PSYCHIATRY DRUG ALERTS

Bringing Clinical Research to Practice

Volume XXXIV / February 2020 / Number 2 www.alertpubs.com

Antipsychotics: Long-Term Morbidity and Mortality

In a nationwide cohort of patients with schizophrenia followed for up to 20 years, long-term antipsychotic use was associated with substantial decreases in all-cause, cardiovascular, and suicide mortality. Hospitalization rates for physical health problems did not differ in individual patients during periods of antipsychotic use and non-use.

Methods: The study population included 62,250 adults who received inpatient treatment for schizophrenia in Finland between 1972 and 2014. Within the cohort, an incident cohort of 8719 first-episode patients initially hospitalized between 1996 and 2014 and with no antecedent antipsychotic use was identified. The study's 2 physical health outcomes—non-psychiatric hospitalizations and cardiovascular hospitalizations—were compared within individuals during periods of antipsychotic use and non-use. The 3 mortality outcomes—all-cause, cardiovascular, and suicide—were compared between individuals for periods of antipsychotic monotherapy, polytherapy, and no antipsychotic therapy, with adjustments for demographics, comorbid physical and psychiatric illnesses, and concurrent pharmacotherapy.

Results: During the 20-year follow-up, cumulative mortality rates were 46% for nonusers of antipsychotics, 26% in those with any use, and 16% in those taking clozapine ($p<0.0001$). In both the full cohort and the incident cohort antipsychotic treatment was associated with reduced mortality rates. (See table.) Significant reductions in mortality were seen with most antipsychotics and were particularly pronounced with clozapine (hazard ratios,* 0.39 all-cause, 0.55 cardiovascular, 0.21 suicide).

Mortality Hazard Ratios over 20 years in antipsychotic users		
Cause	**Full Cohort†**	**Incident Cohort††**
All-cause mortality	0.48	0.64
Cardiovascular	0.62	0.83
Suicide	0.52	0.50
†Between-individual comparison, any antipsychotic use vs. none; ††Within-individual comparison		

Overall, antipsychotic monotherapy was not associated with any difference in cardiac hospitalization or any physical hospitalization between exposure and non-exposure periods. Injectable

PSYCHIATRY DRUG ALERTS (ISSN 2640-7620) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psych@alertpubs.com. Online subscription $105 a year in the U.S.; $113.50 Canada; $123.50 elsewhere; $157 institutional. Subscribers may enroll in the 12-month CME program for an additional $93.00 per year, or enroll in the comprehensive, annual Self-Assessment program for $280 (in the U.S.). M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

fluphenazine was the only individual antipsychotic associated with a statistically significant decrease in hospitalizations for cardiac disease (hazard ratio, 0.46) and for any somatic illness (hazard ratio, 0.69).

Discussion: Patients with schizophrenia have a nearly 15-year shortened average life expectancy compared with the general population. Short-term randomized controlled trials and large observational studies have shown beneficial effects of antipsychotics on mortality, generally attributed to more healthy behaviors and increased contact with the health care system. The present study was large and long enough to allow assessment of long-term outcomes and the effects of specific antipsychotics. Improved control of psychiatric symptoms, allowing for better self-care, may explain why the short-term metabolic adverse effects of antipsychotics did not translate to increased cardiovascular morbidity and mortality.

Taipale H, Tanskanen A, Mehtälä J, et al: 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry* 2020;19 (February):61–68. From the Karolinska Institute, Stockholm, Sweden; and other institutions. **Funded by the Finnish Ministry of Social Affairs and Health. The authors did not include disclosure of potentially relevant financial relationships.**

Common Drug Trade Names*:** **clozapine—*Clozaril*; fluphenazine—*Prolixin

***See Reference Guide.**

Antipsychotics and Ventricular Function

In a cross-sectional controlled study, left ventricular ejection fraction (LVEF) was reduced in medically healthy men receiving longstanding medication for schizophrenia, but not in women. The effect was particularly pronounced for clozapine (*Clozaril*).

Background: Reduced LVEF is an indicator of cardiac dysfunction, with values >50% or >55% considered normal, depending on the guideline. It has recently suggested that clozapine may be associated with subclinical left ventricular dysfunction. The present study was conducted to further explore the reported relationship of low LVEF with antipsychotic medications using computerized magnetic resonance (CMR), a newer and more accurate technique, and to investigate possible gender differences.

Methods: The study included 29 physically healthy patients (18 men) with schizophrenia, recruited from outpatient psychiatric clinics in Sweden. All had a long history of antipsychotic treatment (mean duration, 16.5 years), including clozapine (n=8; 5 as monotherapy), other second-generation antipsychotics (n=14), first-generation agents (n=6), and combined first- and second-generation drugs (n=1). Controls, matched for age, sex, and body mass index, were selected from the general population. LVEF was measured on a single occasion using CMR.

