University at Buffalo
School of Pharmacy and Pharmaceutical Sciences

Drug Information Newsletter

Fall 2017

In this issue…

The University at Buffalo School of Pharmacy and Pharmaceutical Sciences (UB SPPS) Drug Information Newsletter is dedicated to providing timely information relevant to healthcare practitioners in New York. The newsletter supplies information on clinical practice guidelines, medication safety issues, new drug approvals/medications under development, medication shortages, and drug class reviews.

Bevyxa™ (Betrixaban)

Olawonuola Abiona, PharmD

Betrixaban (Bevyxa®) is a factor Xa inhibitor that was approved by the Food and Drug Administration (FDA) in June 2017.[1] It is the only oral anticoagulant indicated for prophylaxis of venous thromboembolism (VTE) specifically in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications. There are several other oral anticoagulants, listed in Table 1.

Clinical pharmacology

Betrixaban works by selectively blocking the active site of factor Xa; it does not require a cofactor for activity.[1] Betrixaban inhibits both prothrombinase as well as free factor Xa activity. Through inhibition of factor Xa, the drug decreases thrombin generation, but it does not have a direct effect on platelet aggregation. The peak concentration of betrixaban occurs within 3 to 4 hours of administration, and the oral bioavailability of an 80 mg dose is about 34%. Betrixaban is metabolized primarily through hydrolysis (independent of cytochrome P450 [CYP] enzymes) but is predominantly found unchanged in the human plasma. Less than 1% of minor metabolites are formed via metabolism by CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4. The volume of distribution is 32 L/kg and in vitro plasma protein binding is 60%. Excretion of the drug occurs mostly in the feces (85%) and in the urine (11%). The elimination half-life is between 19 and 27 hours.

In patients with renal impairment, absorption of betrixaban is increased, with a 2.63-fold change in mean area under the curve (AUC) noted among patients with severe renal impairment (estimated glomerular filtration

rate ≥15 to <30 mL/min/1.73 m^2) compared to healthy volunteers.[1] At this time, studies have not been conducted in patient with hepatic impairment.

Table 1. FDA-approved uses and dosing of oral anticoagulants.[1-6]

Drug name (brand, manufacturer)	Mechanism of action	Indication(s)	Dosing
Apixaban (Eliquis®, Bristol-Myers Squibb)	Factor Xa inhibitor	Reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	5 mg BID, unless:
			2 of the following: Age ≥80 y; Wt ≤60 kg; SCr ≥1.5 mg/dL — 2.5 mg BID
		Prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery	Hip: 2.5 mg BID for 35 days
			Knee: 2.5 mg BID for 12 days
		Treatment of DVT and PE	10 mg BID for 7 days
			▼On Day 8 transition to▼
			5 mg BID
		Reduction in risk of recurrent DVT and PE following initial therapy	2.5 mg BID
Betrixaban (Bevyxa™, Portola)	Factor Xa inhibitor	Prophylaxis of VTE in adult patients hospitalized for an acute medical illness, who are at risk for thromboembolic complications	CrCl ≥30 mL/min: 160 mg x1, then 80 mg once daily, for 35 to 42 days
			CrCl ≥15 to <30 mL/min (or using concurrent P-gp inhibitor): 80 mg x1, then 40 mg once daily, for 35 to 42 days
Dabigatran (Pradaxa®, Boehringer Ingelheim)	Direct thrombin inhibitor	Reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	CrCl >30 mL/min: 150 mg BID
			CrCl 15-30 mL/min: 75 mg BID
		Treatment of DVT and PE in patients previously treated with a parenteral anticoagulant for 5-10 days	CrCl >30 mL/min: 150 mg BID
		Reduction in risk of recurrent DVT and PE following initial therapy	
		Prophylaxis of DVT and PE in patients who have undergone hip replacement surgery	CrCl >30 mL/min: 110 mg x1, then 220 mg once daily for 28-35 days
Edoxaban (Savaysa™, Daiichi Sankyo)	Factor Xa inhibitor	Reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	CrCl >50 to ≤95 mL/min: 60 mg once daily
			Do not use if CrCl >95 mL/min
		Treatment of DVT and PE in patients previously treated with a parenteral anticoagulant for 5-10 days	60 mg once daily, unless:
			CrCl 15-50 mL/min, Wt ≤60 kg, or Concurrent use of certain P-gp inhibitors — 30 mg once daily
Rivaroxaban (Xarelto®, Janssen)	Factor Xa inhibitor	Reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	CrCl >50 mL/min: 20 mg once daily (with evening meal)
			CrCl 15-50 mL/min: 15 mg once daily (with evening meal)
		Treatment of DVT and PE	15 mg BID for 21 days
			▼On Day 22 transition to▼
			20 mg once daily

Drug name (brand, manufacturer)	Mechanism of action	Indication(s)	Dosing
		Reduction in risk of recurrent DVT and PE in patients at continued risk after completion of initial treatment for ≥6 months	10 mg once daily
		Prophylaxis of DVT, which may lead to PE, in patients undergoing hip or knee replacement surgery	Hip: 10 mg once daily, for 35 days
			Knee: 10 mg once daily, for 12 days
Warfarin (Coumadin®, Bristol-Myers Squibb)	Vitamin K antagonist	Prophylaxis and treatment of VTE	Individualize and adjust based on INR
		Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement	
		Reduction in risk of death, recurrent MI, and thromboembolic events after MI	

BID=twice daily, CrCl=creatinine clearance, DVT=deep vein thrombosis, INR=international normalized ratio, MI=myocardial infarction, P-gp=P-glycoprotein, PE=pulmonary embolism, VTE=venous thromboembolism, Wt=weight

Dosing and storage

The manufacturer recommends administering betrixaban at an initial single dose of 160 mg, followed by 80 mg once daily.[1] Betrixaban should be administered with food. The recommended duration of treatment ranges from 35 to 42 days.

Patients who have severe renal impairment (creatinine clearance [CrCl] ≥15 to <30 mL/min, calculated using the Cockcroft Gault equation and actual body weight) should receive a reduced dose of betrixaban.[1] The recommended initial dose in these patients is 80 mg followed by 40 mg once daily. Patients who are concurrently taking P-glycoprotein (P-gp) inhibitors should also receive a reduced dose of betrixaban (80 mg on day 1, followed by 40 mg once daily).

If a dose of betrixaban is missed, patients should take it as soon as possible on the same day; the daily dose should never be doubled to make up for a missed dose.[1] Betrixaban is supplied as oral capsules in 2 different dosages (40 mg and 80 mg) and should be stored at room temperature.

Safety

Warnings and precautions

Betrixaban carries a boxed warning that spinal/epidural hematomas may occur if the medication is used in patients receiving neuraxial anesthesia or undergoing a spinal puncture.[1] There may be an increased risk with use of an in-dwelling epidural catheter or concurrent use of medical products affecting hemostasis. Spinal/epidural hematomas can result in long-term or permanent paralysis. To mitigate this risk, an epidural catheter should not be removed earlier than 72 hours after the last dose of betrixaban, and the next dose of betrixaban should not be given earlier than 5 hours after the catheter is removed.

Patients who receive neuraxial anesthesia while taking betrixaban should be monitored frequently for signs of neurological impairment.[1] The potential risks versus benefits of neuraxial intervention must be assessed before it is administered to an anticoagulated patient.

Adverse reactions

There is an increased risk of bleeding with betrixaban, which can be fatal.[1] Concurrent use of medications affecting hemostasis can increase the risk of bleeding. These medications include heparin, thrombolytic agents, aspirin, other antiplatelet agents, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), and serotonin norepinephrine reuptake inhibitors. Patients should be educated on the signs and symptoms of blood loss. At this time there is no reversal agent for betrixaban, and the drug's effects are expected to persist for at least 72 hours after the last dose. Vitamin K, protamine sulfate, and tranexamic acid are not expected to reverse the anticoagulant effects of betrixaban. If a patient is experiencing an active pathological bleed, betrixaban should be discontinued and, if needed, blood products should be administered.

