PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XL / August 2019/ Number 8 www.alertpubs.com

Celebrating 40 Years of Bringing Clinical Research to Practice

Mirabegron: Cardiac Safety

Despite concerns about cardiac safety based on its mechanism of action, results of a population-based cohort study indicate that mirabegron (*Myrbetriq*) is not associated with greater cardiovascular risk than other overactive bladder (OAB) treatments.

Background: Mirabegron is the first Beta3-adrenoceptor agonist approved for treatment of OAB. Compared with the traditionally used antimuscarinic agents, mirabegron appears to have a positive safety profile. However, the agent increases contractile force and reduces inotropic effects, which raises concerns about cardiovascular adverse effects.

Methods: A cohort of >38,000 patients aged ≥65 years with newly initiated OAB treatment were identified from Canadian administrative health-care databases. Patients who received mirabegron were propensity-score matched* with up to 4 comparison subjects who received other OAB treatments. As the primary outcome, the incidence of arrhythmia and tachycardia was compared between the groups over 1 year of treatment. Secondary outcomes included MI and stroke.

Results: A total of 16,948 mirabegron-treated patients were matched with 21,870 patients receiving other OAB treatments. The average patient age was 76 years in both groups, and about 75% of patients were women. Comorbid hypertension and diabetes were common in the cohort, affecting 78% and 35% of patients, respectively. The 1-year incidence of arrhythmia or tachycardia did not differ between the treatment groups (3.6% for mirabegron and 3.8% for other OAB drugs; hazard ratio,* 0.93). Additionally, mirabegron was not associated with a greater incidence of MI or stroke than other OAB agents (hazard ratio, 1.06).

Subgroup analyses were conducted based on patient age (with a cutoff of 75 years) and history of atrial fibrillation or ventricular arrhythmia. Results of these comparisons were consistent with the primary analysis, indicating no increased risk of any cardiovascular outcome with mirabegron.

Tadrous M, et al: Association of mirabegron with the risk of arrhythmia in adult patients 66 years or older–a population-based cohort study [letter]. *JAMA Internal Medicine* 2019; doi: 10.1001/jamainternmed.2019.2011. From Women's College Institute, Ontario, Canada; and other institutions. **Funded by the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund; and other sources. Four of 7 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Hepatitis C Antiviral Warning

The FDA has issued a drug safety communication regarding risk of worsening liver function and liver failure with several antivirals used to treat hepatitis C. The combination agents, glecaprevir and pibrentasvir (*Mavyret*), elbasvir and grazoprevir (*Zepatier*), and sofosbuvir, velpatasvir, and voxilaprevir (*Vosevi*) are intended for treatment of

Primary Care Drug Alerts® (ISSN 1559-5668) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: donna@alertpubs.com. © 2019 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription $105.00 a year in the U.S.; $113.50 Canada; $123.50 elsewhere; $157 institutional. Individual issues are available for $10.00 each. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

hepatitis C only in patients without or with no more than mild liver impairment. An FDA review identified 63 cases of worsening liver function, some of which were fatal, in patients treated with one of these agents. Most cases occurred in patients with moderate or severe liver impairment or other pre-existing risk factors (e.g., liver cancer, alcohol abuse) who should not have been treated with these medications. In most cases, symptoms resolved or improved after stopping treatment. The FDA will continue to monitor the safety of the agents, but notes that when prescribed as indicated they continue to be both safe and highly effective at clearing the virus.

FDA Drug Safety Communication: FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease. Available at https://www.fda.gov/drugs/drug-safety-and-availability.

Cardiovascular Outcomes With Dulaglutide

In a 5-year placebo-controlled trial, the GLP-1 receptor agonist dulaglutide (*Trulicity*) reduced cardiovascular disease outcomes in patients with type 2 diabetes who also had or were at risk for cardiovascular disease.

Background: Previous trials of other GLP-1 receptor agonists, with shorter durations, have had inconsistent results. Several of the trials suggested the agents may reduce cardiovascular outcomes, but only in patients with existing cardiovascular disease.

Methods: This multicenter, multinational trial, conducted by the manufacturer of dulaglutide, was carried out in patients aged ≥50 years with established or newly diagnosed type 2 diabetes. Patients were receiving stable doses of up to 2 oral antihypoglycemic agents, with or without basal insulin therapy. Participants were required to have cardiovascular risk factors from an age-dependent list (e.g., tobacco use; dyslipidemia; hypertension; abdominal obesity; previous MI, ischaemic stroke, or revascularization; left ventricular hypertrophy). Previous treatment with DPP-4 inhibitors or other GLP-1 receptor agonists was discontinued before study entry, but other diabetes medications were continued. Treating physicians were encouraged to promote a healthy lifestyle and to manage diabetes according to guidelines. Patients were randomly assigned to receive double-blind weekly injections of 1.5 mg dulaglutide or placebo. The primary study outcome was a composite of nonfatal MI, nonfatal stroke, and death from cardiovascular or unknown causes.

