

Case Studies from the Medical Examiner

Accidental Mixed Drug Toxicity Leads to Patient Death

Spring 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 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

SK was a 63-year-old male who was found unresponsive in the front yard of his home on May 6, 2019. He was taken to hospital, but all attempts at resuscitation were unsuccessful.

SK's past medical history included chronic pain (following a fall from his bike with left rib fracture in May 2018), hypertension, and depression. Shortly after his fall, SK visited the emergency room (ER) eight times (between May to July of 2018) requesting opioid analgesics due to ongoing left rib pain interfering with sleep. He was prescribed oxycodone/acetaminophen for the first two visits by ER providers but was not given any opioids in his subsequent six visits and told to follow-up with his regular health care provider. His regular care provider then regularly prescribed acetaminophen/codeine.

The immediate cause of death was determined to be accidental mixed drug toxicity (cocaine, codeine, amitriptyline, gabapentin). A significant condition contributing to death was coronary artery disease.

Discussion and Recommendations

This patient was receiving multiple sedating medications, which is associated with an increased risk of opioid-related deaths.¹⁻⁴ The risk of an opioid-related death is higher in those exposed to

an opioid concurrently with gabapentin (adjusted odds ratio (aOR) 1.49, 95% CI 1.18 to 1.88)¹ and benzodiazepine (aOR 3.86, 95% CI 3.49-4.26)³ compared to those taking an opioid prescription alone. Higher daily doses of sedating medications are more likely to be taken by individuals who experienced an opioid overdose compared to their matched controls.⁵ Pharmacists can play a role in reducing the risk of opioid-related deaths

by re-evaluating the use of combination sedating medications.

One strategy is to **re-assess the efficacy and safety of medications to determine the need for continued use**. For instance, evidence suggests that the efficacy of benzodiazepines diminish and dependence risk increases beyond 4-6 weeks of use, and there is evidence of safety risk associated with long-term use

especially in older adults, such as accidents, injury, and cognitive impairment.⁶ In this case, alprazolam and codeine were being used for a longer period than what would be recommended for anxiety (typically < 8 weeks for benzodiazepine)⁷ or pain management (typically < 1 week for acute pain)⁸.

Identifying barriers to treatment that offer a better efficacy and safety profile long-term (e.g., cognitive behavioural therapy for insomnia, selective serotonin receptor inhibitors for anxiety) and setting realistic functional goals

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Toxicology Results

Drug	Level in blood (ng/mL)	Therapeutic Range (ng/mL)
Benzoylcegonine (main metabolite of cocaine)	827 mg/dL	N/A
Amitriptyline Nortriptyline (active metabolite) Total*	250 ng/mL 63 ng/mL 313 [^] ng/mL	75 - 200
Codeine* Morphine	110 mg/mL 8.9 ng/mL	10 - 100 10 - 80
Alprazolam	41 ng/mL	20 - 70
Gabapentin*	42 ug/mL	2-20
Ethanol	23 ng/mL	N/A

*Above therapeutic range.

[^] Tricyclic antidepressants undergo post-mortem redistribution and levels may be slightly elevated in the toxicology report.

DPIN History Three Months Prior to Patient's Death

Generic Name	Date Dispensed	Strength	Quantity	Days Supply	Prescriber	Pharmacy
Acetaminophen/ codeine	May 5	300/30 mg	120	30	Dr. X	XYZ Pharmacy
	Apr 5		120			
	Mar 17		60			
	Mar 2		60			
	Mar 1		120			
Feb 1	120					
Alprazolam	May 5	0.5 mg	120	30	Dr. X	XYZ Pharmacy
	Apr 5	1 mg	60			
	Mar 17	1 mg	30			
	Mar 2	1 mg	30			
	Mar 1	1 mg	60			
Feb 1	1 mg	60				
Amitriptyline	May 4	25 mg	30	30	Dr. YY	XYZ Pharmacy
	Apr 4					
	Mar 6					
	Feb 11					
Gabapentin	May 4	400 mg	180	30	Dr. YY	XYZ Pharmacy
	Apr 4					
	Mar 6					
	Feb 11					
Zopiclone	Apr 20	5mg	30	30	Dr. X	XYZ Pharmacy
	Mar 21					

can help engage patients in making a change.

Pharmacists can work with prescribers to help create a gradual taper schedule with frequent follow-up to reduce the risk of combination sedating medications.

Asking patients about the use of other substances can help identify potential drug interactions and determine whether safer pharmacotherapy options are available for the patient. This patient was taking amitriptyline in addition to cocaine with underlying coronary artery disease. Both amitriptyline and cocaine have cardiotoxic effects particularly at higher doses. **Providing both patient and prescriber with information on potential risks and alternative options to reduce the risk could be helpful in this case.**

This patient was also receiving an early refill March 2, and different prescribers were prescribing different psychoactive medications. **More frequent follow-up with the patient may be required when dose changes are being made. It is also important to recognize potential red flags for early refill requests for psychotropic medications,** including pattern of running out early, lost or stolen medication, and multiple self-sanctioned dose increases.⁹

Limiting the dispensing quantity could be considered to reduce the risk of overdose or diversion of lost or stolen medication.

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

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