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Psychotic Decompensation after a Change to a Stabilized Medication Regimen

- Conduct a medication review to help determine what, if any, therapeutic consequences may result when changes to a medication regimen are needed.
- Improve software for checking drug interactions to alert prescribers and pharmacists to the implications of eliminating a clinically relevant drug interaction through discontinuation of a drug.

As part of an ongoing collaboration with a provincial death investigation service, ISMP Canada received a report describing an individual whose psychiatric conditions had been stabilized by a medication regimen that included both clozapine and fluvoxamine. A supply shortage of fluvoxamine led to a cascade of events that resulted in the individual's decompensated psychosis. This bulletin shares identified opportunities and related recommendations to avoid similar tragedies.

INCIDENT DESCRIPTION

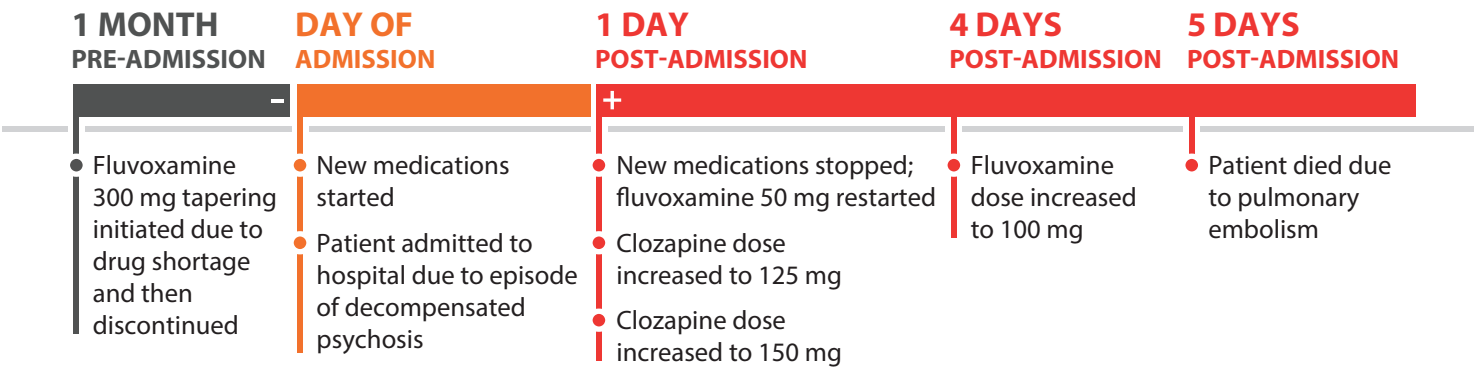
A patient with diagnoses of schizophrenia and obsessive-compulsive disorder had been receiving clozapine 100 mg, fluvoxamine 300 mg, and clomipramine 100 mg daily at bedtime for several years. This medication regimen stabilized the patient's conditions. As a result of a shortage of fluvoxamine supply in the community, the prescriber tapered the patient off fluvoxamine over a period of about a month, with a plan to initiate 2 alternative agents (both antidepressants with serotonergic properties) after discontinuation. During the tapering period, the patient experienced psychotic decompensation.

On the day the new medications were started, the patient required admission to hospital for treatment of decompensated psychosis and symptoms suggestive of serotonin overload. Because the hospital still had a supply of fluvoxamine, this drug was restarted after rapid discontinuation of the new agents. Additionally, the doses of both fluvoxamine and clozapine were increased, in an effort to control the patient's psychotic symptoms. A few days later, the patient died from a pulmonary embolism secondary to deep vein thrombosis in the leg. The timeline shown in Figure 1 outlines the medication changes in the period preceding the patient's death.

BACKGROUND

Schizophrenia is a complex mental illness that affects how a person thinks, feels, behaves, and relates to others.[1] Antipsychotic medications are typically prescribed to reduce the intensity and frequency of the symptoms of schizophrenia. Clozapine is an

Figure 1. Timeline of events just before (-) and after (+) admission to hospital



antipsychotic medication with known serious adverse effects; because of these adverse effects, it is usually reserved for managing schizophrenia that has proven resistant to treatment with other antipsychotic drugs.[2] In particular, clozapine therapy puts patients at risk for granulocytopenia and agranulocytosis; consequently, patients must undergo regular blood monitoring while taking this drug.[3] Venous thromboembolism, including fatal pulmonary embolism, is another adverse effect that has been reported with clozapine, as well as certain other antipsychotic drugs.[4-7] For the period January 1965 to December 2020, the Canada Vigilance Adverse Reaction Online Database contains 188 case reports of pulmonary embolism describing a serious outcome, including 81 fatal cases, in which clozapine administration was a suspected contributing factor.[8]

Fluvoxamine is an antidepressant and selective serotonin reuptake inhibitor that is indicated for the treatment of obsessive-compulsive disorder.[9] Fluvoxamine inhibits metabolism of clozapine, so concurrent administration of the two drugs results in a noticeable increase in plasma clozapine levels.[10] In fact, clinicians sometimes deliberately prescribe fluvoxamine and clozapine together, to take advantage of this interaction and thereby reduce the clozapine dose (and pill burden) required to manage patients with refractory schizophrenia.[11]

Disruptions to the medication supply chain can have a negative impact on patients, health care practitioners, and the health care system as a whole. When a product is unavailable, for any reason, pharmacists make efforts to obtain the needed supply from different wholesalers, manufacturers, or other pharmacies and hospitals in their community. If the product remains unavailable, despite these efforts, a substitute medication may be needed.

