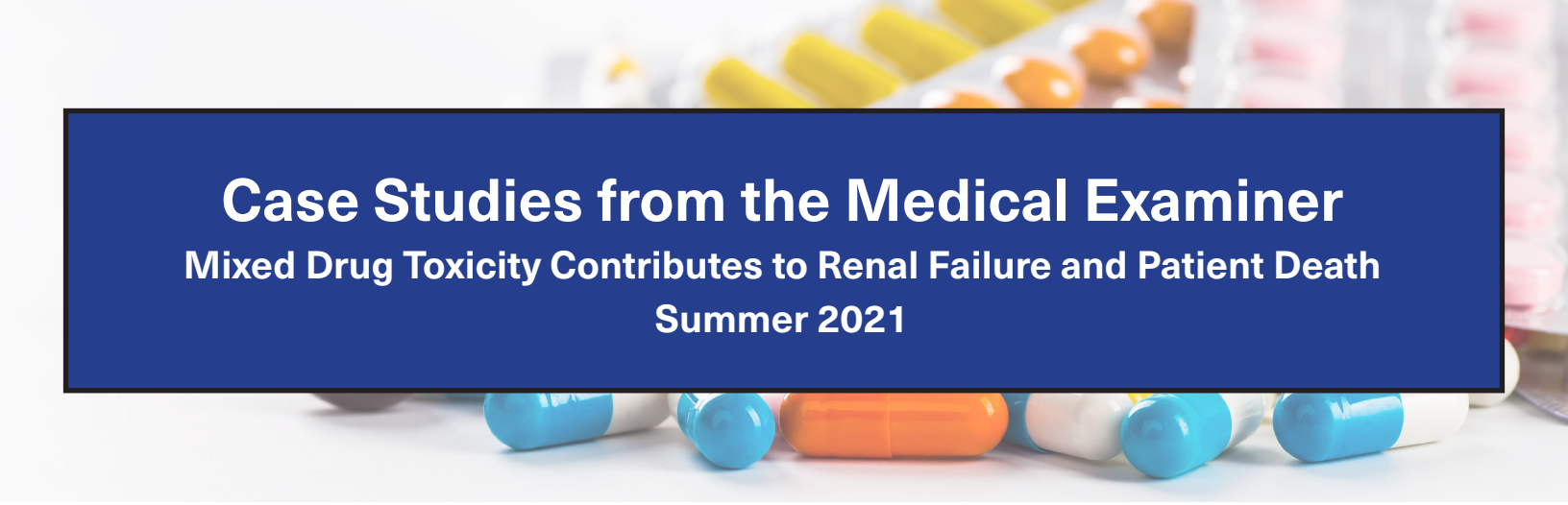

# Case Studies from the Medical Examiner

## Mixed Drug Toxicity Contributes to Renal Failure and Patient Death

## Summer 2021

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-identified to protect the identity of the patient and their family.

## Introduction

NL was a 42-year-old male who was found deceased at his home on Aug 23, 2019. NL's past medical history included bipolar disorder, high cholesterol, obesity (BMI 43), hypertension, and migraines. The immediate cause of death was determined to be accidental mixed drug toxicity (morphine, hydromorphone, cetirizine, cyclobenzaprine, gabapentin, hydroxyzine, mirtazapine and clonazepam). A significant condition contributing to death was renal failure.

## Discussion

NL was receiving all of his medications in bubble packs, dispensed at weekly intervals from the pharmacy. However, a re-evaluation of the safety of long-term combination sedating medications and the use of high-dose (200 mg per day) long-acting morphine is warranted. There is typically little to no dose-response effect of opioids for pain relief and functional recovery[1,2],but there is a dose-dependent increase in the risk of non-fatal and fatal opioid-related overdose[1,3]. Compared to morphine doses of less than 20 mg per day, the risk of experiencing an overdose event is almost four times higher at doses above 50 mg per day, and almost nine times higher at doses above 100 mg per day.[3]

## Recommendations

Patients receiving high-dose opioids, especially in combination with other sedating medications, should be prioritized for opioid tapering.[2] Forming a collaborative relationship with the prescriber on reducing the risk of high-dose opioid use is imperative.