Results: A total of 9901 patients (mean age, 66 years; 46% women) were randomized, 31% of whom had a diagnosis of cardiovascular disease at baseline. The average duration since diagnosis of diabetes was 9.5 years.

After a median follow-up of 5.4 years, the primary composite outcome occurred in 12% of participants assigned to dulaglutide, compared with 13.4% of the placebo group (hazard ratio,* 0.88; p=0.026). The number needed to treat* to prevent 1 adverse cardiovascular event was 18 for people with a previous event and 60 for those with risk factors only. Effects were consistent for all 3 components of the outcome, although the effect was only statistically significant for nonfatal stroke (hazard ratio, 0.76; p=0.017). Effects of treatment were similar in subgroups based on HbA1c levels (< or ≥7.2%), age, sex, duration of diabetes, and body mass index. Dulaglutide was also associated with a mean reduction in HbA1c of 0.6%, without increasing hypoglycemia and with modest reductions in weight, LDL cholesterol, and systolic blood pressure. Microvascular adverse outcomes were less frequent in patients taking dulaglutide than placebo, largely due to fewer adverse renal outcomes. Dulaglutide did not significantly affect the incidence of all-cause mortality, heart failure, revascularization, hospital admission, fractures, or cholelithiasis.

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

Gerstein H, et al: Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised, placebo-controlled trial. *Lancet* 2019;394 (July 13):121–130. doi 10.1016/S0140-6736(19)31149-3. From McMaster University and Hamilton Health Sciences, Canada; and other institutions. **Funded by Eli Lilly and Company. Fifteen of 38 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Istradefylline for Parkinson's Disease

The course of Parkinson's disease is characterized by "off periods" when existing treatment with levodopa/carbidopa (*Sinemet*) becomes less effective and patients experience worsening of motor symptoms. The FDA has approved a new agent, istradefylline (*Nourianz*), for use as an add-on treatment during these "off periods". In clinical

trials with >1100 patients, those who received 12 weeks of istradefylline experienced significant decreases in daily "off" time, compared with those who received placebo. Common adverse effects of istradefylline included dyskinesia, dizziness, constipation, nausea, hallucinations, and insomnia. If psychotic behavior or impulsive/compulsive behaviors develop, istradefylline should be reduced or discontinued. Use of the agent during pregnancy is not recommended and women with childbearing potential should be advised to use adequate contraception.

FDA News Release: FDA approves new add-on drug to treat off episodes in adults with Parkinson's disease. Available at www.fda.gov/news-events/press-announcements/fda-approves-new-add-drug-treat-episodes-adults-parkinsons-disease.

Lefamulin for Bacterial Pneumonia

Antimicrobial-resistant infections are a global health concern, and the FDA has fast-track protocols for approval of new agents designed to treat serious or life-threatening infections. Following a priority review, the new antibiotic lefamulin (*Xenleta*) has received FDA approval for the treatment of community-acquired bacterial pneumonia. In studies comprising >1200 patients, rates of clinical success with lefamulin administered either orally or intravenously were similar to those of existing treatments for bacterial pneumonia (i.e. moxifloxacin with or without linezolid). Common adverse effects of lefamulin included diarrhea, nausea, vomiting, injection-site reactions, and liver enzyme elevations. Lefamulin can prolong the QT interval, and is not recommended for patients with pre-existing QT prolongation or arrhythmia and concurrent use with other agents that prolong the QT interval should be avoided. Additionally, because of potential fetal risks, women should be advised to use effective contraception during treatment and for 2 days following the final dose.

FDA News Release: FDA approves new antibiotic to treat community-acquired bacterial pneumonia. Available at www.fda.gov/news-events/press-announcements/fda-approves-new-antibiotic-treat-community-acquired-bacterial-pneumonia.

Updated Adult Immunization Guideline

The Advisory Committee on Immunization Practices has released an updated guideline for immunization of adult patients.

Influenza—Routine annual influenza vaccination is recommended for all patients aged ≥6 months who have no contraindication. Trivalent formulations of the vaccine protect against H1N1 and H3N2 influenza A strains and 1 influenza B strain. Quadrivalent vaccines also protect against a second influenza B strain. In older patients (aged ≥65 years) the F*luzone* high dose and the *Fluad* adjuvanted trivalent formulations may be more effective than standard dose trivalent formulations. The quadrivalent intranasal vaccine has been reformulated to increase efficacy against H1N1 strains. Severe egg allergy is no longer a contraindication to any influenza vaccine.

