Opioid toxicity due to CNS depressant polypharmacy: A case report

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Abstract

The interaction between methadone and central nervous system depressants can cause serious adverse effects, including profound sedation, respiratory depression, coma, and death. This poses a challenge in the treatment of patients with concurrent psychiatric and substance use disorders as the combined use is often unavoidable. We report a case of a patient with opioid use disorder, mood disorder unspecified, chronic pain, and chronic obstructive pulmonary disease who experienced 2 serious episodes of CNS and respiratory depression due to polypharmacy-induced opioid toxicity. Careful consideration of pharmacokinetics, pharmacodynamics, and patient-specific factors was imperative to identify the suspected contributing medications: methadone, lorazepam, divalproex, gabapentin, and cyclobenzaprine. Cognitive and system factors that contributed to these adverse events and strategies to mitigate risk of recurrence were also identified.

Keywords: central nervous system depression, CNS, methadone, drug interactions, opioid use disorder, concurrent disorder

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Background

Methadone is a μ-opioid receptor agonist used in the treatment of OUD. Its use is associated with increased retention in treatment, suppressed opioid use, and reduced morbidity and mortality.[1] Although it is effective, the long half-life and full-agonist activity carry the risk of opioid toxicity, especially when used in combination with other CNS depressants.[2,3] This poses a challenge for health care providers treating patients with concurrent psychiatric and substance use disorders as the use of psychotropic medications with CNS depressant properties is often unavoidable.[4,5] We report a case of a patient with OUD, mood disorder unspecified, and chronic pain who experienced 2 serious episodes of CNS depression due to polypharmacy-induced opioid toxicity.

Case Report

A 47-year-old white female with MDD, OUD, and chronic pain by history presented to the emergency department with recurrent suicidal ideation. Her medication history included numerous psychotropic medication trials; she had previously been stable for 5 years on the combination of fluoxetine, doxepin, methadone, cyclobenzaprine, gabapentin, and naproxen (see Table for complete dosing regimens). The patient had multiple medical conditions, including COPD, scoliosis, endometriosis, hypertension, and persistent pedal edema.

TABLE: Patient's comprehensive medication list at admission

Medication	Dosage Regimen	Indication
Atenolol	50 mg PO once daily	Hypertension
Cyclobenzaprine	10 mg PO BID	Chronic pain (scoliosis)
Doxepin	150 mg PO once daily	MDD
Estradiol	0.5 mg PO once daily	Endometriosis
Fluoxetine	80 mg PO once daily	MDD
Furosemide	40 mg PO once daily PRN	Pedal edema
Gabapentin	600 mg PO TID	Chronic pain (scoliosis)
Methadone	75 mg PO once daily	OUD
Naproxen	500 mg PO BID PRN	Chronic pain (scoliosis)
Salbutamol	200 mcg inhalations BID PRN	COPD
Tiotropium	5 mcg inhalations once daily	COPD

BID = twice daily; PRN = as needed; TID = three times daily.

On admission, the patient's vitals were as follows: blood pressure (BP) 104/78 mm Hg, heart rate 86 beats/min, respiratory rate (RR) 25 breaths/min, temperature 36.4°C, oxygen saturation (SpO_2) 94%, and QTc 448 ms. BMI was 27.2 kg/m². A urine toxicology test (fluorescence immunoassay) reacted positive to methadone and tricyclic antidepressants as expected. Serum creatinine was elevated at 1.23 mg/dL, and hepatic function, complete blood count, and electrolytes were all unremarkable. Psychiatric evaluation was positive for restlessness, tangential speech, and anxiety. She described her mood as "sad," and her affect was labile. There were no perceptual disturbances. Based on her current presentation and collateral information, which revealed a history of mania, a diagnosis of mood disorder unspecified, current episode mixed was made. Treatment with risperidone 1 mg PO once daily and lorazepam 1 to 2 mg PO 4 times daily as needed was initiated.

