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Efforts to Reduce Concomitant Opioid and Benzodiazepine Prescribing at the Lexington Veterans Affairs Medical Center

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**Executive Summary**

The United States is in the throes of an opioid epidemic. Any person who uses an opioid medication may experience an intentional or unintentional overdose. An overdose is more likely to occur when an individual ingests an opioid in combination with certain classes of medications, such as benzodiazepines or nonbenzodiazepines (Z-drugs). These medications are more likely to cause sedation and respiratory depression when taken together. Veterans, due to their unique mental and physical health challenges, are more likely to experience an overdose when they receive a combination of opioid therapy with benzodiazepine or Z-drug therapy as opposed to a single prescription for either medication.

This descriptive analysis explores the efforts of pharmacists at the Lexington Veterans Affairs Medical Center (VAMC) to reduce concomitant prescribing rates within their institution. Their approach is modeled after another VAMC within their regional cohort that reduced its number of concomitant prescriptions drastically within one calendar year. To assess the efficacy of pharmacist-led provider education efforts, I evaluated concomitant prescribing consultations and interventions for 50 patients. The results of the analysis show a numeric reduction in the number of patients receiving both opioids and benzodiazepines or Z-drugs. The primary goal of prescribing reduction is an increase in patient safety, but the analysis also shows potential for significant cost savings.

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Background and Literature Review

The United States has a drug problem. We air graphic depictions of illicit drug use on network television, romanticize the lives of celebrities who have died of overdose, and glorify the effects of drugs in popular music. Despite the informal and even lighthearted nature of the conversation about substance abuse in the media, illicit drug use is a rapidly growing problem. Increasing use of opioid drugs is especially alarming for two reasons: their ubiquity and their potential for abuse leading to fatal overdose. The CDC implicates opioids in more than 60 percent of all drug overdose deaths. Opioids caused 42,249 overdose deaths in 2016, five times the rate of opioid overdose deaths in 1999. Despite awareness of the opioid epidemic and attempts to stop it, overdose death rates increased in many parts of the nation between 2015 and 2016. The state of Kentucky has the fifth highest rate of death due to drug overdose (“Opioid Overdose,” 2017).

Understanding the opioid abuse epidemic requires an understanding of what opioids do. Opioids are a class of analgesics, also known as pain relievers. Morphine, fentanyl, hydrocodone, and oxycodone are common examples of prescription opioid medications. Heroin is the primary illicit opioid of abuse. All opioids act on opioid receptors in the brain to produce intense feelings of calm and well-being (Baumann, Herndon, & Strickland, 2014). Because of this effect, opioids are used to treat various types of pain. Short courses of opioids can be used to treat both acute and chronic pain. Acute pain is caused by an injury and is not a part of an ongoing process. Chronic pain lasts for three months or more. It can be malignant, a term which refers to cancer-related pain, or non-malignant (Dowell, Haegerich, & Chou, 2016). Opioid receptors in different parts of the body are responsible for common side effects of opioids, such as constipation and respiratory depression. Respiratory depression is the reason that opioid overdose is fatal. Natural breathing mechanisms shut down, resulting in death by suffocation. Opioid receptors also
connect to the reward center of the brain, enforcing repeated use and creating a high potential for addiction (Baumann et al., 2014).

It may be tempting to think that these deaths are primarily the result of illicit drug use, which is the intentional abuse of heroin, prescription opioids, or a mixture of both legal and illegal opioids. However, 40 percent of overdose deaths involve an opioid that was legally prescribed by a healthcare professional (“Opioid Overdose,” 2017). Having a prescription for an opioid does not preclude patients from an overdose. Patients may experience an unintentional overdose if they take more of their opioid than is prescribed to them or if they use certain types of medications in combination with opioid therapy.