Drug interactions

When P-gp inhibitors such as amiodarone, azithromycin, verapamil, ketoconazole, or clarithromycin are used concurrently with betrixaban, there may be an increase in exposure to betrixaban, which can lead to adverse events.[1] Increased monitoring and dose adjustment may be warranted when betrixaban is co-administered with these medications.

Patients using the following medications concurrently with betrixaban may also require frequently monitoring and dose adjustment as these medications may increase the risk of bleeding: anticoagulants, antiplatelet drugs, thrombolytic, aspirin, and NSAIDs.[1]

Efficacy

Betrixaban was granted a Fast Track designation by the FDA and assigned Priority Review, based on its potential to offer a significant improvement in treatment.[7,8] Approval of betrixaban was based on data from 1 phase 3 trial: the APEX study.

APEX was a double-blind, double-dummy, multinational clinical trial in which patients who were hospitalized for acute medical illnesses were randomized to receive betrixaban or enoxaparin for prevention of VTE.[8] This study was conducted to determine if anticoagulation therapy for an extended period (35-42 days) following hospital discharge would be beneficial. Current guidelines recommend the use of low-dose parenteral anticoagulants for 6 to 14 days in patients at high risk for thromboembolism but advise against extended thromboprophylaxis after hospital discharge.[9] However, the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) is still high for at least the first month after discharge.[8] Per APEX investigators, 3 trials were previously conducted, evaluating use of other anticoagulants (enoxaparin, apixaban, and rivaroxaban) in this patient population, but their findings were not positive.[8,10-12]

Patients included in APEX were aged ≥40 years, hospitalized for <96 hours for heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke, with reduced mobility and at least 1 other risk factor for VTE.[8] These risk factors included: age ≥75 years, age 60-74 years with D-dimer ≥2 times the upper limit of normal (ULN), or age 40-59 years with D-dimer ≥2 times the ULN and a history of either VTE or cancer. Betrixaban was administered at a single loading dose of 160 mg followed by 80 mg once daily for an extended duration of 35 to 42 days, while enoxaparin was administered at a dose of 40 mg once daily for a shorter duration of 6 to 14 days. Patients with severe renal impairment received 50% of these doses (for enoxaparin and betrixaban). Those concomitantly receiving a P-gp inhibitor received a reduced dose of betrixaban (1 dose of 80 mg then 40 mg daily).

After about 35% of patients were enrolled in the study an amendment was made to the protocol, based on findings from the MAGELLAN trial, which indicated that patients with high D-dimer levels had more frequent VTE endpoints compared to the overall study population.[1,8,13] Enrollment was restricted to patients aged ≥75 years or with D-dimer levels ≥2 times the ULN, and statistical analyses were planned for 2 cohorts. Cohort 1

included patients with an elevated D-dimer (≥2 times the ULN) and cohort 2 included patients with an elevated D-dimer and aged ≥75 years.

The primary outcome of APEX was a composite of asymptomatic proximal DVT between days 32 and 47, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE between days 1 and 42.[8] The secondary outcomes were a composite of symptomatic venous thromboembolism through day 42 (death, and non-fatal pulmonary embolism) and a composite of asymptomatic proximal DVT between days 32 and 47, symptomatic DVT, nonfatal PE, or death from any cause through day 42. Efficacy was analyzed based on the modified intent to treat (mITT) population. Patients were included in the analysis if they had ≥1 dose of the study drug and had follow-up assessment data on ≥1 of the primary or secondary efficacy outcome components. These analyses were also conducted in the 2 aforementioned cohorts.

A total of 7,513 patients were included in this study: 3,759 in the betrixaban group and 3,754 in the enoxaparin group.[8] Baseline demographics were well-matched; with the exception of the percentage of participants with CrCl 15-30 mL/min, there were no statistically significant differences between groups.[13] Approximately 55% of participants were female and 93% were Caucasian. The mean age was 76.4 years. The most frequently observed acute medical conditions were decompensated heart failure (45%), acute infection (29%), respiratory failure (12%), ischemic stroke (11%), and rheumatic disorders (3%). In terms of risk factors for VTE, 68% of patients were aged ≥75 years, 97% were severely immobilized at study entry, and 62% had D-dimer ≥2 times the ULN. In this study, 8.3 % of patients in the betrixaban group and 7.9% of patients in the enoxaparin group had a history of DVT or PE.

The efficacy results for the primary outcome in the mITT population are described in Table 2.[8] Notably, only 6,286 of the patients (3,112 in the betrixaban arm and 3,174 in the enoxaparin arm) could be evaluated for the primary outcome. In acute medically ill patients with elevated baseline D-dimer levels (cohort 1), the primary outcome was reported in fewer patients receiving betrixaban vs. enoxaparin; however, the difference was not statistically significant. In contrast, among patients with elevated baseline D-dimer levels and age ≥75 years (cohort 2), as well as the overall population, statistically significant differences were observed in the primary outcome, favoring betrixaban.

In all 3 cohorts, key secondary end points (symptomatic VTE, primary efficacy outcome plus death from any cause, and net clinical benefit) were reported less frequently in the betrixaban group versus the enoxaparin group.[8] However, statistically significant differences were only observed in the overall study population; differences observed between treatment groups in each of the cohorts were not statistically significant.

In addition to efficacy outcomes, patients were monitored for bleeding and other adverse events for up to 77 days.[1,8] Major bleeding occurred in 0.7% of the betrixaban group and 0.6% of the enoxaparin group (relative risk [RR]=1.19; 95% confidence interval [CI] 0.67 to 2.12).[8] The incidence of fatal bleeding was similar in the 2 study groups. In cohort 1, no cases of fatal bleedings were reported in the betrixaban group, but 1 case was reported in the enoxaparin group. In cohort 2, 1 case of fatal bleeding was reported in both treatment groups. Major or clinically relevant nonmajor bleeding occurred in 3.1% of the betrixaban group and 1.6% of the enoxaparin group (RR=1.97; 95% CI 1.44 to 2.68).

The APEX clinical trial showed significant reduction in symptomatic events and asymptomatic DVT with betrixaban compared to enoxaparin in patients hospitalized for acute medical illnesses.[8] This study showed that extended administration of oral betrixaban can reduce the rate of VTE in patients who have predefined risk factors. Though the study did not show a significant difference in the primary efficacy outcome in patients with elevated baseline D-dimer levels, their findings in patients with elevated D-dimer levels and age ≥75 years, as well as the overall study population, suggest that there could be significant thromboembolic benefits associated with extended use of betrixaban, compared to shorter term therapy with enoxaparin.

Table 2. Results of the primary and secondary outcomes in the APEX trial and their components.[8]

Outcome	Cohort 1				Cohort 2				Overall Population			
	Betrixaban (N=1914)	Enoxaparin (N=1956)	Relative Risk (95% CI)	P Value†	Betrixaban (N=2842)	Enoxaparin (N=2893)	Relative Risk (95% CI)	P Value†	Betrixaban (N=3112)	Enoxaparin (N=3174)	Relative Risk (95% CI)	P Value†
	no./total no. (%)				*no./total no. (%)*				*no./total no. (%)*			
Primary end point												
Primary efficacy outcome‡	132/1914 (6.9)	166/1956 (8.5)	0.81 (0.65–1.00)	0.054	160/2842 (5.6)	204/2893 (7.1)	0.80 (0.66–0.98)	0.03	165/3112 (5.3)	223/3174 (7.0)	0.76 (0.63–0.92)	0.006
Asymptomatic proximal deep-vein thrombosis	105	129	NA	NA	128	162	NA	NA	133	176	NA	NA
Symptomatic proximal or distal deep-vein thrombosis	14	19	NA	NA	14	21	NA	NA	14	22	NA	NA
Symptomatic nonfatal pulmonary embolism	5	17	NA	NA	9	18	NA	NA	9	18	NA	NA
Death from venous thromboembolism	12	11	NA	NA	13	13	NA	NA	13	17	NA	NA
Key secondary end points												
Symptomatic venous thromboembolism§	30/2314 (1.3)	44/2313 (1.9)	0.67 (0.42–1.07)	0.09	35/3407 (1.0)	49/3407 (1.4)	0.71 (0.46–1.09)	0.11	35/3721 (0.9)	54/3720 (1.5)	0.64 (0.42–0.98)	0.04
Primary efficacy outcome plus death from any cause¶	232/2014 (11.5)	264/2054 (12.9)	0.89 (0.75–1.05)	0.16	291/2973 (9.8)	329/3018 (10.9)	0.90 (0.77–1.04)	0.15	298/3245 (9.2)	359/3310 (10.8)	0.85 (0.73–0.98)	0.02
Net clinical benefit‖	141/1914 (7.4)	174/1956 (8.9)	0.82 (0.66–1.01)	0.07	174/2842 (6.1)	214/2893 (7.4)	0.82 (0.68–1.00)	0.05	179/3112 (5.8)	233/3174 (7.3)	0.78 (0.65–0.95)	0.01

