Case Studies from the Medical Examiner

Accidental Mixed Drug Toxicity Contributes to Patient Death

Winter 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

BC is a 47-year-old female who was found unresponsive in her bedroom on June 7, 2019. Emergency MedicalServices responded but all resuscitation efforts were unsuccessful. Drug paraphernalia was found at the scene. BC had a past medical history of hypertension, hypothyroidism, uncontrolled type I diabetes mellitus, peripheral neuropathy, prior episode of diabetic ketoacidosis and end-stage renal disease requiring hemodialysis. In addition, her history included previous suicidal ideation, suicide attempt, and substance abuse with a recent fentanyl overdose one month prior to her death.

The immediate cause of death was determined to be accidental mixed drug toxicity (cocaine, fentanyl, and multiple non-opioid drugs (alprazolam, clonazepam, diphenhydramine, pseudoephedrine and zopiclone). A significant condition contributing to her death was end-stage renal disease due to type I diabetes mellitus.

Discussion

BC was rapidly tapered off hydromorphone-controlled release (CR) over the span of 13 weeks. Based on recommendations from the 2017 Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain[1], initial dose reductions in the range of 5-10% of the total daily morphine equivalent dose (MED) every 2-4 weeks are reasonable, with frequent follow-up[2]. Once a dose of approximately 1/3 of the original dose is reached, smaller dose reductions (e.g., 5% every 4-8 weeks) may be more suitable and more likely to result in a successful taper[3].

BC's original dose of 72 mg/day of hydromorphone-CR (360 mg/day MED)[4], was decreased to 30 mg/day (150mg MED) on March 2. BC's original hydromorphone-CR dose of 72 mg/ day should have been reduced by 5 -10%, equating roughly to 3 – 7 mg/day (18 – 36 mg/day MED) for two-four weeks. However, as the DPIN history shows, her dose was reduced by 42 mg/day (210mg MED) for two weeks, which is roughly 60% of her total daily MED. After a brief dose re-escalation on March 15, her dose was tapered further to 50%, 33%, 16%, and then 8% of her original daily MED dose at two-week intervals for the subsequent eight weeks, before being completely tapered off.

> **Patients who are given sudden and rapid dose reductions and are physically dependent on opioids can experience serious withdrawal symptoms, uncontrolled pain, psychological distress, and potentially suicide**

The 2017 Guideline states that rapidly decreasing the dose over a few days or weeks can lead to severe withdrawal symptoms and should be carried out in a medically supervised withdrawal centre with an interdisciplinary approach[1]. According to a study by Mark et al., each additional week of tapering time was associated with a 7% reduction in the probability of an emergency department visit or hospitalization secondary to opioid

Toxicology Results

The following chart represents the results of the toxicology report.

Drug	Level in blood	Therapeutic Range
Alprazolam Alpha-hydroxyalprazolam	28 ng/mL 0 ng/mL	25 – 55 ng/mL
Clonazepam 7-Aminoclonazepam (Metabolite of clonazepam)	0 ng/mL 111 ng/mL	20 – 70 ng/mL 20 – 140 ng/mL
Diphenhydramine*	214 ng/mL	14 – 112 ng/mL
Fentanyl	13.9 ng/mL	^within 24 hours of the application of a 100 ug/hr transdermal patch, the expected serum concentration is 1.9 – 3.8 ng/mL
Gabapentin	5 ug/mL	2 – 20 ug/mL
Paroxetine*	341 ng/mL	31 – 62 ng/mL
Pseudoephedrine	286 ng/mL	^following daily 360mg doses, plasma pseudoephedrine concentrations reach 640ng/mL.
Zopiclone	32 ng/mL	25 – 65 ng/mL
Ethanol	11 mg/dL	N/A

* above the therapeutic range

Note: Selective serotonin-reuptake inhibitors like paroxetine undergo post-mortem redistribution and levels may be slightly elevated in the toxicology report.

Relevant DPIN History Prior to Patient's Death

Generic Name	Date Dispensed	Strength (in mg)	Quantity	Days Supply	Prescriber	Pharmacy
Clonazepam	May 11	2	500	100	Dr A.	ABC Pharmacy
Acetaminophen/ Codeine	May 14	300/30	30	3		
Diltiazem	Apr 22 Feb 28	360, 180 360, 180	90, 90 60, 60	90, 90 60, 60		
Gabapentin	Apr 22, 3 Feb 28	100	40, 60 60	40, 60 60		
Hydromorphone (Controlled Release)	May 5 Apr 26, 14, 2 Mar 15, 2 Feb 18,	3 6,12,18 24, 30 12, 24	28 28, 28, 28 28,14 28, 28	14		
Lorazepam	May 27, 5 Apr 31, 21, 14, 1 Mar 15, 1 Feb 25,18	1	84, 84 42, 84 ,84, 84 84, 84 28, 56	14, 14 7, 14, 14,14 14,14 7, 14		
Paroxetine	Mar 1	20	180	90		
Quetiapine	Apr 2	25	90	90		
Zopiclone	May 10	5	180	90		

poisoning or substance use disorder ($p < 0.01$)[5], meaning that slower opioid tapering schedules were associated with improved safety. In 2019, the U.S. Food and Drug Administration (FDA) has released a statement that indicated patients who are given sudden and rapid dose reductions and are physically dependent on opioids can experience serious withdrawal symptoms, uncontrolled pain, psychological distress, and potentially suicide[6].