Benzodiazepines are a class of medications that can exacerbate the side effects of opioids and increase the risk for overdose. Examples of benzodiazepines are alprazolam, diazepam, and clonazepam, marketed under the trade names Xanax®, Valium®, and Klonopin® respectively. Benzodiazepines act on a receptor in the brain that is responsible for inhibitory signaling. Using a benzodiazepine increases the intensity of inhibitory signaling, leading to the primary pharmacologic effects of benzodiazepines: inhibition of anxiety, sedation, anti-seizure activity, and sleep induction (Griffin, Kaye, Bueno, & Kaye, 2013). These pharmacologic effects make short courses of benzodiazepines effective for surgical anesthesia, treatment or prevention of seizures, and treatment or prevention of specific panic and anxiety disorders. The exact mechanism of opioid and benzodiazepine interaction is unknown. It is hypothesized that the two medications have a synergistic effect, increasing the potential for sedation and respiratory depression (Jones & Comer, 2012).

Despite the dangers of concomitant opioid and benzodiazepine prescribing, rates of concomitant prescribing rose in recent years. Sun et al. (2017) conducted a retrospective analysis of concomitant prescribing.
prescribing using insurance claims data from 315,428 privately insured patients aged 18 to 64 years from 2001 to 2013. The primary outcomes for the study included the annual percentage of opioid users with concurrent benzodiazepine use, the annual incidence of emergency room visits, and hospital visits for opioid overdose that resulted in inpatient admission. The researchers found that concomitant prescribing of benzodiazepines and opioids increased from 9 percent in 2001 to 17 percent in 2013; in just over a decade, the rate of concomitant prescribing in the sample nearly doubled. Concomitant prescribing was associated with an adjusted odds ratio for emergency room visits or inpatient admission for opioid overdose of 2.14 (95% CI 2.05, 2.24, p<0.001) among all users (Sun et al., 2017). This odds ratio suggests that patients who use both benzodiazepines and opioids are at a 200 percent higher risk of hospital admission compared with patients who only use opioids.

United States veterans may be particularly sensitive to the dangers of concomitant prescribing. They may bear the emotional and mental scars of combat, physical injuries resulting in chronic pain, or both; these injuries may predispose them to an intentional or unintentional overdose. French et al. (2005) evaluated the prescription medications of 13,745 veterans from 1999 to 2001. The primary outcome of the analysis was the estimated risk of an injury within 30 days for patients who were taking a benzodiazepine and another medication with a “major” interaction severity rating as defined by Micromedex®, a database of clinical resources. A major severity drug interaction implies that the risks of using the medication combination in question outweigh the benefits in a majority of patients. The authors found that concomitant opioid and benzodiazepine prescribing accounted for 79.6 percent of combined therapy. A total of 1,110 veterans experienced an injury, and roughly 71 percent of the injured veterans were taking benzodiazepines with another medication. Although this study did not specifically evaluate the
combination of opioids and benzodiazepines, the results are significant: concomitant use of benzodiazepines with another major interaction medication yielded an odds ratio of 2.31 (95% CI 2.2, 2.4, p<0.0001) versus benzodiazepine use alone (French et al., 2005).

A case-cohort study by Park, Saitz, Ganoczy, Ilgen, & Bonhert (2015) further explored the link between opioid prescribing and drug overdose death in US veterans. The researchers evaluated 422,786 veterans who received medical care through the Veterans Health Administration (VHA) from 2004 to 2009. The sample included all 2,400 veterans who died of a drug overdose during that time and a random sample of 420,386 veterans who received VHA medical services and a subsequent prescription for an opioid. Of the total study population, 27 percent of veterans received concomitant opioid and benzodiazepine prescriptions. Among the 2,400 veterans who died of a drug overdose, 49 percent died during a period in which they had concomitant opioid and benzodiazepine prescriptions. The adjusted hazard ratio for active opioid and benzodiazepine prescriptions was 3.86 (95% CI 3.49, 4.26) versus no benzodiazepine prescription. Higher daily doses of benzodiazepines were associated with increased risk of death. This study shows the additional impact of concomitant prescribing on veterans: more than a quarter of patients who received an opioid through the VHA were almost four times more likely to die of a drug overdose when compared to their peers (Park et al., 2015).