Summary

It remains to be seen whether betrixaban will be widely used for patients who are at risk for thromboembolic complications. Since betrixaban was granted Fast Track approval by the FDA under Priority Review, available data on the drug are limited. While betrixaban seems to have clear benefits, further trials are necessary to elucidate its place in therapy.

References

1. Bevyxxa™ [package insert]. South San Francisco, CA: Portola Pharmaceuticals, Inc; 2017.
2. Eliquis® [package Insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.
3. Pradaxa® [package Insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2017.
4. Savaysa™ [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc.; 2017.
5. Xarelto® [package Insert]. Titusville, NJ: Janssen Pharmaceuticals; 2017.
6. Coumadin® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.
7. U.S Food and Drug Administration. FDA approved Betrixaban (BEVYXXA, Portola) for the prophylaxis of venous thromboembolism (VTE) in adult patients. Available at: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm564422.htm. Accessed September 20, 2017.
8. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med*. 2016;375(6):534-544.
9. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e195S-e226S.
10. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. *Ann Intern Med*. 2010;153(1):8-18.
11. Cohen AT, Spiro TE, Büller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368(6):513-523.
12. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med*. 2011;365(23):2167-2177.
13. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. Supplement. Available at: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1601747/suppl_file/nejmoa1601747_appendix.pdf. Accessed October 31, 2017.

Adjunctive Minocycline in the Treatment of Psychiatric Illness

Emily Leppien, PharmD

Introduction/Background

Recently, the World Health Organization (WHO) reported that antimicrobial resistance is a significant threat to effective prevention and treatment of an increasing range of infections, and the Centers for Disease Control and Prevention (CDC) documented that up to 50% of antibiotics prescribed in acute care hospitals within the United States (US) were either inappropriate or unnecessary.[1,2] The CDC also identified that antimicrobial agents are among the most commonly prescribed medications within nursing homes with up to 70% of long-term care facility patients receiving at least 1 antibiotic prescription annually.[3] These statistics and increasing antimicrobial resistance have led to an emphasis on the need to decrease the inappropriate use of antimicrobial agents within healthcare settings.

At the beginning of 2017, the Joint Commission announced a new medication management (MM) standard for all hospitals and nursing home facilities.[4] This new standard speaks to the increase in inappropriate antimicrobial prescribing by addressing antimicrobial stewardship. Effective January 1, 2017, stewardship interventions must now include both restriction and enablement methods to assist healthcare providers in adherence to guidelines to prevent overuse and misuse of antimicrobial agents. The key requirements of this new standard include establishing a multidisciplinary antimicrobial stewardship committee to assess appropriateness of antibiotics, reporting information on antibiotic use and resistance patterns, and developing protocols or policies/procedures for treatment of common infections, including educating staff on antimicrobial resistance and appropriate use of antibiotics.

Initially, it may seem as if this new standard does not have much relevance within a psychiatric hospital, as antibiotic use is lower in this setting compared to acute care hospitals; however, antibiotic use for the potential treatment of psychiatric illnesses is currently under investigation. Recent scientific literature has suggested that minocycline, a second-generation tetracycline antibiotic, has potential as an adjunctive treatment option in psychiatric illness for schizophrenia, major depressive disorder, bipolar disorder, and obsessive-compulsive disorder (OCD). [5]

Current psychotropic agents used to treat psychiatric illness correct dysfunctional neurotransmitter systems to alleviate a multitude of symptoms. While these treatment options have demonstrated efficacy, patient response to these treatment options may not always be adequate. There is new evidence to suggest that inflammation, oxidative stress, and changes to the glutamatergic pathways can also play a role in many psychiatric illnesses.[6,7] As an inhibitor of microglial activation, minocycline can modulate glutamate-induced excitotoxicity, and it also has anti-inflammatory, antioxidant and neuroprotective effects.[6] This has led to the hypothesis that minocycline may be effective treatment for symptoms of psychiatric illness.

Minocycline: proposed mechanisms of action

Initial evidence of minocycline's mechanism of action was demonstrated in animal studies.[6] High-dose minocycline has been reported to reduce levels of interleukin (IL)-1ß, prostaglandin-E2 (PGE2), superoxide production, and inhibit cyclo-oxygenase-2 (COX-2) in rats and mice. Minocycline also reduced markers of oxidative stress including nitrite, protein carbonylation and thiobarbituric acid in animal models. These results propose that minocycline has robust effects on redox systems.

Minocycline has been shown to exhibit neuroprotective factors by reducing lesion volume and memory degradation caused by ischemia.[6] Minocycline also has documented effects on neurotrophins by reducing expression of brain-derived neurotrophic factor (BDNF). Lastly, following minocycline treatment, rats previously administered glutamate, had increased cell viability compared to controls, which indicated decreased N-methyl-D-aspartate (NMDA) receptor activation and glutamate-induced neurotoxicity. The proposed mechanisms of action of minocycline are illustrated in Figure 1.

Figure 1. Proposed mechanisms of action of minocycline.[6]

