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2019-2020 Food and Drug Administration Drug Safety Communications Update

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One of the key roles of the Food and Drug Administration (FDA) is to monitor medication safety. The FDA collects post-marketing adverse effects of medications and issues Drug Safety Communications when necessary.[1] In the past two years, sixteen drug safety communications have been released. This article will focus on recent warnings for medications more commonly used in the primary care setting, namely montelukast, gabapentinoids, febuxostat, and benzodiazepines. **Table 1** highlights the most relevant aspects of the warnings, followed by a presentation of additional related evidence.

Table 1. Summary of 2019-2020 FDA Drug Safety Communications

Drug Safety Communication	Summary of Evidence	Risk Mitigation Strategies
Montelukast		
Potential risk of serious neuropsychiatric side effects such as suicidal ideation, aggressiveness, and anxiety with montelukast use	Causal relationship inconclusive due to poor quality of evidence	• Use ICS and ICS/LABA for asthma • Use antihistamines for allergic rhinitis
Pregabalin, Gabapentin		
Increased risk of respiratory depression (including risk of death) with concomitant use of gabapentinoids with other CNS depressing medications (including opioids and benzodiazepines)	Increased risk with concomitant CNS depressants likely based on retrospective cohort and case-control analyses	• Avoid co-prescribing of gabapentinoids with other CNS depressants (especially opioids and benzodiazepines) • Initiate pregabalin at low dose (25 mg 1-3 times daily) and up-titrate slowly • Initiate gabapentin at low dose (100 mg 1-3 times daily) and up-titrate slowly
Febuxostat		
Increased risk of cardiovascular and all-cause mortality from use of febuxostat in gout treatment	Increased risk of cardiovascular and all-cause mortality likely from secondary endpoints from CARES trial	• Use renally adjusted allopurinol for chronic urate lowering therapy • Only use febuxostat in those with contraindications to allopurinol
Benzodiazepines		
Increased risk for abuse, addiction, physical dependence, and withdrawal even when used at recommended doses	Increased risk likely (especially when used concurrently with opioids) based on systematic reviews	• Avoid prescribing benzodiazepines for greater than 2-4 weeks in duration • Initiate at low dose • Prescribe only 1-2 week supplies at a time • Avoid alprazolam if possible • Use a discontinuation taper for patients on therapy for at least 2-4 weeks

Abbreviations: CARES - Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities; CNS – central nervous system; ICS – inhaled corticosteroid; LABA – long acting beta agonist

Montelukast:

Montelukast, a leukotriene receptor antagonist, is approved for asthma, prevention of exercise induced bronchoconstriction, and allergic rhinitis.[2] The FDA published a Drug Safety Communication in March 2020 detailing the risk of serious neuropsychiatric (NP) side effects, including suicidal ideation (SI), irritability, and anxiety associated with montelukast use.[3] This risk was escalated to a Black Box Warning (BBW) due to new data indicating an increased risk of SI. A total of 82 suicide cases associated with montelukast use were identified from the FDA Adverse Event Reporting System (FAERS) database, 34 of which contained sufficient data to support montelukast precipitating the suicidal event. However, since many of these 34 cases had additional risk factors for SI, a causal relationship with montelukast could not be established.[3]

A systematic review from 2018 assessed montelukast's relationship with NP side effects. Four of the included studies showed no statistically significant increase in SI following montelukast use. One nested case-control study included in this systematic review noted that the odds ratio (OR) for SI was not statistically significant at 0.70 (95% confidence interval [CI] 0.36-1.39 for *all* ages assessed [ages 5-24 years]). However, the sub-cohort of people aged 19-24 years had an OR of 5.15 (95% CI 1.16-22.86), which was statistically significant.[4] Two additional retrospective studies (one cohort and one case-control) published after the systematic review demonstrated a statistically significant increase in the risk of NP side effects in asthmatic patients 18 years or younger after montelukast exposure. One showed a relative risk (RR) of 12.0 (95% CI 1.6-90.2),[5] and the other showed an OR of 1.91 (95% CI 1.15-3.18).[6]

The evidence for increased NP side effects from montelukast is inconclusive due to the poor quality of evidence (mostly retrospective studies with potential confounders). However, safer alternatives are available for all approved indications of montelukast. Thus, the FDA drug safety communication recommends use of an inhaled corticosteroid (ICS), ICS/long-acting beta-agonist (LABA), or an as needed ICS/LABA for asthma[7] and antihistamines for allergic rhinitis[8] as first-line therapy, especially in patients with pre-existing mental health conditions such as anxiety and previous SI. If montelukast is used, patients should be warned about the possible risk of NP side effects such as increased anxiety, irritability, and sleep disturbances.

