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 together 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-identified 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 identified 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 first 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 filled 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 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) and the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain Practice Toolkit are also great resources that can be used to determine approximate diazepam equivalents.

There is no evidence that combination benzodiazepines improve efficacy, 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 improve efficacy, but combination treatment may increase risk of harm. Safety concerns include increased risk of falls, injury, confusion,
### Toxicology Results

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

*Above therapeutic range

### Recent DPIN History Preceding Patient’s Death

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

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Date Dispensed</th>
<th>Strength</th>
<th>Quantity</th>
<th>Days Supply</th>
<th>Prescriber</th>
<th>Pharmacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>Nov 14, 2017</td>
<td>1 mg</td>
<td>56</td>
<td>28</td>
<td>Dr. Gucci</td>
<td>Ferragamo Drugs</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Nov 14, 2017</td>
<td>30 mg</td>
<td>28</td>
<td>28</td>
<td>Dr. Gucci</td>
<td>Ferragamo Drugs</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>Nov 14, 2017</td>
<td>75 mg</td>
<td>28</td>
<td>28</td>
<td>Dr. Gucci</td>
<td>Ferragamo Drugs</td>
</tr>
</tbody>
</table>

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**


10. NICE Clinical Knowledge Summary – Benzodiazepine and Z-drug withdrawal (http://cks.nice.org.uk/benzodiazepine-and-zdrug-withdrawal#1scenario)