## Introduction

KF was a 40-year-old woman who was found deceased at home in December 2018. She had a past medical history of opioid addiction and was on a methadone maintenance treatment program. There was no suicide note found and no indication of trauma. An autopsy was performed, and cause of death was determined to be multi-drug overdose involving carfentanil and methadone. This case was identified by the College as an important learning opportunity for pharmacists to review dispensing practices.

## Discussion

There are multiple factors that are important to consider.

Although benzodiazepines did not contribute to the patient’s death, it is still important to note that KF was prescribed near or higher than recommended doses of benzodiazepines. 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 Opioid Manager are also excellent resources that can be used to determine approximate diazepam equivalents. Prescribing more than 30-40 mg of diazepam or equivalent per day is generally not recommended. At 2 mg of alprazolam per day (20 to 40 mg diazepam equivalents) and 30 mg of temazepam per day (10 to 15 mg diazepam equivalents), the patient may have received greater than the recommended cumulative dose of benzodiazepines.

Long-term use of benzodiazepines is not supported by evidence and prescribing more than one at a time is not recommended. There is no evidence that combination benzodiazepines improves efficacy, but combination treatment may increase risk of harm. This practice may be an attempt to treat anxiety and insomnia individually without consideration of their common causes. Patients should have a long-term plan for managing anxiety and insomnia in place, 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.

Prescribing benzodiazepines concurrently with methadone can result in excessive sedation and lead to increased risk of respiratory depression. If it is necessary to prescribe them together, daily dispensing or dispensing along with methadone is recommended. For more information about appropriate prescribing practices in opioid...
**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>Methadone</td>
<td>650*</td>
<td>100-400</td>
</tr>
<tr>
<td>EDDP (inactive methadone metabolite)</td>
<td>88</td>
<td>N/A</td>
</tr>
<tr>
<td>Carfentanil</td>
<td>1.11 (The lowest carfentanil is 0.05 ng/mL)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Please note that a level of 650 ng/ml methadone in a long-term, stable opioid replacement therapy (ORT) patient cannot necessarily be interpreted as a toxic level. This level may be appropriate and it cannot be assumed that the methadone was overused.

**Recent DPIN History Preceding Patient’s Death**

KF’s DPIN showed that she was dispensed the following drugs (and had been 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>Methadone</td>
<td>Dec 20, 2018</td>
<td>10 mg/ml</td>
<td>16*</td>
<td>5*</td>
<td>Dr. Psy</td>
<td>TT Pharmacy</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Dec 13, 2018</td>
<td>1 mg</td>
<td>56</td>
<td>28</td>
<td>Dr. Psy</td>
<td>Bullseye Pharmacy</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Dec 13, 2018</td>
<td>30 mg</td>
<td>28</td>
<td>28</td>
<td>Dr. Psy</td>
<td>Bullseye Pharmacy</td>
</tr>
</tbody>
</table>

*Daily dose 3.2 mL (32 mg). Patient received a total of two witnessed doses and five carry doses weekly.

replacement therapy, refer to the Opioid Agonist Therapy (OAT) Guidelines for Manitoba Pharmacists.

Consider providing naloxone kits to patients at risk of opioid overdose (e.g., >90 mg morphine equivalent, ORT patients, multiple prescribers, frequent early refills, frequent emergency visits requesting opioid, history of opioid use disorder, concomitant CNS depressants, during tapering plan). Note that greater than normal doses of naloxone may be required to reverse an overdose for more potent opioids, like fentanyl and carfentanil.

The patient’s benzodiazepines did not appear on the toxicology report. The patient may have been diverting the medication or was not taking them. The patient was supplementing with street drugs (carfentanil) which in combination with the patient’s methadone, resulted in a fatal overdose. Patients showing signs of instability should not be given carries.

It would have been advisable for the pharmacist dispensing the patient’s medications to have a conversation with the prescriber about the combination, dosages, and quantities dispensed of the medications prescribed. 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


4. The Center for Effective Practice (CEP) Practice Tool: Benzodiazepine Use.


12. Canadian Centre on Substance Use and Addiction (CCSA). Resources related to the opioid crisis.