Gabapentinoids (Gabapentin and Pregabalin):

Gabapentin and pregabalin are gamma aminobutyric acid (GABA) analogs approved for partial onset seizures and post-herpetic neuralgia.[9,10] Pregabalin is also approved for diabetic peripheral neuropathy and fibromyalgia.[10,11] The FDA published a Drug Safety Communication in December 2019 detailing an increased risk of respiratory depression in patients with respiratory risk factors, including concurrent use of other central nervous system (CNS) depressants (such as opioids and benzodiazepines), elderly patients, and patients with chronic obstructive pulmonary disease (COPD).[12] The FDA identified 49 case reports of patients experiencing respiratory depression following gabapentinoid administration. Of the cases, 92% of patients had pre-existing loss of lung function or concurrent use of another CNS depressant; 12 of these patients died (all of whom had at least one additional risk factor for respiratory depression in addition to gabapentinoid use). An analysis of which patients had pre-existing loss of lung function, concurrent CNS depressant medication use, or both was not provided. The risk in healthy individuals is less supported.[12] Additional evidence related to the FDA warnings for gabapentinoids is displayed in **Table 2**.

Table 2. Evidence Supporting Risk with Gabapentinoids

Type of Study	RF for RD in the study	Outcomes	Results
Population-based, nested, case-control[13] N = 5875 Ages: 15-105 years	Concurrent opioid use Chronic lung disease (23% of all patients)	Opioid related death following exposure to concomitant gabapentin	Gabapentin + opioid vs. opioid alone OR = 1.49; 95% CI 1.18-1.88
Retrospective, cohort[14] N = 44,152 (gabapentin), 736,835 (opioid), 15,343 (both) Ages: 16-64 years	Concurrent opioid use (2% of all patients)	Risk of IPH or ED visit for RD	When compared to *regular use gabapentin: Gabapentin alone with **sustained overuse: OR = 0.9; 95% CI 0.4-1.7 Concurrent gabapentin + opioid, 1 medication with **sustained overuse: OR = 2.6; 95% CI 2.0-3.5 Concurrent gabapentin + opioid, both medications with **sustained overuse: OR = 4.1; 95% CI 1.8-9.6
*Regular Use: Gabapentin ≤3600 mg/day; opioid ≤50 MME/day **Sustained Overuse: Gabapentin >3600 mg/day; opioid >50 MME/day AND ≥3 rolling calendar quarters at these doses			
Abbreviations: CI – confidence interval; ED – emergency department; IPH – inpatient hospitalization; MME – morphine milligram equivalents; OR – odds ratio; RF – risk factors; RD – respiratory depression			

Based upon the evidence and the increased utilization of gabapentinoids in recent years,[12] providers should be mindful of the increased risk for respiratory depression with gabapentin and pregabalin use, especially when prescribed concurrently with opioids or other CNS depressants. The risk for respiratory depression in elderly patients or patients with compromised lung function (i.e., COPD, obesity, and obstructive sleep apnea) is less clear as there are currently no studies that have specifically assessed these risk factors. If gabapentinoids are used, they should be initiated at a low dose (see **Table 1**) and up-titrated slowly to the minimum effective dose for each patient. Patients should be closely monitored for confusion/disorientation, extreme sleepiness or lethargy, and slowed, shallow, or difficult breathing.

Febuxostat:

In February 2019, the FDA released a Drug Safety Communication about the increased risk of cardiovascular (CV) death from febuxostat, a xanthine oxidase inhibitor.[15,16] The FDA mandated that the labeling include a BBW and updated the indication to "hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable."[16] Data from the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, as outlined in **Table 3**, primarily led to this Drug Safety Communication.[16]

Table 3. Evidence Supporting Risk with Febuxostat

Type of Study	Outcomes	Results
Multicenter, double-blind, non-inferiority (for primary endpoint), superiority (for secondary endpoints)[17] N = 6190 Ages: greater than 18 years	Primary: 4-point MACE (CV death, nonfatal MI, nonfatal stroke, unstable angina with urgent revascularization) Secondary: Death from any cause, death from CV cause	Primary: Febuxostat vs. allopurinol: HR = 1.03; 95% CI 0.87-1.23 Secondary: Death any cause: HR = 1.22; 95% CI 1.01-1.47 Death CV cause: HR = 1.34; 95% CI 1.03-1.73
Abbreviations: CI – confidence interval; CV – cardiovascular; HR – hazard ratio; MACE – major adverse cardiovascular event; MI – myocardial infarction		

Although the data for increased risk of CV death and all-cause mortality with febuxostat is based on secondary endpoints alone, the severity of the risk cannot be ignored. Providers should utilize allopurinol as first-line therapy in patients with gout, especially in patients with pre-existing CV disease or at high CV risk. Febuxostat should generally be reserved for patients whom have contraindications to allopurinol (such as hypersensitivity reactions including Stevens-Johnson Syndrome and Allopurinol Hypersensitivity Syndrome). If used,

the FDA recommends that patients prescribed febuxostat be advised to seek emergency medical attention if they experience any of the following: chest pain, shortness of breath, rapid or irregular heart rate, unilateral numbness, dizziness, trouble speaking, or a sudden and severe headache.[16]