Benzodiazepines are not the only class of medications that can cause the pharmacologic effects mentioned above. Nonbenzodiazepines, informally called Z-drugs or Z hypnotics, are a class of medications intended for short-term use in the treatment of insomnia (Drover, 2004; Gunja, 2013). Examples of Z-drugs include zolpidem (Ambien®), zaleplon (Sonata®), and eszopiclone (Lunesta®). The term nonbenzodiazepine refers only to the structure of the Z-drugs, because their chemical structure is distinct from the chemical structure of benzodiazepines. Despite their structural differences, Z-drugs
act on the same receptor as benzodiazepines to increase inhibitory signaling. The increase in inhibitory signaling produces a sedative effect resulting in sleep induction (Drover, 2004). Early in development and marketing, Z-drugs were thought to be a safer alternative to benzodiazepines for the treatment of insomnia (Gunja, 2013). But Z-drugs are not benign. Adverse effects include dizziness and impaired thinking, which have been linked to an increased number of falls and traffic accidents. Additional research implicates zolpidem in an increasing number of emergency room visits, especially when other medications with similar effects, such as benzodiazepines and opioids, are ingested at the same time (Shayegani et al., 2018).

Shayegani et al. (2018) recognized the implications of these findings for veteran populations and sought to characterize zolpidem use among Iraq and Afghanistan veterans in a retrospective cohort analysis. The analysis included 493,683 veterans who received care from fiscal year 2013 to fiscal year 2014. Of the veterans included in the analysis, 7.6 percent ($n = 37,422$) received zolpidem; of those patients, 77.3 percent were exposed to zolpidem for longer than the FDA-approved treatment duration of 4 weeks and 0.9 percent received high-dose zolpidem. The researchers found that veterans were significantly more likely to receive concomitant benzodiazepine and/or opioid prescriptions in either scenario. They also discovered that zolpidem exposure was associated with depression and PTSD diagnoses. As Shayegani et al. (2018) put it, “…since psychiatric disorders such as PTSD and depression carry an inherent risk for overdose death on their own, the FDA warning for zolpidem regarding an increased risk of worsening depression or suicidality should be considered.” Overall, the study showed many opportunities for improvement in Z-drug prescribing within the VHA (Shayegani et al., 2018).
The concerns addressed in the aforementioned research are echoed by the U.S. Food and Drug Administration (FDA). In a Drug Safety Communication issued on August 31, 2016, the FDA called attention to the increased risk of serious adverse events and death with concomitant use of opioids and other medications, including benzodiazepines and Z-drugs. The FDA assigned its strongest warning to the combination of opioids and other medications or drugs that exert an inhibitory effect. The Communication also urges prescribers to use caution and discretion when prescribing opioids and another inhibitory medication or drug due to the increased risk presented by the combination (U.S. Food & Drug Administration [FDA], 2016).

Studies and cautionary statements provide a strong impetus to change medical care within the VHA. The VHA, a component of the US Department of Veterans Affairs (VA), launched the Opioid Safety Initiative (OSI) in 2013. The OSI measures four dimensions: number of opioid prescriptions, results of urine drug screens, concurrent benzodiazepine and opioid therapy, and number of patients on high opioid dosages. Unfortunately, there is a dearth of published evidence on the efficacy of interventions related to OSI metrics. The lack of publishing is multifactorial, but may be due in part to the VHA’s tendency to emphasize internal improvement processes. Each VA Medical Center (VAMC) is part of a regional office, called the Veterans Integrated Service Network (VISN). Each VISN office compares the OSI metrics to other facilities within the same VISN and to national trends as a method of quality improvement (Gellad, Good, & Shulkin, 2017). The Lexington Veterans Affairs Medical Center (VAMC) is among those facilities working hard to serve veterans through the OSI. Their current focus is reducing the rate of concomitant opioid and benzodiazepine prescribing while maintaining patient satisfaction.
Another facility within VISN 9 has drastically reduced concomitant prescribing rates within a calendar year, and the Lexington VAMC will adopt a similar model in an attempt to develop safer prescribing practices.