Results: On average, patients with schizophrenia had moderately lower LVEF than controls. For male patients, the difference from matched controls was statistically significant (p=0.0076). Compared with male controls, mean LVEF was 10.6% lower in clozapine-treated men and 5.5% lower in those taking non-clozapine antipsychotics. (See table.)

Mean LVEF in patients receiving long-term antipsychotic treatment vs controls

	Controls	Patients	
		Non-clozapine antipsychotics	Clozapine
Men	63.6	56.5	51.7
Women	61.3	64.5	60.7

Two risk factors, reduced physical activity and higher scores on the AUDIT test of alcohol use, were also associated with lower LVEF, but including these risk factors in the statistical model did not affect the relationship between antipsychotic medication and LVEF.

Discussion: The present results suggest there may be a need for routine cardiac monitoring in patients taking antipsychotic medication, at least in men, possibly from the earliest stages in antipsychotic treatment when early prevention measures can be put into effect. While the results were not significant among women, the potential effects should be investigated in studies with more female subjects.

Andreou D, Saetre P, Fors B, et al: Cardiac left ventricular ejection fraction in men and women with schizophrenia on long-term antipsychotic treatment. *Schizophrenia Research* 2020; doi 10.1016/schres.2019.12.042. From the Karolinska Institute and Stockholm Health Care Services, Sweden; and other institutions. **Funded by the Swedish Research Council. Two of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Opioid Use Disorder Treatment Approaches

In a large nationwide sample of insured patients with opioid use disorder, treatment with buprenorphine or methadone was associated with a lower rate of recurrence than other models of treatment. However, few patients received these treatments.

Background: Despite better access to medical care, commercially insured patients with opioid use disorder rarely receive medications and commonly undergo psychosocial-only treatments. The comparative effectiveness of different treatment pathways has not been well studied.

Methods: The investigators analyzed administrative claims data from a large, diverse cohort of patients with opioid use disorder, enrolled in commercial insurance or Medicare Advantage plans. A total of 6 mutually exclusive treatment pathways were compared: no treatment; inpatient detoxification or residential services; intensive behavioral health; buprenorphine or methadone; naltrexone; and nonintensive outpatient counseling. Patients were followed for at least 90 days and up to 1 year after beginning treatment, or from a randomly selected index date for those who received no treatment. As proxies for recurrence, fatal and nonfatal overdose and opioid-related acute hospitalization were the primary study outcomes.

Results: The cohort included nearly 41,000 patients (mean age, 48 years; 54% men), 58% with commercial insurance and 42% covered by Medicare Advantage (the latter including 25% who were aged <65 years). The most common treatment pathway was nonintensive behavioral health (59%), followed by inpatient or residential services (16%) and buprenorphine or methadone (12.5%). Nearly half of patients were no longer enrolled in their insurance plan after 1 year, but it could not be determined whether this was due to death or loss of coverage. Patients treated with medication had the highest coverage discontinuation rates, about 54%.

During 3 months of follow-up, 707 patients (1.7%) experienced an overdose and 773 (1.9%) had a serious episode of opioid-related care. Compared with patients receiving no treatment, those who received buprenorphine or methadone had a lower rate of overdose or acute care within the 3 months after starting treatment. (See table.) Rates of these outcomes were also lower at 1 year. Intensive behavioral health interventions were also better than no treatment. Inpatient detoxification or residential services, intensive behavioral health interventions, and naltrexone were not associated with statistically significant reductions in recurrence outcomes.

Adjusted Hazard Ratios* for Opioid Relapse		
	3 months	**12 months**
Overdose		
Buprenorphine or methadone	0.24	0.41
Non-intensive behavioral health	—	0.79
Opioid-related ER or inpatient stay		
Buprenorphine or methadone	0.68	0.74
Non-intensive behavioral health	0.59	0.60
Only statistically significant hazard ratios are shown		

Compared with buprenorphine or methadone, all other treatment options

were associated with higher rates of eventual admission to inpatient detoxification. Duration of pharmacotherapy was relatively short, with means of 74 and 150 days, in the buprenorphine or methadone and naltrexone groups, respectively. Longer duration of buprenorphine or methadone treatment was associated with lower rates of overdose and acute care use.

Discussion: Most individuals in this cohort received only psychosocial services or inpatient detoxification, both of which were less effective than pharmacotherapy. Numerous barriers, including a lack of access to waivered practitioners, high copayments and/or prior authorization requirements, and other restrictions, limit the use of pharmacotherapy to treat opioid use disorder and can lead to premature discontinuation in patients who do receive it. The present findings suggest coverage of buprenorphine and methadone should be expanded and include fewer restrictions and that patient-centered treatment models should focus on retaining opioid users on medications.