It is also critical to note that sudden discontinuation of opioids may cause vulnerable individuals to resort to illicit, harmful drugs to alleviate their withdrawal symptoms, which may elevate the risk of accidental overdose when opioid tolerance is lowered[7,8]. Tapering should be done slowly to minimize this risk. In this case, BC was at an increased risk for unintentional overdose, as she had a history of suicidal ideation, a previous suicide attempt, and non-prescription fentanyl exposure.

Recommendations

A crucial strategy in tapering opioids would be to engage in active discussions with the patient to establish realistic goals, that include but are not limited to, improvement in mood and function, pain control, reduction in adverse events, and better quality of life. Moreover, a detailed plan must be discussed and should include a set schedule of dose reductions, frequent follow-up visits (e.g., weekly check-ins) and strategies to manage withdrawal symptoms and emerging pain. As pharmacists can assist physicians and patients with scheduling dose reductions, it is vital for the pharmacist and physician to collaborate closely to construct an optimal and personalized opioid tapering strategy that best meets the patient's needs[9]. The patient should be informed of the increased risk for overdose if they quickly return to a previously prescribed higher dose or seek other opioids. Given the patient's history of overdose, this patient may have benefited from daily dispensing of medication. Additionally, according to the Canadian national consensus guidelines for naloxone prescribing by pharmacists by Tsuyuki et. al[10], all patients receiving an opioid should be dispensed take-home naloxone and counselled by a pharmacist.

Providing patients with resources on accessing services for addiction and suicide is recommended, including the following:

- Rapid Access to Addictions Medicine Clinic (RAAM) located across Manitoba is a drop-in clinic for individuals seeking help with high-risk substance use and addictions. Not for individuals needing urgent medical attention. See the website for more information and locations.

- Crisis Response Centre (CRC) located at 817 Bannatyne Avenue is a 24/7 drop-in for adults experiencing a mental health crisis.

- Mobile Crisis Service (204-940-1781) is a 24/7 phone service assisting individuals experiencing a mental health crisis.

To summarize, the pharmacist is primarily responsible for prioritizing patient safety. Pharmacists must ensure they complete a thorough revision of each prescription, as well as address and correct potential issues before the medication is dispensed. All members are reminded of their professional obligation and must take measures 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.

Pharmacists must ensure they complete a thorough revision of each prescription, as well as address and correct potential issues before the medication is dispensed.

References

1. J. Busse, S. Craigie, D. Juurlink, N. Buckley, L. Wang, R. Couban, T. Agoritsas, A. Carrasco-Labra, L. Cooper, C. Cull, B. Da Costa, J. Frank, G. Grant, A. Iorio, N. Persaud, S. Stern, P. Tugwell, P. Vandvik and G. Guyatt, "Guideline for Opioid Therapy and Chronic Noncancer Pain," Canadian Medical Association Journal, pp. 189:E659-66, 2017.

2. L. Murphy, R. Babaei-Rad, D. Buna, P. Isacc, A. Murphy, K. Ng, L. Reiger, N. Steenhof, M. Zhang and B. Sproule, "Guidance on opioid tapering in the context of chronic pain: Evidence, practical advice and frequently asked questions," Canadian Pharmacists Journal (CPJ), p. 151(2): 114–120, 2018.

3. RxFiles Academic Detailing, "Tapering Opioids How to Explore and Pursue the Option for Patients Who Stand to Benefit," Spring 2018. [Online]. Available: https://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Tapering-Newsletter-Compilation.pdf [Accessed August 2021].

4. Centre For Effective Practice, "Opioid Tapering Template," February 2018. [Online]. Available: https://cep.health/media/uploaded/CEP_Opioid_Tapering_Template_2018.pdf [Accessed August 2021].

5. T. L. Mark and W. Parish, "Opioid medication discontinuation and risk of adverse opioid-related health care events," Journal of Substance Abuse Treatment, vol. 103, no. August, pp. 58-63, 2019.

6. U.S. Food and Drug Administration (FDA), "FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering: FDA Drug Safety Communication," 9 April 2019. [Online]. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes. [Accessed August 2021].

7. S. Darke and W. Hall, "Heroin Overdose: Research and Evidence-Based Intervention," Journal of Urban Health: Bulletin of the New York Academy of Medicine, vol. 80, no. No. 2, pp. 189-200, June 2003.

8. A. Agnoli, G. Xing, D. J. Tancredi, E. Magnan, A. Jerant and J. Fenton, "Association of Dose Tapering With Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids," The Journal of the American Medical Association (JAMA), vol. 326, no. 5, pp. 411-419, August 3, 2021.

9. Canadian Institute for Health Information (CIHI), "Opioid Prescribing in Canada: How Are Practices Changing?," Canadian Institute for Health Information, Ottawa, 2019.

10. R. Tsuyuki, V. Arora, M. Barnes, M. A. Beazely, M. Boivin, A. Christofides, H. Patel, J. Laroche, A. Sihota and R. So, "Canadian national consensus guidelines for naloxone prescribing by pharmacists," Canadian Pharmacist Journal (CPJ) , vol. 153, no. 6, pp. 347-351, 2020.