled trial, vilazodone (*Viibryd*) reduced anxiety symptoms and functional impairment in patients with GAD.

Methods: Study subjects were 404 adults (mean age, about 40 years; 68% women) who met DSM-IV criteria for GAD. Participants were required to have a Hamilton Anxiety Rating Scale (HAM-A) score of ≥20, a Clinical Global Impression–Severity (CGI-S) scale* score of ≥4, and a Hamilton Rating Scale for Depression (HAM-D) score of ≤17. Those with treatment-resistant anxiety and those requiring concomitant psychotropics (other than sedative/hypnotics for insomnia) were excluded. Patients received 8 weeks of double-blind treatment with either placebo or vilazodone at 10 mg/day for 1 week, 20 mg/day for the second week, and, if needed, a further increase to 40 mg/day. The primary efficacy outcome was change from baseline in HAM-A score in the intent-to-treat population.

Results: The mean baseline HAM-A score was 25 in both treatment groups. Compared with placebo, vilazodone was associated with a significantly larger reduction from baseline in mean score. At 8 weeks, scores were 12 and 15 in the vilazodone and placebo groups, respectively (p=0.005; effect size,* 0.31). Vilazodone differed significantly from placebo beginning at week 4. Active treatment was also associated with significantly greater improvement in secondary efficacy outcomes, including overall illness severity and functional capacity. (See table, next page.) The numbers needed to treat* were 6 for each additional response on the HAM-D and CGI, and 7 for the Sheehan Disability Scale.

Efficacy outcomes: vilazodone vs placebo in generalized anxiety disorder				
	Vilazodone (n=202)	**Placebo (n=202)**	**Odds Ratio***	**Significance**
HAM-A Response**	57%	39%	2.72	p=0.0034
CGI-Improvement Response†	66%	49%	2.63	p=0.0068
Sheehan Disability Scale Remission‡	49%	34%	2.30	p=0.0307
** ≥ 50% decrease from baseline †score of ≤2 ‡ total score of ≤6 ,and item scores ≤2				

Significantly more patients withdrew from vilazodone treatment than placebo: 29% versus 19% ($p<0.05$), mainly due to adverse events—e.g., nausea (n=6), dizziness (n=5), diarrhea (n=4), and headache (n=2). There were no instances of treatment-related suicidal ideation or behavior. Vilazodone was associated with sexual dysfunction in 17 patients (8%), including erectile dysfunction in 4 and decreased libido in 5.

Discussion: SSRIs are approved as first-line agents for treating GAD. Vilazodone differs from other SSRIs in being a partial 5-HT_{1A} receptor agonist. These results suggest that vilazodone may be an additional therapeutic option for the many patients who experience an inadequate response to existing GAD treatments.

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

Durgam S, Gommoll C, Forero G, Nunez R, et al: Efficacy and safety of vilazodone in patients with generalized anxiety disorder: a randomized, double-blind, placebo-controlled, flexible-dose trial. *Journal of Clinical Psychiatry* 2016;77 (December):1687–1694. From Forest Research Institute, Jersey City, NJ. **Funded by Forest Laboratories, LLC. All study authors declared financial relationships with commercial sources.**

***See Reference Guide.**

Pioglitazone in Depression

The antidiabetic agent pioglitazone may induce remission of depression, according to results of a meta-analysis of 4 clinical trials.[1]

Background: Pioglitazone is 1 of several available peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonists, also known as glitazones or thiazolidinediones, and is the only drug from this class investigated for treatment of depression. Of 4 published randomized trials of pioglitazone for depression, 3 reported the drug resulted in larger reductions in depression symptom scores than control treatments, but only 1 study found a difference in remission rates. The meta-analysis was conducted to compare remission rates by combining studies to increase statistical power.

Methods: For inclusion in the analysis, studies were required to be randomized trials of the use of any PPAR-gamma agonist to treat a major depressive episode (using standardized diagnostic criteria), with outcomes assessed using a standardized rating scale. There were no studies of a PPAR-gamma agonist other than pioglitazone, and all studies measured the outcome using the Hamilton Rating Scale for Depression (HAM-D). Remission was defined as a HAM-D score of <8.

Results: The studies included 161 patients with major depressive disorder or bipolar depression. A total of 81 patients received pioglitazone, and 80 received a control treatment (60 placebo, 20 metformin). Pioglitazone was given as monotherapy in 1 study and as an add-on to anti-depressants or mood stabilizers in the rest. Treatment duration was 6 weeks in 3 studies and

12 weeks in 1. Three studies were of a high quality, and 1 was rated as at serious risk of bias and providing a low level of evidence. Results of the analysis were generally the same whether or not the lower-quality study was included.

Depression remission was achieved by 27% of patients who received pioglitazone, compared with 10% of controls (odds ratio* for remission, 3.3; p=0.08). The number needed to treat* with pioglitazone was 6 patients to have 1 additional remission compared with a control treatment.

Studies differed in terms of inclusion criteria—e.g., the level of depression severity required for enrollment, whether patients with metabolic comorbidities were enrolled, the use of background psychoactive medication, and the use of drugs with potential pharmacokinetic interactions with pioglitazone. None of these factors affected the results of the analysis.

Discussion: The quality of this evidence is limited by the heterogeneity of studies with regard to mood disorder diagnosis, gender ratio, age, baseline severity, use of concomitant drugs, control treatments, and duration of follow-up. Since all studies used a 30-mg/day fixed dose of pioglitazone, there was no evidence of a dose-response effect, which would have provided further evidence of pharmacologic antidepressant effects. It is impossible to know whether the effects of pioglitazone are due to PPAR-gamma inhibition or other properties, such as improvement in insulin resistance or inflammation. Two randomized, controlled trials are underway of pioglitazone as add-on or monotherapy for the treatment of bipolar depression. It should be noted that use of pioglitazone in diabetes is declining because of its adverse effects, which may include heart failure, edema, hepatic effects, bladder cancer, hypoglycemia, and macular edema.[2]

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

[1]Colle R, de Larminat D, Rotenberg S, Hozer F, et al: Pioglitazone could induce remission in major depression: a meta-analysis. *Neuropsychiatric Disease and Treatment* 2017;13:9–16. From University Paris-Sud and Assistance Publique-Hospitaux de Paris, Paris, France; and other institutions. **Source of funding not stated. One study author disclosed financial relationships with commercial sources; the remaining 7 authors declared no competing interests.** See related story in *Psychiatry Drug Alerts* 2015;29 (February):9–10.

[2]Actos [package insert]. Takeda Pharmaceuticals, Deerfield, IL; 2011. http://general.takedapharm.com/content/file.aspx?filetypecode=actospi&cacheRandomizer=3d9b5f7e-8ec6-465c-888d-cd68312eee1a.

Common Drug Trade Names*: metformin—*Glucophage*; pioglitazone—*Actos

***See Reference Guide.**

Rapid Outpatient Opioid Detoxification

In a randomized trial, rapid detoxification with low-dose naltrexone was more effective than standard buprenorphine-assisted detoxification in transitioning opioid-dependent patients to extended-release (XR) naltrexone injection.

Background: Injectable XR naltrexone is FDA approved for relapse prevention after opioid detoxification. However, 7–10 days of abstinence from opioids are required before injection to avoid precipitating withdrawal. While this delay is manageable in inpatient settings, it is problematic for outpatients.

Methods: Two treatment regimens (see table, next page) were compared in 150 patients (mean age, 35 years; 86% men) seeking outpatient treatment for opioid dependence of ≥6 months' duration. Patients with unstable medical or psychiatric disorders and those with alcohol dependence were excluded from the study. On day 1, patients were instructed to abstain from opioids and were randomly assigned to open-label treatment in a 2:1 ratio; more patients received naltrexone detoxification to allow for a closer examination of the safety and efficacy of that regimen. The naltrexone-assisted group was given increasing oral doses on days 4–7, with XR-naltrexone injected on day 8. The buprenorphine-assisted group

received decreasing doses of buprenorphine on days 2–7, followed by a 7-day opioid washout before injection of XR-naltrexone on day 15. After the naltrexone injection, all patients received 4 weeks of outpatient treatment, including adjuvant medication and twice-weekly individual therapy sessions, followed by an additional XR-naltrexone injection at week 5. The primary study outcomes were the rate of successful induction of XR-naltrexone and the rate of receiving the second injection.

Opioid Detoxification Regimens

Day	Naltrexone-Assisted (n=98)	Buprenorphine-Assisted (n=52)
1	Supportive treatment with clonidine, clonazepam, trazodone, prochlorperazine, or zolpidem	
2	2 mg sublingual buprenorphine every 1–2 hours to a maximum of 8 mg	
3	Supportive treatment only	6 mg buprenorphine
4	1 mg naltrexone	4 mg buprenorphine
5	3 mg naltrexone	4 mg buprenorphine
6	12 mg naltrexone	2 mg buprenorphine
7	25 mg naltrexone	1 mg buprenorphine
8	380 mg injectable XR-naltrexone	Washout
15	——	380 mg injectable XR-naltrexone

Results: At baseline, about half of study participants were classified as high users of opioids (>200 mg morphine equivalents per day) and half as low users. About 37% were primary prescription opioid users, and the rest used heroin.

Successful induction of XR-naltrexone was achieved in 56% of the naltrexone-assisted detoxification group and in 33% of the buprenorphine-assisted detoxification group (p=0.01; adjusted odds ratio,* 2.89). Rates of receiving the second injection were 50% and 27%, respectively (p=0.012; adjusted odds ratio, 2.78). Prescription opioid users had a higher rate of successful induction compared with heroin users (p=0.002; odds ratio, 3.8). Other aspects of opioid use—daily opioid dosage and route of administration—were not predictive of successful transition.

Among secondary study outcomes, the rate of moderate-to-severe withdrawal from days 3 to 7 was low and did not differ between treatments. The proportion of patients who completed the 8-day detoxification phase was similar in the 2 groups, as was the rate of opioid abstinence during weeks 4 and 5 after XR-naltrexone induction. Adverse events were similar in the 2 groups and largely consistent with symptoms of opioid withdrawal.

Discussion: The high rate of attrition from outpatient opioid detoxification indicates a need for more rapid transition protocols. The present study suggests the 8-day naltrexone-assisted protocol may have better results than the standard 15-day method with 7 days of buprenorphine. Surprisingly, both groups had similar withdrawal severity and dropout rates during the first 7 days, but almost 30% of patients who completed the buprenorphine taper relapsed during the second week and were unable to receive the naltrexone injection.

Sullivan M, Bisaga A, Pavlicova M, Choi C, et al: Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2016.16050548. From the College of Physicians and Surgeons of Columbia University, New York, NY; and other institutions. **Funded by the National Institute on Drug Abuse. Four study authors disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

Common Drug Trade Names*: buprenorphine, sublingual—*Subutex*; clonazepam—*Klonopin*; clonidine—*Catapres*; naltrexone XR, injectable—*Vivitrol*; naltrexone, oral—*ReVia*; prochlorperazine—*Compazine*; trazodone—*Oleptro*; zolpidem—*Ambien

***See Reference Guide.**

Neuroprotective Effects of Antimanic Drugs

In a randomized trial, lithium, but not quetiapine (*Seroquel*), appeared to prevent loss of white matter in patients experiencing first-episode mania. This finding supports the continuing use of lithium from the earliest stages of the disorder and challenges guidelines that recommend withholding lithium until the patient has experienced several manic episodes.

Methods: The study was conducted in patients, aged 15–25 years, with a first episode of bipolar I disorder, substance-induced mood disorder, or schizoaffective disorder and who had a Young Mania Rating Scale (YMRS) score of ≥20. Patients who had received cytochrome P450 inducing or inhibiting drugs in the previous 14 days were excluded, as were those with uncontrolled diabetes. All patients initially received treatment with open-label lithium and quetiapine until they were deemed clinically stable, after which they were randomly assigned to continue treatment with either double-blind lithium (n=20) or quetiapine (n=19) as monotherapy. Lithium dose was targeted to serum levels of 0.6–0.8 mEq/L, and the quetiapine dose was determined by each patient's clinician. Structural MRI brain images were obtained at baseline and at 3 and 12 months in treated patients and at baseline and 12 months for a group of 30 age-matched healthy controls.

Results: At baseline (after stabilization but before randomized treatment), first-episode patients had reduced regional grey and white matter volume compared with controls ($p<0.01$). Specifically, patients had reduced grey matter volume in the orbitofrontal cortex, anterior cingulate cortex, inferior frontal gyrus, and cerebellum and reduced internal capsule white matter volume bilaterally. Longitudinally, patients who received quetiapine showed significant further loss of white matter of the left internal capsule at 12 months ($p<0.01$). There were no other changes in grey or white matter volume with time in any group.

Discussion: The progressive nature of bipolar disorder is likely related to loss of brain volume over time. According to previous research, structural changes have been inconsistently observed in patients experiencing their first episode, the earliest possible time to begin any treatment with neuroprotective potential. Considerable evidence supports a protective effect of lithium on grey matter, but the evidence on neuroprotection with antipsychotic drugs has been mixed. Results of the present study suggest lithium is associated with effective cessation of white matter loss during the first 3 months, followed by a rate of loss similar to control subjects. Quetiapine appears to have neither a neuroprotective nor neurotoxic effect; alternatively, it appears to have a slow, relatively weak protective effect.

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

Berk M, Dandash O, Daglas R, Cotton S, et al: Neuroprotection after a first episode of mania: a randomized controlled maintenance trial comparing the effects of lithium and quetiapine on grey and white matter volume. *Translational Psychiatry* 2017; doi 10.1038/tp.2016.281. From Deakin University, Geelong, Australia; and other institutions. **Funded by AstraZeneca; and other sources. Five study authors declared financial relationships with commercial sources, including AstraZeneca; the remaining 10 authors declared no competing interests.**

***See Reference Guide.**

Antidepressants and Hyponatremia in the Elderly

A population-based cohort study found that second-generation antidepressants were associated with increased risk of hospitalization for hyponatremia in elderly patients.

Methods: The study was conducted using healthcare databases from Ontario, Canada. Exposed individuals were patients aged >65 years who had a mood or anxiety disorder and were given a prescription for any 1 of 9 second-generation antidepressants (i.e., citalopram,

escitalopram, paroxetine, fluoxetine, fluvoxamine, venlafaxine, duloxetine, mirtazapine, sertraline) in 2003–2012. Those receiving >1 antidepressant concurrently were excluded; however, patients receiving a concurrent mood stabilizer were not excluded. Each patient was assigned an index date, which was the date of the first antidepressant prescription. Index dates were randomly assigned to a control group of patients not receiving any antidepressant therapy. Each exposed patient was individually matched with a control subject based on index date and a propensity score* for being prescribed a second-generation antidepressant that included >100 factors including age, gender, chronic kidney disease, and diuretic use. The primary outcome of interest was hospitalization for hyponatremia within 30 days of the index date. The secondary outcome was hospitalization for concomitant hyponatremia and delirium.

Results: The study cohort comprised >138,000 matched pairs of exposed patients and controls. Patients had a mean age of 76 years, and 68% were women. Nearly half of all antidepressant users (46%) received a prescription for citalopram. Although absolute risks were small (<2%), antidepressants were associated with a >5-fold increase in risk of hospitalization for hyponatremia, and a 4-fold greater risk of hospitalization with hyponatremia and delirium. (See table.) The association was robust in numerous alternative analyses and sensitivity analyses and in different subgroups: patients using different antidepressants or dosages, those with or without chronic kidney disease or congestive heart failure at baseline, and diuretic users and non-users. Venlafaxine was associated with no hospitalizations, but all other antidepressants including mirtazapine, the only other non-SSRI, were associated with increased risk.

Outcomes within 30 days of new antidepressant prescription, or index date in antidepressant non-users			
	Users (n=138,246)	**Non-users (n=138,246)**	**Relative Risk***
Hospitalization for hyponatremia	450 (0.33%)	84 (0.06%)	5.46
Hospitalization for hyponatremia and delirium	28 (0.02%)	7 (0.005%)	4.00

Discussion: Several prior studies found a similar association of antidepressants with hyponatremia, but they were much smaller and provided highly variable estimates of risk. The results of this study are consistent with these, and with the known mechanism of antidepressant-related inappropriate antidiuretic hormone secretion. Hyponatremia can lead to confusion, seizures, and death. Although the excess absolute risk of hyponatremia with antidepressants is small, the widespread use of these drugs suggests thousands of cases may occur each year and there are no guidelines for serum sodium monitoring in this situation.

Gandhi S, Shariff S, Al-Jaishi A, Reiss J, et al: Second-generation antidepressants and hyponatremia risk: a population-based cohort study of older adults. *American Journal of Kidney Disease* 2017;69 (January):87–96. From Western University, London; and St. Michael's Hospital, Toronto, Canada. **Funded by the Canadian Institutes of Health Research; and other sources. The authors declared no competing interests.**

Common Drug Trade Names*: citalopram—*Celexa*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; mirtazapine—*Remeron*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor

***See Reference Guide.**

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

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

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

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 is 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. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

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.

PSYCHIATRY DRUG ALERTS

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Cariprazine vs Risperidone for Negative Symptoms

In a manufacturer-sponsored study, cariprazine monotherapy was superior to risperidone monotherapy at reducing predominant negative symptoms of schizophrenia.[1]

Background: Cariprazine has a unique activity profile, with especially potent affinity for the dopamine D_3 receptor. The importance of this receptor in modulating mood and cognition suggests possible efficacy of cariprazine in treating negative symptoms.

Methods: Study subjects had a diagnosis of schizophrenia (DSM-IV-TR) with a duration of ≥2 years and had been clinically stable for ≥6 months but continued to have a Positive and Negative Syndrome Scale (PANSS) negative symptom score of ≥24 plus a score of ≥4 on at least 2 of the 4 core negative PANSS symptoms: blunted affect, passive social withdrawal, lack of spontaneity, and flow of conversation. Those with a history of nonresponse to risperidone or who had received the drug within the prior 6 weeks were excluded. Participants were randomly assigned to double-blind treatment with either cariprazine or risperidone. During the first 2 post-randomization weeks, study medications were cross-titrated with patients' previous antipsychotics. Following the taper, patients received monotherapy for 26 weeks at target dosages of 4.5 mg/day cariprazine or 4 mg/day risperidone. Patients could receive lorazepam or a similar agent for agitation, sedatives for sleep, or a limited number of agents for extrapyramidal symptoms, but no other psychotropics were permitted. The primary efficacy outcome was change from randomization to treatment week 26 in the PANSS factor score for negative symptoms.

Results: A total of 460 patients (mean age, 40 years; 58% men) received study medication. Of these, 456 completed ≥1 assessment and were included in the intent-to-treat analysis. The mean baseline PANSS negative symptom score was 28 in each treatment group. Patients who received cariprazine had a significantly larger reduction in the negative symptom score than those receiving risperidone (8.6 vs 7.2 points; p=0.0022; effect size*, 0.31). Rates of response, defined as a ≥20% reduction from baseline in PANSS negative symptoms, were 69% with

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cariprazine and 58% with risperidone (odds ratio,* 2.08; p=0.0022). These rates translate to a number needed to treat* of 9 to achieve 1 additional response with cariprazine, relative to risperidone.

Several secondary efficacy measures also favored cariprazine. Statistically significant differences were observed in change from baseline on the Clinical Global Impression–Severity (CGI-S) scale (p=0.0052) and the CGI–Improvement scale (p<0.0001), although the absolute mean differences versus risperidone were small. Scores on the Personal and Social Performance Scale indicated greater cariprazine-related improvement in self-care, personal and social relationships, and socially useful activities, but not in disturbing and aggressive behaviors. Further analysis indicated that improvement in negative symptoms was not related to improvement in positive symptoms, depression, or extrapyramidal symptoms.

Editorial.[2] Although some second-generation antipsychotics may be more effective than conventional agents at reducing negative symptoms, previous research suggests they lack a direct effect on primary negative symptoms and improvement is secondary to reductions in positive symptoms. Although the absolute differences in improvement between the groups in this study were small and effect sizes were not robust, the number needed to treat for cariprazine is below the cutoff of 10 that is generally accepted to indicate clinical significance.

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

[1]Nemeth G, Laszlovszky I, Czobor P, Szalai E, et al: Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet* 2017; doi 10.1016/S0140–6736(17)30060–0. From Gedeon Richter Plc, Budapest, Hungary; and other institutions including Forest Research Institute, Jersey City, NJ. **Funded by Gedeon Richter Plc. Eleven study authors declared financial relationships with commercial sources; the remaining author declared no competing interests.**

[2]Leucht S, Davis J: Schizophrenia, primary negative symptoms, and soft outcomes in psychiatry [editorial]. *Lancet* 2017; doi 10.1016/S0140–6736(17)30060-0. From the Technische Universitat Munchen, Germany; and other institutions.

Common Drug Trade Names*: cariprazine—*Vraylar*; risperidone—*Risperdal

***See Reference Guide.**

Adjunctive Citicoline in Depression

In a randomized trial, adding the dietary supplement citicoline to citalopram (*Celexa*) was superior to citalopram monotherapy at reducing symptoms of depression.

Background: Animal models have shown that citicoline increases the amount of acetylcholine, noradrenaline, dopamine, and serotonin in different parts of the brain. It has shown promise in treating cognitive deficits in patients with brain injury, craving and depression in patients with substance use disorders, and mood in patients with bipolar disorder.

Methods: Study participants (n=54; mean age, 36 years; 15 men) had a diagnosis of major depressive disorder of at least moderate severity. All patients received treatment with citalopram, increasing from 20 mg/day in the first week to 40 mg/day in weeks 2–6. In addition, patients received randomly assigned, double-blind citicoline (100 mg every 12 hours) or placebo. The primary study outcome was change from baseline in Hamilton Rating Scale for Depression (HAM-D) score.

Results: The treatment groups did not differ in depression severity at baseline, with mean HAM-D scores of 25 and 24 in the citicoline and placebo groups, respectively. After 6 weeks of treatment, combined therapy resulted in a larger decrease in HAM-D scores than citalopram monotherapy (mean scores, 6.5 and 10, respectively; p=0.021). The between-group difference was statistically significant as early as treatment week 2. Remission (i.e., HAM-D score of ≤7) occurred by week 6 in 72% of patients receiving combination therapy and 44% of those receiving monotherapy (odds ratio,* 3.27; p=0.04). Rates of response and early improvement

were also higher with combination therapy, although not significantly. Citicoline and placebo were associated with comparable adverse effects, with no serious events or death in either group. Only 4 of the 54 patients (2 from each group) did not complete treatment.

Study Rating*—15 (88%): This study met most criteria for a randomized trial; however, the source of funding was not stated.

Roohi-Azizi M, Arabzadeh S, Amidfar M, Salimi S, et al: Citicoline combination therapy for major depressive disorder: a randomized, double-blind, placebo-controlled trial. *Clinical Neuropharmacology* 2017;40 (January–February):1–5. From Tehran University of Medical Sciences; and Mashad University of Medical Sciences, Iran. **Source of funding not stated. The authors declared no competing interests.**

***See Reference Guide.**

Monthly Aripiprazole Maintenance

Once-monthly injectable aripiprazole delayed the time to mood episode recurrence in a 52-week placebo-controlled withdrawal trial within a 4-phase manufacturer-sponsored study of patients with bipolar I disorder.[1]

Methods: This multicenter study enrolled patients who met DSM-IV-TR criteria for bipolar I disorder and who were currently experiencing a manic episode (excluding those with rapid cycling). In phases 1 and 2, patients not already taking the drug were converted to oral aripiprazole monotherapy over 4–6 weeks and then assessed for clinical stability over the next 2–8 weeks. During phase 3 (this study), all patients received open-label aripiprazole injections every 4 weeks for up to 28 weeks. Finally, those who met the study's stability criteria for ≥8 consecutive weeks were randomly assigned to 52 weeks of double-blind treatment with long-acting injectable aripiprazole or placebo. The primary efficacy endpoint was time from randomization to recurrence of any mood episode, including hospitalization for a mood episode; exceeding thresholds on the Young Mania Rating Scale, the Montgomery-Asberg Depression Rating Scale, or the Clinical Global Impression for Bipolar Disorder-Severity Scale; need for another medication; a serious adverse event; or active suicidality.

Results: A total of 466 patients began treatment with oral aripiprazole, 425 entered the open-label stabilization phase, and 266 (mean age, 41 years; 58% women) began the placebo-controlled phase. The overall recurrence rate in the active treatment group was about half that in the placebo group. (See table.) Recurrence risk with once-monthly aripiprazole was significantly lower for manic episodes ($p<0.0001$) and approached significance for mixed episodes ($p=0.06$). Risk of depressive recurrence was not reduced. However, patients had few depressive symptoms at study entry and the number of depressive recurrences was low. Notably, monthly aripiprazole did not increase the number of depressive recurrences.

Continuation of once-monthly aripiprazole vs placebo in bipolar I disorder: selected outcomes

Outcome	Aripiprazole	Placebo	Significance
Recurrence of any mood episode	27%	51%	p<0.0001
Median time to discontinuation for any reason	345 days	170 days	p=0.0026
Discontinuation for adverse event	17%	26%	p=ns

Adverse events were similar to those reported for oral aripiprazole. There were minimal differences between groups in extrapyramidal symptoms. Aripiprazole was associated with a modestly higher rate of clinically significant weight gain (18% vs 13%), but no clinically significant elevation in prolactin.

Discussion: Currently, injectable risperidone (administered every 2 weeks) is the only long-acting injectable antipsychotic approved for maintenance treatment of bipolar disorder. Results of the present study support the safety and efficacy of once-monthly aripiprazole for these patients and are consistent with a meta-analysis suggesting that the efficacy of long-acting injectable antipsychotics is similar to that of oral agents.[2]

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

[1]Calabrese J, Sanchez R, Jin N, Amatniek J, et al: Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16m11201. From Case Western Reserve School of Medicine, Cleveland, OH; Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ; and H. Lundbeck A/S, Valby, Denmark. **Funded by Otsuka; and Lundbeck. All study authors disclosed financial relationships with commercial sources including Otsuka and/or Lundbeck.**

[2]Kishi T, et al: Long-acting injectable antipsychotics for prevention of relapse in bipolar disorder: a systematic review and meta-analysis of randomized controlled trials. *International Journal of Neuropsychopharmacology* 2016;19:pyw038.

Common Drug Trade Names*:** **aripiprazole, injectable—*Abilify Maintena*; risperidone, injectable—*Risperdal Consta

***See Reference Guide.**

Lithium, Sertraline, and Bipolar Switching

In patients with bipolar II depression, lithium monotherapy, SSRI monotherapy, and the combination were all associated with similar rates of switching to hypomania and similar antidepressant efficacy in a randomized trial. Combination therapy was associated with a higher rate of discontinuation.

Methods: Study subjects (n=142; mean age, 39 years; 54% women) had a structured clinical interview-confirmed diagnosis of bipolar II disorder and were currently experiencing a major depressive episode, with no-or-minimal symptoms of mania. Patients with rapid cycling (42%) were not excluded, nor were those with a history of substance abuse ≥3 months prior to entry. Participants were randomly assigned to 16 weeks of double-blind treatment with lithium at a minimum dosage of 900 mg/day, sertraline at a minimum of 100 mg/day, or combined treatment with both agents. Lithium dosage was guided by the same serum level range as in bipolar I disorder (0.8–1.2 mEq/L), but because the therapeutic range for bipolar II disorder is not precisely known, lower levels were permitted in patients who could not tolerate levels >0.8 mEq/L. To maintain the blind, serum samples were collected from all participants and a single unblinded, nonrating physician at each study site characterized lithium levels as sub-therapeutic, therapeutic, or toxic to guide dosage changes. The primary study outcome was a switch to hypomania or mania, based on scores on the Young Mania Rating Scale or the Clinical Global Impression for Bipolar Disorder (CGI-BP) severity scale. The secondary efficacy outcome was response, defined as a sustained decrease of ≥50% on the Inventory of Depressive Symptomatology–Clinician Rated or a decrease of ≥2 points on the CGI-BP depression severity score, without hypomania or mania.