Wakeman S, Larochelle M, Ameli O, et al: Comparative effectiveness of different treatment pathways for opioid use disorder. *JAMA Network Open* 2020; doi 10.1001/jamanetworkopen.20109.20622. From Massachusetts General Hospital, Boston; and other institutions. **Funded by Boston Medical Center; and other sources. Six of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: buprenorphine—*Subutex*; naltrexone—*ReVia, Vivitrol

***See Reference Guide.**

Buprenorphine/Cannabis Interaction

A small retrospective study in patients undergoing opioid maintenance therapy (OMT) found buprenorphine concentrations were nearly 3-fold higher in patients who used cannabis. Given the increasing medical and recreational use of cannabis, therapeutic drug monitoring of buprenorphine may be prudent.

Methods: Data were analyzed from patients undergoing OMT with either buprenorphine or buprenorphine/naloxone. Patients were required to be receiving OMT for ≥5 years and to be clinically stable while receiving a stable buprenorphine dosage with a take-home prescription. Patients were free of HIV infection and active hepatitis, not using illegal drugs, and not taking medications with known CYP3A4 or CYP2C8 activity, as these enzymes are involved in buprenorphine metabolism. Participants underwent monthly immunologic urine testing for drugs and serum levels of buprenorphine and norbuprenorphine. The probability of a cannabis/buprenorphine interaction was rated using the 10-item Drug Interaction Probability Scale.

Results: A total of 10 patients provided 32 eligible serum buprenorphine measurements over the course of 5 years: 5 patients were consistently negative for all drugs of abuse except nicotine and 5 tested positive for cannabis only. No patient reported cannabis use by prescription. Urine cannabis concentrations in the exposed group were consistent with frequent use of moderate amounts, in agreement with the patients' self-reports of once-daily consumption via smoking.

Mean buprenorphine dosages did not differ between cannabis exposed and unexposed patients (8.6 and 8.8 mg/day, respectively). Cannabis use was strongly associated with serum buprenorphine levels, with mean concentrations of 5.4 ng/mL (range, 2–10) in the cannabis group and 2 ng/mL (range, 0.2–12.6) in the comparison group ($p<0.0002$). On average, norbuprenorphine levels were higher in the cannabis group than controls, although not significantly. The total active moiety and the dose-related active moiety were at least twice as high in the cannabis group as the control group. Three patients who discontinued cannabis use during the study period showed substantial declines in buprenorphine concentrations after cessation, further supporting the probable interaction.

Discussion: These results suggest cannabis consumption lowers the rate of buprenorphine metabolism, most likely due to CYP3A4 inhibition. The possibility of interaction should be

taken into consideration when attempting to wean OMT patients from cannabis use, as it may contribute to buprenorphine withdrawal symptoms and an increased dosage requirement. Caution should be taken when prescribing medical cannabis to patients receiving OMT.

Vierke C, Marxen B, Boettcher M, et al: Buprenorphine-cannabis interaction in patients undergoing opioid maintenance therapy. *European Archives of Psychiatry and Clinical Neuroscience* 2020; doi 10.1007/s00406-019-01091-0. From the University Medical Center Göttingen, Germany, and other institutions. **Funded by the Deutsche Forschungs Gesellschaft. Two of 5 study authors disclosed potentially relevant financial relationships; 2 declared no competing interests; and no disclosure was included for the remaining author.**

Common Drug Trade Names*: buprenorphine—*Subutex*; buprenorphine/naloxone—*Suboxone

SAGE-217 Pharmacokinetics

Pharmacokinetic studies of the investigational $GABA_A$ receptor modulator SAGE-217 indicate that the agent is orally bioavailable in a dose-dependent manner, with low variability, and a relatively short period to reach target concentrations.[1] In addition, minimal accumulation was noted after 7 days of treatment, suggesting that loading doses would not be necessary. The agent has shown preliminary efficacy in major depression.[2]

Methods: Studies were conducted in healthy volunteers, aged 22–55 years, using randomized, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) designs, with 72 and 36 subjects, respectively. Participants in the 9 cohorts of the SAD study received 9 single oral doses, ranging from 0.25 to 66 mg. Dosage in the MAD study were based on results of the SAD study and included 15, 35, and 30 mg/day, administered for 7 consecutive days. One group in the MAD study returned for a second week so that the tolerability of morning and evening dosing could be compared.