The purpose of this study is to evaluate changes in the rate of concomitant opioid and benzodiazepine prescribing at the Lexington VAMC. The necessary changes in prescribing present a unique challenge: patients cannot immediately discontinue either type of medication after long-term use without suffering from withdrawal. Both types of medications must be tapered, sometimes over the course of months, to avoid temporary or permanent harm to the patient. While one medication is being tapered, both prescriptions will appear active and flag a concomitant prescribing alert. If the data collected for this study measured concomitant prescribing rates without considering the necessity of medication tapering, the result of pharmacist efforts to curb prescribing would be obscured. Instead, data analysis will measure the number of pharmacist recommendations and compare that number to the number of interventions implemented. Using the number of interventions implemented will allow a more accurate assessment of changes in prescribing habits at the Lexington VAMC, even before any tapers are complete.

The pharmacist-led effort to curb concomitant prescribing is two-pronged. First, pharmacists from the Lexington VAMC drafted an educational letter to send to all patients with concomitant active opioid and benzodiazepine prescriptions. An active prescription is one that has authorized refills remaining and has not expired. The letter, which can be found in Appendix A, informs patients about the rationale behind the decision to curtail concomitant prescribing. It describes at a basic level the different types of opioids, __________________________

1 VISN 9 comprises 5 health systems: Lexington, KY; Louisville, KY; Memphis, TN; Mountain Home, TN; and Tennessee Valley Healthcare System, which has campuses in both Murfreesboro, TN and Nashville, TN.
different types of benzodiazepines, and the harmful effects that can result from concomitant use. The letter also emphasizes that the patient will need to contact his or her prescriber to make a choice about which medication he or she chooses to taper. The goal of this correspondence is to make patients aware of the dangers of taking both medications and empower them to make a decision with the help of their healthcare provider.

Second, providers are requesting pharmacist guidance in identifying and treating patients receiving concomitant opioid and benzodiazepine or Z-drug prescriptions. The provider or pharmacist can enter a pharmacotherapy consultation into the Computerized Patient Record System (CPRS), the electronic medical record system used by the VHA. The consultation contains active prescriptions, diagnoses, and a summary of evidence supporting concomitant prescribing reduction. If the consultation is initiated by a provider, it contains a request for a tapering schedule for the chosen medication. If the consultation is initiated by a pharmacist, it contains a proposed tapering schedule for the provider to evaluate. Once the pharmacist initiates or responds to the consultation, providers may evaluate the recommendation to determine which interventions they want to implement. In addition to recommendations for tapers, pharmacists developed a talking points sheet to guide provider discussions with patients, which can be found in Appendix B.

**Research Design**

To measure the impact of pharmacy consultations for the purpose of quality and process improvement, this research quantifies the number of pharmacy consultations entered in CPRS to address patients with concomitant prescriptions and the number of interventions resulting from those consultations. Comparing the number of consultations with the number of subsequent changes in prescribing for each patient in question facilitates an assessment of the efficacy of the current interventions. In order to obtain the Staton
number of consultations and subsequent interventions, I conducted a chart review of each patient who received a concomitant prescribing pharmacotherapy consultation from December 1, 2017 to March 31, 2018. Practitioners addressed 50 consultations during this time.

Demographic information collected from CPRS included the patient’s age in years calculated by CPRS, self-reported birth sex, self-reported race, and self-reported ethnicity. I assessed the number of providers prescribing opioids and benzodiazepines or Z-drugs to each patient using the State Prescription Drug Monitoring Program (PDMP) reports available through CPRS, which lists the type of controlled substance prescribed and the name of the provider who prescribed the controlled substance. I also identified non-VA providers using the PDMP reports, since the reports provide a comprehensive list of all prescribers in the state of Kentucky.

I used each patient’s individual pharmacotherapy consultation to identify the active opioid prescription(s) and active benzodiazepine or Z-drug prescription(s) addressed in the consultation. The opioid and benzodiazepine or Z-drug indication was obtained using the active diagnoses listed in the consultation. I estimated the duration of treatment for each opioid and benzodiazepine or Z-drug using outpatient medication dispensing histories available in CPRS. These durations represent total months of continuous therapy from medication class initiation to the date of the pharmacotherapy consultation, rounded down to the nearest whole month. Medication class initiation means the number of continuous months that a patient was receiving any opioid and any benzodiazepine or Z-drug. Most patients had an extensive dispensing history available in CPRS. Some patients transferred care to the VA after they received relevant prescriptions from an outside provider. In these cases, treatment duration was estimated by VA dispensing records and supplemented with reports from the provider about the patient’s duration of
therapy. Treatment duration included any type of opioid, benzodiazepine, or Z-drug as long as therapy with the medication class in question was continuous.