Results: The treatment groups did not differ in likelihood of incurring a treatment-emergent adverse effect, and rates of study drop-out due to adverse effects (24–29%) did not differ between the groups. However, the overall dropout rate was significantly higher for combined therapy (71%) than for lithium or sertraline monotherapy (55% and 42%, respectively; p=0.03). The response rate was 63% overall and did not differ statistically among treatments. Combined therapy did not accelerate the antidepressant response.

During the study period, hypomania developed in 20 patients (14%) and was severe in 3 (1 in each treatment arm). Rates of switching did not differ across treatment groups; nor were rapid-cycling patients at greater risk of a switch than others. There were 5 switches to hypomania

with combination therapy, 7 with lithium, and 8 with sertraline. No patient switched to mania. The majority of patients who switched (75%) did so within 5 weeks of starting therapy. History of substance abuse, in particular stimulant abuse or dependence, was associated with a significantly higher risk of switching ($p<0.001$). In addition, within the lithium groups, patients who switched to hypomania had significantly lower serum levels than those who did not experience a switch ($p=0.03$).

Discussion: There are currently few guidelines for treatment of bipolar II depression; instead, guidelines for bipolar I are often applied. This study adds to the sparse literature on treatment of bipolar II depression and suggests that it may require a different approach than bipolar I depression. Quetiapine is the only FDA-approved drug for treatment of bipolar II depression.

Altshuler L, Sugar C, McElroy S, Calimlim B, et al: Switch rates during acute treatment for bipolar II depression with lithium, sertraline, or the two combined: a randomized double-blind comparison. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2016.15040558. From the David Geffen School of Medicine at UCLA, Los Angeles, CA; and other institutions. **Funded by the NIMH; and other sources. Four study authors disclosed financial relationships with commercial sources; the remaining 8 authors declared no competing interests.**

Common Drug Trade Names*: quetiapine—*Seroquel*; sertraline—*Zoloft

Solifenacin and Donepezil Dosing

In a first-in-patients study, co-administration of solifenacin, a peripheral anticholinergic approved for treatment of overactive bladder, allowed patients to tolerate increased doses of donepezil. The increased donepezil doses resulted in better clinical outcomes.

Background: It has been suggested that profound underdosing contributes to the lack of efficacy of donepezil and other cholinesterase inhibitors in Alzheimer's disease. However, dose-limiting adverse effects are a major factor contributing to underdosing. A 23-mg strength of donepezil was introduced in 2010 but has found limited acceptance due mainly to GI intolerance.

Methods: This single-blind, dose-escalation, crossover study recruited patients, aged 50–89 years, with a diagnosis of probable Alzheimer's dementia, according to standard criteria, and who had Mini-Mental State Examination (MMSE) scores of 10–20, indicating moderate impairment. All patients received 10 mg/day donepezil for ≥12 weeks before study entry. Those taking memantine at stable doses for ≥8 weeks were allowed to continue.

All patients received 6 tablets of single-blind study medication per day throughout the study. At entry, patients received 10 mg/day donepezil plus placebo for 2 days. On day 3, 10 mg/day solifenacin was introduced and then increased to 15 mg/day after 1 week. Remaining placebo tablets were subsequently replaced with donepezil, increasing in weekly 5-mg increments to 25 mg/day and then at biweekly intervals until the patient's first intolerable dose or the protocol-specified maximum of 40 mg/day. When titration was completed, patients were received maintenance with 15 mg/day solifenacin and the maximum tolerated dose of donepezil for 12 weeks. The primary study outcome was the maximum tolerated dose of donepezil during coadministration of solifenacin. Cognitive effects were a secondary study outcome.

Results: The 41 study participants had a mean age of 73 years, and 54% were women. The mean baseline MMSE score was 16.5. The average duration of donepezil treatment before study entry was >2 years, and 61% of patients were also taking memantine. Of the 11 patients who did not complete the study, none withdrew because of a drug-related adverse effect.

Solifenacin was not associated with observable cognitive decline, neuropsychological dysfunction, or other evidence of centrally mediated adverse effects. Of the 33 patients who completed donepezil dose titration, all reached a maximum tolerated dosage of ≥25 mg/day and all but 4 tolerated 40 mg/day. In all patients who completed the study, the maximum titrated dose was

maintained throughout the final 3 months of the study. GI intolerance was the dose-limiting adverse effect in 3 of the 4 patients whose maximum tolerated dose was 25 mg. No clinically meaningful changes in vital signs, electrocardiogram, or laboratory findings occurred.

Mean scores on the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) improved during the study period, reaching a peak at 18 weeks (after completion of donepezil titration), after which scores declined but remained higher than baseline averages at the 26-week endpoint. Final scores averaged about 2.5 points better than would be expected with 10 mg/day donepezil. A total of 14 patients (61%) were judged to be responders, based on stable or improved ADAS-cog scores. In the 16 patients with evaluable Clinical Global Impression–Improvement ratings at 26 weeks, both study clinician and caregiver ratings indicated substantial global improvement ($p<0.01$).

Discussion: The present observations support the suggestion that underdosing contributes to the lack of donepezil efficacy and suggests that more aggressive dosing may now be possible. Further study is now needed in a fully powered, randomized, controlled trial.

Chase T, Farlow M, Clarence-Smith K: Donepezil plus solifenacin (CPC-201) treatment for Alzheimer's disease. *Neurotherapeutics* 2017; doi 10.1007/s13311-016-0511-x. From Chase Pharmaceuticals, Inc., Washington, DC; and Indiana University School of Medicine, Indianapolis. **Funded by Chase Pharmaceuticals Corporation. The authors did not include disclosure of potential conflicts of interest.**

Common Drug Trade Names*: donepezil—*Aricept*; memantine—*Namenda*; solifenacin—*VESIcare

Dopamine-Serotonin Stabilizer in Schizophrenia

In a phase II trial, RP5063, an investigational dopamine-serotonin stabilizer, was superior to placebo in acute exacerbation of schizophrenia or schizoaffective disorder. The agent has a complex profile of partial agonist and antagonist activity of different dopamine and serotonin receptor subtypes, which differentiates it from approved atypical antipsychotics that are either D_2 antagonists or D_2 partial agonists.

Methods: The multinational study enrolled patients who had received a diagnosis of schizophrenia or schizoaffective disorder ≥1 year prior to screening, who were experiencing an acute exacerbation of ≤4 weeks, and who had a history of response to antipsychotic medication. Study patients were randomly assigned to double-blind, inpatient treatment with 1 of 3 dosages of RP5063 (15, 30, or 50 mg/day), placebo, or 15 mg/day aripiprazole (*Abilify*; included as an active control for sensitivity analysis only). Additional antipsychotics and other psychotropics were not permitted. The primary efficacy endpoint, assessed after 28 days of treatment, was change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score.

Results: A total of 234 subjects (mean age, 36 years; 75% men) were randomized; 80% completed the study. Of the patients who withdrew, 3 (1 in the 50 mg RP5063 group and 2 in the aripiprazole group) did so because of adverse effects. About 95% of patients had schizophrenia, and all were markedly ill at baseline (mean PANSS score, 88.2). The 15- and 50-mg doses of RP5063 were associated with significant improvement in the PANSS total score relative to placebo (see table, next page), with statistical differences apparent as early as day 15. The 30-mg dose was numerically superior to placebo, and the lack of significance was attributed to a high rate of discontinuation for reasons that were not related to the medication. Between 37% and 46% of the RP5063 dosage groups had a ≥2-point improvement in the Clinical Global Impression–Improvement scale score by day 28, compared with 19% of the placebo group. RP5063 was associated with improvements in both PANSS positive and negative subscale symptoms. The differences were statistically significant versus placebo for positive symptoms in the 50-mg RP5063 group and for negative symptoms with 15 and 50 mg. There were no significant differences among the groups in changes from baseline on measures of cognition.

Change from baseline to study end in PANSS total score				
	Baseline Mean	Endpoint Mean	Significance vs Placebo	≥30% PANSS Improvement
15 mg RP5063	87.6	67.4	p=0.02	41%
30 mg RP5063	88.7	73.3	p=ns	26%
50 mg RP5063	85.9	66.7	p=0.016	39%
Aripiprazole	91.7	82.4	—	16%
Placebo	89.8	78.4	—	22%

Only 1 patient stopped taking RP5063 because of a drug-related adverse event. Insomnia and agitation were the most frequent adverse events associated with RP5063, and extrapyramidal symptoms and akathisia affected ≤10% of the 3 dosage groups. There were no clinically relevant changes in weight, body mass index, or waist circumference within or between the treatment groups. RP5063 was associated with modest decreases in prolactin and with no changes in laboratory measurements or electrocardiogram.

Discussion: Although preliminary, these results suggest that RP5063 may be effective in schizophrenia and schizoaffective disorder and have a favorable adverse-effect profile that could improve treatment compliance.

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

Cantillon M, Prakash A, Alexander A, Ings R, et al: Dopamine serotonin stabilizer RP5063: a randomized, double-blind, placebo-controlled multicenter trial of safety and efficacy in exacerbation of schizophrenia or schizoaffective disorder. *Schizophrenia Research* 2017; doi 10.1016/j.schres.2017.01.043. From Reviva Pharmaceuticals, Inc., Santa Clara, CA. **Funded by Reviva. Four study authors disclosed financial relationships with commercial sources, including 3 with Reviva; the remaining 2 authors declared no competing interests.**

***See Reference Guide.**

Antipsychotic Adverse Effects: Patient Perspectives

Patient perspectives on the burden of adverse effects associated with atypical antipsychotics differ from those of clinicians, according to a focus group- and interview-based study. Because adverse effects differ substantially among second-generation agents, these observations argue for an adverse event-tailored approach when choosing a treatment.

Methods: The study was carried out at 2 qualitative research centers in the U.S. Study participants were community residents who had previously volunteered to participate in research opportunities, had a clinician-administered diagnosis of major depressive disorder (n=25) or schizophrenia (n=17), received an atypical antipsychotic within the past year, and had experienced ≥1 adverse event. The study also included 4 psychiatrists who provided direct care to patients with these disorders and had experience prescribing second-generation antipsychotics. The patients with depression and the psychiatrists participated in separate guided focus groups, and the patients with schizophrenia were interviewed individually. Patients were asked to list all side effects they had experienced, estimate their frequency, and rank them according to how bothersome they were. Clinicians listed all adverse effects known to them and then ranked them by frequency, clinical importance, and level of patient-perceived aggravation.

Results: The most commonly prescribed antipsychotics for depression were quetiapine and aripiprazole (each 24%), while patients with schizophrenia most often were given a prescription for olanzapine or risperidone (each 24%). The 4 psychiatrists had treated a total of about 600 patients with major depressive disorder and 300 with schizophrenia within the past year, including 35% and 57%, respectively, for whom an atypical antipsychotic was prescribed.

The adverse effects most often reported by all patients were cognitive issues including decreased attention and reduced ability to concentrate, remember, or recall (57%); weight gain and/or increased appetite (55%); low energy (48%); excessive sleepiness (36%); and extrapyramidal symptoms (36%). The most bothersome side effects according to both patient groups were cognitive issues (57%), weight gain and/or increased appetite (55%), extrapyramidal symptoms (36%), and sleepiness (36%). The patterns differed somewhat between patient groups: cognitive issues, weight gain, and excessive sleepiness were the most bothersome in patients with depression, while weight gain, low energy, and anxiety were the most bothersome to patients with schizophrenia. Nearly half of patients in each group reported experiencing reduced sexual desire, but this was not generally rated as among the most bothersome effect.

Adverse effects that were considered the most clinically important by ≥2 of the 4 psychiatrists were metabolic syndrome (all 4 physicians), neutropenia (3), and weight gain, hyperglycemia, and QT prolongation (2 each). Physicians rated weight gain as the most bothersome to patients, followed by reduced sexual desire, extrapyramidal symptoms, akathisia, and hormonal issues.

Discussion: This research is part of an effort to develop a tolerability index that will accommodate patient preference for avoiding specific adverse effects of atypical antipsychotics. Low energy, somnolence or sedation, and cognitive issues were more bothersome to patients than clinicians believed. Many of the effects judged clinically significant by psychiatrists are not amenable to patient self-reporting, and other differences may be attributable to clinical terminology or to patients' greater tendency to attribute their experience to their illness rather than its treatment. Interestingly, cognitive issues, frequently reported by patients as bothersome, are not mentioned in the prescribing information of any of the atypicals studied.

Llorca P-M, Lancon C, Hartry A, Brown T, et al: Assessing the burden of treatment-emergent adverse events associated with atypical antipsychotic medications. *BMC Psychiatry* 2017; doi 10.1186/s12888-017-1213-6. From Universite Clermont-Auvergne, France; and other institutions including Lundbeck and Otsuka Pharmaceutical Development Corporation. **Funded by Otsuka; and Lundbeck. Six study authors disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal

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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 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.

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.

PSYCHIATRY DRUG ALERTS

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Valbenazine for Tardive Dyskinesia

The newly approved vesicular monoamine transporter 2 (VMAT2) inhibitor valbenazine (*Ingrezza*) improved tardive dyskinesia (TD) and was well tolerated in a phase III trial.

Background: Valbenazine is the first FDA-approved drug to treat antipsychotic-induced TD, which affects as many as 20–30% of patients with chronic antipsychotic exposure. Previously, treatment options included stopping the antipsychotic, reducing the dosage, or using off-label medications. VMAT2 inhibitors modulate release of dopamine into the synapse and may offset the movement-related adverse effects of antipsychotics.

Methods: Study subjects, aged 18–85 years, had a diagnosis of schizophrenia, schizoaffective disorder, or mood disorder and had been experiencing moderate-or-severe dopamine receptor blocker-induced TD for ≥3 months. Patients taking strong CYP3A4 inducers, dopamine agonists and precursors, MAOIs, stimulants, or other VMAT2 inhibitors were required to undergo a 30-day washout prior to study screening. Participants received 6 weeks of randomized, double-blind treatment with 40 or 80 mg/day valbenazine or placebo, and TD symptoms were assessed every other week. The study's primary efficacy endpoint was change from baseline to week 6 in the 7-item Abnormal Involuntary Movement Scale (AIMS) dyskinesia score in patients taking the 80-mg dose, compared with placebo. AIMS examinations were video recorded and scored by a pair of expert clinicians. The key secondary endpoint was the Clinical Global Impression of Change–Tardive Dyskinesia (CGI-TD).

Results: A total of 234 patients were randomly assigned to treatment, and 205 (88%) completed the study. Two-thirds had a diagnosis of schizophrenia or schizoaffective disorder, 77% were taking atypical antipsychotics, and 17% were taking first-generation agents. The mean baseline AIMS dyskinesia score was 10. At week 6, treatment with 80 mg/day valbenazine was associated with a mean reduction in the AIMS dyskinesia score of 3.2 points, compared with 0.1 point in the placebo group ($p<0.001$; effect size,* 0.9). Separate analysis, which excluded 9 patients in the valbenazine group who had undetectable plasma drug levels and others who were not assessed, had similar results. The proportion of all patients judged to be responders

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(≥50% reduction in AIMS dyskinesia score) was 40% in the 80-mg/day valbenazine group (p<0.001 vs placebo), 24% in the 40-mg/day group (p=0.02 vs placebo), and 9% in the placebo group. The number needed to treat* with 80 mg/day valbenazine for 1 response was 4. The 2 treatment groups did not differ from placebo in the CGI-TD score. However, an analysis limited to 179 patients with a recorded AIMS score and a detectable plasma level of valbenazine at week 6 (if assigned to valbenazine) and no important efficacy-related protocol deviations showed about a half-point improvement relative to placebo (p=0.011).

The most frequently reported adverse effects of valbenazine were somnolence, akathisia, and dry mouth, each affecting about 1–5% of patients. No deteriorations in psychiatric stability or drug-related changes in laboratory results, physical examinations, vital signs, or electrocardiograms were observed.

Discussion: The present study results provide initial support for a favorable risk–benefit profile for both valbenazine doses. Patients who completed the current trial have gone on to a 42-week extension period of valbenazine treatment, results of which will be reported separately.

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

Hauser R, Factor S, Marder S, Knesevich M, et al: KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.16091037. From the University of South Florida, Tampa; and other institutions including Neurocrine Biosciences Inc., San Diego, CA. **Funded by Neurocrine Biosciences. Eight study authors disclosed financial relationships with commercial sources, including Neurocrine Biosciences; the remaining author declared no competing interests**

***See Reference Guide.**

Antidepressants and Smoking

Smoking tobacco reduces serum levels of several antidepressants, according to a systematic review. While very limited, published data suggest smoking is associated with lower levels of fluvoxamine, duloxetine, venlafaxine, trazodone, and mirtazapine.

Background: There is a lack of consensus on whether clinical outcome is correlated with plasma levels of SSRIs and other newer antidepressants. Nevertheless, it appears that subtherapeutic levels could jeopardize clinical response. Furthermore, most antidepressant adverse effects are dose dependent. Elimination of antidepressants is almost completely dependent on hepatic cytochrome P450 (CYP) enzymes, many of which are induced by compounds in cigarette smoke.

Methods: A comprehensive literature search identified 21 studies comparing steady-state metabolism of newer antidepressants in smokers and nonsmokers. The review included 7 studies of fluvoxamine; 2 each of fluoxetine, sertraline, venlafaxine, duloxetine, and mirtazapine; and 1 each of escitalopram, citalopram, trazodone, and bupropion. The studies comprised a total of 2375 patients, 733 of whom were smokers. No studies of paroxetine, milnacipran, or agomelatine were identified. All of the antidepressants evaluated are metabolized by CYP isoenzymes.

Results: Fluvoxamine levels were consistently decreased in smokers. However, most of the fluvoxamine studies were conducted in Japan in a population that differs from others in CYP enzyme activity. Studies of sertraline, escitalopram, and citalopram have shown no effect of smoking on serum levels, but many of these studies were based on a particularly young study population and did not exclude the possibility of interactions with other drugs. In 1 study, levels of norfluoxetine, the active metabolite of fluoxetine, were significantly higher in smokers than nonsmokers, which could suggest the possibility of accumulation and increased risk of serotonin syndrome.

Study results have been more consistent for SNRIs and other non-SSRI antidepressants. In 2 studies, average venlafaxine levels were significantly lower in smokers than in nonsmokers.

Strong evidence, from 2 large randomized clinical trials, suggests serum levels of duloxetine are significantly lower in smokers than nonsmokers. Smoking was also associated with significantly reduced levels of trazodone and mirtazapine. In a single study that included only 17 smokers, smoking did not influence bupropion levels.

Discussion: Although it is difficult to draw implications from many of the studies because of small sample sizes, failure to account for exposure to other drugs, and limitation to a single ethnic group or age group, these findings may help direct the choice of antidepressant treatments and dosages and highlight the possibility of adverse effects in patients who quit smoking.

Oliveira P, Ribeiro J, Donato H, Madeira N: Smoking and antidepressants pharmacokinetics: a systematic review. *Annals of General Psychiatry* 2017; doi 10.1186/s12991–017–0140–8. From Coimbra Hospital University Centre, Portugal. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names*: agomelatine (not available in U.S.)—*Valdoxan*; bupropion—*Wellbutrin*; citalopram—*Celexa*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; milnacipran—*Savella*; mirtazapine—*Remeron*; paroxetine—*Paxil*; sertraline—*Zoloft*; trazodone—*Desyrel*; venlafaxine—*Effexor

Quetiapine vs Lithium Maintenance

Following a first episode of mania successfully treated with lithium plus quetiapine (*Seroquel*), lithium monotherapy was superior to quetiapine monotherapy as maintenance treatment. This finding, unexpected in the context of other research, suggests that lithium may have greater efficacy in the early stages of bipolar disorder or in more severely affected patients.

Methods: The study recruited patients, aged 15–25 years, who were experiencing a first episode of mania (the majority with psychotic features). Nearly half of the patients had comorbid cannabis use disorder, and nearly one-third had comorbid alcohol use disorder. All patients (n=40; mean age, 21 years; 78% men) received treatment with lithium plus quetiapine as part of a routine care protocol. Quetiapine dosage was determined by the treating clinician, and lithium dosages were based on serum level targets of 0.8–1.0 mEq/L. Following clinical stabilization, 1 of the 2 drugs was gradually withdrawn, by random assignment. Patients and their psychiatrists knew which drug was being continued, but evaluators and others connected with the study did not. Patients were assessed for mania, depression, clinical status, functioning, and other outcomes at regular intervals, ending at 12 months.

Results: After 12 months, patients who received lithium fared significantly better than those who received quetiapine in terms of depression, psychotic symptoms, overall psychopathology, and functional outcomes. However, differences in Young Mania Rating Scale (YMRS) scores did not differ between the 2 treatments, and the Clinical Global Impression for Bipolar Disorder (CGI-BP) mania scale was higher in the quetiapine group only at 9 months. According to post-hoc analyses, although most patients were euthymic at study entry, the quetiapine group showed a significant worsening of depression, measured with the Montgomery Asberg Depression Rating Scale (MADRS) during treatment, while the lithium group did not.

The groups differed significantly at 12 months on the Brief Psychiatric Rating Scale (BPRS) psychosis subscales (p=0.047), and the quetiapine group showed a greater deterioration from baseline than the lithium group (p=0.004), as well as greater severity of positive symptoms (p=0.005). In terms of overall psychopathology, the quetiapine group had a statistically significant worsening in BPRS total score from baseline to 12 months (p=0.008), while the lithium group continued to improve (p=0.023). The lithium group showed improvement in CGI-BP severity scores and measures of function (Global Assessment of Functioning [GAF], Social and Occupational Functioning Assessment Scale [SOFAS]), with only modest differences in Quality of Life Scale scores. (See table, next page.)

Selected Outcomes at 12 Months				
	Lithium		Quetiapine	
	Baseline	Endpoint	Baseline	Endpoint
MADRS	6.9	2.5	7.1	13.4
BPRS Total	33.4	28.1	32.5	39.6
BPRS Positive Symptoms	4.6	4.3	4.3	6.1
GAF	69.1	77.0	68.7	57.0
SOFAS	70.8	77.6	67.7	57.2

Discussion: These results were surprising given the failure of other maintenance studies to find differences in efficacy between typical antipsychotics and mood stabilizers. Patient selection may explain much of the difference. Lithium may be more effective in first-episode patients and in those with an index episode polarity of mania.

Berk M, Daglas R, Dandash O, Yucel M, et al: Quetiapine v. lithium in the maintenance phase following a first episode of mania: randomised controlled trial. *British Journal of Psychiatry* 2017; 10.1192/bjp.bp.116.186833. From Deakin University, Melbourne, Australia; and other institutions. **Funded by Astra Zeneca. Six study authors disclosed financial relationships with commercial sources, including AstraZeneca; the remaining 11 authors declared no competing interests.**

Topiramate for Skin-Picking Disorder

In a pilot study, topiramate (*Topamax*) reduced skin-picking behavior to a clinically significant extent. Other pharmacologic and psychological treatments for this disorder have had limited success.

Methods: Study subjects (n=10; 8 women; mean age, 24 years) were adults who engaged in recurrent skin picking resulting in lesions, with clinically significant distress or impairment and repeated prior attempts to stop. Skin picking was not attributable to the physiological effects of substance use or a medical condition, or to another psychiatric disorder, although comorbid conditions (e.g., social anxiety disorder, major depression, drug/alcohol dependence) were common. After a washout of previous medications, study patients were started on 25 mg/day topiramate, followed by very gradual increases until clinical response, up to a maximum of 100 mg b.i.d. Participants were followed for 12 weeks, and the primary outcome measure was the mean amount of time spent picking per day, as reported in a diary. Other outcome measures were the Skin Picking Impact Scale, a modification of the Yale-Brown Obsessive Compulsive Scale (SPS-Y-BOCS), Beck Anxiety and Depression Inventories, and Clinical Global Impression (CGI) Severity (S) and Improvement (I) scales.

Results: Study patients had skin-picking onset at an average age of about 16 years (range, 12–34 years) and had gone a mean of nearly 5 years before seeking any treatment. All had multiple prior treatments, including antidepressants, antipsychotics, mood stabilizers, habit-reversal therapy, and cognitive behavioral therapy. Patients reported interference with social and work activities, inability to control the behavior, and anxiety, interpersonal rejection, and depression.

By the end of follow-up, the amount of time spent skin picking was reduced from a baseline mean of 85 minutes per day to 30 minutes per day. Seven patients reported no skin picking at follow-up. Clinician-rated measures indicated that 3 patients were much improved and 4 were very much improved on the CGI-I, and the mean CGI-S rating improved from markedly to mildly ill. The patients most likely to improve were those with relatively mild skin picking of short duration, those with good family support systems, and those who were married and more educated. All secondary outcome measures showed improvement, including the SPS-Y-BOCS and measures of anxiety and depression. A single patient dropped out of the study

because of intolerable dizziness and sedation. Three others had milder adverse effects—nausea, drowsiness, headache, confusion—but these were limited to the first week of treatment.

Discussion: These results suggest that topiramate warrants further study for skin-picking disorder, especially in view of the limited success of psychological therapies, SSRIs/SNRIs, opioid antagonists, atypical antipsychotics, and glutamatergic agents. Skin-picking disorder may share a common pathway with other obsessive-compulsive syndromes such as body dysmorphic disorder, Tourette's disorder, and trichotillomania, which suggests a glutamatergic dysfunction and possible efficacy of glutamatergic drugs. Topiramate modulates GABA-ergic neurotransmission and may also help reverse dopamine reward dysfunction.

Jafferany M, Osuagwu F: Use of topiramate for skin-picking disorder: a pilot study. *The Primary Care Companion for CNS Disorders* 2017; doi 10.4088/PCC.16m01961. From Central Michigan University College of Medicine, Saginaw. **This study was conducted without funding. The authors declared no competing interests.**

5-α Reductase Inhibitors and Depression, Suicide

Despite concerns based on pharmacovigilance sources, use of 5-α-reductase inhibitors (5-ARIs) was not associated with an increased rate of suicide in a large cohort of older men with benign prostatic hyperplasia (BPH). The drugs were, however, associated with a temporary increase in depression and self-harm.

Background: The potential adverse neurologic effects of 5-ARIs are a growing concern. There have been postmarketing reports of self-harm, suicidal ideation, and suicide in men taking these drugs, and depression is now included as an adverse event in the product monographs. There are also multiple lines of evidence supporting plausible biological mechanisms, including the role of 5-α reductase in production of neuroactive steroids and the involvement of testosterone in depression via the neuroendocrine stress response.

Methods: A cohort of men, aged ≥66 years, who received treatment with dutasteride or finasteride for BPH between 2003 and 2013, was identified from Canadian healthcare databases. Each patient was matched with a control, who was selected from the general population based on index date, history of depression or self-harm, and a 44-item propensity score.* The index date for cases was the date of prescription filling and for controls, a date was randomly selected. Risk was assessed for the period of continuous drug usage from the index date until 12 months after discontinuing the medication. The primary study outcome was suicide. Secondary outcomes were self-harm requiring emergency treatment or psychiatric hospitalization and new onset of depression.

Results: The study population consisted of >93,000 pairs of exposed and unexposed men with a mean age of 75 years. About half of patients took dutasteride and half finasteride. Baseline rates of psychotropic use, which ranged from <1% for mood stabilizers to about 15% for antidepressants, did not differ between exposed and unexposed men.