Benzodiazepines:

Benzodiazepines (BZDs) bind to post-synaptic GABA-A receptors in the brain, leading to hyperpolarization of neurons and less neuronal firing.[11] This action leads to the anxiolytic, anticonvulsant, and CNS depressive properties of BZDs. The FDA published a Drug Safety Communication in September 2020 detailing an increased risk of abuse, addiction, physical dependence, and withdrawal with BZD use, even when used at recommended doses.[18] The BBW was expanded on the label to reflect this information. From a review of published literature and emerging case reports, the FDA found new information that reinforced the knowledge that BZDs were widely prescribed in the United States (US) and often for longer durations than recommended. In 2018 for example, 50% of patients who were prescribed a BZD received prescriptions for greater than 2 months. In 2019, 92 million BZD prescriptions were dispensed to patients in an outpatient setting, the most common of which were for alprazolam, clonazepam, and lorazepam. The FDA also reviewed 104 cases from the FAERS database detailing abuse, dependence, or withdrawal from BZD monotherapy at recommended doses. Of the cases, 80% of patients described withdrawal symptoms following cessation of the BZD, even when tapered.[18] Additional evidence related to the FDA warnings for BZDs is displayed in **Table 4**.

Table 4. Evidence Supporting Risk with Benzodiazepines

Type of Study	Outcomes	Results
2019 Systematic, epidemiologic review[19] Ages: 12 years and older	Epidemiological findings	• 1 in 20 patients prescribed a BZD • Deaths related to BZD OD increased by 400% from 1996 to 2015 • 2.2% of patients misused BZD, 64% of whom obtained BZD from friend or family • Alprazolam most commonly misused BZD (73% of all misuse)
Systematic review[20] N = 353,658 Ages: 20 years and older	Risk of falls, traffic accidents, and injuries from those accidents for new BZD use vs. non-use	Risk of falls: OR = 2.8; 95% CI, 2.2-3.6 Traffic accidents: OR = 3.4; 95% CI, 1.7-6.8 Injuries from traffic accidents: OR = 3.1; 95% CI, 1.5-6.2
Systematic review[20] N = 14,117 Ages: 18 years and older	Mortality following BZD use	OR = 1.4; 95% CI, 1.1-1.7
Abbreviations: BZD – benzodiazepine; CI = confidence interval; OD – overdose; OR = odds ratio		

For most indications, including generalized anxiety disorder (GAD), BZDs are generally recommended as second or third-line options.[21] First-line options will vary by disease state, but for GAD, selective serotonin reuptake inhibitors are recommended first-line.[21] Based upon the evidence, BZDs should be avoided unless there are no other alternatives available. Alprazolam in particular should be avoided if possible. Alprazolam has an increased risk of misuse, abuse, and withdrawal due to its rapid absorption, low lipophilicity, and short half-life as compared to other BZDs.[22] If BZDs are used, they should be prescribed at the lowest starting dose and for a short amount of time (less than 2-4 weeks). Prescribing limited quantities (i.e., no more than 1-2 weeks at a time) may help to limit misuse.[23] Unfortunately, evidence demonstrating what duration of BZD therapy warrants discontinuation via taper are lacking. However, most guidance statements and guidelines recommend that a taper over *at least* 8-10 weeks be considered for patients prescribed BZDs for at least 2-4 weeks.[23-25] In general, avoiding abrupt discontinuation may be best for all patients on BZDs to avoid severe withdrawal symptoms.

Conclusion

Staying up to date on serious adverse effects of medications is an important responsibility for healthcare providers. Based on this review, montelukast may be associated with serious NP side effects (such as SI) and should generally be reserved as second-line therapy for both asthma and allergic rhinitis. Gabapentin and pregabalin may increase the risk of serious respiratory depression when co-prescribed with opioids (and other CNS depressants such as benzodiazepines), and thus opioid or BZD co-prescribing should be avoided as much as possible. Febuxostat appears to increase the risk of all-cause and CV related mortality, and it should generally be reserved for patients that cannot tolerate allopurinol. Due to increased risk of abuse, physical dependence and withdrawal, BZDs should be reserved for second or third-line therapy. Long-term BZD use should generally be avoided due to an increased risk of morbidity and mortality. If utilized, they should be prescribed at a low dose in limited quantities for less than 2-4 weeks. Pharmacists and other healthcare providers should strive to remain up to date on the ever-changing information about medications to ensure the safety of their patients. Providers should always consider submitting a medication adverse event report to the FAERS database via FDA MedWatch (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) to ensure that unexpected outcomes are incorporated, trended, and investigated, if necessary.[26,27]

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