The patient's psychiatric conditions deteriorated quickly upon admission. She became increasingly disorganized, confused, and intrusive and her mood was extremely labile. To target mood lability, the following changes were made between days 1 and 5: risperidone was changed to divalproex enteric-coated tablets 250 mg PO in the morning and 500 mg PO at bedtime and quetiapine 100 mg extended-release PO at bedtime and 25 to 50 mg immediate-release 4 times daily as needed were added (see Figure). A tapering regimen was initiated for fluoxetine and doxepin discontinuation as these unopposed antidepressants were thought to be contributing to worsening of manic symptoms.

On day 6, the patient was found unresponsive 3 to 4 hours after the administration of her morning medications. On examination, it was found BP 80/50 mm Hg, RR 8 breaths/min, SpO_2 95% to 100%, and QTc 456 ms. Three doses of

naloxone 0.4 mg IM injection were administered with 2 minutes in between doses. The patient responded immediately and became agitated, combative, and reported feeling cold. She scored 8 (*mild withdrawal*) on the Clinical Opiate Withdrawal Scale and was given 1 dose of clonidine 0.1 mg and 3 doses of lorazepam 2 mg for withdrawal symptoms. Her liver function tests and electrolytes were unremarkable. She had a small increase in serum creatinine to 1.37 mg/dL. Creatinine kinase (CK) was elevated to 907 U/L, which was attributed to the use of physical restraints. The patient denied intake of nonprescribed medications, and no substances or substance-related paraphernalia were found in her room or belongings. Results of the urine toxicology test were not clinically meaningful due to a delay in acquiring the sample.

Methadone, quetiapine, divalproex, cyclobenzaprine, fluoxetine, doxepin, and gabapentin were held following this incident due to concerns of repeat CNS depression. When the patient's clinical presentation improved later the same day, gabapentin was restarted for pain management, and the tapering regimens of fluoxetine and doxepin were reinitiated. Methadone was restarted 2 days later (day 8) at 30 mg PO once daily to be titrated by 10 mg each day until at 60 mg daily. Divalproex 250 mg PO in the morning and 750 mg PO at night was restarted on day 8 for mania (valproic acid blood levels recorded 4.8 mcg/mL on day 9), and cyclobenzaprine 10 mg PO twice a day was restarted on day 10. Lorazepam remained available for as-needed use for opioid withdrawal symptoms and anxiety during this time.

On day 11, the patient was found unresponsive 4 hours after administration of her morning medications, which included cyclobenzaprine, divalproex, gabapentin, and methadone. She was having 2 to 3 seconds of apnea,
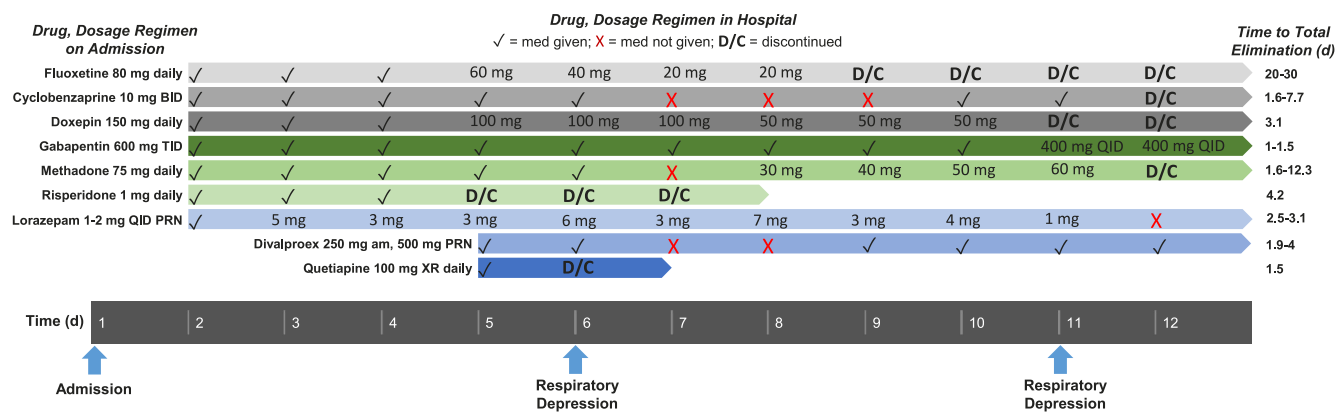
Drug, Dosage Regimen on Admission	Drug, Dosage Regimen in Hospital √ = med given; X = med not given; D/C = discontinued											Time to Total Elimination (d)
Fluoxetine 80 mg daily	√	√	√	60 mg	40 mg	20 mg	20 mg	D/C	D/C	D/C	D/C	20-30
Cyclobenzaprine 10 mg BID	√	√	√	√	√	X	X	X	√	√	D/C	1.6-7.7
Doxepin 150 mg daily	√	√	√	100 mg	100 mg	100 mg	50 mg	50 mg	50 mg	D/C	D/C	3.1
Gabapentin 600 mg TID	√	√	√	√	√	√	√	√	√	400 mg QID	400 mg QID	1-1.5
Methadone 75 mg daily	√	√	√	√	√	X	30 mg	40 mg	50 mg	60 mg	D/C	1.6-12.3
Risperidone 1 mg daily	√	√	√	D/C	D/C	D/C						4.2
Lorazepam 1-2 mg QID PRN	√	5 mg	3 mg	3 mg	6 mg	3 mg	7 mg	3 mg	4 mg	1 mg	X	2.5-3.1
Divalproex 250 mg am, 500 mg PRN	√	√	X	X	√	√	√	√				1.9-4
Quetiapine 100 mg XR daily	√	D/C										1.5