The absolute risk of suicide was low—0.04% in both patients and controls. Use of a 5-ARI was not associated with suicide risk (hazard ratio,* 0.88). Absolute rates of self-harm and depression were 0.18% and 1.95%, respectively in the treated group, compared with 0.14% and 1.37% in controls. Compared with unexposed men, risk of self-harm was increased during the first 18 months of 5-ARI use (hazard ratio, 1.88; $p<0.01$), but not afterward. Risk of depression was increased throughout the period of 5-ARI use, up to >3 years, although the highest risk was in the first 18 months (hazard ratio, 1.94, dropping to 1.22 afterward; $p<0.01$ at all time points).

Discussion: These results suggest that neither finasteride nor dutasteride is associated with increased suicide risk in older men with BPH and that the potential benefits of treatment likely outweigh the small increase in risk of self-harm and depression. However, discontinuation of

these drugs may be appropriate if self-harm or depression occurs shortly after they are started, and the associations should be evaluated in younger men receiving treatment for alopecia.

Welk B, McArthur E, Ordon M, Anderson K, et al: Association of suicidality and depression with 5α-reductase inhibitors. *JAMA Internal Medicine* 2017; doi 10.1001/jamainternmed.2017.0089. From Western University, Canada; and other institutions. **Funded by Western University; and other sources. One study author disclosed a financial relationship with a commercial source; the remaining 5 authors declared no competing interests.**

Common Drug Trade Names*: dutasteride—*Avodart*; finasteride—*Propecia, Proscar

***See Reference Guide.**

Activating and Sedating Effects of Atypicals

Second-generation antipsychotics differ considerably in their propensity to cause activating and sedating side effects, according to an analysis of clinical trial data from multiple sources. Individual patient preferences can vary with regard to which type of adverse effect is least tolerable. Assuming equivalent efficacy, these differences can have important implications for treatment selection.

Methods: The investigators reviewed pivotal clinical trial data from the product labeling as well as the "gray" literature—i.e., unpublished sources available on the Web. For each of the first-line, oral second-generation antipsychotics indicated for treating schizophrenia, the researchers identified frequencies of activating and sedating side effects and calculated the absolute risks and numbers needed to harm (NNH).*

Results: Based on the statistical calculations, the authors separated the atypicals into 4 distinct categories: predominantly activating, predominantly sedating, similarly activating and sedating, and neither activating nor sedating. (See table.)

Categories of Activation/Sedation
Predominantly activating (akathisia) lurasidone cariprazine
Similarly activating and sedating risperidone aripiprazole
Predominantly sedating olanzapine quetiapine IR and XR ziprasidone asenapine iloperidone
Neither activating nor sedating paliperidone brexpiprazole

Among activating effects, akathisia occurred at highly varied rates among the atypicals. Rates were higher with lurasidone, cariprazine, risperidone, olanzapine, asenapine, and aripiprazole than with placebo, with NNH values ranging from 11 to 31. Rates did not differ from placebo for paliperidone, ziprasidone, quetiapine extended release, brexpiprazole, or iloperidone.

Few statistically significant associations were observed for individual agents and other activating effects: iloperidone with agitation and with insomnia (lower risk than placebo) and extended-release quetiapine with insomnia (lower risk than placebo).

Somnolence and sedation are often combined in clinical trial reports and were combined in the present analysis. Risk of sedating adverse effects were higher than placebo for olanzapine, risperidone, quetiapine (extended and immediate release), ziprasidone, lurasidone, asenapine, and iloperidone, with NNH estimates ranging from 10 to 33. Aripiprazole, paliperidone, and brexpiprazole were similar to placebo, and there was no information on cariprazine or risperidone.

Citrome L: Activating and sedating adverse effects of second-generation antipsychotics in the treatment of schizophrenia and major depressive disorder. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000665. From New York Medical College, Valhalla, NY. **Funded by Otsuka Pharmaceutical Development & Commercialization, Inc. The study author disclosed financial relationships with commercial, including Otsuka.**

Common Drug Trade Names*: aripiprazole—*Abilify*; asenapine—*Saphris*; brexpiprazole—*Rexulti*; cariprazine—*Vraylar*; iloperidone—*Fanapt*; lurasidone—*Latuda*; olanzapine—*Zyprexa*; paliperidone—*Invega*; quetiapine—*Seroquel*; risperidone—*Risperdal*; ziprasidone—*Geodon

***See Reference Guide.**

Acute Kidney Injury Risk with Antipsychotics

Risk of hospitalization for acute kidney injury (AKI) was elevated in patients taking certain atypical antipsychotics, relative to haloperidol, according to a retrospective cohort study.[1] However, the absolute excess risk of these events was small.

Background: A recent large database analysis found associations of some earlier second-generation antipsychotics with AKI and related events in patients aged >65 years.[2] The present study adds information about agents that have become more widely used in recent years and in a broader patient population.

Methods: Claims data were analyzed from a managed care prescription database covering >14-million patients in 2007–2013. Patients were included in the analysis if they had a diagnosis of schizophrenia or bipolar disorder and had ≥1 claim for haloperidol, aripiprazole, fluphenazine, olanzapine, quetiapine, risperidone, or ziprasidone. Because AKI hospitalizations are rare, only antipsychotics that had a sufficient number of prescriptions to make reliable incidence estimates were included. The primary outcome was hospitalization for AKI during active treatment with any of the study drugs or within 30 days of discontinuation. Secondary outcomes included any of the known causes of AKI: hypotension, acute urinary retention, neuroleptic malignant syndrome (NMS) and rhabdomyolysis, and pneumonia. Patients receiving haloperidol were the reference group for incidence comparisons. Because events that occurred during overlap of 2 study medications could be attributable to 1 of the drugs or to both drugs, a separate sensitivity analysis using episodes without overlap was conducted to provide a clean comparison.

Results: The final sample consisted of >172,000 patients. The overall incidence of AKI in patients exposed to a study medication was 25 per 1000 exposures, ranging from a minimum of 12.9 per 1000 exposures to fluphenazine, to 29 per 1000 to quetiapine. After adjustment for multiple factors, the incidence was significantly elevated, relative to haloperidol, for olanzapine, quetiapine, and ziprasidone. (See table.) Risks of the 4 predisposing events did not follow a consistent pattern, but risk elevations were statistically significant for: quetiapine and hypotension; quetiapine and NMS or rhabdomyolysis; and olanzapine and pneumonia ($p<0.05$ for all). As a class, second-generation antipsychotics had a significantly higher risk of AKI than first-generation agents (hazard ratio,* 1.3). Results were similar in the sensitivity analysis excluding episodes of medication overlap.

Hospitalization for AKI with atypical antipsychotics, relative to haloperidol**

Antipsychotic	Incidence per 1000 Person-Years	Adjusted Hazard Ratio	Significance
Haloperidol	20.3	—	—
Olanzapine	27.5	1.34	$p<0.05$
Quetiapine	29	1.35	$p<0.01$
Ziprasidone	23.2	1.34	$p<0.05$

****Risk with aripiprazole, fluphenazine, and risperidone did not differ significantly from haloperidol.**

Discussion: These newer data suggest AKI risk is not a class effect of second-generation agents, and that AKI risk should not be a major concern in prescribing antipsychotics. However,

caution may be warranted when prescribing olanzapine, quetiapine, or ziprasidone for elderly patients and those at risk for kidney disease. In addition, high-risk antipsychotics should be considered as a potential cause when AKI occurs.

[1]Jiang Y, McCombs J, Park S: A retrospective cohort study of acute kidney injury risk associated with antipsychotics. *CNS Drugs* 2017; doi 10.1007/s40263–017–0421–4. From the University of Southern California, Los Angeles; and the University of California, Los Angeles. **This study was conducted without funding. The authors declared no competing interests.**

[2]Hwang Y, et al: Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. *Annals of Internal Medicine* 2014;161:242–248.

Common Drug Trade Names*: aripiprazole—*Abilify*; fluphenazine—*Prolixin*; haloperidol—*Haldol*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*; ziprasidone—*Geodon

***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.

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 is the treatment.

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. Through matching and balancing samples, propensity scores help adjust for selection bias, making it possible to obtain average treatment effects.

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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PSYCHIATRY DRUG ALERTS

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Long-Acting Stimulant for Adult ADHD

In a manufacturer-sponsored, placebo-controlled trial, a new triple-bead mixed amphetamine salts formulation, SHP465, improved ADHD symptoms in adults. The formulation was designed to provide drug coverage throughout the day, after once-daily administration, by incorporating beads that provide for immediate release, pulsatile delayed release, and sustained release.

Methods: Study participants (n=411) were adults, aged 18–55 years, with a DSM-IV-TR diagnosis of ADHD who had baseline scores of ≥32 on the ADHD Rating Scale–IV (ADHD-RS-IV). After a washout of previous medication in the 67 patients who reported using ADHD medication in the previous 30 days, patients were randomly assigned to 6 weeks of double-blind treatment with 1 of 3 dosages of SHP465 (25, 50, or 75 mg/day) or placebo. All patients who received SHP465 were started at 25 mg/day, and the 2 higher dosages were force-titrated over the subsequent 2–3 weeks. The primary efficacy endpoint was change from baseline in the ADHD-RS-IV total score.

Results: The study participants had a mean age of 37 years, 56% were men, and most had the combined ADHD subtype. During the study, the mean daily dose of mixed amphetamine salts was 25 mg in the 25-mg/day group, 41 mg in the 50-mg/day group, and 50 mg in the 75-mg/day group. Patients in all groups took ≥95% of the provided study medication.

Mean baseline ADHD-RS-IV total scores averaged about 40 and were reduced in all groups at study end. Efficacy of the 3 dosages did not differ (see table, next page); thus they were combined in the outcome analyses. Relative to placebo, the decrease from baseline in the ADHD-RS-IV total score in the combined SHP465 groups was 10.6 points ($p<0.0001$; effect size,* 0.91). Statistically significant differences from placebo were observed as early as week 1. SHP465 was superior to placebo for both the inattentiveness and hyperactivity/impulsivity subscales of the ADHD-RS-IV ($p<0.0001$ for both). Clinical Global Impression–Improvement ratings were "much improved" or better in 65% of the groups receiving the active drug and in 20% of the placebo group ($p<0.0001$).

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Change in ADHD-RS-IV Score				
	Baseline	**End Point**	**Significance vs Placebo**	**Effect Size**
Placebo	40.2	31.2	——	——
25 mg SHP465	39.9	21.1	p<0.0001	0.85
50 mg SHP465	40.9	21.0	p<0.0001	0.92
75 mg SHP465	40.2	20.0	p<0.0001	0.96

Adverse effects of SHP465 were similar to those reported for other long-acting stimulants. Severe adverse effects associated with SHP465 were dose-related and included insomnia (n=10), headache (n=2), and fatigue (n=2). Side effects leading to treatment discontinuation in ≥2% of patients were insomnia, anxiety, increased blood pressure, flushing, and headache. Other frequent adverse effects were decreased appetite, decreased weight, and dry mouth.

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

Frick G, Yan B, Adler L: Triple-bead mixed amphetamine salts (SHP465) in adults with ADHD: results of a phase 3, double-blind, randomized, forced-dose trial. *Journal of Attention Disorders* 2017; doi 10.1177/1087054717696771. From Shire, Lexington, MA; Endo Pharmaceuticals, Malvern, PA; and New York University, New York. **Funded by Shire Development LLC. Two study authors disclosed financial relationships with commercial sources, including Shire; the remaining author declared no competing interests that were relevant to this study.**

***See Reference Guide.**

Mixed States: Treatment Recommendations

Evidence supports the use of several atypical antipsychotics in the treatment of mixed states, as well as some older mood stabilizers; however, no single agent or combination studied has shown sufficient evidence of efficacy at reducing manic symptoms, depressive symptoms, and relapse risk. (See table, next page.)

By reducing the diagnostic threshold for mixed states in bipolar disorder, the DSM-5 criteria substantially increases their potential identification and improves their characterization. Knowledge about effective treatments is limited because there have been few trials conducted specifically in patients with mixed states; instead, recommendations are based on post-hoc subgroup analyses of wider trials, most of which have been industry sponsored. A comprehensive literature search for trials, including meta-analyses and post-hoc analyses, found 39 published studies.

The available data on lithium in mixed states is inconclusive. However, lithium deserves consideration because it is the only psychoactive drug that has a well-established effect in preventing suicide. Among the other mood stabilizers, valproate significantly reduced manic symptoms in patients with a mixed episode and, in another study, reduced depressive symptoms. It was not superior to placebo in relapse prevention in patients with dysphoric mania. Studies of carbamazepine have shown contradictory results.

Most of the available atypical antipsychotics have been investigated in patients with mixed states. Olanzapine has been studied the most frequently and has demonstrated efficacy on manic symptoms in DSM-IV mixed mood episodes, and a recent post-hoc analysis applied these findings to DSM-5 episodes. There is insufficient evidence of its efficacy for depressive symptoms. Aripiprazole was superior to placebo for both manic and depressive symptoms in patients with DSM-IV mixed states. In several recent trials or post-hoc pooled analyses, asenapine reduced both manic and depressive symptoms in patients with DSM-IV mixed episodes.

Evidence for Pharmacological Treatments of Mixed States			
Agent	**Significant reduction in manic symptoms**	**Significant reduction in depressive symptoms**	**Significant reduction in relapse risk**
Aripiprazole	Yes	Yes	Inconclusive*
Asenapine	Yes	Yes	Inconclusive*
Olanzapine	Yes	Inconclusive*	Yes
Paliperidone	Yes	No	Yes
Quetiapine	Inconclusive*	Inconclusive*	Inconclusive*
Risperidone	Yes	Inconclusive*	Inconclusive*
Ziprasidone	Yes	Yes	Inconclusive*
Lurasidone	Yes	Yes	Inconclusive*
Lithium	No	Inconclusive;* however, antisuicide effects have been demonstrated	No
Valproate	Yes	Yes	No
Carbamazepine	Inconclusive*	Yes	Inconclusive*
Lamotrigine	No	Inconclusive*	Inconclusive*
Valproate + Olanzapine	Yes	Yes	Inconclusive*
Lithium + Olanzapine	Yes	Inconclusive*	Inconclusive*
Lithium + Quetiapine	Inconclusive*	Inconclusive*	Yes
Lithium or Valproate + Aripiprazole	Yes	Yes	Inconclusive*
*Insufficient or contradictory data			

Betzler F, Stover L, Sterzer P, Kohler S: Mixed states in bipolar disorder—changes in DSM-5 and current treatment recommendations. *International Journal of Psychiatry in Clinical Practice* 2017; doi 10.1080/13651501.2017.1311921. From Charite Universitatsmedizin Berlin, Germany. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; asenapine—*Saphris*; carbamazepine—*Tegretol*; lamotrigine—*Lamictal*; lurasidone—*Latuda*; olanzapine—*Zyprexa*; paliperidone—*Invega*; quetiapine—*Seroquel*; risperidone—*Risperdal*; valproate—*Depakene, Depakote*; ziprasidone—*Geodon

Cholinesterase Inhibitors for Cognitive Effects of ECT

According to a systematic review of the limited available research, acetylcholinesterase inhibitors may prevent cognitive side effects of electroconvulsive therapy.

Methods: A comprehensive literature search for all published trials or reviews of acetylcholinesterase inhibitors' effects on cognition in adults undergoing ECT identified only 5 studies. Because of differing designs, medications, patient populations, and outcome measures, the studies could not be pooled for a meta-analysis.

Results: Of the 5 studies, 4 were placebo-controlled trials and 1 was a non-blinded pilot study; all were parallel-group studies except for a single crossover trial. Sample sizes were generally small, ranging from 17 to 45. Four different medications were investigated: IV physostigmine, and oral donepezil, galantamine, and rivastigmine. Each of the studies found a positive effect of acetylcholinesterase-inhibitor treatment on cognitive function. A single IV administration of physostigmine after the 5th or 6th session of ECT was associated with improved memory function and fluency, assessed 90 minutes after the session. Use of 5 mg/day donepezil throughout the treatment course was associated with significantly better cognitive recovery from ECT, compared with placebo, within the first 90 minutes after the ECT. Cognitive function, measured a maximum of 48 hours after ECT, was superior when patients received 4 mg/day galantamine, compared with the same patients' performance with no cholinesterase inhibitor treatment. Cognitive function was superior in patients receiving 4.5 mg/day rivastigmine for 4 weeks, compared with placebo, up to but not including an evaluation 4 weeks after the last ECT. Finally, flexible-dose galantamine appeared to prevent delayed memory deficits up to 48 hours after an ECT session. Use of cholinesterase inhibitors did not substantially affect ECT parameters (e.g., stimulus strength, number of sessions).

Discussion: Modifications of ECT modalities to limit the treatment's cognitive side effects have had limited success, as have a number of medications. The consistent results with acetylcholinesterase inhibitors support cholinergic mechanisms in the cognitive side effects of ECT; additional research appears to be warranted.

Henstra M, Jansma E, van der Velde N, Swart E, et al: Acetylcholinesterase inhibitors for electroconvulsive therapy-induced cognitive side effects: a systematic review. *International Journal of Geriatric Psychiatry* 2017; doi 10.1002/gps.4702. From the University of Amsterdam, the Netherlands; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names: **donepezil—*Aricept*; galantamine—*Razadyne*; physostigmine—*Antilirium*; rivastigmine—*Exelon***

Brexanolone for Postpartum Depression

In a small proof-of-concept study, brexanolone, a neuroactive hormone, was safe and well tolerated and showed promising effects in women with postpartum depression. Brexanolone is a proprietary hormone preparation that can be titrated to provide third-trimester levels of allopregnanolone, a hormone whose rapid postpartum decline may be associated with postpartum depression.

Background: Allopregnanolone is the major metabolite of progesterone. The hormone increases during pregnancy and decreases rapidly after delivery. Failure of $GABA_A$ receptors to adapt to the abrupt decline in allopregnanolone may be associated with symptoms of postpartum depression.

Methods: The open-label study was conducted in women admitted to an inpatient perinatal psychiatry unit for a major depressive episode between 14 days and 20 weeks postpartum. Participants were required to have a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥20 and were allowed to continue on stable doses of background antidepressant medication. Brexanolone was given by infusion at a dose targeted to achieve a steady-state plasma allopregnanolone concentration of about 150 nM, approximately matching levels in the third trimester. Dosing was titrated over the first 12 hours, continued at the maintenance level until the end of the second day, and then tapered over the final 12 hours to allow physiologic adjustment to lower levels. Outcomes were assessed at 12-hour intervals beginning 12 hours after the start of the infusion and lasting throughout the infusion (hour 60) and at 1 additional point (hour 84). Safety and tolerability were the primary study outcomes. Efficacy was assessed, as a secondary outcome, as change from baseline in the HAM-D.

Results: Planned enrollment was 10 patients, but the trial was stopped prematurely after positive results in the first 4, in order to accelerate further clinical development. Mean HAM-D scores were decreased at the 12-hour assessment (from 26.5 at baseline to 4.8), reached a maximum decrease to 1.8 at end of infusion, and remained low through the 12-hour taper. HAM-D scores for all patients were consistent with remission (i.e., ≤7) from hour 24 onward. Secondary measures of depression and anxiety showed similar patterns. Mean Clinical Global Impression–Improvement ratings were much or very much improved from the first assessment through study end.

All patients experienced adverse events: sedation; infusion site discomfort, pain, or erythema; rash; thyroid stimulating hormone increase; dizziness; flushing; and oropharyngeal pain. These were mild to moderate and 3 women had precautionary dosage adjustments. There were no important changes in laboratory parameters or electrocardiograms and no reports of suicidal behavior or ideation.

Discussion: Although this study had important methodological limitations and a very small sample size, the rapid antidepressant effects of brexanolone infusion appear to warrant further study, particularly in light of the time required for SSRIs to have therapeutic effects.

Kanes S, Colquhoun H, Doherty J, Raines S, et al: Open-label, proof-of-concept study of brexanolone in the treatment of severe postpartum depression. *Human Psychopharmacology: Clinical and Experimental* 2017; doi 10.1002/hup.2576. From Sage Therapeutics, Inc., Cambridge, MA; and other institutions. **Funded by Sage Therapeutics, Inc. All study authors declared financial relationships with commercial sources, including Sage Therapeutics.**

Gender Differences: Risk Factors for Antidepressant Mania

Men and women with bipolar disorder have different risk profiles that predict the onset of antidepressant treatment emergent mania (ATEM), according to a retrospective clinical study.

Methods: The study population consisted of 210 adult patients with a diagnosis of DSM-IV bipolar I or II disorder who were attending psychiatric clinics in 4 French cities over a 13-year period. Patients were classified as having ATEM (n=75) if they had onset of full DSM-IV syndromal mania or hypomania within 90 days of starting an antidepressant, either as monotherapy or combined with a mood stabilizer. The comparison group (n=135) consisted of patients with bipolar disorder, similar in all respects except that they had ≥1 lifetime depressive episode but did not have onset of ATEM despite ≥90 days' treatment with antidepressant monotherapy. A variety of potential predictive factors for ATEM were examined in the sample as a whole and separately in men and women.

Results: Of the 75 cases of ATEM, 61 (87%) occurred during antidepressant monotherapy. SSRIs were prescribed in 46% of ATEM episodes and tricyclics in 21%. Prescribing patterns were similar for patients with bipolar I and II disorder and for men and women. Patients in the ATEM case and control groups had a mean age of 43 years and had received the bipolar disorder diagnosis 18–19 years in the past. Patients with ATEM differed from the comparison group by having a higher prevalence of rapid cycling (25% vs 12%; p=0.02) and a higher rate of depression as the disorder onset polarity (81% vs 64%; p=0.02). Patients with emergent mania/hypomania also had a higher mean number of depressive episodes and a higher lifetime rate of alcohol use disorder. Additional predictive factors emerged when the analysis was stratified by gender. (See table.)

Multivariate risk factors for ATEM in men and women with bipolar disorder

Risk Factor	Odds Ratio*
Men	
Alcohol use disorder	6.37
Lifetime history of suicide attempts	4.19
Depressive episodes per year	1.71
Women	
Thyroid disorder	3.23
Family history of bipolar I	2.68
Depressive onset polarity	2.01

Discussion: Results of this study provide some insight into risk factors for ATEM in patients with bipolar disorder. However, as this is the first study to explore gender differences in ATEM risk, the results require replication.

Scott J, Brichant-Petitjean C, Etain B, Henry C, et al: A re-examination of antidepressant treatment-emergent mania in bipolar disorders: evidence of gender differences. *Acta Psychiatrica Scandinavica* 2017;135:479–488. From Newcastle University, Newcastle upon Tyne, U.K.; and other institutions. **Source of funding not stated. All study authors declared financial relationships with commercial sources.**

***See Reference Guide.**

Cariprazine Tolerability in Acute Mania

According to pooled data from phase 2/3 clinical trials, cariprazine (*Vraylar*) was generally well tolerated and safe in patients with bipolar I disorder. Akathisia and extrapyramidal symptoms were the most commonly observed adverse events, but they were generally mild to moderate and manageable with medication.

Methods: The investigators analyzed pooled data from 3 short-term (3 weeks) placebo-controlled trials from the manufacturer's clinical-development program for cariprazine in bipolar I disorder. Participants were adults, aged 18–65 years, who met DSM-IV-TR criteria for bipolar I disorder, manic or mixed type. In 2 studies, patients received flexibly dosed cariprazine at 3–12 mg/day, or placebo. In the third study, patients were randomly assigned to 2 different cariprazine dose ranges, 3–6 mg/day or 6–12 mg/day, or to placebo. In all 3 studies, dosing was started at 1.5 mg on the first day and increased based on response and tolerability.

Results: The pooled safety population was 1065 patients: 263 patients who received 3–6 mg/day cariprazine, 360 who received 9–12 mg/day cariprazine, and 442 in the placebo groups. The treatment groups had similar mean treatment durations of 17–18 days and similar overall completion rates.

Adverse events and withdrawal for adverse events (see table) were numerically more frequent with cariprazine than with placebo. (Differences between groups were not subjected to statistical analysis.) Rates of most adverse events were similar for the 2 cariprazine dose ranges. The incidence of extrapyramidal symptoms may have been dose-related (26% vs 29% for the lower and higher dose cariprazine groups, respectively), as was the frequency of constipation (6% vs 11%). Three-fourths of all adverse events were considered mild to moderate. Depressive symptoms did not worsen in the cariprazine or placebo groups, rates of suicidal ideation were low (about 2% in all groups), and there were no instances of suicidal behavior.

Frequency of selected treatment-emergent adverse events (TEAEs)

	Placebo	Cariprazine (merged dosage groups)
Any TEAE	67%	80%
TEAE resulting in discontinuation	7%	12%
Extrapyramidal symptoms	12%	28%
Akathisia	5%	20%
Discontinuation for mania	3%	0%
Glucose levels: Shift from normal to impaired	6%	10%
Blood pressure: Shift from normotensive to elevated	5%	10%

Extrapyramidal symptoms were mild or moderate in >90% of patients who experienced them and rarely led to drug discontinuation. Onset of akathisia and extrapyramidal symptoms peaked within 2 weeks of treatment initiation, coinciding with the acquisition of steady state for cariprazine and its active metabolites. About half of patients used permitted antiparkinsonian medication.

Cariprazine had few effects on lipid metabolism but was associated with a greater increase in fasting glucose levels than placebo. Patients receiving cariprazine gained about 1 lb on average. Mean prolactin levels decreased in all treatment groups. Cardiovascular safety assessments showed few differences between groups, but more patients receiving cariprazine than placebo shifted from normal or borderline to high blood pressure levels. Liver enzymes were also increased to a slightly larger degree with cariprazine than with placebo and these increases may have been dose-related. However, no cariprazine-treated patient met Hy's Law criteria (i.e., alanine aminotransferase or aspartate aminotransferase levels of ≥3 times the upper limit of normal plus total bilirubin level of ≥2 times the upper limit of normal and an alkaline phosphatase level of <2 times the upper limit of normal).

Earley W, Durgam S, Lu K, Debelle M, et al: Tolerability of cariprazine in the treatment of acute bipolar I mania: a pooled post hoc analysis of 3 phase II/III studies. *Journal of Affective Disorders* 2017;215 (June):205–212. From Allergan, Jersey City, NJ; Gedeon Richter PLC, Budapest, Hungary; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

SNRIs and Stroke Risk

In a population-based study, new users of an SNRI had an elevated risk of nonfatal stroke compared with new users of an SSRI.

Methods: The study was a retrospective analysis of health care data from the Canadian province of Manitoba. It included all patients who received a new prescription for an SSRI or an SNRI in 1998–2014, after ≥1 year free of antidepressant therapy. Hospitalized patients and those with a recent cardiovascular or cerebrovascular event were excluded. The primary study outcome was a composite of hospital admission for acute myocardial infarction, fatal or nonfatal stroke, or other cardiovascular illness. Patients were followed until the first occurrence of a study outcome or 1 year after the new prescription because these effects are known to occur early in treatment.

Results: The study population consisted of >225,000 patients given a prescription for an SSRI and nearly 55,000 given an SNRI. The most frequently prescribed drugs in either class were citalopram (42% of SSRI prescriptions) and venlafaxine (94% of SNRI prescriptions). There were no meaningful baseline differences between the 2 patient groups.

After propensity score matching* to adjust for baseline differences between those receiving an SSRI or an SNRI, new users of SNRIs had a significantly higher risk of the primary composite outcome than users of an SSRI (propensity-weighted hazard ratio,* 1.13). This increase was entirely due to increased risk of nonfatal stroke (hazard ratio, 1.20). Among nonfatal stroke events, ischemic stroke incidence was elevated in SNRI users (hazard ratio, 1.32) but hemorrhagic stroke was not.