To assess the efficacy of the consultation process, I determined who initiated the consultation if a formal consultation was present in CPRS. I used the pharmacotherapy consultation to determine the pharmacist recommendations, then reviewed provider responses and notes from each patient’s chart to determine the intervention chosen by the provider. I also recorded planned taper lengths and alternative treatments used to replace the tapered medication for patients who received intervention. I measured the number of adverse events experienced by reviewing each patient’s medical records for evidence of calls to their provider, emergency room visits, or complaints during follow-up appointments.

Results

Demographic Information: Forty-nine of the patients were male and one patient was female. The average age for patients was approximately 65 years, with a range of 29 years old to 89 years old. Forty-eight of the patients identified as white, one patient identified as American Indian/Alaskan Native, and one patient declined to provide a response. Forty-eight of the patients identified as not Hispanic/Latino, one patient was unsure of ethnicity, and one patient declined to provide a response.
Opioid Use: The 50 patients had a total of 53 active opioid prescriptions, because 3 patients had multiple active prescriptions for more than one type of opioid. Figure 1 depicts the frequency of each type of medication in the active prescriptions; hydrocodone with acetaminophen (abbreviated APAP) was the most prevalent opioid prescribed in the sample. The average estimated treatment duration for opioid therapy was approximately 117 full months, or 9.75 years. The minimum estimated treatment duration was 2 months and the maximum was 273 months. The 50 patients carried a total of 81 pain-related diagnoses, with an average number of diagnoses per patient of 1.64 active pain-related diagnoses. The most common indication for opioid prescription was back pain, followed by osteoarthritis and neck pain. Further details regarding opioid therapy indications can be found in Appendix C.

Benzodiazepine and Z-drug Use: The 50 patients had a total of 57 active prescriptions, because 7 patients had multiple active prescriptions for multiple benzodiazepines or a benzodiazepine and a Z-drug. Figure 2 depicts the frequency of each type of medication in the active prescriptions. Zolpidem is the only Z-drug included in the analysis; the remaining medications listed are benzodiazepines. Diazepam was the most prevalent benzodiazepine prescribed in the sample. The average estimated treatment duration of benzodiazepine or Z-drug therapy was approximately 94 months, or 7.8 years. The minimum estimated treatment duration was 2 months.
and the maximum was 233 months. The 50 patients carried a total of 59 diagnoses related to their benzodiazepine and/or Z-drug prescriptions. The most common indication was insomnia, followed by anxiety disorder and PTSD. Further details regarding benzodiazepine and Z-drug therapy indications can be found in Appendix C.

Number of providers and non-VA providers: Twenty-seven patients used a single VA provider to obtain both opioids and benzodiazepines and/or Z-drugs. Twenty-three patients used more than one provider; of those 23 patients, 2 patients got their benzodiazepine or Z-drug from an outside provider and 1 patient got his or her opioid from an outside provider.

Consultation initiation, recommendations, and interventions: A total of 46 consultations were officially entered into CPRS as a unique document. Of these 46 consultations, the majority (n = 43) were initiated by providers; the remainder (n = 3) were initiated by pharmacists. Four of the consultations were not entered into CPRS as a unique document, and information from those consultations was obtained from notes and addenda written on the subject of concomitant prescribing.
Figure 3 and Table 1 show an overview of pharmacist recommendations for each patient, if available, and the resulting interventions by providers. The three categories of pharmacist recommendations are listed on the X-axis of Figure 3, and the subgroups within each of the three categories represent which medication was discontinued or tapered by the provider. Pharmacist recommendations were unavailable for two of the patients, represented as “None” in Figure 3 and Table 1. Both of these consultations were not entered officially into CPRS and consisted of conversations between providers. Roughly a quarter \((n = 13)\) of patients did not receive any interventions. Of the 37 interventions, over half \((n = 20)\) resulted in tapering of a benzodiazepine or Zdrug. Provider intervention aligned with pharmacist recommendation in approximately 30 percent \((n = 15)\) of the 48 consultations where a recommendation was given. Note that this is a conservative estimate; in many cases, the pharmacist recommended that both medications ultimately be tapered and discontinued, but that only one taper should occur at a time. This recommendation gave providers and patients a choice on which drug to taper first. Because this study was conducted before all drug tapers were complete, it was not possible to
assess whether or not a second medication was discontinued at the time of data collection. This means that provider interventions might align more closely with pharmacist recommendations at a later date.