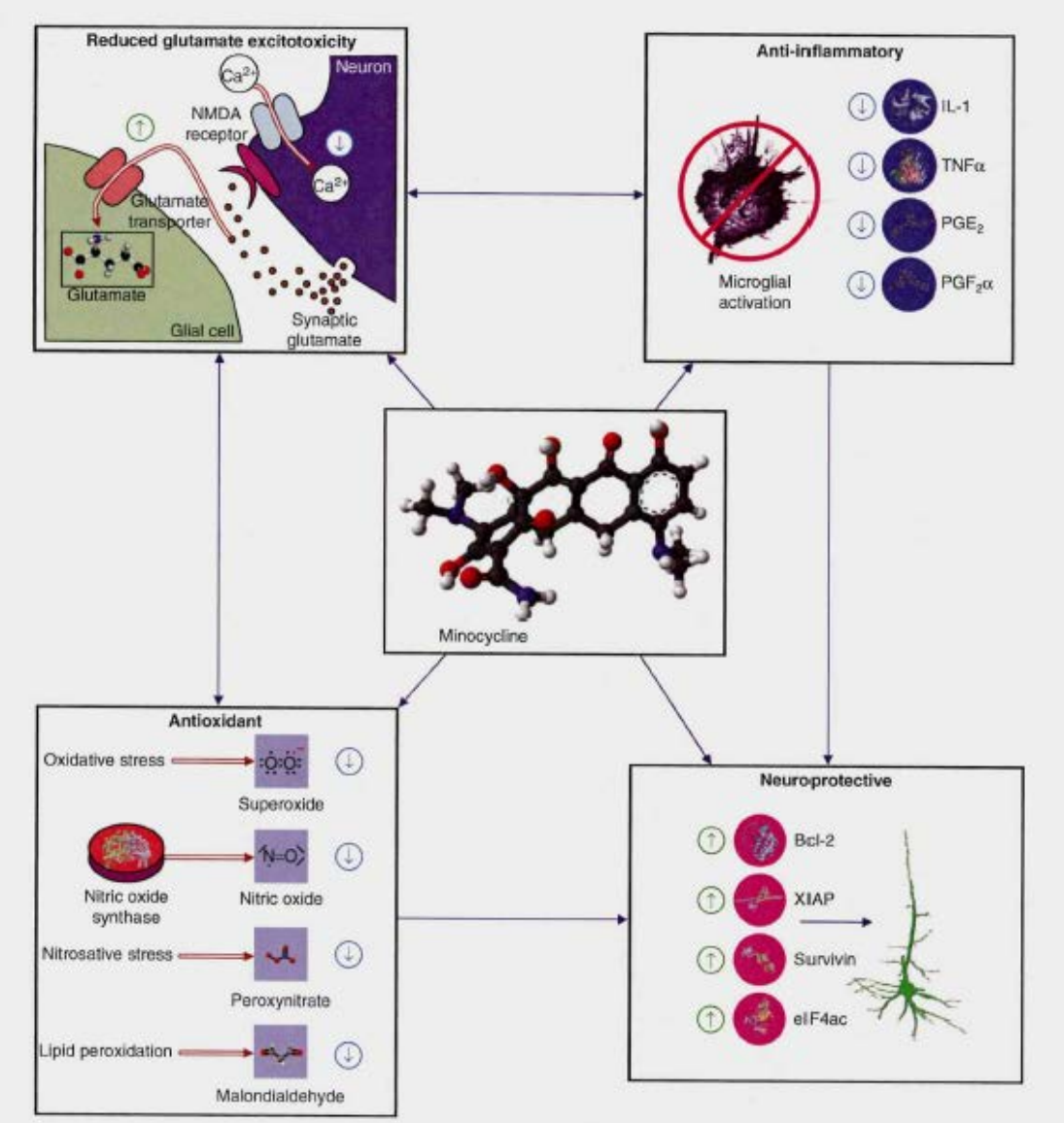


Fig. 1. Proposed mechanisms of action, including reduced glutamate excitotoxicity, inflammation, oxidative stress and augmented neurogeneis, targeted by minocycline that may benefit the symptoms of psychiatric illness. **IL-1** = interleukin-1; **PGE_2** = prostaglandin-E_2; **$PGF_2\alpha$** = prostaglandin $F_2\alpha$; **TNFα** = tumour necrosis factor-α; ↑ indicates increases; ↓ indicates decreases.

Minocycline efficacy in psychiatric illness

The efficacy and safety of adjunctive minocycline for the treatment of bipolar disorder, depression, or OCD was investigated in 3 clinical trials.[8-10] Selected findings and characteristics of the methods used in these studies are outlined in Table 1. In all 3 trials, minocycline was titrated to a dose of 100 mg twice daily. The primary endpoint varied based on the psychiatric condition being evaluated.

Table 1. Summary of selected trials evaluating efficacy and safety of minocycline in psychiatric illness.[8-10]

Trial	Design & Duration	Population	Interventions	Efficacy Outcomes	Safety Outcomes
Soczynska et al[8] 2017	OL 8 weeks	27 outpatients in Canada, aged 18-65 years, meeting DSM-IV criteria for **BD-I/II with depressive episode**, HAM-D ≥20, receiving prior, individualized therapy for ≥4 weeks	Adjunctive minocycline 100 mg PO BID	Comparing baseline to 8-week scores: • MADRS: difference=0.835, p<0.001* • HAM-D: difference=0.949, p<0.001* • CGI-S: difference=1.09, p<0.001* Adjunctive minocycline was associated with a significant reduction in depressive symptom severity from baseline to week 8 using MADRS, HAM-D and CGI-S scales.	• 2 serious ADE: mixed episode with psychotic features and severe abdominal pain resulting in hospitalization → determined that emergent hypomania was not a result of adjunctive minocycline as measured by YMRS (p=0.624) • No significant effect of time on intensity of SI as measured by C-SSRS (p=0.145) → emergence of SI in 1 individual that became serious at week 8; no identified cases of suicidal behavior
Dean et al[9] 2017	R, DB, PC 12 weeks	71 outpatients in Australia and Thailand, mean age of 50 years, meeting DSM-IV criteria for **depression**, MADRS ≥25, receiving prior, individualized therapy for ≥2 weeks	Adjunctive minocycline 100 mg PO BID vs. placebo	Between-group difference (95% CI); p-value: • MADRS: -2.0 (-7.1, 3.2); p=0.624 • CGI-S: -0.4 (-1.0, 0.3); p=0.483 • CGI-I: -1.0 (-1.8, -0.3); p=0.022* • PGI: -0.9 (-1.5, -0.2); p=0.084 • Q-LES-Q: 0.1 (0.0, 0.2); p=0.0048* The difference between minocycline and placebo in the MADRS, CGI-S and PGI scores were not significant. There were significant improvements in global impression, functioning and quality of life, which are being recognized as more comprehensive measures of clinical outcomes, as these are specific to how the patients rate their symptoms.	No significant difference in the total number of ADE (p=0.999)

Trial	Design & Duration	Population	Interventions	Efficacy Outcomes	Safety Outcomes
Esalatmanesh et al[10] 2016	R, DB, PC 10 weeks	94 outpatients in Iran, aged 18-50 years, with **moderate-to-severe OCD** (Y-BOCS-T ≥21), receiving fluvoxamine 100 mg/day for 4 weeks followed by 200 mg/day for 6 weeks	Adjunctive minocycline 100 mg PO BID vs. placebo	Between-group difference (95% CI); p-value: • Y-BOCS-T: 3.21 (0.84, 5.58); p=0.008* • Y-BOCS-O: 2.12 (0.75, 3.50); p=0.002* • Y-BOCS-C: 1.53 (0.21, 2.84); p=0.02* • # remitters: 2.50 (1.06, 5.90); p=0.03* The result showed that minocycline significantly reduced OCD symptoms as an adjuvant agent to fluvoxamine in moderate-to-severe OCD patients compared to placebo.	Frequency of ADE (i.e. GI effects, sedation, insomnia, dizziness and headache) did not differ significantly between the 2 groups (p>0.05)

ADE=adverse drug event, BD=bipolar disorder, BID=twice daily, CI=confidence interval, DB=double-blind, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, EPS=extrapyramidal symptoms, GI=gastrointestinal, OCD=obsessive-compulsive disorder, OL=open-label, PC=placebo-controlled, PO=by mouth, R=randomized, SI=suicidal ideation

CGI-I=Clinical Global Impression-Improvement Scale (range 1-7), CGI-S=Clinical Global Impression-Severity Scale (range 1-7), C-SSRS=Columbia Suicide Severity Rating Scale (series of yes vs. no questions), HAM-D=Hamilton-Depression Rating Scale (range 0-52), MADRS=Montgomery-Asberg Depression Rating Scale (range 0-6), PANSS=Positive and Negative Syndrome Scale (range 0-210), PGI=Patient Global Impression Scale (range 1-7), Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire (range 14-70), SANS=Scale for Assessment of Negative Symptoms (range 0-125), Y-BOCS-C=Yale-Brown Obsessive Compulsive Compulsion Subscale Score (range 0-20), Y-BOCS-O=Yale-Brown Obsessive Compulsive Scale Obsession Subscale Score (range 0-20), Y-BOCS-T=Yale-Brown Obsessive Compulsive Scale (range 0-40), YMRS=Young Mania Rating Scale (range 0-60)