When the analysis was stratified into 2 age groups, the nonfatal stroke risk increase with SNRIs was confined to patients aged >40 years. Drug-related differences in some outcomes were significant in different risk groups: All-cause and cardiovascular-related deaths were more frequent in SNRI users without a history of mood and anxiety disorders, but nonfatal strokes were elevated regardless of this history. Risks of the composite outcome, nonfatal stroke, and cardiovascular-related hospitalizations were increased in SNRI users with a history of cardiovascular disease, but not in those without such a history.

Discussion: SNRIs increase norepinephrine levels and related sympathetic activity, which can induce hypertension, tachycardia, and cardiotoxicity when these drugs are taken in high doses or in overdose. The present study extends the limited existing epidemiologic data on adverse clinical outcomes by examining risk in new users, regardless of treatment indication, and in a

wide age range of patients. The authors note that while this study was designed to compare 2 classes of antidepressants, the vast majority of patients in the SNRI group received venlafaxine (94%); further study to investigate the risk associated with individual SNRIs is needed.

Leong C, Alessi-Severini S, Enns M, Nie Y, et al: Cerebrovascular, cardiovascular, and mortality events in new users of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors: a propensity score-matched population-based study. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000701. From the University of Manitoba, Canada. **Funded by the university. The authors declared no competing interests.**

Common Drug Trade Name*s: citalopram—*Celexa*; venlafaxine—*Effexor

***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.

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. Through matching and balancing samples, propensity scores help adjust for selection bias, making it possible to obtain average treatment effects.

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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PSYCHIATRY DRUG ALERTS

Volume XXXI / June 2017 / Number 6 www.alertpubs.com

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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.

FDA approves two-month Aristada for treatment of schizophrenia [press release]. Dublin, Ireland; Alkermes PLC: June 6, 2017. Available at http://www.alkermes.com.

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.)

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Fetal antidepressant exposure and risk of autism spectrum disorders, adjusted for past maternal depression			
Exposure Period	**Number of Studies**	**Odds Ratio***	**Significance**
Pre-conception	4	1.77	p<0.001
First trimester	5	1.79	p<0.001
Second trimester	4	1.67	p=0.009
Third trimester	4	1.54	p=ns
Pregnancy total	5	1.52	p=0.01

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 Bicetre, 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 dispensations 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.

Viktorin A, Ryden E, Thase M, Chang Z, et al: The risk of treatment-emergent mania with methylphenidate in bipolar disorder. *American Journal of Psychiatry* 2017;174 (April):341–348. From Karolinska Institutet, Stockholm, Sweden; and other institutions. **Funded by the Swedish Research Council; and other sources. Three study authors disclosed financial relationships with commercial sources; the remaining 8 authors declared no competing interests.**

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.

Adherence to initially prescribed drug by class at 6 months		
Drug Class	**Odds Ratio***	**Significance, compared with SSRIs**
SNRIs	1.23	p<0.0001
MAOIs	Similar to SSRIs	p=ns
TCAs	0.45	p<0.0001
Other antidepressants	0.77	p<0.0001

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.

Adjusted hazard ratios* for fracture associated with use of psychotropic medications		
	Major osteoporotic fracture	Hip fracture
SSRIs	1.43±	1.48±
Other antidepressants	1.27±	1.06
Mood stabilizers	1.41±	1.24
Antipsychotics	1.43±	2.14±
Benzodiazepines	1.15±	1.24±
±p<0.05		

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.

PSYCHIATRY DRUG ALERTS

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Antipsychotics and Endometrial Cancer

Prolactin-elevating antipsychotics were not associated with increased risk of endometrial cancer in a population-based study.[1] This finding suggests that prolactin may not play an important role in endometrial cancer pathogenesis.

Background: A possible long-term association of prolactin-elevating antipsychotics with hormone-sensitive cancer has been primarily investigated for breast cancer. There has been very little research on endometrial cancer, although these cancers express prolactin receptors and respond to prolactin in vitro; plus prolactin levels are elevated in women with endometrial cancer. A single study found a 5-fold increase in endometrial cancer risk in women who received treatment with antipsychotics, compared with untreated women.[2]

Methods: Data were extracted from the U.K. Clinical Practice Research Datalink, covering >13-million patients enrolled in British general practices. A nested case-control analysis was conducted within a cohort of all women given a first-ever prescription for an antipsychotic in 1990–2013, excluding those with a history of prolactinoma, endometrial cancer, or hysterectomy at cohort entry. To account for latency and minimize detection bias, follow-up commenced 1 year after the first antipsychotic prescription. Each case—a woman in whom endometrial cancer developed—was matched with up to 20 controls of similar age, year of cohort entry, and duration of follow-up. Antipsychotics were divided into 2 categories: prolactin-elevating (all first-generation agents plus the second-generation agents amisulpride, paliperidone, risperidone, and zotepine) and prolactin-sparing (all other second-generation agents). Exposure was defined as ≥3 prescriptions within a 12-month period. The analysis was adjusted for multiple confounders including comorbid medical conditions and use of medications that have been associated with endometrial cancer risk or that suppress prolactin levels.

Results: Nearly 66,000 women were given a new prescription for an antipsychotic during the study period. Prolactin-elevating antipsychotics were not associated with an elevated risk of

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endometrial cancer compared with prolactin-sparing antipsychotics (adjusted odds ratio,* 1.00). Risk did not differ in subgroups stratified for duration of antipsychotic use. However, risk was slightly elevated, although nonsignificantly, in women under menopausal age and those aged ≥75 years, but decreased, again nonsignificantly, in women aged 51–74 years.

Discussion: Data on prolactin levels were not available for evaluation. Nevertheless, the results suggest that prolactin may merely be a mediator of estrogen-induced tumorigenesis, not an independent risk factor.

[1]Klil-Drori A, Yin H, Abenhaim H, du Fort G, et al: Prolactin-elevating antipsychotics and the risk of endometrial cancer. *Journal of Clinical Psychiatry* 2017;78 (June):714–719. From Jewish General Hospital, Montreal, Canada; and other institutions. **Funded by the Canadian Institute of Health Research. The authors declared no competing interests.**

[2]Yamazawa K, et al: A case-control study of endometrial cancer after antipsychotics exposure in premenopausal women. *Oncology* 2003;64:116–123.

Common Drug Trade Names*: amisulpride (not available in the U.S.)—*Solian*; paliperidone—*Invega*; risperidone—*Risperdal*; zotepine (not available in the U.S.)—*Losizopilon

***See Reference Guide.**

Adjunctive Minocycline for Bipolar Depression

In a pilot study, adjunctive minocycline (*Minocin*) improved depressive symptoms in patients with bipolar disorder.

Background: Evidence suggests that chronic low-grade inflammation may be involved in the pathophysiology of bipolar disorder and that pharmacological modulation of inflammation reduces symptoms of depression in patients with mood disorders. Minocycline is a second-generation tetracycline that readily crosses the blood-brain barrier and has antiinflammatory activities independent of its antibiotic effects.

Methods: The pilot study was an open-label, uncontrolled, 8-week trial of minocycline in patients with bipolar I or II disorder who were currently experiencing a major depressive episode. Patients were required to have a screening score of ≥20 on the 17-item Hamilton Rating Scale for Depression (HAM-D) and to have been experiencing depression for ≥1 month but <1 year. Those whose current depressive episode had been resistant to ≥2 drugs were excluded. All participants received 100 mg minocycline b.i.d in addition to their previous medications, which were to remain unchanged. The primary efficacy outcome was change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS). Because early life adversity is a known risk factor for bipolar disorder and has been shown to condition immune responses to danger signals, a standardized scale was also administered to assess the indirect effects of childhood trauma.

Results: Of the 27 patients (mean age, 42 years; 13 men) in the intent-to-treat analysis, 12 had a diagnosis of bipolar I and 15 had a diagnosis of bipolar II disorder. Most patients (n=22) were receiving combinations of anticonvulsants and atypical antipsychotics. The mean duration of the current depressive episode was about 22 weeks. Adverse events—i.e., emergent mania with psychotic features, severe abdominal pain, hyperpigmentation, hives, fever and joint pain, esophageal swelling, and emergent hypomania in 1 patient each—lead to withdrawal of 7 patients by the investigators. A total of 19 patients completed treatment as planned.

Patients showed a significant reduction in mean MADRS score during treatment (effect size,* 0.835; $p<0.001$). Secondary efficacy measures also indicated significant depression improvement: the HAM-D (effect size, 0.949; $p<0.001$), the Clinical Global Impression (CGI)–Severity scale (effect size, 1.09; $p<0.001$), and the CGI–Improvement scale (effect size, 0.557; $p=0.041$). Improvement was evident at the first week post-baseline and remained significant throughout treatment. Response rates (≥50% decrease in HAM-D or MADRS score) ranged from 22% to 33% depending on the measure.

A subset of 20 study participants completed neurocognitive testing. There was a significant decline in verbal memory from baseline, which was limited to patients whose depression did not improve during the study. Psychomotor speed improved only in those whose depressive symptoms were ameliorated. The 19 patients with a history of early-life adversity showed significant improvement in depression throughout treatment, while those without early adversity showed no change.

Although 2 patients had emergent mania/hypomania, overall symptom ratings for mania in the study group did not worsen. Eight patients had worsening of suicidal ideation, which persisted in 4. Treatment had mixed effects on circulating inflammatory cytokine levels.

Discussion: The potential for antiinflammatory treatments to improve depression is supported by preclinical studies and other preliminary clinical evidence. Despite significant improvement in depressive symptoms in study patients, many did not achieve treatment response with minocycline; the results need to be replicated in more rigorous studies.

Soczynska J, Kennedy S, Alsuwaidan M, Mansur R, et al: A pilot, open-label, 8-week study evaluating the efficacy, safety and tolerability of adjunctive minocycline for the treatment of bipolar I/II depression. *Bipolar Disorders* 2017;19 (May):198–213. From the University of Toronto, Canada; and other institutions. **Funded by the Mood Disorders and Psychotherapy Unit of the University of Toronto; and other sources. Seven of 10 authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Brexanolone for Postpartum Depression

In a multicenter, placebo-controlled trial, brexanolone (a proprietary form of an endogenous neurohormone believed to be involved in postpartum depression) significantly improved symptoms of postpartum depression.[1]

Background: The neurohormone allopregnanolone—a GABA receptor modulator and a major metabolite of progesterone—increases throughout pregnancy and decreases rapidly upon childbirth. Failure of GABA receptors to adapt to the decrease in allopregnanolone is hypothesized to contribute to postpartum depression. Brexanolone is a formulation of allopregnanolone that can be administered intravenously to produce stable serum concentrations equivalent to third-trimester levels. A small proof-of-concept study suggested potential efficacy in postpartum depression.[2]

Methods: Study subjects were 21 women currently experiencing a major depressive episode with onset during the third trimester or within 4 weeks after delivery. Participants had to be within 6 months postpartum at the time of enrollment and to have a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥26, indicating severe depression. Patients were allowed to continue any ongoing antidepressants while receiving the study drug but were required to suspend breastfeeding during treatment and for the following 12 days. Women were randomly assigned to receive brexanolone or placebo in a continuous 60-hour infusion during inpatient care and were then followed as outpatients for a total of 30 days. The primary study outcome was change from baseline to 60 hours in HAM-D score. Secondary outcomes included response (≥50% reduction in HAM-D score) and remission (HAM-D score, ≤7).

Results: Mean baseline HAM-D scores were 28 and 29 in the brexanolone and placebo groups, respectively. Following infusion, women who received brexanolone experienced a mean 21-point reduction in HAM-D score, compared with an 8.8-point reduction in the placebo group (mean difference, 12.2 points; p=0.0075; effect size,* 1.2). Significant differences in the HAM-D between groups first appeared at the 24-hour assessment and persisted at the 7- and 30-day follow-up evaluations.

Response rates did not differ significantly between the active-treatment and placebo groups immediately following infusion (7 vs 4 women, respectively). However, the difference reached significance at 72 hours (80% vs 27%; p=0.037) and persisted at 7 days (80% vs 20%; p=0.033). Remission occurred within 60 hours in 7 of 10 patients receiving brexanolone and in 1 of 11 receiving placebo (odds ratio,* 23.33; p=0.036).

Brexanolone was well tolerated, and no serious adverse events or treatment discontinuations were reported. Common adverse events with brexanolone included dizziness (n=2), somnolence (n=2), sedation (n=1), and sinus tachycardia (n=1). At baseline, 2 patients in the brexanolone group reported active suicidal ideation with a plan; neither patient continued to have suicidal ideation during or after infusion.

Discussion: This study is the initial placebo-controlled trial in the ongoing clinical development program of brexanolone. Potential advantages of the treatment, relative to conventional antidepressants, include its large effects and rapid onset of action.

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

[1]Kanes S, Colquhoun H, Gunduz-Bruce H, Raines S, et al: Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. *Lancet* 2017; doi 10.1016/S0140-6736(17)31264–3. From Sage Therapeutics, Inc., Cambridge, MA; and other institutions. **Funded by Sage. Of 15 study authors, 14 disclosed financial relationships with commercial sources, including SAGE; the remaining author declared no competing interests.**

[2]Kanes S, et al: Open-label, proof-of-concept study of brexanolone in the treatment of severe postpartum depression. *Human Psychopharmacology: Clinical and Experimental* 2017; doi 10.1002/hup.2576. See *Psychiatry Drug Alerts* 2017; 31 (May):36–37.

***See Reference Guide.**

Stimulant Effects in Depression

Psychostimulants may reduce depressive symptom severity in patients with major depressive disorder or bipolar disorder, according to a meta-analysis of clinical trials.

Background: Stimulants and agents with stimulant-like activity are frequently prescribed off-label for adults with mood disorders. Their use is often empirical—i.e., they are prescribed for target symptoms that are frequent complaints in patients with depression, such as fatigue and apathy.

Methods: The analysis was based on a comprehensive search of English-language reports published before January 2016. Included were all randomized placebo-controlled trials of any FDA-labeled stimulant in adults with clinically significant depressive symptoms as part of major depressive disorder or bipolar disorder. Studies limited to patients with bipolar disorder were excluded. Stimulants were used as either adjunctive therapy or monotherapy and included armodafinil/modafinil, amphetamine, dextroamphetamine, lisdexamfetamine, and methylphenidate. The analysis included 21 studies with a total of 1900 patients (mean age, 44 years) who received treatment with a stimulant and 1823 controls (mean age, 43 years). The primary endpoint was investigator-identified response, measured in each study with a standardized rating scale for depression.

Results: Stimulant treatment was associated with a greater response rate for depressive symptoms than placebo (odds ratio [OR]* for response, 1.41; p=0.003). Response rates did not differ between patients with unipolar depression and those with bipolar disorder. In 10 studies with a total of nearly 2200 subjects, modafinil/armodafinil was superior to placebo (OR, 1.47; p=0.0002). Dextroamphetamine was statistically superior to placebo (OR, 7.11; p=0.04), but the comparison was based on a single, 2-week study in 22 patients. Other agents were numerically but not statistically superior to placebo. The analysis showed that adjunctive stimulants were associated with higher response rates than adjunctive placebo (OR, 1.39), but stimulant

monotherapy was not superior to placebo. In the few studies that reported data on mania, the incidence of manic or hypomanic induction was similar in patients receiving stimulants and controls.

Discussion: While these results suggest adjunctive psychostimulants may improve symptoms of depression, the analysis did find evidence of publication bias, and strong conclusions about their efficacy cannot be drawn. The pharmacodynamic profile of stimulants suggests that their clinical effects may be centered in specific symptom domains or dimensions, such as cognitive-emotional and neurovegetative symptoms.

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

McIntyre R, Lee Y, Zhou A, Rosenblat J, et al: The efficacy of psychostimulants in major depressive episodes: a systematic review and meta-analysis. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000723. From the University of Toronto, Canada; and other institutions. **Source of funding not stated. Four of 9 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: amphetamine—*Evekeo*; armodafinil—*Nuvigil*; dextroamphetamine—*Dexedrine*; lisdexamfetamine—*Vyvanse*; methylphenidate—*Ritalin*; modafinil—*Provigil

***See Reference Guide.**

Metformin in Alzheimer's Disease

Treatment with metformin (*Glucophage*) showed promising effects on cognition and biomarkers of Alzheimer's disease in a placebo-controlled pilot study.

Background: Insulin resistance has been associated with Alzheimer's-like biomarkers, reduced activation of cerebrocortical insulin receptors, and decreased cerebral glucose metabolism that correlates with memory impairment. Clinical trials with intranasal insulin and other antidiabetic drugs in patients with Alzheimer's disease with have had mixed results. Treatment with metformin, an insulin sensitizer, is a promising alternative approach, avoiding the risks of chronic insulin administration.

Methods: Study participants were patients aged 55–80 years with a diagnosis of mild cognitive impairment or early dementia due to Alzheimer's disease, and with no history of diabetes or prediabetes. Eligibility criteria included fasting glucose <110 mg/dL or HbA1c <6.0, at least 1 positive biomarker for Alzheimer's disease, a lack of evidence for vascular dementia, and a baseline Mini-Mental State Examination (MMSE) score >19. Patients taking a cholinesterase inhibitor were allowed to continue on a stable dose. Study treatment consisted of 8 weeks of randomly assigned metformin (titrated to 1000 mg b.i.d. or maximum tolerated dose) or placebo, followed by 8 weeks of the crossover treatment. Outcomes in this exploratory trial included cerebrospinal fluid (CSF) sampling, magnetic resonance imaging (MRI) to assess cerebral blood flow in specified regions, and testing with the Alzheimer's Disease Assessment Scale-cognitive subscale, computerized neuropsychological assessments, the Geriatric Depression Scale, and the Dementia Severity Rating Scale.

Results: Study participants (n=20; 9 women) had a mean age of 70 years and baseline MMSE scores averaging 26. After 8 weeks of active treatment, metformin was detectable in CSF at average levels of about 10% of mean fasting plasma levels. There were no changes in CSF markers of Alzheimer's disease. Functional MRI studies showed no statistically significant treatment effect in any of the predefined regions of interest, but patients who completed scans before and after both metformin and placebo exposure (n=17) showed a significant increase in superior and middle orbitofrontal cerebral blood flow with metformin but not placebo ($p<0.05$ for both regions). Cognitive testing showed a statistically significant improvement in 1 measure of executive function after metformin treatment ($p<0.05$).

Statistical trends favoring metformin were observed on measures of learning and memory, but not language or motor speed.

Common adverse effects of metformin were anorexia, diarrhea, nausea, hypoglycemia, and weight loss. Transient lactic acidosis developed in 2 patients. Metformin was not associated with changes in plasma glucose or insulin, depression, or functional status.

Discussion: Regardless of important limitations, including the small sample and crossover without a washout period, results of this study indicate that metformin crosses the blood-brain barrier and may improve executive function in patients with Alzheimer's dementia. Additional studies appear to be warranted.

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

Koenig A, Mechanic-Hamilton D, Xie S, Combs M, et al: Effects of the insulin sensitizer metformin in Alzheimer disease: pilot data from a randomized placebo-controlled crossover study. *Alzheimer Disease and Associated Disorders* 2017;31 (April–June):107–113. From the University of Pennsylvania, Philadelphia. **Funded by the BrightFocus Foundation; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Antipsychotics: Real-World Effectiveness Compared

According to a registry-based observational study, among available antipsychotics, oral clozapine and long-acting injectables (LAIs) are associated with the lowest rates of re-hospitalization and treatment failure.

Methods: Study data were collected from Swedish national health care databases for all patients aged 16–64 years with a diagnosis of schizophrenia between mid-2006 and 2013. The primary study outcomes were psychiatric rehospitalization and treatment failure, a composite outcome that included rehospitalization, discontinuation or switch to another medication, or death. The rate of each outcome was compared within individual patients during outpatient treatment with different antipsychotics versus periods of non-use of the same antipsychotic or no antipsychotic use. The analyses were adjusted for time-dependent covariates, such as the order of treatment and time since diagnosis.

Results: Of nearly 30,000 patients followed for a mean of 6 years, 44% were rehospitalized and 72% experienced a treatment failure. In within-patient comparisons (periods of use vs non-use of medication), the lowest rates of rehospitalization were found for oral clozapine (hazard ratio [HR],* 0.53) and for LAI paliperidone, zuclopenthixol (not available in the U.S.), perphenazine, and olanzapine (HRs, 0.51–0.58). Oral flupenthixol (not available in the U.S.) and quetiapine were associated with the highest rates of rehospitalization (HRs, 0.92 and 0.91, respectively). When compared with oral olanzapine, the most frequently used antipsychotic, risk of rehospitalization was significantly lower with LAI zuclopenthixol and oral clozapine (HRs, 0.83 and 0.84, respectively); oral flupentixol, quetiapine, and haloperidol had significantly higher risk (HRs, 1.28–1.46).

Results were similar for the treatment failure outcome. The lowest rates of treatment failure were observed with clozapine (HR, 0.58) and the LAI agents (HRs, 0.65–0.80). Because patients' probability of switching from clozapine to another medication is low, the analysis was repeated without medication switching as part of the composite outcome; clozapine was still associated with the best outcome.

Discussion: Efficacy comparisons of antipsychotic agents are generally based on randomized controlled trials, which exclude a large proportion of patients, often because of factors that may affect treatment outcome such as treatment refusal, substance abuse, or comorbidity.

Observational studies, which are more inclusive, have shown the best results with clozapine, olanzapine, and LAI agents; however, even these studies are vulnerable to selection bias. The present study showed LAI formulations were particularly beneficial in a sub-analysis of newly diagnosed patients. Rates of psychiatric hospitalization were 40–70% higher with quetiapine than the best-performing agents, which suggests quetiapine may not be a good monotherapy option in schizophrenia.

Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtala J, et al: Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.1322. From the Karolinska Institutet, Stockholm, Sweden; and other institutions. **Funded by Janssen-Cilag. Seven of 11 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: clozapine—*Clozaril*; olanzapine—*Zyprexa*; LAI paliperidone—*Invega Sustenna, Invega Trinza*; quetiapine—*Seroquel

***See Reference Guide.**

Lithium in Pregnancy and Cardiac Malformations

In a large, Medicaid-based, retrospective cohort study, lithium use in early pregnancy was found to be associated with a modest increase in the risk of cardiac malformations in infants.[1] The results confirm an association reported in the 1970s and reflected in the product labeling of lithium, but the increase in risk was much smaller than suggested by the earlier data.

Methods: The study cohort included all Medicaid-covered pregnancies resulting in a live birth in women aged 12–55 years in 46 states and the District of Columbia in 2000–2010. Exposure was defined as ≥1 filled prescription for lithium during the first trimester and no prescriptions during the 3 months before conception, to allow for possible overlap. The primary comparison group consisted of all women with no filled prescriptions for lithium or lamotrigine (*Lamictal*). A second comparison group consisted of women who filled a prescription for lamotrigine (not known to be associated with increased risk of congenital malformations) during preconception or early pregnancy. Women exposed to both drugs were excluded. The primary study outcome was the presence of any cardiac malformation in the infant. A secondary outcome was right ventricular outflow tract obstruction defects, a category that includes Ebstein's anomaly, a defect associated with lithium in early data.

Results: The cohort consisted of >1.3 million pregnancies, including 663 in women exposed to lithium in the first trimester and 1945 in women exposed to lamotrigine. After adjustment for propensity scores and other covariates (e.g., age, comorbid conditions, concomitant medications), lithium was associated with an increased overall rate of cardiac malformations compared with lamotrigine (risk ratio,* 2.25) and with use of neither medication (risk ratio, 1.65). The adjusted increase in malformations with lithium was nearly 1 case per 100 births compared with no drug exposure and 1.45 cases per 100 births compared with lamotrigine exposure. Right ventricular outflow tract obstruction defects were found in 0.6 per 100 lithium-exposed pregnancies, a somewhat higher rate than in unexposed pregnancies (risk ratio, 2.66). None of these were specifically coded as Ebstein's anomaly.

In a dose-response analysis, risk of cardiac malformation increased with the dosage of lithium, but not lamotrigine. All cases of right ventricular outflow obstruction defect occurred with a lithium dose of >600 mg/day.

Discussion: The final report of the International Register of Lithium Babies, published in 1979, was based on 18 infants with cardiac malformations from a total of 225 exposed pregnancies.[2] This study lacked a control group and may have been subject to biases. Despite warnings based on these data, lithium remains first-line treatment for bipolar disorder in

women of reproductive age, based on strong evidence of its efficacy. The present study suggests the increased risk is real but smaller than previously reported, and that risk is dose-dependent.

[1]Patorno E, Huybrechts K, Bateman B, Cohen J, et al: Lithium use in pregnancy and the risk of cardiac malformations. *NEJM* 2017:376 (June 8):2245–2254. From Brigham and Women's Hospital; and other institutions, Boston, MA. **Funded by the NIMH. Six of the 8 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Weinstein M (1980). Lithium treatment of women during pregnancy and in the post-delivery period. In Handbook of Lithium Therapy (421–430). Lancaster, U.K.: MTP Press.

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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.

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.

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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Fluvoxamine Augmentation of Clozapine

In a placebo-controlled trial, adjunctive fluvoxamine blunted weight gain and metabolic adverse effects in patients taking clozapine, without any loss of clinical effect. However, caution is warranted in considering this strategy because fluvoxamine can increase clozapine levels by a factor of ≥5 in some patients.

Methods: The study enrolled patients with treatment-resistant schizophrenia, with poor response to ≥2 first- or second-generation antipsychotics, a poor level of functioning over the past 5 years, and persistent scores indicating at least moderate severity on the Positive and Negative Syndrome Scale (PANSS). Patients were randomly assigned to receive clozapine monotherapy or clozapine–fluvoxamine. Based on the average dosage in Taiwan, where the study was conducted, clozapine monotherapy was titrated to a target of 300 mg/day. Because 50 mg/day fluvoxamine can increase plasma clozapine levels >2-fold, clozapine was titrated to 100 mg/day in the combined medication group. The primary study outcome was change in body weight from the start of treatment to 12 weeks.

Results: Of 85 randomized patients (average age, about 45 years; 72% men), 77 completed the trial. Patients who received clozapine monotherapy gained an average of 5.5 lbs over 12 weeks, compared with 1.5 lbs in the clozapine–fluvoxamine group ($p<0.0001$). Combined treatment was also associated with smaller changes in insulin resistance (HOMA-IR) and in levels of insulin, glucose, and triglycerides ($p=0.005$ for insulin and <0.0001 for the rest). Changes in mean white blood cell count were small and did not differ between the 2 groups at 12 weeks. Compared with baseline, both groups had similar significant improvements in PANSS total and negative symptom scores and scores on the Montgomery-Asberg Depression Rating Scale. The combined-therapy group had a larger decrease in PANSS general psychopathology ($p=0.009$). PANSS positive symptoms changed little with either treatment. The 2 groups showed no significant difference in plasma clozapine levels, but the monotherapy group had significantly higher levels of the metabolites norclozapine and clozapine N-oxide and a lower ratio of clozapine to norclozapine. Adverse effects were generally mild and did not differ between the 2 groups.

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Discussion: Fluvoxamine, approved in the U.S. for treatment of obsessive-compulsive disorder, is a potent inhibitor of CYP1A2, which metabolizes clozapine to norclozapine. Fluvoxamine may have reduced metabolic adverse effects of clozapine by decreasing levels of the metabolite norclozapine.