Of the 37 patients who received an intervention, 31 patients entered at least one tapering process at the time of data collection. Five patients were taking the medication intermittently or rarely, so their prescription was discontinued without a taper. The remaining patient had a prescription discontinued without a taper; it was unclear whether or not this patient was taking the medication infrequently enough to safely discontinue without a taper. The minimum planned taper length was 1.5 weeks (10 days) and the maximum planned taper length was 26 weeks, with an average of roughly 7 weeks. The majority of patients did not receive any alternative pharmacologic treatment during their taper, depicted in Figure 4. The 18 patients who received alternative pharmacologic treatment received a total of 21 alternatives, meaning that 3 patients received multiple alternatives. Details regarding the choice of alternative treatments can be found in Appendix D. Two patients reported adverse effects related to their drug tapers. One experienced insomnia related to discontinuation of a benzodiazepine. The other experienced insomnia and anxiety related to a benzodiazepine taper, despite the implementation of an alternative sleep aid. Neither situation resulted in serious adverse events, such as hospitalization or death.

**Implications for Hospital Policy Decisions**
The results of this interim quality improvement research are promising for the Lexington VAMC. The majority of consultations were initiated by providers instead of pharmacists. The motivation to initiate consultations implies provider acceptance of policies related to concomitant prescribing reduction. Entering a consultation to request pharmacist guidance also shows that providers are willing to work with other members of the interdisciplinary healthcare team to achieve safer medication outcomes for their patients. Equally reassuring is the fact that 74 percent of consultations resulted in an intervention designed to reduce concomitant prescribing. If results are extrapolated to all patients who are receiving concomitant prescriptions, the Lexington VAMC could see safer medication use in hundreds of patients who are at increased risk of overdose. The reduction in potentially harmful prescribing habits is a testament to the power of an interdisciplinary healthcare team and the role that pharmacists can play in keeping patients safe.

Although patient safety is the primary goal of these interventions, cost savings opportunities are an added benefit. A 2017 study by Stevens et al. examined Intensive Care Unit (ICU) admissions due to opioid overdose from 2009 to 2015 based on data provided by Vizient, Inc. During this time period, nearly 22,000 patients required ICU care following opioid overdose. The researchers found that the average cost of an ICU admission for an opioid overdose was approximately $92,000 per patient in 2015. Based on this number, hospital systems with large populations of high-risk patients could see significant cost savings with prevention of even a single overdose.

Cost savings opportunities are also available from a pharmacy purchasing perspective. The 37 interventions resulted in an average prescription cost reduction of $43.63 per patient per year based on pricing from VA purchasing contracts. There are 427 patients with identified concomitant prescriptions;
an extrapolation to 300 patient interventions would yield an annualized outright cost savings of approximately $13,000. The CDC estimates the life expectancy of an average US citizen at nearly 79 years (“Life Expectancy,” 2017). If we assume an average age of 65 years for veterans, the resulting prescription cost savings totals over $180,000 over the lives of the veterans. Non-VA health systems may use actual wholesale price (AWP) to calculate cost savings. If AWP of the medications is used, the average prescription cost reduction is $857.82 per patient per year with an annualized cost savings of nearly $32,000 for 37 patients. Extrapolating to 300 patient interventions using AWP yields an annualized cost savings estimate close to $260,000.
Limitations

This descriptive research addresses a relatively small number of patients who received concomitant opioid and benzodiazepine or Z-drug prescriptions in the initial stages of intervention and tapering. It was not possible to evaluate the true length of each patient’s taper, since patients may require a faster or slower taper than originally intended based on their clinical response and any reported adverse effects. It is possible that more adverse effects, including relapse or use of illicit substances, will be reported as patients progress further into the tapering process. It is also possible that a higher quantity of alternative medication treatments will be prescribed to help patients cope with the eventual discontinuation of their opioid, benzodiazepine, or Z-drug. The consultations included in the analysis were not randomized; they reflect patterns of pharmacist-led provider education efforts.