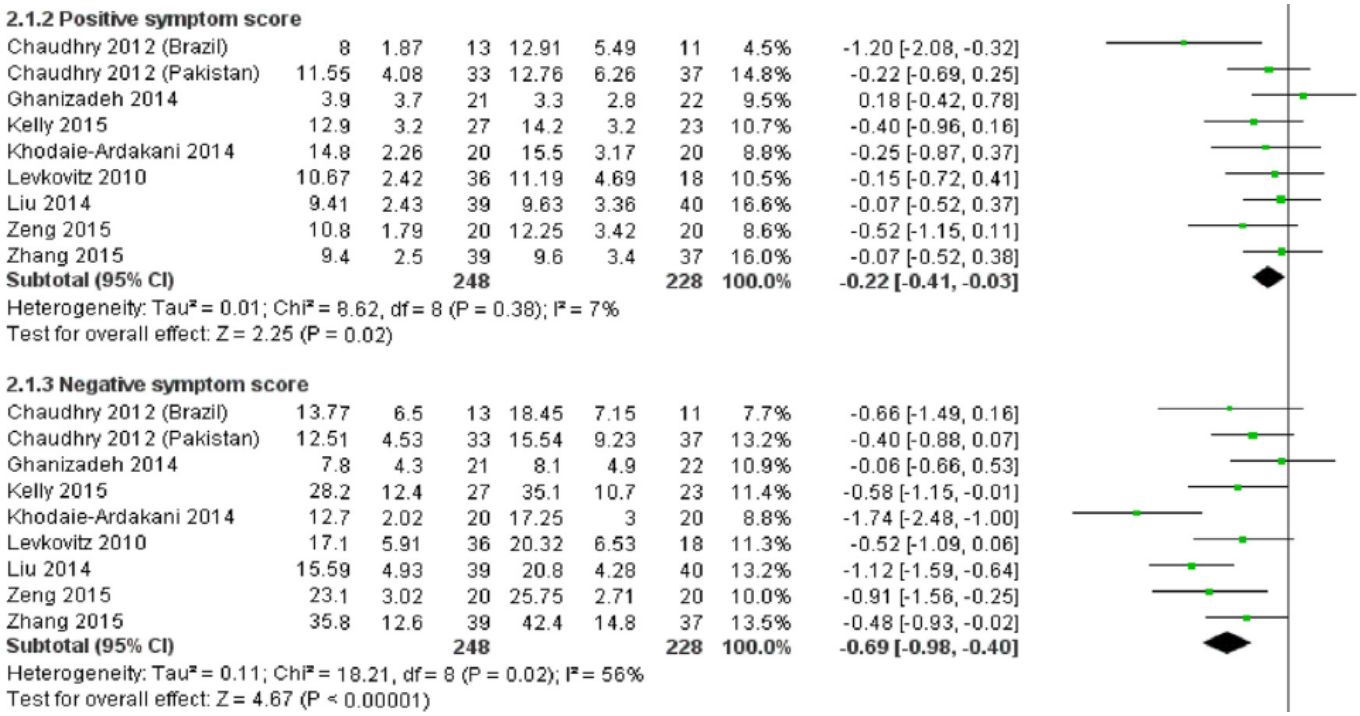
*=significant difference

A recently published meta-analysis included 8 studies comparing adjunctive minocycline versus placebo in patients with schizophrenia.[11] The investigators included randomized controlled trials published through January 2016 in both Chinese and English databases. A total of 548 patients, majority male (63.5%), were included, with ages ranging from 25 to 43 years. The dosage of minocycline in these studies ranged from 50 to 200 mg/day, with a median of 175 mg/day, given over 18.57 ± 13.4 weeks (range of 8-48 weeks, median 14 weeks).

The primary outcome was symptomatic improvement assessed using the Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS).[11] Secondary outcome measures included Scale for Assessment of Negative Symptoms (SANS), positive and negative subscales of the PANSS/BPRS, Abnormal Involuntary Movement Scale (AIMS), Extrapyramidal Symptoms Rating Scale (ESRS), and discontinuations due to adverse drug reactions (ADRs).

Minocycline was found to be superior to placebo when comparing total PANSS and BPRS scores (95% confidence interval [CI] -0.9, -0.18; p=0.004).[11] Comparative analyses of positive symptom scores and negative symptom scores also revealed superiority of minocycline to placebo (standard mean difference [SMD] -0.22; 95% CI -0.41, -0.03; p=0.02, and SMD -0.69; 95% CI -0.98, -0.40; p<0.00001, respectively), as seen in Figure 2.

Figure 2. Selected findings from a meta-analysis of randomized controlled trials evaluating efficacy of adjunctive minocycline for schizophrenia.[11]



Xiang et al found all-cause discontinuation was not significantly different between adjunctive minocycline treatment and placebo (relative risk [RR]=1.11; 95% CI 0.85, 1.46; p=0.44).[11] No statistically significant differences were observed between groups in terms of discontinuation due to inefficacy/relapse (RR=0.80; 95% CI 0.26, 2.40; p=0.69) or intolerability (RR=1.85; 95% CI 0.59, 5.86; p=0.29). Seven of the 8 trials reported ADRs, with weight gain (11.3%), dizziness (9.1%), and nausea/vomiting (7.6%) being the most common in the minocycline group. Comparisons of ADRs between the 2 groups (including akathisia, weight gain, dizziness, nausea/vomiting, EPS, anticholinergic effects, or sedation) revealed no statistically significant differences (RR=0.59–2.00; 95% CI 0.08, 12.37; p=0.12–1.00), confirming minocycline's safety profile.

Discussion/Conclusion

Current FDA-approved treatment options for psychiatric disorders have substantial documented efficacy; however, there are instances in which response to these treatment options is suboptimal. While traditional psychotropic treatment options focus on correcting neurotransmitter dysfunction to improve psychiatric symptoms, there is growing evidence that inflammation, oxidative stress, and glutamate pathological changes have an effect in psychiatric conditions. Minocycline's proposed mechanisms overlap with these newly understood pathological changes that occur in patients with psychiatric disorders.

The efficacy of adjunctive minocycline in the treatment of psychiatric illness has been demonstrated in the aforementioned trials.[8-11] A major limitation of the available evidence, however, is the limited number of published studies and the small sample sizes. Adjunctive minocycline does appear to be efficacious and safe in the treatment of bipolar disorder, major depressive disorder, OCD, and schizophrenia. Although the optimal therapeutic dose of minocycline that should be used in the treatment of psychiatric illnesses is not as clear, it appears that 100 mg twice daily may be effective in the studied conditions.

The available evidence suggests that minocycline may potentially play a role in the adjunctive treatment of psychiatric illness;[8-11] however, more research is needed to confirm its place in therapy. Based on the recent literature, use of minocycline for the treatment of psychiatric illnesses may increase. If minocycline is used, clinicians should carefully monitor for symptomatic improvement with appropriate rating scales, as well as ADRs, to ensure safe and effective use. With the new MM standard from the Joint Commission, minocycline use in psychiatric hospitals will be closely monitored through antimicrobial stewardship committees.

References

1. World Health Organization. Antimicrobial Resistance. Updated April 2015. http://www.who.int/mediacentre/factsheets/fs194/en/#. Accessed October 27, 2017.
2. Centers for Disease Control and Prevention. Core Elements of Hospital Antibiotic Stewardship Programs. http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html. Accessed October 27, 2017.
3. Centers for Disease Control and Prevention. Antibiotic Use in Nursing Homes. November 5, 2013. https://www.cdc.gov/longtermcare/prevention/antibiotic-stewardship.html. Accessed October 27, 2017.
4. Joint Commission on Hospital Accreditation. New antimicrobial stewardship standard. *Jt Comm Perspect*. 2016;36(7):1,3-4,8.
5. Beovic B, Plesnicar BK, Potocan M, et al. Antibiotic prescribing in psychiatric hospitals and interactions between antibiotics and psychotropic drugs: a prospective observational study. *Infect Control Hosp Epidemiol*. 2016;37(2):233-235.
6. Dean OM, Data-Franco J, Giorlando F, Berk M. Minocycline: therapeutic potential in psychiatry. *CNS Drugs*. 2012;26(5):391-401.
7. Zhang L, Zhao J. Profile of minocycline and its potential in the treatment of schizophrenia. *Neuropsychiatr Dis Treat*. 2014;10:1103-1111.
8. Soczynska JK, Kennedy SH, Alsuwaidan M, 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 Disord*. 2017;19(3):198-213.
9. Dean OM, Kanchanatawan B, Ashton M, et al. Adjunctive minocycline treatment for major depressive disorder: a proof of concept trial. *Aust N Z J Psychiatry*. 2017;51(8):829-840.
10. Esalatmanesh S, Abrishami Z, Zeinoddini A, et al. Minocycline combination therapy with fluvoxamine in moderate-to-severe obsessive-compulsive disorder: A placebo-controlled, double-blind, randomized trial. *Psychiatry Clin Neurosci*. 2016;70(11):517-526.
11. Xiang YQ, Zheng W, Wang SB, et al. Adjunctive minocycline for schizophrenia: a meta-analysis of randomized controlled trials. *Eur Neuropsychopharmacol*. 2017;27(1):8-18.