Requesting information on renal function could be suggested to help re-evaluate the safety of medications. In particular, metabolites of morphine (e.g., morphine-6-glucuronide) can accumulate in renal insufficiency and contribute to central nervous system depression and prolonged respiratory depression.

Although wait times may limit the availability of a Sleep Study Assessment, referral to a respirologist may be of benefit for patients with an underlying respiratory disease, high BMI, and those receiving high-dose opioids.

An evaluation of medications contributing to sedation and weight gain, including quetiapine, mirtazapine, and gabapentin could also be re-assessed.

**Strategies to help engage patients on reducing the risk of high-dose opioid use include**

- providing education on the benefits and harms of remaining on high-dose opioids compared to alternative options;
- identifying specific, measurable, and relevant functional goals for the patient;
- having a plan for managing withdrawal symptoms, emerging pain, or reduced functioning during a tapering schedule, re-assuring changes to the dose would be done slowly;
- offering an opioid rotation; and
- recommending the patient take home a naloxone kit.

## Toxicology Results

The following chart represents the results of the toxicology report.

| Drug | Level in blood | Therapeutic Range |
|---|---|---|
| Cetirizine | 1400 ng/mL | N/A |
| Cyclobenzaprine* | 100 ng/mL | 3 - 32 ng/mL |
| Clonazepam | 0 | 20 - 70 ng/mL |
| 7-aminoclonazepam (active metabolite) | 18 ng/mL | 20 - 140 ng/mL |
| Gabapentin* | 26 ug/mL | 2 – 20 ug/mL |
| Hydromorphone | 3 ng/mL | 1 - 30 ng/mL |
| Hydroxyzine | 39 ng/mL | 20 – 80 ng/mL |
| Mirtazapine | 37 ng/mL | 28 – 64 ng/mL |
| Morphine* | 310 ng/mL | 10 – 80 ng/mL |
| Quetiapine | 110 ng/mL | 100 – 1000 ng/mL |

* above the therapeutic range

## Relevant Three-Month DPIN History Prior to Patient's Death

| Generic Name | Date Dispensed | Strength | Quantity | Days Supply | Prescriber | Pharmacy |
|---|---|---|---|---|---|---|
| Clonazepam | Aug 21,14, 7<br>Jul 31, 24, 17, 10, 3<br>Jun 26,19,12, 5, 2<br>May 29, 22 | 2 mg | 21 | 7 | Dr. X | XYZ Pharmacy |
| Cyclobenzaprine | | 10 mg | 21 | | | |
| Duloxetine | | 60 mg | 7 | | | |
| Gabapentin | | 600 mg | 28 | | | |
| Hydroxyzine | | 25 mg | 21 | | | |
| Mirtazapine | | 30 mg | 7 | | | |
| Morphine SR | | 100 mg | 14 | | | |
| Prazosin | | 2 mg | 14 | | | |
| Quetiapine | | 300 mg | 14 | | | |
| Salbutamol | 100 mcg | 100 mcg | 200 | 21 | | |
| Fluticasone/vilanterol | 200/25 mcg | 200/25 mcg | 30 | 30 | | |

**It is a pharmacist's primary responsibility to ensure patient safety when dispensing a prescription medication.** All members are reminded of their professional obligation to ensure that each prescription is reviewed thoroughly, and potential issues addressed, even if it means there may be a difficult patient encounter. Measures must be taken to address issues with appropriateness of drug therapy, drug interactions, therapeutic duplication, and inappropriate or unsafe dosing. Pharmacists do not have the obligation to dispense medications that they believe may cause patient harm. In such cases, the patient must be referred appropriately according to the Referring a Patient Practice Direction.

# References


1. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. CMAJ 2017;189(18):E659-666.
2. Rauck R, Rapoport R, Thipphawong J. Results of a double-blind, placebo-controlled, fixed-dose assessment of once-daily OROS(R) hydromorphone ER in patients with moderate to severe pain associated with chronic osteoarthritis. Pain Pract 2013;13:18–29
3. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med 2010;152(2):85-92.