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

Lu M-L, Chen T-T, Kuo P-H, Hsu C-C, et al: Effect of adjunctive fluvoxamine on metabolic parameters and psychopathology in clozapine-treated patients with schizophrenia: a 12-week, randomized, double-blind, placebo-controlled study. *Schizophrenia Research* 2017; doi 10.1016/j.schres.2017.06.030. From Taipei Medical University, Taiwan; and other institutions. **Funded by the National Health Research Institute; and other sources. The authors declared no competing interests.**

Common Drug Trade Names*:** **clozapine—*Clozaril*; fluvoxamine—*Luvox

***See Reference Guide.**

Fluoxetine, CBT, or Both for Hypochondriasis

In a randomized trial, fluoxetine (*Prozac*) improved symptoms of hypochondriasis in nearly half of treated patients. Combining cognitive behavioral therapy with fluoxetine produced little additional benefit.[1]

Methods: Study participants were adults, recruited through advertising and clinical referrals, who had DSM-IV hypochondriasis of at least moderate severity. Following stratification by presence or absence of depression or dysthymia, patients were randomly assigned to 1 of 4 treatment groups: fluoxetine, CBT, both treatments together, or placebo. Patients who had received any psychoactive medication in the previous 2 weeks and those with any comorbid DSM-IV disorder rated as severe were excluded. CBT was delivered according to a scripted manual and consisted of 6 hour-long weekly sessions, followed by 2 biweekly sessions, and then 3 monthly booster visits. CBT emphasized psychoeducation, reformulation of dysfunctional assumptions about symptoms, modification of confirmatory bias, reduction of sick role behaviors, identification of situations that exacerbated health anxiety, and reduction of bodily hypervigilance. Exposure therapy was not included in the CBT program. Patients who received medications (either active or placebo) also had 20- to 30-minute medication management visits on a similar schedule to CBT, but without any psychotherapeutic elements. Outcomes were evaluated at weeks 6, 12, and 24. The primary efficacy outcome was treatment response, defined as a ≥25% improvement in scores from baseline on both the Whiteley Index, a 14-item self-report scale, and a modified version of the clinician-rated Yale-Brown Obsessive Compulsive Scale for hypochondriasis (H-YBOCS-M) at 24 weeks. After 12 weeks, patients with minimal improvement (i.e., <15% reduction in the H-YBOCS-M) were removed from the study and offered alternative treatment.

Results: The study was terminated before it reached its target enrollment because only a small proportion of interested patients met eligibility criteria. A total of 195 patients (mean age, 40 years; 44% women) were enrolled and comprised the intent-to-treat population. Of these patients, 123 completed treatment and underwent the week-24 evaluation. There were no between-group differences in drop-out rates.

In the intent-to-treat analysis,* rates of response were 47% for combined treatment, 44% for fluoxetine, 40% for CBT, and 30% for placebo (p=0.03 for trend). Numbers needed to treat* relative to placebo were 6 for combined treatment, 7 for fluoxetine, and 10 for CBT. In pairwise comparisons of patients who completed treatment, fluoxetine was superior to placebo (p=0.02; effect size,* 0.36), while other treatments were not. Fluoxetine was also associated with a faster rate of symptom decline than placebo (p=0.043) in this group, while CBT and combined treatment were not. One-third of patients had comorbid major depression and changes in their

depression ratings over time were not significant, suggesting that the effects of fluoxetine on hypochondriasis symptoms are not due to improved depression.

Discussion: Although fluoxetine was effective in this study, >50% of patients did not meet response criteria, highlighting the need for new treatment approaches to hypochondriasis.

Editor's Note: While hypochondriasis was a valid DSM diagnosis at the time of this study, it has been replaced in the DSM-5 by somatic symptom disorder and illness anxiety disorder.[2]

[1]Fallon B, Ahern D, Pavlicova M, Slavov I, et al: A randomized controlled trial of medication and cognitive-behavioral therapy for hypochondriasis. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.16020189. From the New York State Psychiatric Institute, New York; and Brigham and Women's Hospital, Boston, MA. **Funded by the NIMH. The authors declared no competing interests.**

[2]American Psychiatric Association, 2013 (Somatic Symptom and Related Disorders) Diagnostic and Statistical Manual of Mental Disorders 5th Edition, Washington, DC.

***See Reference Guide.**

APA Consensus Statement on Ketamine

A recent meta-analysis conducted by an American Psychiatric Association task force determined that compelling evidence supports the rapid, robust antidepressant effects of ketamine.[1] However, there are major uncertainties in almost every aspect of its use. There have been no large-scale clinical trials to establish its benefits and safety over time; the treatment is off-label and has not been subject to FDA review; and there are no post-marketing surveillance data on the use of ketamine for any psychiatric disorder. The present consensus statement is not intended to be a firm treatment guideline but rather to facilitate evidence-based treatment decisions, and provides guidance in 7 specific areas.[2]

Patient Selection. The consensus statement recommends a 7-step preprocedural evaluation, including a urine toxicology screen for possible substance use and an informed consent process. Patients should be encouraged to enroll in ongoing federally or privately funded studies assessing the long-term effects of ketamine.

Clinical Experience and Training. Training and credentialing requirements similar to that for anesthetic use of ketamine are recommended, and clinicians should be prepared to manage potential cardiovascular events. The consensus statement suggests that treatment be delivered by a licensed clinician who can administer a Drug Enforcement Agency schedule-III medication and who has advanced cardiac life support certification. Clinicians should also be competent to manage transient dissociative or psychotomimetic treatment effects. They should be prepared to manage emergency behavioral situations and provide psychiatric follow-up as needed.

Treatment Setting. Facilities in which ketamine is administered should have the capacity to monitor basic cardiovascular and respiratory function. Measures should be in place to immediately address cardiovascular and/or respiratory events if they arise. These may include a means of delivering oxygen to patients with reduced respiratory function; medication and/or restraints to manage behavioral symptoms; advanced cardiac life support capabilities; and the means to transfer patients to a hospital setting if necessary.

Medication Delivery. The majority of reports in the literature detail intravenous ketamine use at a dosage of 0.5 mg/kg per 40-minute infusion. Other delivery routes and dosages have received little study. However, dose adjustment may be required for patients with a body mass index of ≥30, in whom greater hemodynamic changes have been observed. A standard operating procedure for infusion should be developed that includes pre-dosing considerations (e.g., informed consent, baseline evaluation), ongoing assessment during the infusion, and post-treatment evaluations.

Follow-Up. Very little data exist on the benefits of repeated ketamine infusions, making it difficult to provide recommendations on frequency or duration of treatment. However, there are a few reports of patients experiencing response with ketamine after >3 infusions. Patients should be monitored closely using a standardized rating instrument to assess clinical change and to help evaluate the risk–benefit ratio of continued treatment.

Repeated Administration. Little data exist to support the determination of a standard number of treatments that should be administered to optimize long-term benefits of ketamine infusion. The consensus statement strongly recommends that the relative benefit of each ketamine infusion be weighed against the potential risks of longer-term ketamine exposure and the lack of published evidence for prolonged efficacy with ongoing administration.

Safety Measures and Continued Treatment. Both cognitive impairment and cystitis have been associated with chronic, high-frequency ketamine use; the agent has a known abuse liability. In light of these concerns, cognitive function, urinary discomfort, and substance use should be assessed if repeated administrations are considered. To minimize these and other risks, the number and frequency of ketamine infusions should be limited to the lowest number necessary to achieve clinical response.

[1]Newport D, et al: Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *American Journal of Psychiatry* 2015;172:950–966.

[2]Sanacora G, Frye M, McDonald W, Matthew S, et al: A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.0080. From Yale University School of Medicine, New Haven, CT; and other institutions. **Funded by the American Psychiatric Association. Seven of 8 study authors disclosed financial relationships with commercial sources.**

Triple-Bead Mixed Amphetamine Salts

A new once-daily triple-bead mixed amphetamine salts formulation (*Mydayis*) has received FDA approval for the treatment of ADHD in adults and adolescents aged ≥13 years. In clinical trials, the agent was shown to significantly improve symptoms beginning at 2–4 hours and lasting for up to 16 hours postdose. Common adverse effects were similar to those with other amphetamine formulations and included insomnia, decreased appetite, and weight loss in adults and adolescents; dry mouth, increased heart rate, and anxiety in adults; and irritability and nausea in adolescents. *Mydayis* is expected to become available in the U.S. later this year at strengths of 12.5, 25, 37.5, and 50 mg.

U.S. FDA approves Mydayis ™ (mixed salts of a single-entity amphetamine product)—a new once-daily option for ADHD symptom control in patients 13 years and older [press release]. Lexington, MA; Shire PLC: June 20, 2017. Available at https://www.shire.com/en/newsroom/2017/june/w6x937. See related story in *Psychiatry Drug Alerts* 2017;31 (May):33–34.

Non-Dopaminergic Drug for Negative Symptoms

In a phase-IIB clinical trial, MIN-101, an experimental drug with primarily anti-sigma-2 and 5-HT_{2A} receptor activity, reduced negative symptoms and was well tolerated in patients with schizophrenia.

Methods: The trial, conducted in multiple European countries, enrolled 244 patients with stable schizophrenia who had been experiencing negative symptoms of at least moderate severity (i.e., score ≥20 on the negative symptom subscale of the Positive and Negative Syndrome Scale [PANSS]) for ≥3 months. After withdrawal of prior antipsychotic medications and hospitalization, patients were randomly assigned to 12 weeks of treatment with 32 mg/day (n=78) or 64 mg/day MIN-101 (n=83), or placebo (n=83). After randomization, patients had to remain hospitalized for ≥36 hours and could remain in hospital or be discharged at the investigators' discretion. The primary study outcome was change from

baseline in the PANSS negative factor score, which is based on 4 negative items and 6 general psychopathology items previously shown to discriminate treatment outcomes well.

Results: At baseline, patients (mean age, 40 years; 56% men) were at least moderately ill, with a mean PANSS total score of 80 and a mean negative-symptom score of 27. A total of 102 patients did not complete the study. Withdrawal rates were similar across treatment groups, with the most common reasons for discontinuation being lack of efficacy and withdrawal of consent: 30 patients in the placebo group and 23 and 16 patients in the low- and high-dose MIN-101 groups, respectively. The intent-to-treat analysis* included 234 patients who received ≥1 dose of medication and underwent ≥1 post-baseline assessment.

After 12 weeks, PANSS negative factor scores decreased by a mean of about 1.5 points with placebo, compared with 3 points with 32-mg/day MIN-101 (p=0.024 vs placebo; effect size,* 0.45), and 3.5 points with 64-mg/day MIN-101 (p=0.004; effect size, 0.57). Statistically significant improvement appeared after 2 weeks with the lower dose and after 8 weeks with the higher dose.

Significant improvements, relative to placebo, were also observed for secondary study outcomes including the PANSS total and negative-symptom scores for both MIN-101 dosages, as well as Clinical Global Impression–Severity scores and the Calgary Depression Scale for Schizophrenia (CDSS) with the higher dose only. The improvement in negative symptoms was independent of the improvement in depression, as shown by a low correlation between the primary outcome and CDSS scores and by adjusting the analysis for changes in CDSS score. Positive symptoms did not differ between the active-treatment and placebo groups and did not worsen during the study.

MIN-101 was well tolerated and did not result in weight gain, prolactin elevation, extrapyramidal symptoms, or suicidality. The most commonly reported events in patients receiving MIN-101 were headache (7.5% vs 3.6% with placebo), anxiety (6.8% vs 6% with placebo), insomnia (5.6% vs 9.6% with placebo), schizophrenia symptoms (5.6% vs 10.8% with placebo), asthenia (5.6% vs 2.4% with placebo), nausea (3.7% vs 3.6% with placebo), and somnolence (3.7% vs 0% with placebo). Serious adverse events were recorded for 6 patients taking MIN-101: 4 hospitalizations for worsening schizophrenia, vomiting with abdominal pain in 1 patient, and syncope with bradycardia in 1. Two patients in the placebo group were hospitalized for worsening schizophrenia.

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

Davidson M, Saoud J, Staner C, Noel N, 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. From Tel Aviv University, Israel; and other institutions. **Funded by Minerva Neurosciences. All study authors disclosed financial relationships with commercial sources including Minerva Neuroscience.**

***See Reference Guide.**

Antidepressant Switching vs Augmentation

In patients with depression unresponsive to a first-line antidepressant, augmentation with aripiprazole was modestly superior to switching to bupropion monotherapy in bringing about remission, according to a large study conducted by the U.S. Department of Veterans Affairs (VA).[1]

Methods: The VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) trial enrolled VA patients with unipolar major depressive disorder who had experienced a suboptimal response to ≥1 course of an antidepressant other than bupropion.

Participants were required to have a baseline Quick Inventory of Depressive Symptomatology (QIDS) score of ≥16 (indicating severe depression) after 6 weeks of treatment or of ≥11 (indicating moderately severe depression) after ≥8 weeks of treatment. Patients were randomly assigned to 1 of 3 treatment strategies: switch to 300 or 400 mg/day sustained-release bupropion; augmentation of the current antidepressant with bupropion; or augmentation with 5, 10, or 15 mg/day aripiprazole. Acute treatment lasted 12 weeks and, if effective, was continued for up to 24 additional weeks. The primary outcome was remission, defined as a QIDS score of ≤5 (indicating no or minimal symptoms) at 2 consecutive visits.

Results: More than 500 patients were enrolled in each of the 3 treatment arms. Patients had a mean age of 54 years, 85% were men, and nearly 50% had comorbid PTSD. They had received a median of 2 prior antidepressant courses. Rates of retention in the 12 weeks of study treatment ranged from 69% in the switch group to 80% in the aripiprazole-augmentation group.

The rate of remission was modestly higher with aripiprazole augmentation than with the other treatments: 29% versus 27% with bupropion augmentation (p=ns) and 22% in the group that switched to bupropion (p=0.02). Bupropion augmentation was not significantly better than switching to bupropion. An analysis of time to remission showed no statistically significant difference among the 3 treatments. Response, a secondary outcome defined as a ≥50% reduction in the QIDS score, occurred in 74% of patients who received augmentation with aripiprazole, a significantly higher proportion than with bupropion augmentation (66%) or switching (62%). Among the 396 patients whose depression remitted with acute treatment, cumulative relapse rates during the continuation phase did not differ according to treatment.

Anxiety, decreased appetite, dry mouth, and increased blood pressure were more frequent with bupropion than with aripiprazole. (See table.) Patients who received aripiprazole were more likely to experience fatigue, increased appetite, weight gain, akathisia, somnolence, and abnormal values for some laboratory tests. In the aripiprazole group, 10% of patients had weight gains of ≥7% during acute treatment, as did 25% during continuation treatment.

Adverse effects present in >5% of patients with significant between-group differences

Adverse Event	Switch to bupropion	Bupropion augmentation	Aripiprazole augmentation	Significance
Anxiety	24%	23%	17%	p=0.007
Irritability	6%	3%	1%	p<0.001
Somnolence	7%	8%	15%	p<0.001
Akathisia	4%	5%	15%	p<0.001
Tremor	6%	10%	4%	p<0.001
EPS	8%	9%	19%	p<0.001
Nausea	17%	12%	13%	p=0.02
Dry mouth	10%	7%	3%	p<0.001
Decreased appetite	16%	12%	8%	p=0.001
Increased appetite	7%	9%	16%	p<0.001
Weight gain ≥7%	5%	5%	25%	p<0.001
Weight loss ≥7%	13%	12%	5%	p=0.02

Editorial:[2] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, a large-scale, NIMH-funded study designed to evaluate next-step treatments in resistant depression, was completed before atypical antipsychotics were approved to treat depression. The VAST-D results extend those findings to include atypical antipsychotic augmentation. According to a recent survey, psychopharmacologists generally consider atypical antipsy-

chotic augmentation as a fourth-line approach, indicating some reluctance to use it. Results of the present study suggest atypicals might be considered earlier. Although the VAST-D population was predominantly male, other research suggests aripiprazole augmentation may be more effective in women than men. The modest advantage of aripiprazole in the VAST-D study may be partly explained by its previously reported efficacy in PTSD, which affected nearly half of the VAST-D population. The marked differences in tolerability of the treatments investigated can help clinicians choose the next step in treating unresponsive depression.

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

[1]Mohamed S, Johnson G, Chen P, Hicks P, et al: Effect of antidepressant switching vs augmentation on remission among patients with major depressive disorder unresponsive to antidepressant treatment: the VAST-D randomized trial. *JAMA* 2017;318 (July 11):132–145. From the VA Connecticut Healthcare System, West Haven; and other institutions. **Funded by the VA. Five study authors disclosed financial relationships with commercial sources; the remaining 11 authors declared no competing interests.**

[2]Fava M: Lessons learned from the VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) study [editorial]. *JAMA* 2017;318 (July 11):126–128. From Massachusetts General Hospital, Boston. **The author disclosed financial relationships with commercial sources.**

Common Drug Trade Names*:** **aripiprazole—*Abilify*; bupropion—*Wellbutrin

***See Reference Guide.**

Lithium, Valproate, and Suicidal Behavior

In a large, well-controlled longitudinal study, lithium was associated with reduced risk of suicidal behavior in patients with bipolar disorder. Valproate had no effect on suicide risk.

Methods: Study subjects were enrolled in Sweden's population register and in various national health care databases. The authors identified nearly 52,000 patients with bipolar disorder type I or II, bipolar disorder NOS, or schizoaffective disorder, who were followed from October 2005 until 2013. The main analysis was limited to about 4400 patients who attempted or committed suicide during follow-up. Each patient served as his or her own control, and medication use was extracted from a prescription registry. Suicide rates were compared within-patient for periods of use of lithium, valproate, or neither drug.

Results: In the cohort, lithium was the most often used antimanic drug (41%), followed by valproate (16%). Nearly half of the patients were not exposed to either drug during the study period. During follow-up, 10,648 suicide-related events occurred. Among patients taking lithium, risk of suicide-related events was 14% lower during use compared with periods of non-use (hazard ratio,* 0.86). During valproate use, risk was slightly increased (hazard ratio, 1.11). Although the agents were not directly compared, the difference between the hazard ratios significantly favored lithium (p=0.001). Results were unchanged in sub-analyses by disorder subtypes and exposure periods and after adjustment for concurrent medications. The beneficial effect of lithium was undiminished in patients with substance use disorder, who made up about half of the group with suicidal behavior.

The population attributable fraction—i.e., the proportion of suicide events that could have been prevented by prescribing lithium throughout follow-up—was 12%. Suicide risk with lithium monotherapy was the same as risk with lithium–valproate combination therapy.

Discussion: Previous evidence suggests lithium may protect against suicide attempts, but results have been inconclusive. Studies of valproate also have had conflicting results. The evidence is based largely on randomized trials, which exclude patients at risk for suicide and are not generalizable. Observational studies avoid some of these problems and generally have larger sample sizes and long periods of observation, but these studies are prone to

confounding by indication. The within-subject design avoids some biases. However, physicians may be less likely to prescribe potentially lethal lithium for high-risk patients, and the need for close clinical monitoring of lithium therapy may have unmeasured benefits. Despite these limitations, the data suggest lithium should be considered as a suicide-prevention strategy in patients with bipolar disorder and suspected suicidal intentions.

Song J, Sjolander A, Joas E, Bergen S, et al: Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.16050542. From the Karolinska Institutet, Stockholm, Sweden; and other institutions. **Funded by the Swedish Research Council; and other sources. Three of 8 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***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.

Intent-to-Treat Analysis (ITT): An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone who begins treatment is included regardless of treatment completion.

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 is 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.

PSYCHIATRY DRUG ALERTS

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Lisdexamfetamine Maintenance for Binge Eating Disorder

In a multicenter, placebo-controlled withdrawal trial, lisdexamfetamine (*Vyvanse*) prevented relapse of binge eating. The stimulant has shown short-term efficacy and is FDA approved for treating moderate-to-severe binge eating disorder in adults.

Methods: The study enrolled patients, aged 18–55 years, with DSM-IV-TR binge eating disorder, who reported ≥3 binge-eating days per week for the 2 weeks before enrollment and had a Clinical Global Impression–Severity (CGI-S)* score of ≥4, indicating at least moderate severity. All patients received treatment for 12 weeks with open-label lisdexamfetamine at dosages of 50 or 70 mg/day. Response was defined as ≤1 binge-eating day per week for 4 consecutive weeks and a CGI-S rating of ≤2. Patients who met response criteria were then randomly assigned to continue receiving lisdexamfetamine or switch to placebo and were followed for up to 6.5 months. The primary outcome was time to relapse, defined as ≥2 binge-eating episodes per week for 2 consecutive weeks and a ≥2-point increase in CGI-S score.

Results: A total of 411 patients (mean age, 38 years; 87% women) received treatment during the open-label phase. At open-label baseline, the mean number of binge-eating episodes per week was 4.8. In the 275 patients who met criteria to enter the randomized withdrawal phase, the number of binge-eating days per week decreased to 0.13 after 12 weeks of lisdexamfetamine treatment.

During the randomized withdrawal phase, 5 patients receiving lisdexamfetamine and 42 receiving placebo experienced a relapse (4% vs 32%; hazard ratio,* 0.09; $p<0.001$). Time to relapse was also significantly longer with lisdexamfetamine ($p<0.001$). At study end, 102 patients in the lisdexamfetamine group and 50 in the placebo group were still receiving randomized medication and continued to meet response criteria (75% vs 38%). The majority of patients who withdrew from the placebo group did so because of relapse (n=40) or patient choice (n=25). In the lisdexamfetamine group, the most frequent reasons for withdrawal

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were patient choice (n=9), followed by adverse events (n=6) and relapse (n=5). The safety and tolerability of lisdexamfetamine were consistent with previous reports in adults with binge eating disorder.

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

Hudson J, McElroy S, Ferreira-Cornwell C, Radewonuk J, et al: Efficacy of lisdexamfetamine in adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.1889. From McLean Hospital and Harvard Medical School, Belmont, MA; and other institutions including Shire Development LLC, Lexington, MA. **Funded by Shire. All 5 study authors disclosed financial relationships with commercial sources, including Shire.**

***See Reference Guide.**

Long-Term Safety of Asenapine

In a 26-week extension study in adults with schizophrenia, asenapine was well tolerated and associated with less weight gain than olanzapine.

Methods: Participants in this study had completed a 6-week phase III trial comparing fixed-dose 2.5 or 5 mg asenapine b.i.d. with 15 mg/day olanzapine and placebo. Patients were enrolled in the extension study based on their clinician's opinion that they would benefit from further treatment. Participants continued to receive their initial double-blind randomly assigned medication and dose during the extension study, with the exception of those who initially received placebo who were switched to 2.5 mg asenapine b.i.d. (This dosage did not differ in efficacy from placebo in the 6-week trial and is below the FDA-approved dosage of 5 or 10 mg b.i.d.). Adverse events were assessed at clinic visits every 4 weeks. The study did not include a primary efficacy analysis. The prespecified key safety endpoint was change from baseline in body weight.

Results: The analysis included a total of 119 patients. Mean ages across the treatment groups ranged from 37 to 41 years; 60% of patients were men. The mean length of exposure to study medication during the extension phase was about 21 weeks in the low-dose asenapine groups, 19 weeks with higher-dose asenapine, and 18 weeks with olanzapine.

Overall, patients switched from placebo to low-dose asenapine, and therefore naive to recent antipsychotic treatment, had the highest incidence of adverse events: 71% compared with 39% and 38% in the continued low- and high-dose asenapine groups, respectively, and 25% in the olanzapine group. (See table.) Akathisia, dizziness, increased creatine phosphokinase and insulin levels, and hypertension were reported only in patients newly switched to asenapine from placebo and each affected ≤2 patients.

Treatment-Emergent Adverse Events of Special Interest				
	Switched to 2.5 mg asenapine b.i.d (n=31)	**2.5 mg asenapine b.i.d. in both stages (n=31)**	**5 mg asenapine b.i.d. (n=42)**	**15 mg/day olanzapine (n=16)**
≥7% weight gain	4 (13%)	2 (6.5%)	5 (12%)	4 (27%)
Insomnia	2 (6.5%)	2 (6.5%)	2 (5%)	None
Somnolence, sedation, or hypersomnia	2 (6.5%)	1 (3%)	1 (2%)	None
Extrapyramidal symptoms	4 (13%)	1 (3%)	None	1 (6%)
Worsening schizophrenia	2 (6.5%)	2 (6.5%)	5 (12%)	1 (6%)

Patients gained less weight on average with asenapine than with olanzapine, but differences were small (<2 lbs in each asenapine group vs >3 lbs with olanzapine) and did not reach statistical significance. Changes in laboratory values—including insulin, fasting glucose, HbA1c,

total cholesterol, and triglycerides—did not differ among the treatment groups. Prolactin levels decreased from the start of extended treatment in all groups. Suicidal ideation developed in 1 patient receiving continued low-dose asenapine, and 1 olanzapine-treated patient attempted suicide. Worsening of schizophrenia was the most common adverse event leading to discontinuation in all treatment groups.

Discussion: Asenapine has a unique activity profile among atypical antipsychotics, with potent antagonism for dopamine, serotonin, noradrenaline, and histamine receptors, but no affinity for muscarinic receptors, thus minimal potential to induce anticholinergic effects. Asenapine-associated treatment-emergent adverse effects in this extension study were similar to those previously reported in short-term trials and most were mild to moderate. Weight gain, which can be indicative of metabolic syndrome and lead to cardiovascular events, was less problematic with asenapine than with olanzapine. Although differences in weight gain between the groups were not significant, the study may have been underpowered to detect statistical differences.

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

Durgam S, Landbloom R, Mackle M, Wu X, et al: Exploring the long-term safety of asenapine in adults with schizophrenia in a double-blind, fixed-dose, extension study. *Neuropsychiatric Disease and Treatment* 2017;13:2021–2035. From Allergan, Inc., Jersey City, NJ; and other institutions. **Funded by Forest Laboratories, LLC, an Allergan affiliate. All study authors disclosed financial relationships with commercial sources.**

Common Drug Trade Names*:** **asenapine—*Saphris*; olanzapine—*Zyprexa

***See Reference Guide.**

Lithium Dosing During Pregnancy

Findings of the first large observational study of lithium blood levels in pregnancy and the postpartum period suggest that lithium blood levels should be monitored closely (e.g., every 3 weeks) until the 34th week of pregnancy, at least weekly until delivery, and then twice-weekly for the first 2 postpartum weeks. Previous recommendations have been based on the general knowledge that increased glomerular filtration leads to decreased lithium blood levels in pregnant women, but data to support a more precise approach have been lacking.

Methods: The investigators reviewed the records of women referred to 2 outpatient psychiatry and obstetric clinics between 2003 and mid-2015. Women were included if they received lithium during pregnancy and had ≥1 lithium blood-level measurement. For each woman, data were obtained during the period from 25 weeks before conception through 25 weeks postpartum. The peripartum time course of lithium levels was synchronized between women based on the date of delivery.

Results: The study included 85 women who received lithium treatment during a total of 113 pregnancies: 75 with bipolar disorder and the rest with schizoaffective disorder, depressive disorder, or borderline personality disorder. Lithium was started prior to conception and maintained throughout pregnancy and the postpartum period in 100 of the women. Deliveries were classified as preterm in 20% of the pregnancies.

A total of 1101 lithium blood-level measurements were included in the analysis. During trimesters 2 and 3, the average lithium dose was increased. Dosing frequency was twice-daily or more during 98% of pregnancies. After delivery, the mean daily dose decreased somewhat, and about 80% of women returned to once-daily dosing. Overall, the lowest lithium blood levels were found during the second trimester, specifically during the 17th week of pregnancy, at a time when women were receiving the highest mean daily dose. Lithium levels were below the therapeutic threshold for mood stabilization in 15% of preconception samples, 62% of first- and second-trimester samples, 39% in the third trimester, and 10% postpartum. When creatinine levels were examined as a measure of renal function, these levels closely paralleled decreases

in lithium levels. No change in the relationship of lithium dose to blood levels was observed between the final week of pregnancy and the first postpartum week.