$SGLT_2$ Inhibitors: Safety Update

Katie Frieling, PharmD

According to the National Institutes of Health, diabetes mellitus affects nearly 30.3 million Americans, which represents roughly 9.4% of the population in the United States.[1] It is a complex disease that requires both non-pharmacologic and pharmacologic treatment in order to meet diabetes treatment goals. The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) both recommend that sodium-glucose cotransporter 2 ($SGLT_2$) inhibitors be used early in diabetes management.[2,3]

While a variety of medications have demonstrated effectiveness in the management of type 2 diabetes, some have been associated with cardiovascular adverse events. In 2007, a meta-analysis was published showing an increased risk of myocardial infarction (MI) in patients taking rosiglitazone.[4] This led to a new Food and Drug Administration (FDA) requirement for evaluation of cardiovascular safety of diabetes medications, not only for medications in development, but also for already approved medications. The FDA defines the acceptable safety standard as the study drug being non-inferior to placebo using a composite outcome that includes a minimum of cardiovascular mortality, non-fatal MI, and non-fatal stroke.

The following will review the safety of $SGLT_2$ inhibitors, which include canagliflozin (Invokana®), empagliflozin (Jardiance®), and dapagliflozin (Farxiga®). These medications work by inhibiting $SGLT_2$ found in the proximal renal tubules.[5] Inhibition of $SGLT_2$ results in decreased reabsorption of glucose back into the blood stream. By blocking the reabsorption and ultimately enhancing the excretion of glucose, plasma glucose levels decrease along with glycosylated hemoglobin (A1c) values.

As with every medication, there are risks and benefits that should be considered when determining appropriateness of therapy. While the risk of hypoglycemia of $SGLT_2$ inhibitor monotherapy is low, because its mechanism of action is not associated with insulin secretion, hypoglycemia has been reported when an $SGLT_2$ inhibitor is used in combination with other antidiabetic medications.[4,5]

There are case reports suggesting that $SGLT_2$ inhibitors are associated with the development of diabetic ketoacidosis (DKA).[6] The authors suggest that $SGLT_2$ inhibitors may cause an increase in glucagon secretion by the alpha cells in the pancreas, which then leads to a decrease in insulin production. From what has been reported, the majority of DKA cases are in type 1 diabetes mellitus patients; the incidence is low in patients with type 2 diabetes.[5] Of note, the AACE does not consider the risk of DKA to be relevant to clinical use of $SGLT_2$ inhibitors in patients with type 2 diabetes.[6,7]

In addition to the above, manufacturers of $SGLT_2$ inhibitors warn that hypotension may develop, as a result of a decrease in intravascular volume.[5,8,9,10] Hypotension appears to be worse in patients who are concurrently taking diuretic medications. Discontinuation of the diuretic is recommended upon initiation of an $SGLT_2$ inhibitor; patients should be reassessed for continued need of the diuretic.

Further, there is a warning for increased risk of bone fractures with $SGLT_2$ inhibitors, and it is recommended to avoid use of these drugs in patients with additional risks for fractures.[5,8,9,10] It is thought that the risk for fractures may increase due to alteration of absorption and excretion of calcium and phosphate which negatively impacts bone health. Researchers found that canagliflozin led to decreased bone mineral density in the hip and lower spine.[11]

Moreover, the labeling mentions the potential for $SGLT_2$ inhibitors to increase low-density lipoprotein (LDL) cholesterol levels.[8,9,10] As such, it is recommended to monitor cholesterol levels and treat patients accordingly.

Additionally, the manufacturers note that $SGLT_2$ inhibitors can cause acute kidney injury (AKI).[8,9,10] Per the product labels, $SGLT_2$ inhibitors should be temporarily discontinued in patients who are experiencing

decreased oral intake or experiencing fluid losses. It is recommended to monitor renal function upon initiation of the medication and periodically throughout treatment.

Though not previously mentioned, $SGLT_2$ inhibitors are also associated with increased risk for genital mycotic infections and urinary tract infections (UTIs).[5] However, they are generally mild and respond to treatment.

In order to meet the FDA requirement regarding cardiovascular safety concerns, the manufacturers of $SGLT_2$ inhibitors are performing long-term studies focusing on cardiovascular outcomes. The first study was the EMPA-REG OUTCOME trial, published in 2015.[12] This was a randomized, double-blind, placebo-controlled trial designed to assess the cardiovascular outcomes of empagliflozin versus placebo against a background of standard diabetes care. This trial included adult patients with type 2 diabetes with a body mass index (BMI) of ≤45 kg/m^2 and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2. Patients were required to have a history of cardiovascular disease and either received no glucose-lowering therapy for at least 12 weeks prior to randomization (with A1c between 7 and 9%), or received stable glucose-lowering therapy for at least 12 weeks prior to randomization (with A1c between 7 and 10%). Patients were randomized in a 1:1:1 manner to empagliflozin 10 mg/d, empagliflozin 25 mg/d, or placebo based on their baseline A1c, BMI, renal function, and geographic region. The patients were monitored for approximately 124 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke and was assessed in the pooled empaglifozin group vs. the placebo group. Secondarily, researchers assessed the composite of the primary outcome components plus hospitalization for unstable angina. The safety endpoints addressed included confirmed hypoglycemic adverse events, urinary tract infections (UTIs), genital infections, volume depletion, acute renal failure, bone fractures, DKA, and thromboembolic events.

Findings from EMPA-REG OUTCOME met the FDA requirement with significantly fewer primary events observed in the empagliflozin groups compared to the placebo group (37.4 vs. 43.9 events/1,000 patient years; hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.74-0.99).[12] The results concerning the primary outcome plus hospitalization for unstable angina showed no statistically significant difference between empagliflozin and placebo (46.4 vs. 52.5 events/1,000 patient years; HR 0.89, 95% CI 0.78-1.01). With regard to safety, significant differences were observed between groups in genital infections (6.4% with empagliflozin, 1.8% with placebo, $p<0.001$) and acute renal failure (5.2% with empagliflozin, 6.6% with placebo, $p<0.01$). Similar rates were observed between groups for hypoglycemia, UTIs, volume depletion, and bone fractures. Confirmed hypoglycemic adverse events occurred in 27.8% of empagliflozin subjects and 27.9% of placebo subjects (p=not reported). UTIs occurred in 18% of empagliflozin subjects and 18.1% of placebo subjects (p=not reported). Volume depletion occurred in 5.1% of empaglifozin subjects and 4.9% of placebo subjects (p=not reported). Researchers found that 3.8% of empagliflozin subjects developed bone fractures vs. 3.9% with placebo (p=not reported). In addition, DKA was documented for 0.1% of empagliflozin subjects and <0.1% of placebo subjects (p=not reported). Also, thromboembolic events occurred in 0.6% of empagliflozin subjects and 0.9% in placebo subjects (p=not reported).

The second cardiovascular trial for the class, CANVAS, was published in June 2017 and evaluated canagliflozin.[13] This was a prospective, randomized, placebo-controlled trial. Participants included patients with type 2 diabetes, aged ≥30 years, with a history of symptomatic atherosclerotic cardiovascular disease; OR aged ≥50 years with ≥2 risk factors for cardiovascular disease. All patients were required to have eGFR >30 mL/min/1.73 m^2. The primary outcome was defined as a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The secondary outcomes included death from any cause, death from cardiovascular causes, progression of albuminuria, and the composite of death from cardiovascular causes and hospitalization for heart failure.