Time (d): 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12

Admission (day 1) — Respiratory Depression (day 6) — Respiratory Depression (day 11)

FIGURE: Patient's total exposure to CNS depressants

RR 4 to 6 breaths/min, SpO_2 of 86%, and BP of 88/51 mm Hg. One dose of naloxone 0.4 mg IM was administered with good response; an increase in RR, BP, and SpO_2 were noted, and the patient reported feeling cold, nauseated, and restless. The patient's RR decreased again 90 minutes later to 6 breaths/min with periods of apnea from 11 to 15 seconds long, and another dose of naloxone 0.4 mg IM was given with good response. She received clonidine in tapering doses, 1 IM dose of lorazepam 1 mg and 1 PO dose of lorazepam 1 mg for opioid withdrawal symptoms. Urine toxicology tested positive to methadone, tricyclic antidepressants, and benzodiazepines. Her creatinine levels (0.81 mg/dL) and liver function tests were normal. CK was elevated (1305 U/L) as it had been from days 7 to 10 and normalized on day 16 (150 U/L).

Following this incident, cyclobenzaprine and methadone were discontinued, and a trial of buprenorphine/naloxone was initiated using a microdosing protocol from days 12 to 23.[6] However, due to patient dissatisfaction of suboptimal pain control, cyclobenzaprine was reinitiated on day 23, and buprenorphine/naloxone was changed back to methadone on day 24. Of note, lorazepam was used as needed for anxiety at doses between 1 and 7 mg/d until day 23. The patient was discharged on day 26 with marked improvement in her psychiatric condition. At time of discharge, the patient was being managed on divalproex 750 mg/d (at a therapeutic level of 75.7 mcg/mL), methadone 30 mg/d, and cyclobenzaprine 10 mg 3 times daily as needed. Informed consent was provided by the patient for the preparation of this case report.

Discussion

Upon analyzing the time of administration, dosage, and combination of medications given prior to each adverse event, it was strongly suspected that the combined use of methadone, lorazepam, divalproex, gabapentin, and cyclobenzaprine contributed to opioid toxicity in our patient. A review of the literature identified reports of interactions between methadone, lorazepam, divalproex, and gabapentin. Methadone and lorazepam have a pharmacodynamic interaction increasing methadone action at μ-opioid receptors.[7] A few in vitro studies suggest a pharmacokinetic interaction between benzodiazepines and methadone via competitive inhibition on methadone N-demethylation, but its clinical importance has not been confirmed.[8] Various guidelines and national organizations suggest against their combined use due to the risk of profound sedation, respiratory depression, coma, or death.[9-11] The FDA[12] also published a warning regarding the risk of respiratory depression from concomitant gabapentin and CNS depressant use.