Five women experienced a relapse during pregnancy: 3 who had subtherapeutic blood levels, 1 who stopped taking her medication, and 1 with no recent blood-level information. Relapse occurred in the postpartum period in 5 women, including 1 with a subtherapeutic lithium level. Supratherapeutic levels were observed in 8 women, including 4 who had preeclampsia and decreased renal function.

Recommendations: In addition to frequent monitoring of lithium levels, the authors recommend obtaining reference lithium and creatinine levels before conception and using these to determine patients' lowest possible therapeutic blood level. Twice-daily lithium dosing can minimize peak lithium levels. Creatinine blood-level monitoring should be considered. Lithium and creatinine monitoring should be increased if women show signs of preterm delivery, preeclampsia, or other illness that can affect renal function. Target lithium blood levels should be increased immediately after delivery to optimize relapse prevention.

Wesseloo R, Wierdsma A, van Kamp I, Munk-Olsen T, et al; Lithium dosing strategies during pregnancy and the postpartum period. *British Journal of Psychiatry* 2017;211 (July):31–36. From Erasmus Medical Centre, Rotterdam, the Netherlands; and other institutions. **Funding by the NIMH; and other sources. The authors declared no competing interests.**

Adjunctive Memantine in Schizophrenia

Memantine, added to background treatment with atypical antipsychotics, was associated with improvement in positive and negative symptoms, general psychopathology, and depression in a placebo-controlled trial in patients with schizophrenia.

Background: Many patients with schizophrenia have comorbid depression. Although most atypical antipsychotics have antidepressant properties, they have not proven effective for treating depression in patients with schizophrenia. Memantine acts as an uncompetitive NMDA receptor blocker, like ketamine, and also has neuroprotective effects, making it a candidate treatment for depression in schizophrenia. Multiple previous studies of memantine for depression in schizophrenia have had inconclusive results.

Methods: Study subjects were 64 inpatients (28 women) with schizophrenia who had received stable doses of an atypical antipsychotic for ≥3 months before admission. Participants were randomized to receive 12 weeks of double-blind adjunctive treatment with either memantine, started at 5 mg/day and increased weekly to a target of 20 mg/day, or placebo. Treatment outcomes were measured using the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS).

Results: Four patients dropped out of the study prematurely, for unstated reasons, and were not included in the analysis. The remaining study group included patients who received treatment with risperidone (n=31), olanzapine (n=17), clozapine (n=9), or aripiprazole (n=3). The 2 adjunctive treatment groups were generally similar, except that the placebo group had significantly higher PANSS total scores and general psychopathology scores at baseline. Mean age was 32 years in the memantine group and 34 years in the placebo group. The outcome analysis was adjusted for these differences.

Treatment response was evaluated at the end of weeks 4, 8, and 12. During the first 4 weeks of treatment, CDSS depression scores were essentially unchanged with memantine and increased slightly with placebo. However, by the end of week 12, adjunctive memantine was superior to placebo with regard to depression improvement. In addition, improvements in PANSS total score and each of the 3 PANSS subscales also significantly favored adjunctive

memantine. (See table). Adverse effects reported with memantine were constipation and headache, each in 2 patients, and dizziness in 1. None were serious or severe.

Change from Baseline to Week 12 in Depression and Schizophrenia Symptoms					
	Memantine		Placebo		Between-Group Significance
Symptom Scale	Baseline	Study End	Baseline	Study End	
CDSS	11.3	8.8	12.1	12	p<0.001
PANSS Total Score	107.4	93	114.9	105.9	p<0.001
PANSS Positive	25.4	21.3	26.9	23.9	p=0.03
PANSS Negative	26.8	21.4	28.5	25.5	p=0.004
PANSS General Psychopathology	55.5	50.2	59.6	56.1	p<0.001

Discussion: This study was conducted only in an inpatient population, which makes the results less generalizable. However, the apparent safety and efficacy of adjunctive memantine in these patients supports further research in more diverse populations.

Omranifard V, Rajabi F, Mohammadian-Sichani M, Maracy M: The effect of add-on memantine on positive, negative and depressive symptoms of schizophrenia: a double-blind, randomized, controlled trial. *Actas Espanolas de Psiquiatria* 2017;45:107–115. From Noor Hospital and Isfahan University of Medical Sciences, Iran. **Funded by the university. The authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; clozapine—*Clozaril*; memantine—*Namenda*; olanzapine—*Zyprexa*; risperidone—*Risperdal

Acute Treatment of First-Episode Psychosis

Second-generation oral antipsychotics appear to be similarly effective and better than haloperidol in the treatment of first-episode psychosis, according to a pairwise and network meta-analysis.* Drug selection should be based on each medication's adverse effects, which are generally similar to those reported in patients with chronic schizophrenia.

Methods: The analysis included all available randomized controlled trials in patients of any age with a first episode of schizophrenia or a related disorder. Studies were excluded if they were conducted in treatment-resistant patients, those with predominantly negative symptoms, or those with stable disease, and if a depot formulation was used. All available first- and second-generation oral antipsychotics were considered. The preferred primary outcome of interest was change from baseline in Positive and Negative Syndrome Scale (PANSS) total score, followed in order of preference by change in the Brief Psychiatric Rating Scale (BPRS) score, the mean scores for either of these instruments at the study endpoint, or change from baseline in any other standardized rating scale. The analysis included both placebo-controlled trials and comparison studies, including open-label studies.

Results: The authors identified 19 studies, published between 1987 and 2015, involving 2669 participants and investigating 12 different drugs. There were 11 studies of haloperidol, 13 of risperidone, 7 of olanzapine, 4 of quetiapine, and 1 each of ziprasidone, zuclopenthixol, molindone, flupenthixol, pimozide, aripiprazole, amisulpride, and sertindole. The mean age of participants in the individual studies was 24 years, and the mean duration of illness before study enrollment was 1.5 years. Patients received treatment for a median of 8 weeks (range, 4–13 weeks). Five studies were judged to have a high risk of bias due to attrition and 2 due to selective reporting. About half of the studies were funded by drug manufacturers.

The results of pairwise and network meta-analyses were consistent, except that, as expected, network meta-analysis gave more highly significant results. In this analysis amisulpride, olanzapine, ziprasidone, and risperidone were significantly superior to haloperidol, and

amisulpride was significantly superior to quetiapine. The analysis showed no differences among medications for positive symptom improvements, but olanzapine was superior to risperidone and haloperidol for negative symptoms. Categorical response to treatment, as defined in the individual studies, did not differ among the drugs.

There were significant differences in adverse events among the medications. Compared with other antipsychotics, olanzapine was associated with less use of antiparkinsonian agents, and quetiapine with less akathisia and sedation. Molindone, aripiprazole, olanzapine, and haloperidol were associated with less prolactin elevation than risperidone, and molindone and olanzapine with less prolactin elevation than haloperidol. Molindone and haloperidol were associated with less weight gain than olanzapine.

Discussion: There is little evidence that treatment recommendations for second-generation antipsychotics can be based on differences in efficacy. Moreover, many second generation agents are available as generics, which removes cost as a consideration. It is important to note that the second-generation antipsychotics brexpiprazole, cariprazine, iloperidone, lurasidone, and paliperidone, which were the latest to enter the market, were not included in the analysis because randomised controlled trials of these agents were not found. According to these results, until better evidence becomes available, treatment decisions should be guided mainly by adverse effects, for which the general patterns are similar to those found in chronic schizophrenia.

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

Zhu Y, Krause M, Huhn M, et al: Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses. *Lancet Psychiatry* 2017; doi 10.1016/S2215-0366(17)30270-5. From Technische Universitat Munchen, Munich, Germany; and other institutions. **Funded by the German Federal Ministry of Education and Research. Two of 9 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: amisulpride (not available in the U.S.)—*Solian*; aripiprazole—*Abilify*; brexpiprazole—*Rexulti*; cariprazine—*Vraylar*; flupenthixol (not available in the U.S.)—*Depixol, Fluanxol*; haloperidol—*Haldol*; iloperidone—*Fanapt*; lurasidone—*Latuda*; molindone—*Moban*; olanzapine—*Zyprexa*; pimozide—*Orap*; quetiapine—*Seroquel*; risperidone—*Risperdal*; sertindole (not available in the U.S.)—*Serdolect, Serlect*; ziprasidone—*Geodon*; zuclopenthixol (not available in the U.S.)—*Clopixol

***See Reference Guide.**

Akathisia in First Episode Psychosis

Antipsychotic medications differ dramatically in their propensity to induce acute akathisia in patients with first-episode psychosis, according to a pooled analysis of prospective studies in a large population of drug-naive patients.

Methods: During a 15-year period, all first-episode patients admitted to a hospital in Spain were enrolled in clinical trials of different antipsychotic medications. Patients were aged 15–60 years, untreated except for brief prior exposures to antipsychotic medication, and had received a diagnosis of a nonaffective psychosis. The present analysis includes data from 3 prospective, open-label, flexible-dose clinical trials of haloperidol, quetiapine, olanzapine, ziprasidone, risperidone, and aripiprazole. Akathisia diagnosis was based on a score of ≥2 on the Barnes Akathisia Scale (BAS), which rates symptom severity on a scale of 0 to 5. The BAS was administered to patients at baseline and after 6 weeks of randomized treatment. Patients receiving the antiparkinsonian agent biperiden at week 6 who had akathisia symptoms noted in their records were considered to be experiencing akathisia, regardless of the BAS score.

Results: The cohort was comprised of 493 patients (282 men) with an average age of about 30 years. The prevalence of akathisia at week 6 was 20%. Demographic, clinical, and laboratory variables did not appear to influence akathisia risk. However, the onset of akathisia was signifi-

cantly associated with the antipsychotic drug initiated at baseline (see table), and 3 agents—haloperidol, risperidone, and aripiprazole—were considered by the investigators to be pro-akathisic. The other 3 agents—ziprasidone, olanzapine, and quetiapine—were considered non-akathisic.

Incidence of acute akathisia in patients with first-episode psychosis

Drug	# of patients	% with akathisia
Haloperidol	54	57%
Risperidone	125	20%
Aripiprazole	143	18%
Ziprasidone	58	17%
Olanzapine	58	4%
Quetiapine	58	4%

After adjustment for multiple comparisons, the incidence of akathisia with haloperidol was significantly greater than with any other agent ($p<0.001$ for all comparisons). Incidence was similar for risperidone and aripiprazole and significantly greater than with olanzapine and quetiapine ($p\leq0.03$ for all comparisons). Ziprasidone did not differ significantly from any other investigated agent. Incidence did not differ significantly between olanzapine and quetiapine.

Use of a pro-akathisic drug was associated with increased risk of akathisia by a large multiple in a multivariate model that included other predictors (odds ratio,* 21.3; $p<0.001$). Other significant predictive factors were hospitalization (odds ratio, 2.6; $p=0.05$) and the total score on the Brief Psychiatric Rating Scale (BPRS) at baseline (odds ratio, 1.05 per BPRS point; $p=0.03$).

Discussion: The overall akathisia incidence in this study is in general agreement with other studies in first-episode patients, which tended not to evaluate individual drugs. Whether akathisia risk is determined by the type or the dosage of antipsychotic is controversial. The drug-related difference in the present study is probably not a function of dosage, since the highest mean chlorpromazine-equivalent doses in this study were found in patients taking olanzapine and quetiapine.

Juncal-Ruiz M, Ramirez-Bonilla M, Gomez-Arnau J, Ortiz-Garcia de la Foz V, et al: Incidence and risk factors of acute akathisia in 493 individuals with first episode non-affective psychosis: a 6-week randomised study of antipsychotic treatment. *Psychopharmacology* 2017;234:2563–2570. From the University of Cantabria, Santander, Spain; and other institutions. **Funded by the Instituto de Salud Carlos III; and other sources. Four of 9 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; biperiden—*Akineton*; haloperidol—*Haldol*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*; ziprasidone—*Geodon

***See Reference Guide.**

Linezolid and Serotonin Syndrome

The incidence of serotonin syndrome in patients taking the antibiotic linezolid is low and not increased with concomitant use of serotonin reuptake inhibitors, according to a hospital-based retrospective study.

Background: Linezolid, a weak, reversible inhibitor of monoamine oxidase, carries an FDA warning to discontinue serotonergic antidepressants during its use. Given the rise in drug-resistant bacterial infections and the generic availability of linezolid, its use can be expected to increase, and delaying antibiotic treatment to discontinue an antidepressant is impractical.

Methods: Investigators reviewed records for adults given linezolid during admission to a single university-based hospital over a 4-year period. Patients who also received an SSRI or SNRI at the same time or up to 2 weeks before were compared with those with no SSRI/SNRI exposure. Serotonin syndrome was identified either as a diagnosis in the record or as clinical features consistent with either the Sternbach criteria (≥3 of 10 items) or the Hunter criteria (≥1 of 5 items).

Results: During the study period, a total of 348 patients (mean age, 54 years; 53% women) received treatment with linezolid and met other study criteria. Of these, 87 also received an SSRI or SNRI, with citalopram representing 41% of SSRI/SNRI use. Nearly 90% of patients overall were exposed to other serotonergic medications—e.g., other antidepressants, analgesics, and antimigraine therapies.

Medical records showed a diagnosis of serotonin syndrome during hospitalization in only 2 patients: 1 patient with cystic fibrosis, receiving escitalopram and multiple pain medications; and 1 receiving cancer chemotherapy and concomitant olanzapine, ondansetron, and other drugs, but no antidepressant treatment. Both patients with diagnosed serotonin syndrome were identified using the less-rigorous Sternbach criteria, and symptoms resolved with linezolid discontinuation. Another 13.8% of patients receiving an SSRI or SNRI met ≥3 Sternbach criteria for serotonin syndrome, compared with 13.4% of patients receiving linezolid monotherapy. Using the more-stringent Hunter criteria (requiring ≥1 identified symptom) rates were 1.1% and 1.9%, respectively. Rates did not differ statistically between the 2 groups using either set of criteria.

Discussion: In 2011, the FDA recommended the immediate discontinuation of SSRI/SNRI antidepressants in patients requiring emergency treatment with linezolid or postponement of linezolid until 2 weeks after antidepressant discontinuation. In practice, stopping antidepressants is risky, delaying linezolid is rarely indicated, and avoiding linezolid may result in use of a less effective antibiotic.

Karkow D, Kauer J, Ernst E: Incidence of serotonin syndrome with combined use of linezolid and serotonin reuptake inhibitors compared with linezolid monotherapy. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000751. From the University of Iowa, Iowa City. **Source of funding not stated. One of 3 study authors disclosed financial relationships with a commercial sources.**

Common Drug Trade Names*: citalopram—*Celexa*; escitalopram—*Lexapro*; linezolid—*Zyvox*; olanzapine—*Zyprexa*; ondansetron—*Zofran

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

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.

Network Meta-Analysis: A method that extends the traditional meta-analytic technique to allow comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common when direct comparisons are unavailable. 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 2 trials would allow a researcher to conclude that treatment option A is more effective than option C, even though the 2 options have never been directly compared.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

PSYCHIATRY DRUG ALERTS

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Methylphenidate Dosing in Substance Use Disorders

Adults with comorbid ADHD and substance use disorders were prescribed a 40% higher stimulant dose than those with ADHD alone, according to a population-based observational study. The stimulant dose stabilized over time, indicating that patients with substance use disorder were not experiencing continuously increasing tolerance.

Methods: The registry-based study included all adults, aged 18–59 years, living in Sweden who received an initial prescription for methylphenidate between 2006 and 2009. Patients with a substance use disorder at the time of their first methylphenidate prescription were identified based on diagnostic codes or prescription of a drug used exclusively to treat substance abuse. The prescribed dose was calculated every 100 days. Daily doses were stratified into 0–72 mg or >72 mg, based on published treatment guidelines (which recommend maximum dosages ranging from 60 to 100 mg/day) and the availability of OROS methylphenidate, the most commonly prescribed formulation in Sweden, in 18-mg increments.

Results: Of >14,000 adults who received treatment for ADHD, nearly 4900 had a comorbid substance use disorder. After 1 year of treatment, patients with comorbid substance use disorder were receiving higher dosages of methylphenidate than those with ADHD alone: 77 mg/day versus 59 mg/day. The difference persisted at 2 years when mean dosages were 87 mg/day versus 61 mg/day, respectively, in the nearly 4500 patients who remained in follow-up. Compared with patients with no substance use disorder, the odds of receiving a methylphenidate dosage of >72 mg/day were significantly higher in patients with the comorbidity at 1 year (37% vs 21%; p<0.0001; odds ratio,* 2.12) and at 2 years (44% vs 23%; p<0.0001; odds ratio, 2.65). Risk was increased in those with a diagnosis of drug abuse, both drug and alcohol abuse, and psychoactive stimulant use. Before the 2-year evaluation, the mean daily methylphenidate dose increased by 3.2 mg/100 days in patients with a substance use disorder, compared with 1.1 mg/100 days in those with ADHD only, but no significant increase occurred in either group after that time. At the 3-year evaluation, the mean dosage was slightly reduced in patients with a substance use disorder and remained the same in those without.

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Discussion: Treatment guidelines for stimulant dosage in adults with substance use disorders are conflicting. Underdosing by following current recommendations may explain why some studies have failed to show a benefit of stimulants in patients with substance use disorders. The early dose increases in the present study may reflect an initial reluctance to prescribe adequate doses due to lack of clear clinical guidelines or prescribers' inappropriate beliefs. Adequate dosing may increase these patients' motivation to stay in treatment and prevent relapses to illegal drug use.

Skoglund C, Brandt L, D'Onofrio B, Larsson H, et al: Methylphenidate doses in attention deficit/hyperactivity disorder and comorbid substance use disorders. *European Neuropsychopharmacology* 2017; doi 10.1016/j.euroneuro.2017.08.435. From Karolinska Institute, Stockholm, Sweden; and Indiana University, Bloomington. **Funded by Karolinska Institute; and other sources. The authors declared no competing interests.**

Common Drug Trade Names*: methylphenidate—*Ritalin*; OROS methylphenidate—*Concerta

***See Reference Guide.**

PPIs and Depression in Elderly

In a community-based sample of elderly patients, use of proton pump inhibitors was associated with increased risk of depression.[1] The calculated population attributable risk* indicates that in this population, 14% of depression cases could be avoided by withdrawing PPIs.

Background: Research has suggested that PPIs are associated with neuropsychological adverse effects. A large cohort study recently found a significantly increased incidence of dementia in elderly patients receiving PPIs.[2] An incidental finding in that study was a higher prevalence of PPI use among patients with depression. Case reports also support the association. However, in the World Health Organization's adverse drug reactions database, depression is rarely associated with PPI use.

Methods: The study population consisted of all persons aged ≥75 years living in a single town in Italy (n=344; mean age, 80 years; 55% women). No study subjects had active peptic ulcer or were receiving *H. pylori* eradication therapy, although neither was an exclusion criterion. Depressive symptoms were assessed with the 30-item Geriatric Depression Scale (GDS), with a score of ≥11 indicating depression and scores of 21–30 indicating severe depression. The investigators also compiled data on medications, medical diagnoses, physical activity, cognitive performance, and functional ability.

Results: Although no patient had a definitive DSM-IV diagnosis of major depressive disorder, depression was recorded in the medical records of 38% of the patients and the mean GDS score was 11. Using the GDS cutoff, 163 participants (47%) reached the study-defined threshold for depression. Of these patients, 44 (13%) were receiving treatment with a PPI, most commonly omeprazole (*Prilosec*), which was used by 29 people.

In the PPI-treated group, 73% had GDS scores above the cutoff for depression, compared with 48% of those not taking PPIs (p=0.002). The mean GDS score was 15 in patients taking PPIs and 10 in others (p<0.0001). In contrast, patients taking H2-receptor antagonists or other antacids did not have elevated average GDS scores or rates of depression. Measurements of physical activity and functional ability were also significantly decreased in patients taking PPIs, and cognitive function was somewhat worse, although not significantly. Depression was associated with PPI use in a multivariate model that accounted for the influence of peptic ulcer disease and SSRI use (odds ratio,* 2.38; p=0.045). PPI use was associated with both severe and milder depression. Increasing PPI dosages were associated with higher rates of depression (p for linear trend=0.014).

Discussion: PPIs are often prescribed inappropriately, and in older patients they are generally prescribed on a long-term or continuous basis. They have not been associated with depression

in younger patients taking them for shorter periods. Several mechanisms may link PPIs to depression: They may affect cognition, leading to depression as a prodromal symptom of dementia; they increase gastrin-releasing peptide, which may affect brain structures, leading to behavioral alterations found in anxiety, depression, and dementia; and hypergastrinemia may stimulate cholecystokinin B receptors in the CNS that regulate anxiety. While these results suggest an association between PPI use and depression, because the study was cross-sectional, causality could not be evaluated and unmeasured factors could confound the association.

[1]Laudisio A, Incalzi R, Gemma A, Giovannini S, et al: Use of proton-pump inhibitors is associated with depression: a population-based study. *International Psychogeriatrics* 2017; doi 10.1017/S1041610217001715. From Campus Bio-Medico di Roma University, Rome, Italy; and other institutions. **Funded by the Italian Ministry of Health. The authors declared no competing interests.**

[2]Gomm W, et al: Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurology* 2016;73:410–416.

***See Reference Guide.**

Iloperidone for Bipolar Mixed Episodes

In a manufacturer-sponsored study, open-label, adjunctive iloperidone significantly improved both manic and depressive symptoms in patients with bipolar mixed states. While iloperidone is not an FDA-approved treatment for mixed states, studies of agents that are approved (i.e., divalproex, olanzapine, risperidone, ziprasidone, aripiprazole) have all had shorter durations and did not evaluate individual symptom domains.

Methods: Study participants, recruited from an outpatient clinic, were currently experiencing a mixed state, defined by simultaneous scores of ≥14 on the Young Mania Rating Scale (YMRS) and the Montgomery-Asberg Depression Rating Scale (MADRS). All met DSM diagnostic criteria for either a mixed manic episode, a manic/hypomanic episode, or a major depressive episode in bipolar I or II disorder. Patients were receiving stable doses of lithium, divalproex, or lamotrigine for ≥2 weeks before initiation of iloperidone and throughout the study. The daily iloperidone dose was titrated in 4-mg increments as tolerated, to a minimum of 12 mg/day and a maximum of 24 mg/day. The primary efficacy outcome was improvement in mania and depression, measured as separate domains with the 42-item Bipolar Inventory of Symptoms Scale (BISS-42). The remaining 3 domains rated with the BISS-42, irritability, anxiety, and psychosis, served as secondary outcomes.

Results: Of the 31 patients started on iloperidone, 16 (52%) completed 20 weeks of treatment. Patients who completed the study experienced significant reductions in BISS-42 scores for depression, mania, and irritability, a modest decline in anxiety, and a reduction in psychosis from a low baseline. (See table.) Defining response as a ≥50% reduction in score, 11 of these patients (68%) achieved YMRS response and 8 (50%) achieved MADRS response. Overall Clinical Global Impression–Severity* scores improved by 1.4 points on average (p=0.0008), and scores on the Global Assessment of Function also improved (p=0.003). The full sample analysis that included patients who discontinued treatment before 20 weeks showed the same pattern,

Change from baseline to 20 weeks in BISS-42 symptom domains with adjunctive iloperidone

BISS Domain	Baseline Score	Final Score	Percent Reduction	Significance
Depression	27	16	41%	p=0.01
Mania	18	7	60%	p<0.001
Irritability	9	4	58%	p<0.001
Anxiety	8	6	21%	p=NS
Psychosis	0.7	0	100%	p=0.06

with smaller but still statistically significant improvement for most outcomes. Improvement was observed as early as treatment week 4.

Of the 15 patients who did not complete the study, 12 withdrew because of adverse events. Study withdrawal was associated with increased heart rate or palpitations in 5 patients and urinary urges or incontinence in 3. One patient had an increase in the Abnormal Involuntary Movement Scale score. Common adverse effects of iloperidone treatment included dry mouth (39%), weight gain (32%), increased heart rate (32%), dizziness/lightheadedness (26%), drowsiness/fatigue (26%), and body aches/muscle stiffness (19%).

Discussion: Iloperidone is currently FDA approved only for treatment of schizophrenia. The adverse effects observed with the medication are likely the result of its α-1 antagonistic properties, and less aggressive dosing titration may reduce adverse effects and increase retention in treatment. While the results are positive, the authors do note study limitations including the lack of a comparison group and use of unblinded symptom ratings. In addition, naturalistic episode remission may have contributed to clinical improvement.

Singh V, Arnold J, Prihoda T, Martinez M, et al: An open trial of iloperidone for mixed episodes in bipolar disorder. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000764. From Texas Tech University Health Sciences Center at El Paso; and the University of Texas Health Science Center at San Antonio. **Funded by Novartis; and Vanda Pharmaceuticals. The authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; divalproex—*Depakene, Depakote*; iloperidone—*Fanapt*; lamotrigine—*Lamictal*; olanzapine—*Zyprexa*; risperidone—*Risperdal*; ziprasidone—*Geodon

***See Reference Guide.**

Relapse Prevention in Anxiety Disorders

In patients with anxiety disorders, continuation of effective antidepressant therapy was associated with a 3-fold lower risk of relapse, according to a meta-analysis of placebo-controlled drug withdrawal trials. This finding suggests that for maximum efficacy, antidepressants prescribed to treat anxiety disorders should be continued for ≥1 year in patients who experienced response.

Methods: A comprehensive literature search was undertaken to identify relapse-prevention studies in patients with panic disorder, agoraphobia, social phobia, generalized anxiety disorder, OCD, PTSD, or specific phobia. In the studies, participants had been classified as antidepressant responders and had been randomized to continue the antidepressant or to switch to placebo. The primary outcomes of the meta-analysis were proportion of relapse and/or time to relapse, using each study's definition of the term.

Results: The search identified 28 studies with >5000 patients who had experienced response to initial antidepressant treatment lasting from 8 to 52 weeks. There was a wide representation of disorders and antidepressant classes, and studies were fairly evenly divided with regard to whether or not they enrolled patients with comorbid disorders, allowed concurrent psychotherapy, and discontinued the antidepressant abruptly or with a taper. Follow-up periods generally ranged from 24 to 28 weeks, although several studies had extended follow-up lasting as long as 56 weeks.

Overall, rates of relapse were 16% in patients who continued antidepressant therapy and 36% in those switched to placebo. Relative to those who received continued antidepressant therapy, the odds ratio* for relapse in those switched to placebo was 3.1. Risk of relapse between weeks 24 and 28 (the follow-up period for all studies examining time to relapse), calculated as the hazard ratio,* was also 3-fold higher with placebo. Subgroup analyses according to type of disorder, mode of discontinuation, use of psychotherapy, and exclusion of comorbidity did not identify any groups whose results differed from the study population as a whole.

Most studies reported on adverse events and concluded that continued antidepressant therapy was well tolerated. Dropout rates, excluding those for lack of efficacy, were higher in placebo-treated patients than those receiving active treatment (odds ratio, 1.31).

Discussion: Anxiety disorders are often chronic, and most guidelines recommend 1 year of follow-up; some advise shorter periods for specific disorders. The present results support continuing therapy for 1 year to protect against relapse; however, because no study had a follow-up of >1 year, the results do not indicate that discontinuing therapy at 1 year is safe or advisable.