The mean follow-up period for CANVAS was 188.2 weeks.[13] The CANVAS results met the standards set by the FDA with significantly fewer participants in the canagliflozin arm experiencing a primary outcome event compared to the placebo arm (26.9 vs. 31.5 events per 1,000 patient-years; HR 0.86, 95% CI 0.75-0.97; $p<0.001$). However, a new safety concern was identified with canagliflozin: an increased risk of lower limb

amputations (canagliflozin vs. placebo: 6.3 vs. 3.4 participants per 1000 patient years; HR 1.97, 95% CI 1.41-2.75). Researchers are not sure of the connection between canagliflozin and lower limb amputations or if amputations will be seen as a class effect. It is recommended for patients to closely monitor their lower extremities, stay well hydrated, and report any new pain, tenderness, or infections that develop.[14] Based on this finding, the FDA issued an additional boxed warning for lower limb amputation, only applicable to canagliflozin.[8]

The cardiovascular study of dapagliflozin, DECLARE-TIMI 58, is currently in progress and should be completed by the Spring of 2019.[15,16] Outcomes to be evaluated include cardiovascular events and, also, lower limb amputations.

A meta-analysis regarding empagliflozin examined data from 14 phase I-III trials and 4 extension studies that looked for trends concerning safety and tolerability.[17] The analysis included trials that varied in length from 8 days to 72 weeks. The studies consisted of empagliflozin as monotherapy, added on to metformin, added on to metformin and a sulfonylurea, added to pioglitazone with or without metformin. The assessment was performed based on the adverse events reported by the trial investigators.

Findings from the meta-analysis indicated no significant difference in limb amputations in patients treated with empagliflozin or placebo.[17] However, these data should be interpreted cautiously because many of the studies included were of varying duration and the amputation rate data were rarely provided in the articles. Data were manually collected and showed a lower limb amputation frequency of 1.1% in all study groups (empagliflozin 10 mg/d, 25 mg/d, and placebo). The majority of the events were from the EMPA-REG OUTCOME trial.[12,17]

The risk of lower limb amputation associated with $SGLT_2$ inhibitors is being addressed in Europe as well. The European Medicines Agency stated that while there is not enough evidence to support the risk in all 3 medications within the class, based on the available data, concern is warranted for all of the $SGLT_2$ inhibitors.[18]

These medications have a mechanism of action that, when used alone, seemingly reduce the risk of hypoglycemia, but at the same time, increase the chance of developing DKA, hypotension, bone fractures, increased LDL, AKI, genital yeast infections, UTIs, and now lower limb amputations. The ADA and AACE recommend use of $SGLT_2$ inhibitors early in diabetes management, but it is important to be aware of the potential risks and discuss them with the patient.[2,3] As with any new class of medication, information regarding the benefits and risks is still being determined; therefore use of $SGLT_2$ inhibitors should only be recommended after careful evaluation of the individual patient.

References

1. National Institute of Diabetes and Digestive and Kidney Diseases. What is Diabetes? https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes. November 2016. Accessed September 27, 2017.
2. Marathe PH, Gao HX, Close KL. American Diabetes Association standards of medical care in diabetes 2017. *J Diabetes*. 2017;9(4):320-324.
3. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2017 executive summary. *Endocr Pract*. 2017;23(2):207-238.
4. Secrest MH, Udell JA, Filion KB. The cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors. *Trends Cardiovasc Med*. 2017;27(3):194-202.
5. Gomez-Peralta F, Abreu C, Lecube A, et al. Practical approach to initiating SGLT2 inhibitors in type 2 diabetes. *Diabetes Ther*. 2017. Epub ahead of print. doi: 10.1007/s13300-017-0277-0.
6. Bloomgarden ZT. Sodium-glucose cotransporter 2 inhibitors and diabetic ketoacidosis. *J Diabetes*. 2016;8(2):175-176.

7. Handelsman Y, Henry RR, Bloomgarden ZT, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. *Endocr Pract*. 2016;22(6):753-762.
8. Invokana® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b9057d3b-b104-4f09-8a61-c61ef9d4a3f3. Accessed October 1, 2017.
9. Jardiance® [package insert]. Indianapolis, IN: Boehringer Ingelheim Pharmaceuticals, Inc.; 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=faf3dd6a-9cd0-39c2-0d2e-232cb3f67565. Accessed October 1, 2017.
10. Farxiga® [package insert]. Mount Vernon, IN: AstraZeneca Pharmaceuticals LP; 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=72ad22ae-efe6-4cd6-a302-98aaee423d69. Accessed October 1, 2017.
11. US Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. September 10, 2015. https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm. Accessed October 1, 2017.
12. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
13. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS program collaborative group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
14. Prasanna Kumar KM, Ghosh S, Canovatchel W, Garodia N, Rajashekar S. A review of clinical efficacy and safety of canagliflozin 300 mg in the management of patients with type 2 diabetes mellitus. *Indian J Endocrinol Metab*. 2017;21(1):196-209.
15. Clinicaltrials.gov. Multicenter trial to evaluate the effect of dapaglifozin on the incidence of cardiovascular events (DECLARE-TIMI58). https://clinicaltrials.gov/ct2/show/NCT01730534. Accessed October 31, 2017.
16. TIMI study group. DECLARE-TIMI 58. http://www.timi.org/index.php?page=declare-timi-58. Accessed October 1, 2017.
17. Kohler S, Zeller C, Iliev H, Kaspers S. Safety and tolerability of empagliflozin in patients with type 2 diabetes: pooled analysis of phase I-III clinical trials. *Adv Ther*. 2017;34(7):1707-1726.
18. Tucker ME. Medscape. EMA: Amputation warning with SGLT2 inhibitors must be on label. February 10, 2017. https://www.medscape.com/viewarticle/875649. Accessed October 1, 2017.

New York State Implements a Naloxone Copayment Assistance Program

Ivan Alvarez, PharmD

Unintentional drug-induced deaths are rising faster than ever and have reached a public health crisis level.[1] In the United States, drug overdose now exceeds automobile accidents as a preventable cause of death. According to the National Center for Health Statistics, provisional counts of drug overdose deaths from April 1, 2017, through March 31, 2017 exceeded 65,000 in the United States, equivalent to an average of about 178 deaths per day.[2] Opioid medications have been the major component of drug overdose deaths.[1]

Opioid overdose deaths may be prevented through a comprehensive approach that includes raising public awareness, responsible opioid prescribing, prevention and treatment of opioid use disorder, and increased access to naloxone.[3] Increased access to naloxone is important because overdoses are commonly witnessed in the company of others.[4] Administration of naloxone by bystanders has been reported in several studies with reversal rates ranging from 75 to 100%.

Naloxone is a pure opioid antagonist that is safe and has not been shown to be abused.[5,6] Naloxone is used as an emergency medical treatment for the reversal of life-threatening opioid effects.

A study in Massachusetts evaluated the impact of overdose education and naloxone distribution (OEND) programs on rates of opioid-related death within nineteen communities.[7] OEND programs trained people at risk for overdose and potential bystanders how to prevent, recognize, and respond to an overdose. The programs distributed naloxone to participants and were shown to be effective in reducing opioid overdose deaths within the communities. OEND programs trained 2912 potential bystanders who reported 327 rescues. Both community-year strata with 1-100 enrollments per 100,000 population (adjusted rate ratio 0.73, 95% confidence interval [CI] 0.57 to 0.91) and community-year strata with greater than 100 enrollments per 100,000 population (adjusted rate ratio 0.54, 95% CI 0.39 to 0.76) had significantly reduced adjusted rate ratios for annual deaths related to opioid overdose and utilization of acute care hospitals compared with communities with no implementation. Providing increased access to naloxone for overdose prevention can have a dual benefit: naloxone can be used to reverse an overdose experienced by the individual, and/or the individual could administer naloxone to reverse an overdose that he/she witnesses.