A less studied interaction is that of divalproex and lorazepam. Both medications are metabolized by uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes.[13] Divalproex is an inhibitor and a substrate of UGT, decreasing glucuronidation and possibly increasing plasma concentration of lorazepam up to 31%.[13] A few case reports[14,15] have implicated this interaction to cause stupor and coma in patients. Our patient was consistently given 1 to 7 mg of lorazepam per day during her admission. When combined with divalproex, the serum concentration of lorazepam and, subsequently, the chance of interaction with methadone may have increased.

Pharmacodynamic additive interactions were also deemed crucial in this case. Caring for this patient was a balancing act between sufficient psychiatric and pain symptom control and the management of CNS depression. Despite the patient having high risk factors for opioid toxicity at baseline, such as COPD and the use of multiple CNS depressants, she was also considered to have high tolerance based on her medication history. The patient was taking the combination of methadone, divalproex, gabapentin, and lorazepam from days 8 to 10 without significant adverse effects. The addition of cyclobenzaprine at bedtime on day 10 seemed to have tipped the balance and contributed to the episode on day 11

although there is only 1 in vitro study to support cyclobenzaprine's potential to inhibit opioid metabolism.[16] Further, a number of CNS depressants were administered throughout this patient's hospital admission (see Figure). Many of the medications have a moderately long half-life of 5 to 72 hours, and as complete elimination takes 4 to 5 half-lives, these medications could have remained in the patient's system and increased the risk of additive CNS depression.[17,18]

This case prompted a retrospective investigation as it is uncommon to have serious, repeated cases of CNS depression requiring naloxone on an inpatient psychiatric unit. On top of pharmacologic factors, some cognitive and system factors were identified that may have contributed to the adverse events. Cognitively, *initial anchoring* was noted as the patient was presumed to have a high tolerance for CNS-depressing medications given her history, and as a result, she was treated with standardized orders for psychiatric medications that may have been dosed too high when combined with methadone.[19] *Premature closure bias* was also notable in the assumption that nonprescribed opioids were taken by the patient and the cause of the episodes of CNS depression. This further contributed to *search satisficing* in that the patient responded to naloxone, and therefore, alternative causes of CNS depression were not explored at the time of the event.[19] Furthermore, a *triage cueing bias* was noted as the patient was experiencing a medical emergency on a psychiatric unit, which articulates systemic issues that played a role.[19] This inpatient unit was ill-equipped with respect to access to addictions specialists, guidelines for monitoring OUD patients, standardized orders for naloxone, and staff training on opioid overdose management.

After reflection on this case, system changes were proposed to mitigate risk of recurrence. The need for education on the more judicial use of lorazepam in patients receiving methadone and the preferential use of nonbenzodiazepine supportive medications, such as clonidine, for opioid withdrawal symptoms was identified.[11,20] Additionally, the preferential use of buprenorphine/naloxone over methadone in patients requiring benzodiazepines was proposed. The interaction between lorazepam and divalproex was proposed to be added to the clinical pharmacy software to enhance identification of this potentially serious interaction. The addition of a naloxone standing order to the psychiatry admission order set was also proposed to increase accessibility to naloxone and to serve as a reminder for nursing staff on how to respond to opioid toxicity. Finally, the need for increased training on chronic pain and concurrent disorders was discussed.

Limitations of this case study include the inability to determine causation due to the retrospective nature of the analysis and confounding factors, such as the patient's clinical status. Further, the analysis was based on the assumption that a single underlying combination was responsible for both episodes of CNS depression, which may be incorrect. Finally, the aforementioned cognitive and system factors may have contributed to drug toxicity.

Conclusion

The combined use of methadone and psychotropic medications is often necessary in the treatment of concurrent disorders despite the known risk of CNS depression. This case of a patient with OUD, mood disorder, and chronic pain suggests avoiding combined use of methadone, lorazepam, divalproex, gabapentin, and cyclobenzaprine or, if required, to use the lowest effective doses with careful monitoring. It also exemplifies the importance of individualized consideration of pharmacokinetics, pharmacodynamics, and patient-specific factors in identifying and managing drug interactions. Additionally, the potential impact of cognitive bias and system factors in this case highlights the need to routinely review health care system processes to ensure appropriate policies, procedures, and educational strategies are in place to mitigate risk of opioid toxicity on inpatient psychiatry units.

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