

Case Studies from the Medical Examiner

Uncoordinated Care Contributes to Accidental Drug Intoxication Death

Fall 2020

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

ML was a 32-year-old female whose medical history included end-stage renal disease (ESRD) requiring hemodialysis, obesity, hypertension, depression, and reported opioid dependence. On December 26, 2019, she experienced chest pain and shortness of breath and was admitted to the hospital for systemic candida infection. On January 3, 2020, she was granted a two-hour pass in the evening for a funeral. She returned to the hospital in the early hours of January 4, several hours after she was due to return. ML then went to bed and was discovered dead later that morning. Her immediate cause of death was cardiac arrhythmia due to cardiomegaly. Mixed drug intoxication was a significant contributory cause, and the manner of death was reported as accidental.

Discussion

ML's care was complicated and involved twelve different physicians, including multiple hospital prescribers from nephrology and internal medicine, as well as more than one primary care physician. The days' supply of medication dispensed changed frequently, and she attended several pharmacies numerous times a month. She also received multiple sedating medications.

Uncoordinated care can put patients at risk of prescription-related harm, and mitigation strategies should be implemented to support and protect the patient.

Recommendations

Patients on multiple sedating agents are at higher risk of experiencing an accidental overdose.^{1,2} Both venlafaxine and diphenhydramine can also contribute to cardiac conduction abnormalities in overdose.^{3,4} **ML could have benefited from coordinated care that involved as few prescribers as possible, allowing for regular evaluation of all medications' efficacy and safety and suggesting tapering or deprescribing if the patient is on many sedating medications.** Pharmacists are encouraged to reach out to prescribers and formulate a care plan.

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Communicate to the patient that it is in their best interest to choose one pharmacy. Using a single pharmacy for all medications (prescription and non-prescription) and as a source of drug information will lower the risk of medication errors, especially during transition points of care.⁵ Seeking to understand the patient's reasoning and priorities for utilizing multiple pharmacies (e.g. proximity, hours of operation, delivery services, etc.) will help develop a coordinated plan. Patients are much more likely to follow a plan they were involved in establishing. If valid reasons exist for using multiple pharmacies, collaboration between pharmacies is expected to provide the best possible care for the patient.

Toxicology Results

Drug	Level in blood (ng/mL)	Therapeutic Range (ng/mL)
Diphenhydramine [^]	447*	14-112
Oxycodone	100	10-100
Trazodone	262	500-1200
Venlafaxine O-desmethylvenlafaxine#	366* 2600*	62-138 118-252
Gabapentin	25*	2-20

[^] Diphenhydramine is the primary constituent of dimenhydrinate

*Above therapeutic range.

O-desmethylvenlafaxine is the major metabolite of venlafaxine

Recent DPIN History Preceding Patient's Death

ML was receiving several medications for ESRD; however, the DPIN history below only includes a summary of the medications relevant to her toxicology results for the six months prior to her death:

Generic Name	Date Dispensed	Strength	Quantity	Days Supply	Prescriber	Pharmacy
Oxycodone/ Acetaminophen	Dec 18, 17	5/325 mg	120, 10	30, 1	Dr. Bow, Dr. BB	GHI Pharmacy
	Nov 20		120	30	Dr. J. Doe	
	Sept 25		120	30	Dr. J. Doe	
	Aug 31, 4		120, 120	30, 30	Dr. J. Doe	
	July 28, 21, 14, 7		28, 28, 28, 28	7, 7, 7, 7	Dr. Vee	
	June 30, 23		28, 28	7, 7	Dr. Vee	
	June 14		56	14	Dr. Elle	
Diphenhydramine	Dec 24,	50 mg	15	5	Dr. KP	XYZ Pharmacy
	Dec 9		30	15	Dr. Hicks	ABC Pharmacy
	Nov 26		30	15	Dr. Psy	ABC Pharmacy
	Sept 28		60	60	Dr. Gucci	DEF Pharmacy
	Aug 30		30	8	Dr. Elle	ABC Pharmacy
Gabapentin	Dec 26, 19	600 mg	14, 14	14, 14	Dr. BB	ABC Pharmacy
	Nov 26		28	28	Dr. Bow	ABC Pharmacy
	Nov 7		28	28	Dr. Psy	ABC Pharmacy
	Oct 8		30	30	Dr. Iris	DEF Pharmacy
	Sept 22		14	14	Dr. Gucci	ABC Pharmacy
	Sept 8		14	14	Dr. Elle	DEF Pharmacy
	Aug 10		28	28	Dr. Vee	ABC Pharmacy
Venlafaxine	Dec 26	150 mg	14	14	Dr. BB	ABC Pharmacy
	Dec 19		14	14	Dr. Kim	ABC Pharmacy
	Nov 26		28	28	Dr. Elle	ABC Pharmacy
	Nov 7		28	28	Dr. Bow	ABC Pharmacy
	Oct 8		30	30	Dr. Vee	DEF Pharmacy
	Sept 26		14	14	Dr. Smith	EFG Pharmacy
	Sept 12		14	14	Dr. Smith	XYZ Pharmacy
	Aug 16		28	28	Dr. Gucci	XYZ Pharmacy
Trazodone	Dec 26, 19	50 mg	14, 14	14, 14	Dr. BB	ABC Pharmacy
	Nov 6		14	14	Dr. Vee	