Future research can build on this foundation in many exciting ways. An analysis conducted after the completion of all interventions can address the true length of each patient’s taper and associated adverse effects reported during the tapering process. This could help guide providers at other institutions as they decide how to implement tapers in their own patients. The data could also guide providers in selecting alternative treatments for their patients to help ease any adverse effects. Although these aspects are clinically important, I believe that future research should also address the variables that affect prescriber decisions. A more robust data set would allow researchers to analyze which, if any, have a statistically significant impact on prescriber behavior. Factors that would warrant consideration in such an analysis might include patient’s age, duration of therapy for all relevant medication classes, interdisciplinary education efforts, recommendations from other practitioners, or the patient’s underlying mental health-related diagnoses, among others. Once the factors responsible for prescriber habits were identified, education efforts could be tailored to those specific needs, making an intervention more likely.
Conclusion

Using an approach modeled by another VAMC within VISN 9, providers at the Lexington VAMC were able to reduce the rates of concomitant opioid and benzodiazepine prescribing in a sample of 50 patients. Overall, prescribers appeared to be receptive to pharmacist-initiated education efforts. This outcome showcases the efficacy of pharmacists as a vital part of the interdisciplinary healthcare team. Though there is room to improve on these results with future research, I recommend that other healthcare systems adopt a similar approach to reduce concomitant opioid and benzodiazepine prescribing rates. Reducing concomitant prescribing rates of opioids and benzodiazepines or Z-drugs increases patient safety and results in cost savings for a healthcare system. I have highlighted evidence regarding increased overdose risk in veteran populations, but any patient receiving an opioid and a benzodiazepine at the same time is at an increased overdose risk. Pharmacists, the medication experts of the interdisciplinary team, are well equipped to champion concomitant prescribing reduction efforts within their health systems.

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Appendix A: Educational Letter to Patients

IMPORTANT SAFETY INFORMATION

January 12, 2018

To whom it may concern,

The Lexington VA Medical center has created a policy that will restrict the concomitant prescribing of an opioid and a benzodiazepine or two other similar sedative sleep-aides. This policy is based off a similar and successful policy implemented last year at the Memphis VA Medical Center. The medications included are listed below:

**Sedative medications include:**
- Alprazolam
- Clonazepam
- Diazepam
- Lorazepam
- Oxazepam
- Temazepam
- Eszopiclone
- Zolpidem

**Opioid medications include:**
- Codeine
- Hydrocodone
- Fentanyl
- Methadone
- Morphine
- Oxycodone
- Tramadol

This decision was made based on clear evidence that this combination has been shown to drastically increase the risk of accidental overdose in the veteran population. Veterans on a combination of sedatives and opioids are almost 4 times more likely to die from an overdose than those just on opioids. In the United States, Veterans that have died of opioid overdose have had a concurrent benzodiazepine prescribed 49% of the time. Opioids increase respiratory depression and that risk is amplified when benzodiazepines are co-prescribed. While the risk of respiratory depression is less with the non-benzodiazepine sedatives included in this policy, there are clear cognitive, memory, and fall risks associated with their combined prescribing and the decision was made to include them.

Over the next several months, our prescribers will clinically evaluate each Veteran affected (roughly 500) and will provide them with therapeutic alternatives and establish a safe taper process for one of these medications. Veterans on hospice, palliative care, or those receiving less than a 14-day supply of this combination will not be affected by this policy.

This policy has the support of facility leadership as well as our clinicians. We are working to ensure that we provide the most safe and effective care possible when treating our Veterans. It will be very important to reinforce to Veterans that the reason behind this change is risk reduction. Our patient advocates can direct you to the correct clinician to answer any questions you may have.

