Case Studies from the Medical Examiner

Benzodiazepines Near or Higher than Recommended Dose Leads to Overdose Death
Summer 2019

Case Studies from the Medical Examiner are a deliverable of the collaborative work of the Adult Inquest Review Committee. The College of Pharmacists of Manitoba, the College of Physicians and Surgeons of Manitoba, and the Chief Medical Examiner's Office work togeter to learn from deaths related to prescription drugs, focusing on opioids and other drugs of misuse. All dates, patient initials, names of pharmacies, and prescribers have been changed and de-identifi d to protect the identity of the patient and their family.

Introduction

LV was a 59-year-old woman who was found dead in November 2017. She was found mid-afternoon in her home by a family member. She had a past medical history of headaches and depression. There was no suicide note found and no indication of trauma. LV's family mentioned that she had been experiencing extreme duress due to a job loss and accrued debt. An autopsy was performed, and cause of death was determined to be suicide due to multidrug overdose. This case was identifi d by the College as an important learning opportunity for pharmacists to review dispensing practices.

Discussion

The toxicology report was positive for codeine, temazepam, clonazepam and venlafaxine. The levels of codeine and venlafaxine were both above the acceptable therapeutic range. Clonazepam was found in her blood; however, the levels were below the sensitivity of the test. Acetaminophen was also present (see chart, right page).

LV passed away from a multidrug overdose. There are multiple factors to consider:

The prescriptions for clonazepam, temazepam and venlafaxine were the fi st and only prescriptions that appeared on LV's DPIN in the past 6 months (see chart, right page) It is unknown if LV had been previously prescribed these medications or had them fill d outside of Manitoba, but it appears that LV was initiated on two benzodiazepines at near or higher than recommended dosages.

Prescribing more than 30-40 mg of diazepam or equivalent per day is generally not recommended. At 2 mg of clonazepam per day (10 to 40 mg diazepam equivalents) in addition to 30 mg of temazepam per day (10 to 15 mg diazepam equivalents), this patient may have exceeded the recommended dose of benzodiazepine prescribing. Prescribing high doses of benzodiazepines in a benzo-naïve patient can result in excessive sedation, respiratory depression and, ultimately overdose. The Ashton Manual[1] is an excellent benzodiazepine reference and includes a chart for determining approximate oral dosages of benzodiazepines in diazepam equivalents. The Compendium of Pharmaceuticals and Specialties (CPS)2and the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain Practice Toolkit3are also great resources that can be used to determine approximate diazepam equivalents.

There is *no evidence* that combination benzodiazepines improves effic y, but combination treatment may increase risk of harm.

Prescribing more than one benzodiazepine at a time is not recommended. There is no evidence that combination benzodiazepines improves efficacy, but combination treatment may increase risk of harm. Safety concerns include increased risk of falls, injury, confusion,

Toxicology Results

Drug	Level in blood (ng/mL)	Therapeutic Range (ng/mL)
Codeine (free)	489*	10-100
Temazepam	538	600-900
Venlafaxine	610*	62-138
O-desmethylvenlafaxine	1010*	118-252
Clonazepam and metabolites	0	20-70

*Above therapeutic range

Recent DPIN History Preceding Patient's Death

LV's DPIN showed only the following for the preceding six months:

Generic Name	Date Dispensed	Strength	Quantity	Days Supply	Prescriber	Pharmacy
Clonazepam	Nov 14, 2017	1 mg	56	28	Dr. Gucci	Ferragamo Drugs
Temazepam	Nov 14, 2017	30 mg	28	28	Dr. Gucci	Ferragamo Drugs
Venlafaxine XR	Nov 14, 2017	75 mg	28	28	Dr. Gucci	Ferragamo Drugs

cognitive impairment, reduced physical function, tolerance, dependence, and abuse. This practice may be an attempt to treat anxiety and insomnia individually without considering their common causes.

Patients should also be told of treatment expectations including a strategy for discontinuing the benzodiazepine once the effects of long-term treatment (e.g., SSRI/SNRI, psychotherapy) begin to take effect. Buspirone could also be considered an alternative to a benzodiazepine for anxiety.

Patients starting antidepressant therapy may experience new or worsening symptoms, including worsening depression and suicide ideation. It is important for healthcare providers to counsel patients appropriately and follow up to reduce risks for self-harm. Improving patients' understanding of treatment expectations is important.

The patient can be made aware that physical symptoms of depression (e.g., sleep, energy) should improve within 3 weeks and cognitive and emotional symptoms (e.g., anxiety, guilt, helplessness, memory, sadness, thoughts of self-harm) usually improve within 6 weeks. Patients should be advised that if they experience new or more intense thoughts of suicide to contact their primary care provider right away.

Codeine was not prescribed to the patient. The patient was self-medicating in addition to seeking out prescription medications. The patient should be counselled on the risks of combining benzodiazepines with other sedating medications.

Upon review of this case it would have been advisable for the pharmacist dispensing these medications to contact the prescriber to discuss the combination of benzodiazepines and the dosages. Dispensing a shorter days supply of the benzodiazepine is also recommended. These conversations should always be documented appropriately.

It is a pharmacist's primary responsibility to ensure patient safety when dispensing prescription medication. All members are reminded of their professional obligation to ensure that each

prescription is reviewed thoroughly. Proper measures must be taken to address issues with appropriateness of drug therapy, drug interactions, therapeutic duplication as well as correct dosage.

Additional Reading

1. The Ashton Manual https://www.benzo.org.uk/manual/bzcha01.htm#24

2. Canadian Pharmacists Association. Compendium of Pharmaceuticals and Specialties (CPS) Available: https://www.pharmacists.ca/products-services/compendium-of-pharmaceuticals-and-specialties/

3. Michael G. DeGroote National Pain Centre. McMaster University. Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain Practice Toolkit. Available: http://nationalpaincentre.mcmaster.ca/documents/practicetoolkit.pdf

4. Swinson RP et al., Clinical Practice Guidelines: Management of Anxiety Disorders. Can J Psychiatry 2006;51(Suppl 2). Available: http://ww1.cpa-apc.org.8080/Publications/CPJsupplements/July2006/anxiety_guidelines_2006.pdf.

5. CADTH. High dose and watchful dosing of benzodiazepines: A review of the safety and guidelines. November 21, 2012. Available: https://www.cadth.ca/high-dose-and-watchful-dosing-benzodiazepines-review-safety-and-guidelines.

6. Choosing Wisely. Pharmacists. Recommendation 6. Don't prescribe or dispense benzodiazepines without building a discontinuation strategy into the patient's treatment plan (except for patients who have a valid indication for long-term use. Available: https://choosingwiselycanada.org/pharmacist/.

7. Choosing Wisely. Drowsy without feeling lousy. A toolkit for reducing inappropriate use of benzodiazepines and sedativehypnotics among older adults in primary care. Version 10. July 2017.

8. CADTH. Discontinuation Strategies for Patients with Long-term Benzodiazepine Use: A review of clinical evidence and guidelines. July 29, 2015. Available: https://www.cadth.ca/sites/default/fil_s/rc0682-bzd_discontinuation_strategies_final_0.pd .

9. CCSA. Effective Interventions to Manage Symptoms of Benzodiazepine Withdrawal in Seniors. November 2014. Available: http://www.ccsa.ca/Resource%20Library/CCSA-Benzodiazepine-Withdrawal-Seniors-Rapid-Review-2014-en.pdf.

10. NICE Clinical Knowledge Summary – Benzodiazepine and Z-drug withdrawal (http://cks.nice.org.uk/benzodiazepine-and-zdrug-withdrawal#!scenario)