Tetanus, diphtheria, pertussis (Tdap or Td)—The tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine is recommended for adults once in their lifetime. There is no minimum time interval between doses of tetanus toxoid, reduced diphtheria toxoid (Td) and Tdap.

Herpes Zoster—*Shingrix*, a new recombinant herpes zoster vaccine is more effective than the older live attenuated *Zostavax* and is recommended for all immunocompetent persons, for those with chronic medical conditions, and for persons aged ≥50 years receiving low-dose immunosuppressive therapy.

Human papilloma virus (HPV)—*Gardasil 9* is the only available HPV vaccine and offers protection against 9 serotypes of the virus. It is recommended for all patients aged ≤26 years who have not been previously vaccinated. It may also be considered for patients up to age 45 years.

Pneumococcal disease—A single dose of pneumococcal 13-valent conjugate vaccine (PCV13; *Prevnar 13*) can be offered to patients aged ≥65 years who are not immunocompromised. Younger adults at increased risk of invasive pneumococcal disease, including those with an immunocompromising condition, should continue receiving a single dose of PCV13. When possible, PCV13 should be administered before the pneumococcal polysaccharide vaccine (PPSV23; *Pneumovax 23*), which protects against 23 types of pneumococcal bacteria, because higher antibody responses are achieved against serotypes common to both vaccines when administered in this order. For high-risk patients, PPSV23 can be given ≥8 weeks after PCV13, but the interval should be ≥12 months for adults aged ≥65 years who are not immunocompromised. If the PPSV23 is administered first, PCV13 should not be administered for

≥12 months. A maximum of 3 doses of PPSV23 are recommended for high-risk persons, with the first booster dose ≥5 years after the initial dose.

Hepatitis—Routine hepatitis A vaccination is now recommended for all homeless adults. A new recombinant hepatitis B vaccine (*Heplisav-B*) has been approved by the FDA for adults. While the ACIP does not endorse one hepatitis B vaccine over another, the *Heplisav-B* vaccine requires only 2 doses and evidence suggests it is more immunogenic.

Meningococcal disease—A routine Meningococcal ACWY vaccine (*Menactra*, *Menveo*) is recommended for all adolescents at age 11–12 years with a booster at age 16 years, and for military recruits, first-year college students residing in residence halls, travelers to endemic areas, and those with HIV. Immunocompromised patients should receive a 2-dose primary series of MenACWY separated by ≥8 weeks. Those with ongoing risk should receive MenACWY boosters every 5 years. Meningococcal B vaccine (*Bexsero*, T*rumenba;* noninterchangeable) is recommended for at-risk patients including college students.

Sha B: Adult Immunization Update. *JAMA* 2019; doi:10.1001/jama.2019.12739. From Rush University Medical Center, Chicago, Il. **The author declared no competing interests.**

Adult Immunization Guidelines	
Influenza inactivated, influenza recombinant, or influenza live attenuated	1 dose annually
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose of Tdap, with Td booster every 10 years
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born after 1956)
Varicella	2 doses (if born after 1979)
Zoster recombinant (RZV; preferred) or zoster live (ZVL)	2 RZV doses in patients aged ≥50 years or 1 ZVL dose in patients aged ≥60 years
Human papilloma virus (HPV)	Patients aged 19–26: 3 doses if not previously vaccinated Consider up to age 45 years
Pneumococcal conjugate (PCV13)	Patients aged 19–64 years: 1 dose if at risk Patients aged ≥65 years: 1 dose
Pneumococcal polysaccharide (PPSV23)	Patients aged 19–64 years: 1 or 2 doses depending on indication if at risk Patients aged ≥65 years: 1 dose
Hepatitis A	2 or 3 doses depending on vaccine if at risk
Hepatitis B	2 or 3 doses depending on vaccine if at risk
Meningococcal A. C, W. Y	1 or 2 doses depending on indication if at risk, with boosters every 5 years if risk remains
Meningococcal B	2 or 3 doses depending on vaccine if at risk, with boosters if risk remains
Haemophilus influenza type b	1 or 3 doses depending on indication if at risk

Reference Guide

Hazard Ratio: A measure of the risk of an event relative to exposure. 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 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. 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 rating checklists are posted at www.alertpubs.com.

Executive Editor**: Trish Elliott** Associate Editor: **Tara Hausmann**
Assistant Editor: **Donna Foehner** Contributing Editor: **Kate Casano, MsHyg**
Founding Editor: Michael J. Powers