Results: Following a single dose, SAGE-217 reached maximum concentrations after 1 hour and had a terminal-phase half-life of 16–23 hours. These parameters were not dose-dependent, but bioavailability was dose-proportional. Accumulation after 7 days of dosing was less than twofold. The maximum tolerated doses of SAGE-217, determined by prespecified stopping criteria, were 55 mg/day in the SAD study and 30 mg/day in the MAD study, 1 level below the maximum dose in each study. Adverse effects of SAGE-217—primarily sedation—were dose-dependent and were less frequent with evening dosing than morning dosing. In the SAD study, 4 patients experienced severe adverse effects (all at the highest dose): changes in mental status (2 patients) and unresponsiveness to stimuli and somnolence in 1 patient each. No patient in the MAD study reported severe adverse effects.

[1]Hoffman E, Nomikos G, Kaul I, et al: SAGE-217, a novel GABAA receptor positive allosteric modulator: clinical pharmacology and tolerability in randomized phase I dose-finding studies. *Clinical Pharmacokinetics* 2020;59:111–120. doi 10.1007/s40262-019-00801-0. From Sage Therapeutics Inc., Cambridge, MA; and other institutions. **Funded by Sage. All study authors disclosed potentially relevant financial relationships with industry sources, including Sage.**

[2]Gunduz-Bruce H, et al: Trial of SAGE-217 in patients with major depressive disorder. *NEJM* 2019;381 (September 5):903–911. See *Psychiatry Drug Alerts* 2019; 33 (September):67–68.

RimabotulinumtoxinB for Sialorrhea

In a phase 3 trial rimabotulinumtoxinB injections (RIMA; *Myobloc*) reduced saliva production in patients with sialorrhea. Treatment was safe and was not associated with the common concerns of oral anticholinergic treatment.

Background: Sialorrhea is often treated with anticholinergic medications. Evidence for their efficacy is limited and adverse effects, including bradycardia, cognitive impairment, drowsiness, and urinary retention, may be particularly troubling in patients with neurologic disorders. Both botulinum toxin A and B are approved for treatment of sialorrhea, but the B type may be particularly effective in secretory disorders due to its greater activity at the cholinergic receptors responsible for salivation.

Methods: The study enrolled adults, aged 18–85 years, with a ≥3-month history of troublesome sialorrhea of any etiology (e.g., Parkinson's disease, stroke, medication-induced). For inclusion, patients were required to meet minimum severity criteria on the Drooling Frequency and Severity Scale (DFSS) and to have an unstimulated salivary flow rate (USFR) of 0.2 g/min. Those who had received prior botulinum toxin injection into the salivary glands were excluded, and all oral and transdermal sialorrhea treatments were discontinued ≥30 days prior to the baseline assessment. By random assignment, patients received RIMA 2500 U or 3500 U or an equivalent volume of placebo injected into both submandibular glands and both parotid glands. The primary study endpoints, assessed at week 4, were change from baseline in the salivary flow rate (USFR) and the Clinical Global Impression–Improvement Scale (CGI-I).

Results: A total of 184 patients (mean age, 64 years; 79% men) were enrolled and treated. Two-thirds had sialorrhea secondary to Parkinson's disease. Both doses of RIMA reduced USFR scores to a similar and significantly greater degree than placebo. Reductions averaged about 0.30 g/min in the active treatment groups, compared with 0.5 g/min in the placebo group ($p<0.001$). CGI-I scores at week 4 were also significantly better with both RIMA doses than with placebo ($p<0.001$ for both). Improvements were evident at week 1 and continued through week 8. At the last visit, weeks 11–15, only the lower dose remained significantly better than placebo. Patient ratings of overall improvement were similar to clinician ratings, with greater improvement in those receiving the lower dose. Although the sample sizes were too small for statistical comparisons, efficacy did not appear to differ based on the cause of sialorrhea.

The most common adverse effects of RIMA were dry mouth, dysphagia, and dental caries. One case of dry mouth led to study discontinuation. One serious adverse event, aspiration pneumonia, was attributed to RIMA. Choking, always considered related to treatment, occurred in 2 patients received RIMA and 2 who received placebo. Little systemic or local spread of the RIMA was identified.

Discussion: Although the present results are positive and support the use of RIMA for sialorrhea, the study sample was primarily male and sialorrhea was due to Parkinson's disease in the majority of patients. The results require replication in larger, more diverse populations.

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

Isaacson S, Ondo W, Jackson C, et al: Safety and efficacy of rimabotulinumtoxinB for treatment of sialorrhea in adults. : a randomized clinical trial. *JAMA Neurology* 2020; 10.1001/jamaneurol.2019.4565. From the Parkinson's Disease and Movement Disorder Center of Boca Raton, FL; and other institutions. **Funded by USWorldMeds LLC. All study authors disclosed relevant financial relationships with commercial sources including USWorldMeds LLC.**

***See Reference Guide.**

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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.

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

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