As of August 9, 2017, the New York State (NYS) Department of Health Acquired Immunodeficiency Syndrome (AIDS) Institute implemented a pharmacy benefit: the Naloxone Copayment Assistance Program (N-CAP).[8] N-CAP aims to remove the financial barriers of obtaining naloxone. The program provides co-payments for naloxone of up to $40.[9] N-CAP is available to all individuals in NYS who have prescription drug coverage through their health insurance plans. Enrollment for individuals is not necessary; however, pharmacies must be enrolled in the AIDS Drug Assistance Program (ADAP) in order to participate in N-CAP.

Individuals at risk for an opioid overdose or their family members may obtain naloxone via a patient-specific prescription, or a standing order. (There are over 2000 pharmacies in NYS that have naloxone available via a standing order). The following formulations are eligible for N-CAP coverage: Narcan® nasal spray (4 mg/0.1 mL), naloxone used for intranasal administration (1 mg/mL in 2 mL Luer-Jet™ pre-filled glass syringes), and naloxone for intramuscular injection (0.4 mg/mL in 1 mL single-dose vials).[9] Specific health insurance plans may limit the monthly amount of naloxone that they will cover. Uninsured individuals and those without prescription drug coverage can still obtain naloxone at no cost through New York's network of registered opioid overdose prevention programs.[8] There are 450 registered opioid overdose prevention programs in NYS (list available at www.health.ny.gov/overdose). Individuals who have a deductible may receive naloxone through a registered opioid overdose prevention program if they have not already met their deductible. Once the deductible has been reached, the N-CAP copayment will be applied.

Several counseling points should accompany distribution programs for naloxone, including signs and symptoms of opioid overdose, need for contact of emergency medical services, and effects of naloxone. Common signs of overdose include failure to be roused or decreased breathing and blue lips (signs of inadequate ventilation).[10] The importance of contacting emergency medical services and the need for hospital evaluation after an overdose must be stressed because of the complications that can arise. The effects of naloxone dissipate after 30-60 minutes. Revived individuals may experience post-treatment respiratory depression requiring further medical assistance when the naloxone wears off. Administration of a second dose of naloxone may be necessary to manage reoccurring respiratory depression.

N-CAP is a first-in-the-nation program that can help put this lifesaving treatment into more hands; however,

naloxone is not a silver bullet.[8] Naloxone does not treat addiction or change behavioral habits but it can reverse an overdose to give individuals a second chance. NYS is at the forefront of designing initiatives to fight the opioid epidemic and should serve as a model for other states to follow.

References

1. Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths — United States, 2010–2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(5051):1445-1452.
2. National Center for Health Statistics. Provisional drug overdose death counts. October 12, 2017. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. Accessed November 1, 2017.
3. Penm J, MacKinnon NJ, Boone JM, Ciaccia A, McNamee C, Winstanley EL. Strategies and policies to address the opioid epidemic: a case study of Ohio. *J Am Pharm Assoc (2003)*. 2017;57(2S):S148-S153.
4. Doyon S, Aks SE, Schaeffer S. Expanding access to naloxone in the United States. *J Med Toxicol*. 2014;10(4):431-434.
5. Substance Abuse and Mental Health Services Administration. SAMHSA opioid overdose prevention toolkit. HHS Publication No. (SMA) 16-4742. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2016. https://store.samhsa.gov/shin/content/SMA14-4742/Overdose_Toolkit.pdf. Accessed November 10, 2017.
6. Naloxone hydrochloride [package insert]. Eatontown, NJ: West-Ward Pharmaceuticals; 2015.
7. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013;346:f174.
8. New York State Department of Health AIDS Institute Office of Drug User Health. Naloxone Co-payment Assistance Program (N-CAP): frequently asked questions and answers. October 2017. https://www.health.ny.gov/diseases/aids/general/opioid_overdose_prevention/docs/n-cap_faqs.pdf. Accessed October 25, 2017.
9. New York State Department of Health. Availability of naloxone in pharmacies. https://www.health.ny.gov/diseases/aids/general/opioid_overdose_prevention/directories.htm. Accessed September 25, 2017.
10. Wermeling DP. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. *Ther Adv Drug Saf*. 2015;6(1):20-31.

Authors

Olawonuola Abiona, PharmD
Dr. Abiona received her Doctor of Pharmacy degree from Touro College of Pharmacy in New York City. Prior to that, she received a Bachelor of Science in Biology from Temple University. She completed her PGY-1 residency at Saint Barnabas Medical Center in Livingston, NJ and is currently the PGY-2 ambulatory care pharmacy resident at Lifetime Health Medical Group. Dr. Abiona is actively involved in education and clinical research. Her goal is to become an ambulatory care clinical pharmacist and to make a difference in healthcare, both in America and in her home continent of Africa.

Ivan Alvarez, PharmD
Dr. Alvarez received his Doctor of Pharmacy degree from the University of Rhode Island. He is the current PGY-1 managed care pharmacy resident at BlueCross BlueShield of Western New York. Dr. Alvarez is currently interested in formulary development and management. He would like to pursue a career in managed care after completing his residency program.

Katie Frieling, PharmD
Dr. Frieling received her Doctor of Pharmacy degree from Union University College of Pharmacy in Jackson, Tennessee and completed her PGY-1 pharmacy practice residency at Ochsner Medical Center in New Orleans, Louisiana. She is the current PGY-2 ambulatory care pharmacy resident at Buffalo Medical Group. Her professional interests include managing chronic diseases, teaching, and precepting student pharmacists.

Emily Leppien, PharmD
Dr. Leppien received her Doctor of Pharmacy degree from the Albany College of Pharmacy and Health Sciences and completed her PGY-1 pharmacy practice residency at the Buffalo Psychiatric Center. She is the current PGY-2 psychiatric pharmacy resident at the Buffalo Psychiatric Center and is Chief Resident among the UB SPPS-affiliated residents. Her professional interests include clinical psychopharmacology, inpatient psychiatry, substance abuse, and pharmacy education. Upon completion of her program, Dr. Leppien plans to pursue a career as a clinical pharmacist in an inpatient psychiatric hospital, continue to teach and precept pharmacy students, and obtain certification as a pharmacotherapy specialist and as a psychiatric pharmacist.

Editors

Linda Catanzaro, PharmD
Dr. Catanzaro received her PharmD from the UB SPPS and subsequently completed a specialty residency in HIV informatics. She also developed and directed the UB SPPS PGY-2 drug information residency program. She is currently a Clinical Assistant Professor at the UB SPPS and staffs the New York State Medicaid Drug Information Response Center.

Holly Coe, PharmD
Dr. Coe received her PharmD from the UB SPPS after receiving her BS in Neuroscience from the University of Rochester. She completed PGY-1 and PGY-2 residencies at the UB SPPS specializing in drug information/pharmacoinformatics. She is currently a Clinical Assistant Professor at the UB SPPS and she staffs the New York State Medicaid Drug Information Response Center.

Terry Dunn, PharmD
Dr. Dunn received both her BS in Pharmacy and PharmD from the UB SPPS. She also completed a hospital pharmacy residency at New England Medical Center in Boston. She has had extensive experience as a pharmacist in various settings, including practicing in a traditional role in hospitals as a Clinical Pharmacy Specialist. She has also served as a Science Specialist at a law firm, working with a team of lawyers defending pharmaceutical companies in product liability lawsuits. In addition, she has participated on an FDA contract updating and rewriting drug labels. She is currently a Clinical Assistant Professor at the UB SPPS and Coordinator for the Center for Health Outcomes, Pharmacoinformatics, and Epidemiology (HOPE).

Irene Reilly, PharmD, BCPS
Dr. Reilly received her PharmD from the University of Illinois at Chicago (UIC) College of Pharmacy after receiving her BA in Economics from the University of Chicago. She completed PGY-1 and PGY-2 residencies at the UIC College of Pharmacy, specializing in drug information. She is currently a Clinical Assistant Professor at the UB SPPS and she leads the New York State Medicaid Drug Information Response Center.

Please address any comments or corrections to Dr. Reilly at irenehon@buffalo.edu.