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

Batelaan N, Bosman R, Muntingh A, Scholten W, et al: Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials. *BMJ* 2017; doi: 10.1136/bmj.j3927. From VU University Medical Center; and the Academic Outpatient Department for Anxiety Disorders, Amsterdam, the Netherlands. **This research was conducted without funding. The authors declared no competing interests.**

***See Reference Guide.**

Ketamine: Potential for Drug Interactions

According to a review, it appears unlikely that ketamine will cause clinically significant interactions with most other drugs. The evidence, while sparse, does suggest drugs that induce or inhibit certain hepatic enzymes may alter the availability of ketamine, but clinical effects of these alterations have not been reported. Data from clinical trials suggest ketamine, when used in subanesthetic doses to treat depression, can be safely combined with most conventional antidepressants.

Ketamine, which is gaining interest as an off-label treatment for severe and resistant depression, is metabolized mainly by hepatic cytochromes (CYP) 2B6, 2C9, and 3A4. Theoretically, medications that induce these enzymes would be expected to reduce exposure to ketamine, and those that inhibit the enzymes would increase exposure. Studies in animals suggest that prolonged, high dosing is required for enzyme induction, and the effects are small. Therefore, it is unlikely that ketamine in the infrequent, subanesthetic doses used to treat depression would cause clinically significant interactions.

However, studies in small numbers of healthy volunteers have shown that rifampin, a potent CYP3A4 and 2B6 inducer, reduces exposure to ketamine, and both ticlopidine and clarithromycin, which are inhibitors of 2B6 and 3A4 respectively, increase exposure. Grapefruit juice inhibits CYP3A4 in the intestinal lining and may potentially induce clinically significant increased exposure to orally administered ketamine. In contrast, St. John's wort, which induces CYP3A4, reduced ketamine exposure in a small group of healthy volunteers. Dose adjustments may be necessary to provide therapeutic levels of ketamine or to reduce adverse effects. Because these adjustments are largely a matter of guesswork, it may be preferable just to avoid drugs that may cause interactions.

Polymorphisms in the CYP2B6 enzyme may also influence ketamine metabolism. Patients with the CYP2B6*6 allele, particularly if it is homozygous, may require reduced doses of ketamine. The allele occurs mostly in African, African-American, and Asian populations. However, it is also possible that the alternative CYP3A4 pathway compensates, and no dosage adjustment is needed.

Ketamine is classified mainly as a noncompetitive NMDA receptor antagonist. Pharmacodynamic interactions may occur with drugs that influence glutamatergic neurotransmission. This includes memantine, a drug that is unlikely to be used in patients who require ketamine

for depression. Lamotrigine and possibly clozapine may reduce the acute perceptual, cognitive, and schizophrenia-like adverse effects of ketamine. There is no information on whether these drugs also blunt the antidepressant effects of ketamine. Reports have suggested concomitant benzodiazepines may attenuate the antidepressant response to ketamine. In 1 small observational study, patients with depression who were taking benzodiazepines took longer to experience response and remission and relapsed earlier than those not taking benzodiazepines. Ketamine has shown safety and efficacy in many trials in patients taking antidepressant drugs, which suggests no compromise in efficacy or tolerability.

Andrade C: Ketamine for depression 5: potential pharmacokinetic and pharmacodynamic drug interactions. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.17f11802. From the National Institute of Mental Health and Neurosciences, Bangalore, India.

Common Drug Trade Names*: clarithromycin—*Biaxin*; clozapine—*Clozaril*; ketamine—*Ketalar*; lamotrigine—*Lamictal*; memantine—*Namenda*; rifampin—*Rifadin*; ticlopidine (no longer available in the U.S.)—*Ticlid

Maternal Antidepressants and Psychiatric Disorders

According to a Danish population-wide study, maternal antidepressant use during pregnancy is associated with increased risk of various psychiatric disorders in the offspring. Risk is increased in children whose mothers continue antidepressant use during pregnancy, compared with those never exposed to antidepressants as well as those whose mothers stop taking the antidepressant.

Background: Previous studies of antidepressant use during pregnancy and risk of disorders in the offspring have largely focused on autism spectrum disorder and ADHD, and results have been mixed. The present study included all psychiatric diagnoses, with separate analyses of autism and of the 4 diagnostic categories most common in Danish children: mood disorder; neurotic, stress-related, and somatoform disorders; behavioral and emotional disorders; and mental retardation.

Methods: The study population consisted of all singleton infants born in 1998–2012 who were followed for up to 16.5 years. Children's exposure was classified as: unexposed, discontinuation (maternal use before but not during pregnancy), continuation (use before and during pregnancy), and new user (only during pregnancy).

Results: Of >905,000 children included in the study, 2.3% were born to mothers who used antidepressants during pregnancy. The majority of mothers used SSRI monotherapy. During follow-up, 32,400 children received a psychiatric disorder diagnosis. Children exposed to antidepressants during gestation had increased rates of psychiatric disorders, whether their exposure was before, during, or throughout pregnancy. The weighted, cumulative, 15-year incidence of any psychiatric disorder was 8% in unexposed children, compared with 11.5% in children whose mothers discontinued antidepressant therapy during pregnancy, 13.6% in those whose mothers continued therapy, and 14.5% in those whose mothers received new antidepressant therapy during pregnancy.

Risk of specific disorders in offspring, relative to maternal continuation or discontinuation of antidepressants during pregnancy

	Hazard Ratio*
All disorders	1.27
Autism spectrum disorder	1.23
Mood disorder	2.76
Somatoform disorder	1.62
Behavioral disorder	1.13

In children whose exposure was continued throughout gestation, risk was increased overall and for most individual categories of disorder (see table), compared with those whose mothers stopped taking antidepressants during the pregnancy. The risk did not differ in

children exposed to SSRIs versus non-SSRI monotherapy (hazard ratios, 1.25 and 1.15), but was higher in children whose mothers took a combination of SSRIs and non-SSRIs (either switching from one to the other or polypharmacy; hazard ratio, 1.72). The analysis showed no great difference among individual drugs, although statistical precision was low for the less commonly used antidepressants. Risk was also elevated with >180 days of antidepressant exposure, compared with shorter durations.

Discussion: Children exposed to antidepressants in utero are at increased risk of psychiatric disorders regardless of whether the agent is discontinued during pregnancy. However, risk is greater when antidepressants are initiated during pregnancy or continued throughout. It is possible that in children whose mothers discontinued antidepressants during pregnancy, the increased risk is driven by the underlying maternal disorder, which may be transmitted to the child via shared genetic susceptibility or environmental stress. Offspring of mothers who receive antidepressants throughout pregnancy may also be affected by greater severity of the maternal disorder, as well by the drugs themselves.

Liu X, Agerbo E, Ingstrup K, Musliner K, et al: Antidepressant use during pregnancy and psychiatric disorders in offspring: Danish nationwide register based cohort study. *BMJ* 2017; doi 10.1136/bmj.j3668. From Aarhus University, Denmark; and other institutions. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Methylphenidate for Apathy in Mild Alzheimer's

In a placebo-controlled trial, methylphenidate (*Ritalin*) reduced apathy in men with mild Alzheimer's disease. Improvement occurred relatively early in treatment and was followed in time by improved cognition and function and reduced caregiver burden.

Background: Apathy is the most common behavioral problem in Alzheimer's disease and may have a greater impact on function than diminished cognition. It also increases caregiver burden and service utilization.

Methods: Study participants were community-dwelling veterans, aged ≥60 years, recruited from the service records of a VA hospital. Patients were enrolled if they had a diagnosis of Alzheimer's disease (made by the study psychiatrist), had a caregiver, and scored ≥18 on the Mini-Mental State Examination (MMSE) and >40 on the Apathy Evaluation Scale–Clinician version (AES-C), a cutoff that is considered clinically significant in patients with the disease. Participants were randomly assigned to receive 12 weeks of treatment with either placebo or methylphenidate started at 5 mg b.i.d., and increased to 10 mg b.i.d. at 2 weeks. To avoid insomnia, the last dose was taken no later than 3 PM. The primary outcome measure was the AES-C, an 18-item scale that measures behavioral, cognitive, and emotional domains of apathy. Scores on the AES-C range from 18 to 72, and a change of 3.3 points is considered clinically meaningful.

Results: Of 60 patients enrolled, 1 withdrew from each group because of caregiver unavailability. Nearly all patients completed all study visits. Participants had a mean age of 77 years, all were men, and the mean baseline AES-C score was 50. The methylphenidate group had significantly greater improvement in the AES-C score than the placebo group, beginning at week 4 and reaching a maximum decrease at the 12-week endpoint (10-point difference; $p<0.001$). The difference was driven by improvements in multiple apathy domains, with behavioral and cognitive scores improving significantly by week 8 and emotional scores by week 12. There was improvement in the other domains, novelty and persistence, but it did not reach statistical significance. Patients who received methylphenidate also showed a mean 2.6-point improvement in the MMSE by week 12 ($p=0.001$), along with significant

improvement on other measures of cognition, instrumental activities of daily living, caregiver burden, depressive symptoms, and Clinical Global Impression–Improvement and Severity measures.

Adverse events generally did not differ between the treatment groups. Compared with baseline, mean systolic blood pressure was significantly increased in methylphenidate-treated patients at 12 weeks; however, the between-group difference was not significant. One patient in the methylphenidate group had a serious adverse event possibly related to medication: seizures requiring hospitalization. Five patients receiving each treatment experienced dizziness and insomnia.

Discussion: The efficacy of methylphenidate in this study and in previous, smaller trials is consistent with the dopaminergic hypothesis of apathy. The ideal treatment duration may be longer than the 12 weeks provided in this study, as suggested by patients' continuing improvement over the study period.

Padala P, Padala K, Lensing S, Ramirez D, et al: Methylphenidate for apathy in community-dwelling older veterans with mild Alzheimer's disease: a double-blind, randomized, placebo-controlled trial. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17030316. From the Central Arkansas Veterans Healthcare System, Little Rock; and other institutions. **Funded by the VA. One study author disclosed relevant financial relationships; the remaining 10 authors declared no competing interests.**

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

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.

Population-Attributable Risk: The portion of the incidence of a disease in the population (exposed and nonexposed) that is due to exposure. It is the incidence of a disease in the population that would be eliminated if exposure were eliminated.

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.

PSYCHIATRY DRUG ALERTS

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Minocycline for Depression

According to a systematic review and meta-analysis, preliminary evidence supports significant antidepressant effects of minocycline (*Minocin*) in patients with unipolar major depression

Background: The immune system has been identified as a novel target in the treatment of depression, and replicated evidence clearly supports the strategy. Minocycline, a tetracycline antibiotic with potent antiinflammatory and neuroprotective effects, has been evaluated in several small controlled trials in both unipolar and bipolar depression. The present analysis was undertaken to synthesize these results.

Methods: A comprehensive literature search was performed to identify reports, including clinical trials, case reports, and observational studies, of minocycline as a treatment for a major depressive episode in unipolar or bipolar depression. All identified studies were included in a qualitative review, and randomized controlled trials of minocycline—as either adjunctive treatment or monotherapy—were included in a meta-analysis. A total of 17 studies were identified: 3 published controlled trials; 2 open-label studies; 1 case report; 3 clinical trials that have been completed but have not yet been published; 1 study that was terminated for product supply issues; and 7 additional studies that are ongoing.

Results: Both open-label studies evaluated adjunctive minocycline (1 in unipolar and 1 in bipolar depression) and reported significant improvements in depression rating scale scores following 6–8 weeks of treatment ($p<0.001$ in bipolar depression and $p<0.008$ in unipolar depression). The single case report also described improved depression with adjunctive minocycline. Preliminary results were available online for 2 of the 3 unpublished studies. Both evaluated open-label treatment and reported 8–15-point reductions in Montgomery-Asberg Depression Rating Scale (MADRS) scores in treated patients. No serious adverse events were described in any of the reports.

The 3 randomized controlled trials comprised a total of 162 patients (52% women) with mean ages ranging from 35 to 51 years. All patients had a diagnosis of unipolar major depression, and

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minocycline was an adjunct to treatment as usual in 2 of the studies. In the pooled analysis, minocycline was significantly superior to placebo at reducing MADRS or Hamilton Rating Scale for Depression scores with a standardized mean difference* of -0.78 (p=0.005). Minocycline was well tolerated; adverse effects were similar to placebo, and none were serious.

Discussion: Although the number of studies and enrolled patients was small, the results of this meta-analysis do provide preliminary support for the efficacy of minocycline in patients with depression; the additional studies support these findings. Several larger-scale ongoing trials evaluating minocycline efficacy in both unipolar and bipolar depression continue to recruit patients, and the full results of the completed but as-yet unpublished studies should help to clarify the robustness of minocycline efficacy and tolerability.

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

Rosenblat J, McIntyre R: Efficacy and tolerability of minocycline for depression: a systematic review and meta-analysis of clinical trials. *Journal of Affective Disorders* 2017; doi 10.1016/j.jad.2017.10.042. From the University of Toronto, Canada. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

Pharmacogenetic-Guided Treatment

In a randomized trial, pharmacogenetic-guided drug selection resulted in improved treatment efficacy in patients with depression and/or anxiety. The trial, funded by the manufacturer of the genetic test, is notable for including patients from both diagnostic categories and from both psychiatric and primary-care practices.

Background: The NeurolDgenetix® Test is based on a panel of 10 genes and accounts for concomitant medications, over-the-counter treatments, and lifestyle factors such as supplements, diet, alcohol, and smoking. The test results in recommendations based on gene/drug and drug/drug interactions for >40 medications used to treat depression and anxiety. The report classifies medications as either "use as directed" or "use with caution and/or increased monitoring," the latter including reasons for caution and recommendations for appropriate action.

Methods: Study participants were adults with DSM-5 unipolar depression and/or anxiety, enrolled from 20 U.S. clinical sites representing psychiatry, internal medicine, OB-GYN, and family practice. Patients were randomly assigned to the experimental group whose treatment was guided by NeurolDgenetix results or a control group receiving usual treatment. Before randomization, all patients had specimens collected (buccal swabs) for genetic testing, but physicians only received the results for patients in the experimental group. Patients returned for assessment at weeks 4, 8, and 12. Treatment outcomes were assessed by raters, unaware of patients' treatment assignment and therapeutic decisions made by the treating physician, using the Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A). Response was defined as a ≥50% reduction in score, and remission as a final score of ≤7. Adverse drug events were also rated by a blinded observer. While the treating physicians could not be blinded to patient arm assignment, they were blind to symptom severity scores (raters categorized symptoms as either mild, moderate, or severe based on score cutoffs), thus ensuring that any expectancy bias did not affect clinical outcome measures.

Results: Of 685 patients enrolled, 579 (85%) completed the study. Patients had a mean age of 48 years, 73% were women, and 18% were African-American. The sample was about evenly divided among patients with depression alone, anxiety alone, and both diagnoses.

Patients with mild depression (i.e., HAM-D scores ≤17) did not improve with treatment, which is consistent with research suggesting medication is ineffective in mild depression. For patients

with severe depression (i.e., HAM-D scores >24), pharmacogenetic testing was associated with higher rates of response at 12 weeks: 73% vs 36% (p=0.001) with an odds ratio* (OR) of 4.72 favoring the pharmacogenetic-guided group and a number needed to treat* (NNT) of 2.7. When patients with moderate depression were included, results were attenuated but remained significant (p=0.01; OR, 2.03; NNT, 5.8). Results for remission in patients with severe depression showed a similar pattern: 35% vs 13% (p=0.02) with an OR of 3.54 and an NNT of 4.6. Remission rates in the group with moderate-to-severe depression were not reported.

Pharmacogenetic-guided treatment was also associated with significantly better outcomes in patients with anxiety. At 12 weeks, HAM-A reductions were 54% in the experimental group and 42% in the control group (p=0.02). Response rates were 63% and 50%, respectively (p=0.04; OR, 1.76; NNT, 7.3). Patients with anxiety and comorbid depression also improved significantly, but to a lesser degree than patients with anxiety alone.

Physicians implemented or modified therapy during the trial in more patients in the experimental group than the control group (p<0.0001; overall percentages not reported). Most medication changes occurred at the 2-week visit (81% of the experimental group and 64% of controls), and changes continued throughout the study. Medication changes in the experimental group were aligned with recommendations 70% of the time. No differences in adverse event rates or severity were observed between groups, suggesting medication changes were not driven by adverse effects.

Discussion: These results support the use of pharmacogenetics to improve outcomes in depression and to a lesser extent, anxiety. While patients with both depression and anxiety also improved, the effects of pharmacogenetic testing in these patients were smaller; additional research is needed to examine this difference.

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

Bradley P, Shiekh M, Mehra V, Vrbicky K, et al: Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: a randomized clinical trial demonstrating clinical utility. *Journal of Psychiatric Research* 2017; doi:10.1016/j.jpsychires.2017.09.024. From Mercer University School of Medicine, Savannah, GA; and other institutions including AltheaDx , San Diego, CA. **Funded by AltheaDx, manufacturer of the NeurolDgenetix® test. Five of 10 study authors disclosed financial relationships with AltheaDx; the remaining authors declared no competing interests.**

***See Reference Guide.**

Ramelteon for Agitation in Delirium

According to the results of a retrospective chart review, the melatonin receptor agonist ramelteon (*Rozerem*) is associated with reduced use of as-needed antipsychotics for agitation in elderly inpatients with delirium. This finding suggests that correcting circadian-rhythm disturbance may be a potential treatment for delirium.

Background: There is no drug FDA-approved to treat delirium. Antipsychotics are often prescribed, despite their risks and an FDA black box warning about mortality risk in elderly patients with dementia. Research has identified degeneration of the suprachiasmatic nucleus of the hypothalamus resulting in reduced melatonin secretion and disrupted circadian rhythm in patients with delirium.

Methods: Data from a single general hospital between May and October 2015 were analyzed retrospectively. The study sample included 125 patients (52% women), aged ≥65 years, who had a diagnosis of delirium, were on continuous observation, and had no standing orders for antipsychotics. Continuous observation included 1-on-1 observation for those experiencing suicidality or at risk of harming themselves or others, and safety watch for those with cognitive deficits or impaired judgment leading to agitation, risky actions, or falls.

Patients with underlying psychiatric disorders were excluded. In the 60 patients (48%) who received ramelteon treatment, the prescription had been based on the clinicians' judgment that they would benefit from the regulation of circadian rhythm. As-needed antipsychotics were used to treat agitation, regardless of ramelteon use. The primary outcome of the analysis was use of as-needed antipsychotics.

Results: During their hospital stay, as-needed antipsychotics were used by 60% of the patients who received ramelteon, compared with 86% of those who did not (p=0.001). In a multivariate analysis adjusted for race, gender, age, and length of stay, patients who did not receive ramelteon had a significantly higher likelihood of receiving an antipsychotic (odds ratio,* 4.3; p=0.002). Among patients who received antipsychotics, the groups did not differ in the type of drug or the dosage. Average length of stay did not differ significantly between the groups.

Discussion: While these results suggest ramelteon may reduce use of as-needed antipsychotics, the study design precluded evaluation of potential confounders and selection bias could not be prevented. Further research with well-designed, prospective studies appears to be warranted.

Pinkhasov A, James S, Fazzari M, Singh D, et al: Role of ramelteon in reduction of as-needed antipsychotics in elderly patients with delirium in a general hospital setting. *Clinical Drug Investigation* 2017; doi 10.1007/s40261-017-0573-5.
From NYU Winthrop Hospital, Mineola; and St. John's University, Queens, NY. T**he study was conducted without funding. The authors declared no competing interests.**

***See Reference Guide.**

Mood Stabilizers in Older Patients

Lithium and divalproex had similar overall efficacy and tolerability in a 9-week randomized comparison trial in older patients with bipolar mania.[1] Contrary to expectations, dosing was not limited by adverse effects to a greater extent with lithium than with divalproex.

Background: Lithium has the strongest evidence supporting its efficacy in adults with bipolar disorder. However, older patients may be unable to tolerate lithium at the concentrations recommended for younger patients, and concerns about tolerability may lead to use of lower doses or alternative medications, such as divalproex.

Methods: Study participants were recruited from 6 U.S. academic medical centers and included both inpatients and outpatients. For inclusion, patients were required to: be aged ≥60 years; meet DSM-IV criteria for bipolar 1 disorder with a current manic, mixed, or hypomanic episode; and have a Young Mania Rating Scale (YMRS) score of ≥18. Following taper and discontinuation of antidepressants and other non-study medications, patients were randomly assigned to 9 weeks of double-blind treatment with either lithium or divalproex. Lithium was initiated at 300 mg/day and titrated to a target serum concentration of 0.80–0.99 mEq/L. Divalproex was initiated at 500 mg/day and titrated to a target of 80–99 µg/mL. Participants who did not have an adequate response at week 3 were given adjunctive risperidone. Those who could not tolerate dosing that achieved the minimal serum targets were withdrawn. The study had 3 primary outcomes: clinical tolerability, measured using the UKU Side Effect Rating Scale sleepiness/sedation item; pharmacologic tolerability, which was the proportion of patients who achieved serum concentrations within the target range; and efficacy, measured as the change from baseline in the YMRS score.

Results: A total of 224 patients (mean age, 68 years; age at first onset of mania, 9–82 years) entered the study. Similar proportions of both groups did not complete 9 weeks of study treatment: 51% with lithium and 44% with divalproex. Reasons for attrition—nonadherence, intolerance, or lack of efficacy—did not differ between the groups. Similar proportions of the lithium and divalproex groups used adjunctive risperidone: 17% and 14%, respectively.

Levels of sleepiness/sedation, the primary tolerability outcome, rated at 3 and 9 weeks did not differ between the 2 drugs. Tremor occurred somewhat less often with divalproex, but the difference was not significant, and there were no significant differences in nausea/vomiting or weight gain. Similar proportions of patients in both groups achieved target drug concentrations: about one-third at week 3 and about 55% at week 9.

Significant differences between the 2 drugs in YMRS improvement, favoring lithium, were observed at week 3 (between group difference, 1.6 points; effect size,* 0.18) and week 9 (mean difference, 4 points; effect size, 0.54). Further analysis indicated that the difference in efficacy was limited to patients with a baseline YMRS score >30. The groups did not differ in rates of response, defined as a ≥50% reduction in YMRS total score: about two-thirds at week 3 and three-fourths at week 9. Remission (i.e., YMRS total score ≤9) occurred in nearly half of patients at week 3 and two-thirds at week 9. Neither agent was associated with worsening of depressive symptoms.

Discussion: Older patients appear to tolerate treatment with lithium or divalproex with conservative serum concentration targets, as well as limited use of rescue and adjunctive medication. Based on their findings, the authors recommend greater use of lithium, which may have neuroprotective and antisuicide effects. However, according to an accompanying editorial,[2] the choice of an acute therapy should include considerations for maintenance therapy, and maintenance treatment with lithium in the elderly may be limited by a higher risk of long-term toxicity, particularly renal and cardiac effects.

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

[1]Young R, Mulsant B, Sajatovic M, Gildengers A, et al: GERI-BD: a randomized double-blind controlled trial of lithium and divalproex in the treatment of mania in older patients with bipolar disorder. *American Journal of Psychiatry* 2017;174 (November):1086–1093. From Weill Cornell Medicine, New York; and other institutions. **Funded by the NIH. Six of 18 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Dunner D: Treatment of bipolar disorder in the elderly [editorial]. *American Journal of Psychiatry* 2017;174 (November): 1032–1033. From the Center for Anxiety and Depression, Mercer Island, WA; and the University of Washington, Seattle. **The author disclosed financial relationships with commercial sources.**

Common Drug Trade Names*: divalproex sodium (valproic acid and derivatives)—*Depakene, Depakote*; risperidone—*Risperdal

***See Reference Guide.**

Venlafaxine and Bone Turnover

In older patients with depression treated with venlafaxine (*Effexor*), antidepressant response appeared to protect against an increase in markers of bone resorption associated with SRI treatment.[1] This observation suggests the possibility that when serotonergic antidepressants are ineffective in treating depression, a switch to a different class of antidepressant rather than augmenting the SRI may have favorable effects on bone turnover.

Background: Bone cells have functional serotonin receptors, and SRI therapy has been associated with accelerated bone loss and increased fracture risk in some studies of older patients. SRIs affect bone cells via the serotonin transporters and receptors. Results of a previous trial, conducted by several of the present study authors and at the same institutions, indicated that patients whose depression remitted with venlafaxine had minimal changes in bone turnover markers, suggesting successful antidepressant response may mitigate bone turnover.[2] However, the study sample (n=73) was small. The present report pools those patients with an additional 95 to increase statistical power and to explore additional variables.

Methods: Participants in this open-label study of venlafaxine were aged ≥60 years and experiencing a major depressive episode, of at least moderate severity, for ≥4 weeks. Those receiving bisphosphonates were excluded, but other bone-protective treatments (vitamin D, calcium, and

estrogen), taken consistently throughout the study, were permitted. All participants received 12 weeks of treatment with venlafaxine, titrated to a target dosage of 150 mg/day. Those whose depression did not remit (i.e., Montgomery-Asberg Depression Rating Scale score of ≤10) after 6 weeks received a further titration to a maximum of 300 mg/day. Blood samples were obtained at baseline and 12 weeks and assayed for CTX, a marker of osteoclast activity and bone resorption, and P1NP, a marker of osteoblast activity and bone formation. Patients were also genotyped for numerous polymorphisms in the serotonin transporter (HTTLPR) and receptor (HTR1B) genes, which were grouped as having high or low activity.

Results: The 168 participants had a mean age of 69 years, 61% were women, and 92% were Caucasian. They were generally physically healthy and cognitively intact. A total of 80 patients (48%) experienced remission of depression. The mean venlafaxine dose at study end was about 200 mg/day in remitters and 268 mg/day in nonremitters.

Overall, the mean levels of CTX increased significantly in patients who received venlafaxine (p=0.02 for mean change from baseline), and levels of P1NP significantly decreased (p=0.01). CTX increased in 55% of the venlafaxine-treated patients, and P1NP decreased in 61%. The increase in CTX was significant in patients who did not achieve remission (p=0.009), while levels showed no change in those whose depression did remit. P1NP decreases occurred in both nonremitters and remitters. In a multivariable model controlling for baseline biomarker levels and other potentially confounding factors, remission status was correlated with end-of-treatment CTX levels (p=0.008), but not P1NP. Levels of P1NP were also lower in patients who had a depressive episode lasting >2 years.

Among Caucasian patients, 30% had a low-expressing serotonin receptor genotype and 29% a low-expressing serotonin transporter genotype. In the multivariable model, the receptor genotype predicted end-of-treatment P1NP (p=0.03), but not CTX. The serotonin transporter genotype was not associated with end-of-treatment levels in either marker.

Discussion: Although still preliminary, the present results support the hypothesis that accelerated bone loss in older individuals taking antidepressants is an effect of the drug, not of depression, and that it can be moderated by antidepressant response. Venlafaxine has binding affinity that is predominantly serotonergic, which suggests that the findings may be broadly applicable to serotonergic antidepressants in general; however, other individual agents should be evaluated. Regardless of the causation of the association, these results suggest that depression of long standing, treatment response, and serotonin receptor genotype may be useful in identifying patients at risk of accelerated bone loss.

[1]Rawson K, Dixon D, Civitelli R, Peterson T, et al: Bone turnover with venlafaxine treatment in older adults with depression. *Journal of the American Geriatric Society* 2017;65 (September):2057–2063. From Washington University, St. Louis, MO; and other institutions. **Funded by the NIMH; and other sources. Four of 7 study authors disclosed potentially relevant relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Shea M, et al: Serotonin-norepinephrine reuptake inhibitor therapy in late-life depression is associated with increased marker of bone resorption. *Osteoporosis International* 2013;24:1741–1749.

