

Case Studies from the Medical Examiner

Over-the-Counter Drugs Contribute to Patient Death

Winter 2019

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

DN was a 52-year-old female found dead in her home in 2015, where she was discovered by her spouse. No evidence of foul play or suicide note was at the scene, however, empty bottles of quetiapine with another individual's name were uncovered. DN struggled with depression, alcohol abuse and smoking, regularly used prescribed opiates for arthritis pain, and had an episode of "substance intoxication" in the previous year. According to her spouse, DN also suffered from insomnia, and regularly used over-the-counter (OTC) acetaminophen products.

DN was consistently requesting and receiving early refills of acetaminophen/codeine/caffeine (300/30/15). A month prior to her death, she was started on citalopram for depression, and her amitriptyline was discontinued.

Although intended for the treatment and relief of allergies, insomnia and motion sickness, diphenhydramine (e.g. Benadryl) or dimenhydrinate (e.g. Gravol) misuse are ... seen frequently in post-mortem toxicology reports.

Discussion

An autopsy was performed, and DN's cause of death was determined to be probable cardiac arrhythmia, and mixed drug intoxication was a contributing factor.

The toxicology report was positive for amitriptyline, codeine, quetiapine, and diphenhydramine, all of which were above the acceptable therapeutic range (see Toxicology Results, right). Acetaminophen was also present and alcohol was involved.

Although DN's DPIN history (see Six-Month DPIN History, right) shows a typical combination of drugs at doses that are within the recommendations, it was the combined effects of the four sedatives ingested (as shown on the toxicology report) that ultimately resulted in death. The learnings from this case will specifically focus on the harms of OTC drugs when combined with other sedative prescription or street drugs.

DN's toxicology report showed high levels of diphenhydramine (DPH), indicating that she likely ingested large amounts of DPH (e.g. Benadryl) or dimenhydrinate (DMH) products (e.g. Gravol).

First generation antihistamines like DPH and DMH are easily accessible in single entity or combination OTC products. Although intended for the treatment and relief of allergies, insomnia and motion sickness, their abuse is commonly cited in literature^{1,2,3} and seen frequently in post-mortem toxicology reports in the medical examiner files. DMH is composed primarily of DPH and 8-chlorotheophylline in a salt form. It has lower potency than pure DPH, as the addition

Toxicology Results

Drug	Level in blood (ng/mL)	Therapeutic Range (ng/mL)
Amitriptyline	523	75 - 200
Nortriptyline (active metabolite)	104 [∞]	
Total	627* [^]	
Codeine (free)	400*	10-100
Morphine (free)	15	10-80
Diphenhydramine#	1540*	14-112
Quetiapine	2439*	100-1000

* Above therapeutic range.

∞ Nortriptyline is an active metabolite of amitriptyline.

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

#Diphenhydramine is the primary constituent of dimenhydrinate.

Six-Month DPIN History Preceding Patient's Death

Generic Name	Date Dispensed	Strength	Quantity	Days Supply	Prescriber	Pharmacy
Acetaminophen/ codeine/caffeine	Aug 18	300/30/ 15 mg	240	30	Dr. Vee	XYZ Pharmacy
	Jul 25					
	Jun 5, 30					
	May 12					
	Apr 19					
	Mar 22					
Feb 26						
Citalopram	Aug 13	20 mg	60	30	Dr. Vee	XYZ Pharmacy
	Jul 11					
Esomeprazole	Aug 13	40 mg	60	30	Dr. Vee	XYZ Pharmacy
	Jul 11					
	Jun 10					
Amitriptyline	Jun 10	50mg, 25mg	30	30	Dr. Vee	XYZ Pharmacy
	May 8	50mg, 25mg				
	Apr 9	50mg, 25mg				
	Mar 10	50mg, 25mg				
	Feb 9	50mg, 25mg				

of 8-chlorotheophylline was initially intended to counteract the sedative effects of DMH⁴. DMH breaks down into DPH to achieve its therapeutic action, and thus appears as DPH in toxicology reports.

In therapeutic doses, DPH side-effects include mild sedation, dizziness, and mild anticholinergic effects. However, when used in large doses (between 200-1200 mg depending on body weight), the drug

has psychedelic properties characterized by hallucinations, delirium, euphoria, and disorientation resembling a "high."⁵ In cases of severe toxicity, it can cause irregular heartbeat, seizures, and coma⁶. When combined with other sedative prescription drugs, as in DN's case, or when combined with street drugs, mixed drug toxicity can lead to death.^{7,8}

According to the Addictions Foundation of Manitoba, approximately one-fifth of teenagers have said they use over-the-counter (OTC) medications to experience euphoria⁹. A study by Thomas et al¹⁰ speculated that DPH abuse may occur in patients with psychiatric comorbidity and antipsychotic treatment, because of the combination of anti-extrapyramidal, euphoria, and stimulant effects.

The OTC availability of these products make their abuse more difficult to detect and monitor, however, findings from the AIRC show that in the last five years, these medications have been linked to at least one hundred deaths in Manitoba. Other notable OTC drugs of abuse also include doxylamine, chlorpheniramine, pseudoephedrine, and dextromethorphan (DM).¹¹

Recommendations

Pharmacists must be well informed of the OTC medications that have an abuse potential, as pharmacist vigilance can play a positive role in the management of OTC medication abuse. To strike a balance between patient/public safety and the patient's right to access needed medications, the following intervention strategies are recommended:

- Entering all purchases of DPH and DMH medications on patient profiles, especially for adolescents, patients with mental health conditions, or those prescribed antipsychotic medication, thereby creating a tracking system of the quantity and frequency consumed by patients. Directing patients to their prescriber or specialist as required can mitigate risks.
- It is strongly recommended that DPH and DMH stock be kept behind the counter, requiring an interaction and assessment by the pharmacist prior to purchase.
- Stocking and dispensing packs of 30 tablets is strongly recommended over packs of 100 tablets, limiting the number of milligrams that can be ingested at once. Most self-limiting conditions can be managed well with 30 tablets of DPH/DMH.
- If DPH and/or DMH is kept over the counter, consider stocking only a limited number of packs for patient self-selection. This lessens the chances of an individual buying a large number of packs at once.
- If DPH and/or DMH is kept over the counter, ensure it is within the direct line of sight from the dispensary (e.g. immediately adjacent to the cash register), so that staff can monitor purchases and pharmacists can intervene more readily.

- Inquire about OTC medication use when taking a drug history. Patients must be warned that opioids and benzodiazepines should never be combined with alcohol or OTC antihistamines as their combined effects could lead to lifethreatening respiratory depression.
- Mitigation strategies to prevent patient drug diversion can include opting to dispense a shorter days supply, switching to other agents with less potential for diversion, offering lockboxes, and discussing with the patient the dangers of diverted medications for other people.
- To prevent stockpiling of medications, it is strongly recommended to ask patients to return their old medications and encourage them to bring it to the pharmacy for disposal, especially if the patient is known to have a history of substance misuse, or is within an environment that may encourage drug diversion and misuse.

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It is a pharmacist's primary responsibility to ensure patient safety when dispensing a prescription medication. All registrants are reminded of their professional obligation to ensure that each prescription is reviewed thoroughly. Measures must be taken to address issues with appropriateness of drug therapy, drug interactions, therapeutic duplication, and inappropriate or unsafe dosing.

References

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