Respectfully,

Lexington VA Medical Center
Appendix B: Provider Discussion Guide

Opioid + Benzo Talking Points

1. Veterans on a combination of sedatives and opioids are almost 4 times more likely to die from an overdose than those just on opioids.

2. In Veterans, 49% of opioid overdose deaths (OD) have a concurrent benzodiazepine prescribed.

3. Beyond the increased risk of accidental OD death, patients on both opioids and benzodiazepines have worse health outcomes, greater utilization of healthcare resources, and higher mental health comorbidities.

When used together, even at prescribed doses, these medications may:

- Slow or stop your breathing
- Cause an accidental overdose

What is an accidental overdose?

An accidental overdose is when your body has too much medication but you didn’t know it was going to be too much. An accidental overdose can cause you to stop breathing and die.

Do not stop your medications on your own before talking to your prescriber

There are many alternatives, both medication and non-medication that your prescriber will talk to you about when making a joint decision moving forward. This will take some input and commitment from you and will be much safer for you in the long run.
Provider Talking Points for Benzo Discontinuation

Patient Argument:
If I stop my benzodiazepine, I’ll experience withdrawals.

Provider Response:
• A tapering schedule will be individualized to your needs
• Tapering minimizes withdrawal symptoms and discomfort
• Tapering safely reduces the need for benzodiazepine therapy

Patient Argument:
My benzodiazepine is the only thing that controls my PTSD symptoms.

Provider Response:
• Evidence does not support utility of benzodiazepines in PTSD
• Inappropriate use of benzodiazepines has been found to worsen PTSD symptoms
• We will work to find safer, more effective treatments for your PTSD symptoms

Patient Argument:
The VA is trying to save costs/cut corners by taking veterans off their prescriptions.

Provider Response:
• VA takes pride in staying at the forefront of patient care/updated guidelines while keeping patients safe
• Combination of benzos and opiates is extremely dangerous due to the risk of respiratory depression/death
• We hope to use less harmful medications to control anxiety and minimize overdose risks

Patient Argument:
I’ve been on my benzodiazepine for years, why should I discontinue it now?

Provider Response:
• American Geriatrics Society recommends AGAINST use of benzodiazepines in patients >65
• Benzos put patients at greater risk of respiratory depression, fractures, falls, car accidents, decreased cognition
• The combination of benzos and opiates is most concerning as it greatly increases your risk of respiratory depression/death

Patient Argument:
I only take my benzodiazepine as needed, what’s the big deal?

Provider Response:
• Medication sensitivity changes with age
• Body may become more sensitive to medication side effects with periodic use
• Periodic use of benzodiazepines may increase risk of overdose
**Patient Argument:**
I can’t sleep without my benzodiazepine.

**Provider Response:**
- Review proper sleep hygiene
- Many pharmacologic and non-pharmacologic alternatives available that are not accompanied by a risk of deadly side effects (melatonin, trazodone, CBT-I, etc)

**Patient Argument:**
If benzodiazepines are so harmful, why did my [Mental Health, etc] provider prescribe it in the first place?

**Provider Response:**
- Benzodiazepines, while possibly effective in the short-term, are not meant for long-term use
- All medications have side effects, but the combination of benzos and opiates is what is most concerning

**Patient Argument:**
My benzodiazepine is the only thing that gets me through the day.

**Provider Response:**
- Empathize with patient
- Benzodiazepines can be effective in the short-term
- No MH indication for long-term use
- Studies show patients on benzos experience MORE anxiety because of peaks/troughs
- Benzodiazepines make it more difficult for psychotherapy to be effective

**Appendix C: Detailed Indication Information**
Appendix D: Alternative Treatments
Number of Patients Receiving Benzodiazepine/Z-drug Alternative Treatments

- Buspirone: 5
- Hydroxyzine: 2
- Melatonin: 1
- Mirtazapine: 1
- Ropinirole: 3
- Trazodone: 1

Number of Patients Receiving Opioid Alternative Treatments

- Acetaminophen: 1
- Gabapentin: 1
- Ibuprofen: 1
- Lidocaine (topical): 2
- Naproxen: 1
- Venlafaxine: 1