Naltrexone for Opioid Dependence

In a randomized trial, injectable extended-release naltrexone was as effective as daily oral buprenorphine–naloxone in the short-term treatment of opioid dependence. Buprenorphine–naloxone is among the most commonly prescribed opioid medication treatments but requires daily or alternate-day dosing. An important potential advantage of extended-release naltrexone is once-monthly injection.

Methods: The trial recruited patients from 5 urban addiction clinics in Norway. Participants met DSM-IV criteria for opioid dependence, but were not dependent on other drugs or alcohol and

did not have other serious psychiatric illness. All participants received treatment as outpatients after discharge from detoxification units, inpatient treatment, or prison. Patients were randomly assigned to receive naltrexone injections (380 mg every 4 weeks) or flexible-dose, daily oral buprenorphine–naloxone, given in a controlled environment. Treatment was provided for 12 weeks. The primary outcomes were retention in the study, the number of weekly urine drug tests free of opioids, and the patient-reported number of days of use of heroin and other illicit opioids. Missing drug screens were considered to be positive for opioids.

Results: Of 232 patients assessed for the study, 51 refused to participate. After exclusions for other reasons, 159 (mean age, 36 years; 28% women) were randomized. Patients had an average of >6 years of heavy heroin use. Similar numbers of patients completed 12 weeks of treatment: 56 in the naltrexone group and 49 in the buprenorphine–naloxone group.

The treatments were similar with regard to the mean proportion of opioid-negative urine tests: 90% for naltrexone, 80% for buprenorphine–naloxone. Naltrexone was noninferior with regard to the mean number of days of heroin use (mean difference, 3.2 days) and days of use of other opioids (mean difference, 2.7 days). However, patients who received naltrexone used significantly less heroin at all 3 time points and significantly less other illicit opioids at weeks 4 and 8. At all time points, patients receiving naltrexone reported less craving and thoughts about heroin. They also had a higher level of satisfaction with treatment and were more likely to recommend it to others than those in the buprenorphine–naloxone group.

Adverse events related to opioid withdrawal—e.g., nausea, chills, and diarrhea—were more common in the naltrexone group (39% vs 14%). Insufficient detoxification appeared to be a factor, and the incidence of these adverse effects declined when the detoxification strategy for the study was strengthened.

Discussion: These results apply to illicit opioids but are likely clinically relevant for people addicted to prescribed opioids as well. The relatively high level of patient satisfaction with naltrexone may be related to the feeling of being protected against relapse and the freedom from having to attend supervised medication intake. Study participants were highly motivated to achieve opioid abstinence, and it is unknown whether extended-release naltrexone would be as effective in a less motivated population.

Tanum L, Solli K, Latif Z, Benth J, et al: Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3206. From the University of Oslo, Norway; and other institutions. **Funded by the Research Council of Norway; and other sources. The authors declared no competing interests.**

Common Drug Trade Names*: buprenorphine–naloxone—*Suboxone*; naltrexone, injectable extended release—*Vivitrol

Monthly Buprenorphine for Opioid Use Disorder

The Psychopharmacologic Drugs and Drug Safety and Risk Management Advisory Committees of the FDA have recommended approval of an investigational once-monthly sustained-release buprenorphine injection (RBP-6000) for the treatment of moderate-to-severe opioid use disorder.

The new buprenorphine formulation makes use of the Atrigel® delivery system, which consists of a biodegradable polymeric solution and a water-miscible biocompatible solvent. After subcutaneous injection, the solvent diffuses out of the polymer matrix and the polymer precipitates, trapping buprenorphine inside and forming a solid depot at the injection site. The depot then releases buprenorphine over a 1-month period by diffusion as the polymer biodegrades. In clinical trials, RBP-6000 produced significantly greater abstinence rates than

placebo, with a safety profile similar to that of oral transmucosal buprenorphine (*Subutex*). Injection-site reactions resulted in <1% of patients withdrawing from the trials.

While the recommendations of the FDA advisory committees are not binding, they do play a major role in the decision process. The FDA expects to take action on the decision by the end of November.

FDA advisory committees recommend approval of Indivior's RBP-6000 for the treatment of opioid use disorder [press release]. Richmond, VA; Indivior PLC: October 31, 2017. Available at https://www.prnewswire.com/news-releases/fda-advisory-committees-recommend-approval-of-indiviors-rbp-6000-for-the-treatment-of-opioid-use-disorder-300546838.html.

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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: 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 is 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.

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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Valbenazine for Tardive Dyskinesia

Long-term treatment with valbenazine (*Ingrezza*) was safe and well tolerated in a 42-week extension of a phase-III clinical trial.[1] Efficacy at reducing symptoms of tardive dyskinesia was also sustained during the long-term study.

Methods: Study participants were enrolled after completing a 6-week double-blind, placebo-controlled trial of valbenazine.[2] Entry criteria for the acute trial included a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or mood disorder; stable medical, psychiatric, and medication status; and moderate-to-severe tardive dyskinesia symptoms, rated through video by independent observers using the Abnormal Involuntary Movement Scale (AIMS). Patients entering the extension study continued to receive their randomly assigned valbenazine dosage of 40 or 80 mg/day. Those initially in the placebo group were switched to valbenazine, with the dose assigned randomly. Extended treatment was continued for 42 weeks and then followed by a 4-week washout. The primary aim of the extension study was to evaluate the long-term safety of valbenazine. Efficacy, a secondary outcome, was assessed using the AIMS, the Clinical Global Impression of Change–Tardive Dyskinesia scale, and the Patient Global Impression of Change.

Results: Of 205 patients who completed the randomized trial, 198 (mean age, 56 years; 54% men) entered the extension study, 69 of whom had received placebo in the earlier phase. A total of 124 patients (63%) completed the extension period; 31 participants (15% of the total) discontinued due to adverse effects, only somnolence (n=3) and suicidal ideation (n=2) led to discontinuation in >1 patient. The suicidal ideation resolved after valbenazine was stopped but was not considered drug related. About one-third of participants had a lifetime history of suicidal ideation and/or behavior, and these symptoms worsened during the trial in 13 patients. A total of 29 serious adverse events occurred, syncope affected 3 patients and the remaining events occurred in ≤2 patients each. During washout after the extension study, anxiety affected 2 patients. There were no clinically important changes in weight, vital signs, electrocardiography, or lab results.

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Improvements in tardive dyskinesia observed with active treatment during the clinical trial were sustained during extended treatment. All 3 measures of tardive dyskinesia showed a similar pattern: improvement relative to baseline, followed by a return to baseline levels during the 4 weeks of drug withdrawal. Rates of response (≥50% improvement in AIMS score) at the end of the acute study were 40% with the 80-mg dose and 24% with the 40-mg dose. At the end of extension treatment, rates were 52% and 28%, respectively. About half of these patients lost their response status after 4 weeks off the medication. Ongoing psychiatric evaluation using standard instruments showed that patients' psychiatric status remained stable during the extension and washout periods, indicating that valbenazine did not interfere with the action of antipsychotic or antidepressant medication.

Discussion: Tardive dyskinesia is a persistent, often disabling, and sometimes irreversible effect of antipsychotic treatment. First-line treatment for emergent tardive dyskinesia is usually antipsychotic dosage reduction or discontinuation, which can lead to uncontrolled symptoms of the underlying disorder. While many agents have been used off-label to treat tardive dyskinesia, valbenazine (1 of 2 selective vesicular monoamine transporter 2 inhibitors FDA approved to treat tardive dyskinesia)[3] appears to control symptoms safely over the long term without interfering with efficacy of background medications.

[1]Factor S, Remington G, Comella C, Correll C, et al: The effects of valbenazine in participants with tardive dyskinesia: results of the 1-year KINECT 3 extension study. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.17m11777. From Emory University, Atlanta, GA; and other institutions including Neurocrine Biosciences, Inc., San Diego, CA. **Funded by Neurocrine Biosciences, Inc. All study authors disclosed financial relationships with commercial sources, including Neurocrine Biosciences.**

[2]Hauser R, et al: KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.16091037. See *Psychiatry Drug Alerts* 2017;31 (April):25–26.

[3]Valbenazine. Drug Facts and Comparisons. Facts & Comparisons [database online]. St Louis, MO: Wolters Kluwer Health, Inc; October 2017. Accessed December 6, 2017.

Cariprazine: Response and Remission

According to a post-hoc analysis of pooled data from the manufacturer-sponsored clinical trials, cariprazine (*Vraylar*) produces response and remission in a substantial percentage of patients with bipolar I mania. Outcomes of the individual studies, including mean change from baseline on mania rating scales, are important for approval purposes but may be less meaningful from a clinical standpoint. Knowing how many patients' symptoms will respond or remit with treatment may be more important. Full remission, although not fully operationalized, is considered the treatment goal for bipolar mania.

Methods: The analysis was based on pooled data from 3 similarly designed, placebo-controlled, multicenter trials consisting of 3 weeks of treatment with cariprazine or placebo. The trials differed mainly in whether a fixed or fixed/flexible cariprazine dose was used. Dosage groups were pooled for the present analysis. Participants were adult inpatients with bipolar I disorder and a Young Mania Rating Scale (YMRS) score of ≥20, high scores on ≥2 of the 4 core YMRS items (irritability, speech, content, disruptive/aggressive behavior), and minimal depressive symptoms. The analysis included all patients who received ≥1 dose of study medication and ≥1 post-baseline evaluation. Multiple definitions of response and remission, based on YMRS, Montgomery-Asberg Depression Rating Scale (MADRS), and Clinical Global Impression (CGI) ratings, were evaluated.

Results: The analysis included 608 patients who received treatment with cariprazine and 429 who received placebo. Baseline ratings indicate that patients had manic symptoms of moderate severity. Cariprazine produced significantly higher rates of response and remission

regardless of the definition. (See table.) Numbers needed to treat* (NNT) for each outcome reported were clinically meaningful.

Treatment outcomes in pooled analysis of cariprazine vs placebo in bipolar I disorder

	Cariprazine	Placebo	Odds Ratio*±	NNT	Significance
Response: ≥50% decrease in YMRS total score	57%	36%	2.30	5	p<0.001
Global response: CGI-Improvement* score ≥2	64%	42%	2.42	5	p<0.001
Remission: YMRS total score ≤12	46%	30%	2.08	7	p<0.001
Remission: CGI-Severity* score ≤2	32%	22%	1.73	10	p<0.001
Unstable or emerging depression: MADRS total score ≥15	8%	11%	NS	—	NS
Composite remission: YMRS and MADRS total scores ≤12	45%	29%	2.15	—	p<0.001
Composite remission (stringent): YMRS and MADRS total scores ≤8	29%	19%	2.03	—	p<0.001
Cumulative remission: YMRS total score ≤12 maintained from first occurrence to study end	46%	30%	—	—	p<0.001
Composite symptomatic and functional remission: YMRS total score ≤12 plus CGI-Severity ≤2	29%	19%	1.85	—	p<0.001

±All odds ratios favored cariprazine
Note: Odds ratios and NNTs were not provided for all outcomes

Discussion: Because residual manic symptoms increase the risk of recurrence of both mania and depression, full remission is an important treatment goal in bipolar disorder. Remission rates with active treatment in the present analysis were in the same range as those reported for other second-generation antipsychotic monotherapies.

Earley W, Durgam S, Lu K, Ruth A, et al: Clinically relevant response and remission outcomes in cariprazine-treated patients with bipolar I disorder. *Journal of Affective Disorders* 2018;226 (January 15):239–244. From Allergan, Jersey City, NJ, and other institutions including Gedeon Richter, Budapest, Hungary. **Funded by Forest Research Institute, Inc., an Allergan affiliate; and Gedeon Richter Plc. The authors did not include disclosure of potentially relevant relationships.**

***See Reference Guide.**

Risperidone ISM

According to the results of a phase-II study, an investigational formulation of long-acting injectable risperidone (*Risperdal*) provides therapeutic blood levels rapidly without a loading dose or oral supplementation. The ISM formulation consists of an injectable fluid that precipitates in the body, forming a solid or semisolid depot that biodegrades slowly, delivering sustained drug release for up to 1 month.

Methods: Study subjects with DSM-IV schizophrenia were receiving maintenance therapy with oral risperidone and had symptoms that were stable and no more than moderately severe. After a 5–7-day washout of oral risperidone, patients received 4 consecutive IM injections of open-label risperidone ISM at 28-day intervals. The injection site—either gluteal or deltoid—was randomly assigned. The primary objective of the study was to examine the pharmacokinetics of the active moiety, consisting of risperidone and the active metabolite, 9-OH-risperidone. Safety, tolerability, and efficacy were assessed as secondary, exploratory outcomes.

Results: A total of 67 patients (mean age, 43 years; 82% men) were randomized and received ≥1 injection. Of these, 36 (54%) received all 4 doses and completed all evaluations. Concentrations above the estimated lower therapeutic threshold of 10 ng/mL were achieved within 2 hours of injection, reaching a maximum in 24–48 hours. Time to peak was highly variable among patients, ranging from 2 hours to 21 days. After reaching the peak level following the final dose, the mean plasma half-life of the active moiety was about 11 days. Drug exposure was somewhat higher for the deltoid injection site, but the difference was not clinically significant. There was no drug accumulation after 4 injections.

Adverse effects were as expected for an injectable risperidone formulation and included hyperprolactinemia (54%), injection-site pain (33%), injection-site erythema (15%), and injection-site induration (8%). All episodes of hyperprolactinemia and injection-site reactions were mild or moderate. Other common adverse effects included oromandibular dystonia (13%), sedation (13%), and somnolence (12%).

On average, scores on the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) Severity scale did not change from baseline, indicating symptom control was not compromised by the new formulation. One patient experienced a worsening in the PANSS total score, with active moiety levels slightly below the threshold. Average CGI–Improvement scores indicated minimal improvement.

Discussion: Cytochrome P450 metabolism profiles can affect pharmacokinetics. However, the contribution of these phenotypes (e.g., ultra-rapid, extensive, poor metabolizer) could not be evaluated in the present sample because nearly all patients were identified as extensive metabolizers. An ongoing phase-III trial is expected to provide additional information on optimal dosing and regimens.

Carabias L, Llaudo J, Ayani I, Martinez J, et al: A phase II study to evaluate the pharmacokinetics, safety, and tolerability of risperidone ISM multiple intramuscular injections once every 4 weeks in patients with schizophrenia. *International Clinical Psychopharmacology* 2017; doi 10.1097/YIC.0000000000000203. From Laboratorios Farmaceuticos Rovi, Madrid, Spain; and CBH Health, LLC, Rockville, MD. **Funded by Laboratorios Farmaceuticos Rovi; and other sources. All 6 study authors disclosed financial relationships with commercial sources including Rovi.**

Low Antipsychotic Levels Common in Refractory Schizophrenia

In a cross-sectional study, a clinically significant proportion of patients considered to have treatment-resistant schizophrenia were found to have subtherapeutic antipsychotic plasma levels. Although routine therapeutic drug monitoring is not recommended for patients taking non-clozapine antipsychotics, these results suggest it may be warranted in the assessment of treatment resistance.

Methods: Blood samples were obtained at the time of first assessment in a consecutive series of 99 patients referred to a British community mental health service for assessment and management of treatment-resistant schizophrenia over a 5-year period. Participants had a current prescription for a non-clozapine oral antipsychotic as monotherapy. Therapeutic thresholds were drug specific: 200 µg/L amisulpride; 150 µg/L aripiprazole; 5 µg/L haloperidol; 20 µg/L olanzapine; 100 µg/L quetiapine; 20 µg/L risperidone (total and 9-hydroxy); and 200 µg/L sulpiride. Study patients were followed for a mean of about 1.5 years after their assessment.

Results: Of the 99 patients (median age, 40 years; 64% male; 48% self-reported black ethnicity) evaluated for treatment resistance, 12 had undetectable drug levels and 23 had detectable but subtherapeutic levels (35% in total). Only 2 patients had levels measured in the year prior to their referral. Subtherapeutic levels were associated with black ethnicity and a lower prescribed antipsychotic dose. During follow-up, 31% of patients with a subtherapeutic drug level were hospitalized, compared with 11% of those with a therapeutic level (hazard ratio,* 1.8; p=0.019).

Discussion: Clozapine is the only licensed treatment with proven efficacy in refractory schizophrenia, but subtherapeutic plasma levels should be investigated before prescribing it. If the patient is nonadherent, a long-acting injectable drug should be tried before determining treatment resistance. Other potential causes of low drug levels include rapid metabolism due to genetic variants and enzyme induction secondary to smoking or other medications. It is also possible that some patients with therapeutic levels may not have adequate dopamine receptor occupancy in the brain. Dose increases should be considered when other reasons for a low antipsychotic level have been excluded. Individuals with a subtherapeutic level should be monitored closely.

In the study, plasma samples were not taken at a set time following patients' last dose. For most antipsychotics, the recommendation is to measure trough levels immediately before the next dose, however, this is difficult to carry out in practice. As a result of collection times, the nearly 35% prevalence of subtherapeutic levels may be an underestimate.

McCutcheon R. Beck K, D'Ambrosio E, Donocik J, et al: Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia. *Acta Psychiatrica Scandinavica* 2017; doi 10.1111/acps.12825. From King's College, London U.K.; and other institutions. **Funded by the Medical Research Council–UK; and other sources. Two of 11 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: amisulpride (not available in U.S.)—*Solian*; aripiprazole—*Abilify*; clozapine—*Clozaril*; haloperidol—*Haldol*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*; sulpiride (not available in U.S.)—*Dolmatil, Sulpor

***See Reference Guide.**

Antipsychotics and GI Hypomotility

According to the results of a population-wide retrospective cohort study in patients with schizophrenia or schizoaffective disorder, rates of constipation and other consequences of gastrointestinal (GI) hypomotility are increased with clozapine and quetiapine relative to other antipsychotics. To prevent progression to a more severe outcome, patients taking either of these drugs should be closely monitored for constipation.

Background: Antipsychotic treatment has consistently been associated with constipation. However, previous observations of antipsychotic-associated constipation have been limited to cross-sectional studies or other weaker designs and have not examined the entire spectrum of drugs or GI hypomotility disorders.

Methods: The analysis was based on data from the Taiwan National Health Insurance program and included all adults with schizophrenia or schizoaffective disorder who received a prescription for an antipsychotic for the first time in 2001–2011. Antipsychotics were classified into 6 categories, based in part on their anticholinergic activity: high- and low-potency first-generation agents; clozapine; olanzapine; quetiapine; and all other second-generation agents. The 3 outcomes of interest were constipation, ileus (i.e., paralytic ileus, intestinal pseudo-obstruction, bowel obstruction, and fecal impaction), and ischemic bowel disease. The analysis was adjusted for multiple covariates, including age, gender, medical comorbidities, and the use of tricyclic antidepressants and other anticholinergic medications.

Results: The study cohort consisted of >27,000 patients. Because only 9 cases of ischemic bowel disease occurred, this outcome was not analyzed further. The cumulative incidence of constipation in all antipsychotic users was about 27% (42.5 cases per 1000 person-years), and ileus occurred in about 3% of patients (4.4 cases per 1000 person-years). The drug-specific relative risks of constipation (see table, next page) were increased for clozapine, olanzapine, and quetiapine and decreased for other second-generation agents. Risks of ileus followed a similar pattern. First-generation antipsychotics were associated with increased risk of both outcomes. In

the large subgroup of patients who had ever taken anticholinergics, comprising about two-thirds of the entire cohort, risks of constipation or ileus were further increased in users of high-potency first-generation drugs or clozapine.

Risks of constipation and ileus relative to non-use of the agent		
	Hazard Ratio*	
	Constipation	Ileus
Clozapine	1.64 ‡	1.95 ‡
Quetiapine	1.16‡	1.10
Low-potency first-generation agents	1.14‡	1.28‡
Olanzapine	1.09†	1.22‡
High-potency first-generation agents	1.07‡	1.30 ‡
All other second-generation	0.94†	0.93
†p<0.05 ‡ p<0.001		

Discussion: The present study confirms previous observations, especially regarding clozapine, which is reportedly associated with constipation rates of one-third or higher. Clozapine is associated with a 4-fold higher median colonic transit time than other antipsychotics. Quetiapine has received little attention as a cause of constipation, despite its known anticholinergic effects. Ileus was a rare adverse effect in the present study but is clinically relevant due to its potentially severe consequences.

Chen H-K, Hsieh C-J: Risk of gastrointestinal hypomotility in schizophrenia and schizoaffective disorder treated with antipsychotics: a retrospective cohort study. *Schizophrenia Research* 2017; doi 10.1016/j.schres.2017.10.024. From Tzu Chi University, Taiwan; and other institutions. **Funded by the university. The authors declared no competing interests.**

Common Drug Trade Names*: clozapine—*Clozaril*; olanzapine—*Zyprexa*; quetiapine—*Seroquel

***See Reference Guide.**

Sertraline Efficacy in Kidney Disease

In a placebo-controlled trial, sertraline (*Zoloft*) did not improve depressive symptoms in patients with non-dialysis-dependent chronic kidney disease (CKD).[1] This finding adds to growing evidence that results of large-scale clinical trials, with their conventional selection criteria, may not be applicable to patients with complex multiple illnesses, according to an editorial.[2]

Methods: The trial, conducted at 3 medical centers in Texas, enrolled patients with non-dialysis-dependent stage 3, 4, or 5 CKD and depressive symptoms, with a screening score of ≥11 on the 16-item Quick Inventory for Depressive Symptomatology, self-reported version (QIDS-SR). Patients receiving psychotherapy or a serotonergic drug were excluded. After a 1-week placebo run-in, patients who still met DSM-IV criteria for unipolar major depression were randomly assigned to receive double-blind treatment with 50 mg/day sertraline or placebo. The sertraline dosage was titrated to a maximum of 200 mg/day and kept constant for the final 6 weeks of the 12-week study. The primary study endpoint was change from baseline to week 12 on the clinician-rated QIDS (QIDS-C) score. Among the prespecified secondary endpoints were response (≥50% decrease in the QIDS-C) and remission (final score ≤5).

Results: Of about 1000 patients who met screening criteria, nearly 700 declined participation. A total of 193 completed the placebo run-in and were included in the primary analysis. Patients' average age was 58 years, three-fourths were men, and the mean baseline QIDS-C score was 14. The median sertraline dosage was 150 mg/day. Patients took about 95% of their study medication, 92% completed 6 weeks of treatment, and 84% completed the full 12 weeks.

On average, the QIDS-C decreased by about 4 points in both the sertraline and placebo groups. Remission occurred in about 15% of each treatment group, and response in 32% of the sertraline group and 25% of the placebo group, a nonsignificant difference. Secondary outcomes of function and quality of life also did not differ between the groups.

Discussion: Previous studies investigating the efficacy of antidepressants in patients with CKD are few and of low methodologic quality. Participants in this trial had high prevalences of comorbid illnesses such as diabetes, metabolic syndrome, and congestive heart failure.

The results are consistent with other studies suggesting that SSRIs are not superior to placebo in patients with depression and chronic illnesses such as asthma, ischemic heart disease, and congestive heart failure.

Editor's Note: Reasons for the high refusal rate (70%) were not discussed, and differences in patient characteristics between those who agreed to participate and those who did not could potentially affect the generalizability of the study results.

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

[1]Hedayati S, Gregg L, Carmody T, Jain N, et al: Effect of sertraline on depressive symptoms in patients with chronic kidney disease without dialysis dependence: the CAST randomized clinical trial. *JAMA* 2017;318 (November 21):1876–1890. From the University of Texas Southwestern Medical Center, Dallas; and other institutions. **Funded by the National Institute of Diabetes and Digestive and Kidney Diseases; and other sources. Three of 8 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Walther C, Shah A, Winkelmayer W: Treating depression in patients with advanced CKD: beyond the generalizability frontier [editorial]. *JAMA* 2017;318 (November 21):1873–1874. From Baylor College of Medicine, Houston, TX; and other institutions. **One of 3 authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Abilify MyCite

The recent FDA approval of *Abilify MyCite* (aripiprazole tablets with sensor) marks the first available drug with a digital ingestion tracking sensor embedded in the pill that records medication consumption. The new product is approved for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and for use as an add-on treatment for depression in adults. The digital ingestion tracking system works by sending a message from the pill's sensor to a patch worn by the patient. The patch transmits the information to a smart phone application where patients can track the ingestion of the medication. They can also permit their caregivers and physician to access the information through a web-based portal. It should be noted that the ability of the product to improve medication compliance has not been proven, and *Abilify MyCite* should not be used to track drug ingestion in "real-time" or in emergency situations because detection may be delayed or may not occur.

FDA News Release: FDA approves pill with sensor that digitally tracks if patients have ingested their medication. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm584933.htm.

Antidepressants and Seizure Risk

SSRIs, SNRIs, and some other new-generation antidepressants were associated with increased risk of new-onset seizure in a population-based study. Risk was further increased in adolescent and young adult patients and with higher doses of some agents.

Methods: Study data were collected from the Taiwanese National Health Insurance Research Database, which covers >99% of the population. Study patients were aged ≥10 years, received a prescription for an antidepressant to treat depression in 2002–2012, and had a new diagnosis of epilepsy or convulsions. More than 10,000 patients met these criteria. The data were analyzed with a case-crossover design, comparing antidepressant use during the 30 days before the seizure with antidepressant use during the control period, which was the 91st–120th day before seizure onset. Each patient served as his/her own control. Antidepressants were classified according to their mechanism of action: tricyclics, SSRIs, SNRIs, and others. The analysis was adjusted for use of other medications that could affect seizure thresholds, including antipsychotics, benzodiazepines, mood-stabilizing antiepileptics, and others.

Results: Seizures were uncommon in this population, with a cumulative rate of 0.68% over a mean of 5.4 years of follow-up. Patients who experienced new onset of seizures were an average age of 53 years and were evenly divided between genders. Overall antidepressant use was asso-

ciated with a higher rate of seizures, as was prescription of SSRIs, SNRIs, mirtazapine, and bupropion. (See table). Tricyclics were not associated with seizure risk; nor were the "other" agents moclobemide and trazodone. Risk was increased for each individual SSRI and, among SNRIs, for duloxetine but not milnacipran or venlafaxine. A dose-response association with seizure risk was identified for SSRIs and SNRIs as classes and for bupropion and mirtazapine.

Seizure risk during 30-day periods of antidepressant use vs non-use		
Antidepressant Use	**Adjusted Odds Ratio***	**Significance**
All antidepressants	1.48	p=0.001
SSRIs	1.76	p=0.001
SNRIs	1.40	p=0.01
Mirtazapine	1.38	p=0.05
Bupropion	2.23	p=0.001

Antidepressant-associated seizure risk was highest for patients aged <25 years (adjusted odds ratio, 2.73; p=0.01). Risk was also elevated to a greater degree with major versus minor depression. Gender and medical comorbidity did not influence seizure risk.

Discussion: The lack of an association between tricyclics and seizure was unexpected, as associations with this antidepressant class have been reported in the literature. In the present population, the lack may be due to conservative prescribing of tricyclics; the majority of prescriptions were for <50% of the defined daily dose. In addition, these results may have limited generalizability because the Taiwanese population includes a high proportion of slow metabolizers of antidepressant drugs.

Wu C-S, Liu H-Y, Tsai H-J, Liu S-K: Seizure risk associated with antidepressant treatment among patients with depressive disorders: a population-based case-crossover study. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16m11377. From National Taiwan University, Taipei; and other institutions. **Funded by National Taiwan University Hospital; and the National Health Research Institutes, Taiwan. The study authors declared no competing interests.**

Common Drug Trade Names*: bupropion—*Wellbutrin*; duloxetine—*Cymbalta*; milnacipran—*Savella*; mirtazapine—*Remeron*; moclobemide (not available in U.S.)—*Manerix*; trazodone—*Desyrel*; venlafaxine—*Effexor

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Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

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

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 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 is 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.

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.