Recommending and gradually implementing controlled dispensing to the patient and prescribers may help patients at risk of opioid dependence, diversion, and/or overdose (see the CPhM Summer 2020 Medical Examiner Case Study for more information). Blister packaging of medications may also help reduce the risk of overdose.⁶ It should be emphasized to both patients and providers that such interventions are not meant to impede patient care but rather ensure patient safety and allow for regular follow-up.

If you have a patient with reported opioid dependence, consider speaking to them or their prescriber regarding opioid agonist therapy (OAT). Buprenorphine-naloxone and methadone are evidence-based OAT, which have been found to retain individuals in treatment, maintain abstinence from illicit opioid use, and reduce morbidity and mortality.⁷ Rapid Access to Addictions Medicine (RAAM) clinics are also available for those seeking help with substance use and addictions, which are accessible without an appointment or referral.⁷

Educate patients about the risks of combining opioids and benzodiazepines with over the counter (OTC) medications. High concentrations of diphenhydramine were found in ML's toxicology report. Although ML had been prescribed diphenhydramine, patients often supplement with OTC diphenhydramine or dimenhydrinate (including combination products, in which the patient may be unaware). Pharmacists are reminded to consider keeping diphenhydramine and dimenhydrinate behind the counter (or only keep a limited stock and smaller pack sizes OTC) and entering all purchases of these medications into patient profiles whenever possible.

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 and that potential issues are addressed — even if it means there may be a difficult patient encounter. Measures must be taken to address issues with the appropriateness of drug therapy, drug interactions, therapeutic duplication, and inappropriate or unsafe dosing. Pharmacists do not have an 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. Smolina K, Crabtree A, Chong M, Zhao B, Park M, Mill C, et al. Patterns and history of prescription drug use among opioid-related drug overdose cases in British Columbia, Canada, 2015-2016. *Drug and Alcohol Dependence* 2019;194:151-158.
2. Gjelsvik B, Heyerdahl F, Hawton K. Prescribed medication availability and deliberate self-poisoning: a longitudinal study. *J Clin Psychiatry* 2012;73(4):e548-554.
3. Howell C, Wilson AD, Waring WS. Cardiovascular toxicity due to venlafaxine poisoning in adults: a review of 235 consecutive cases. *Br J Clin Pharmacol* 2007;64:192-197.
4. Zareba W, Moss AJ, Rosero SZ, Hajj-Ali R, Konecki J, Andrews M. Electrocardiographic findings in patients with diphenhydramine overdose. *Am. J. Cardiol.* 1997; 80: 1168–73
5. World Health Organization. The nine Patient Safety Solutions, 2007: Assuring medication accuracy at transitions in care. Available: https://www.who.int/patientsafety/events/07/02_05_2007/en/. Accessed October 8, 2020.
6. Hawton K, Ware Ch, Mistry H, Hewitt J, Kingsbury S, Roberts D, et al. Paracetamol self-poisoning characteristics, prevention and harm reduction. *British Journal of Psychiatry* 1996;168:43-48.
7. Bruneau J, Ahamad K, Goyer M-E, Poulin G, Selby P, Fischer B, et al. Management of opioid use disorders: a national clinical practice guideline. *CMAJ* 2018;190(9):E247-57.
8. Shared Health Manitoba. Rapid Access to Addictions Medicine (RAAM) Clinic. Available: <https://sharedhealthmb.ca/services/mental-health/raam-clinic/>. Accessed October 8, 2020.
9. Sinyor M, Howlett A, Cheung AH. Substances used in completed suicide by overdose in Toronto: An observational study of coroner's data. *Can J Psychiatry* 2012;57(3):184-191.