When a new medication is being added to a patient's medication profile, health care practitioners, including pharmacists and prescribers, use drug interaction–checking software in pharmacy and electronic medical record (EMR) systems to support identification of potential drug interactions.[12] Currently, such software does not have the functionality to alert practitioners to the therapeutic effect, if any, of discontinuing one of the interacting drugs, nor do such programs provide related clinical decision support.

DISCUSSION

Drug Shortages

In the context of a drug shortage, a change to an established medication regimen should be considered only if no additional product can be obtained and the shortage will be prolonged. In making changes to a patient's regimen, health care providers need to assess how critical the drug is for the patient and if any clinical ramifications will result from making the change.[13] In the incident described above, the

prescriber altered the patient's previously stable medication regimen when fluvoxamine was unavailable, which in turn led to an episode of decompensated psychosis. The patient required admission to hospital for this episode.

Functionality of Drug Interaction Software

It would be advantageous to expand the functionality of software in pharmacy and EMR systems to alert practitioners when changing a patient's medication regimen (i.e., adding or discontinuing a medication) might affect an existing, clinically desirable drug interaction. Such functionality could be further enhanced with clinical decision support to promote optimal prescribing and safe medication-use practices.

In this case, the original prescriber had intentionally prescribed clozapine and fluvoxamine together to take advantage of the drug-drug interaction. More specifically, concomitant therapy with the 2 drugs allowed the patient's conditions to be stabilized at a lower dose of clozapine, thus reducing not only the risk of dose-related adverse effects, but also the pill burden. When a different prescriber (who may have been unfamiliar with this interaction and its benefit) discontinued fluvoxamine because of the supply shortage, neither the pharmacy software nor the EMR software flagged the clinical implications.

STRATEGIES TO IMPROVE MEDICATION SAFETY

Recommendations to improve medication safety were presented by the death investigation service. These included standardization of protocols for testing plasma levels of clozapine, enhancement of EMR systems to facilitate access to information about previous treatments and their results, improvement of communication between practitioners about the management of patients affected by a drug shortage, and expanded functionality of drug interaction-checking software. The following strategies focus on improving communication (both among practitioners and with patients) related to drug shortages, and enhancing software functionality.

Pharmacists and Community Pharmacy Teams

- When a drug shortage is directly affecting patient care, check all potential medication supply avenues. The Canadian Pharmacists Association's Drug Shortages Guide presents a systematic approach to assessing the impact of drug nonavailability and subsequent patient management.
- For any patient whose therapy will be affected by a drug shortage, conduct a medication review. Discuss care options with prescribers.
- Counsel patients and/or their caregivers about substitute drug therapies and any potential consequences of changing the regimen.
- Add notes to the patient profile to communicate clinically significant information (such as an intentional, desirable drug interaction) to other team members.
- Advise patients to keep an up-to-date medication list and to maintain a record of why medication changes have been made in the past. The 5 Questions to Ask About Your Medications and the MyMedRec app can help patients clarify, record and share this information with the health care team.

Prescribers

- When medication therapy for a patient whose condition has been stabilized by means of a multidrug regimen must be changed for a nonclinical reason, such as a drug shortage, ensure that a medication review has been conducted to identify any potential unintended effects (e.g., due to elimination of a known and desirable drug interaction).
- Document in the patient's EMR the rationale for each medication in the regimen and any changes that are made.
- Communicate to the pharmacist, via the prescription (whether written, verbal, or electronic), the rationale for each medication in the regimen and any changes that are made.
- Set reminders in the patient's EMR following a significant change in the medication regimen for clinical monitoring and, if appropriate, lab tests.
- Ensure that the patient and/or their caregiver is aware of the reasons for a medication change and

ensure their ability to consent to the change. For some patients, especially those receiving psychiatric care, an advocate may be needed to help with the process.[13]

Pharmacy and EMR Software Vendors

- Enhance drug interaction-checking software to alert practitioners to the discontinuation of a medication linked to a clinically relevant, desirable interaction.
- Provide clinical decision support within the interaction software, where possible.

CONCLUSION

Learning from this death investigation illustrates the need to improve communication within the health care team, particularly by ensuring that all care providers have access to medication history notes about treatment decisions. There is a need to develop protocols for changing therapy safely in high-risk patients (i.e., by means of a full medication review). As well, there are opportunities to improve the functionality of drug interaction–checking software (for alerting practitioners to the consequences of discontinuing specific medications) and to enhance clinical decision support software (so as to promote optimal care).

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As part of its mandate, ISMP Canada participates in medication incident investigations across Canada. ISMP Canada's role during these investigations focuses on incident analysis, identification of strategies to prevent recurrence of similar errors, and promotion of safe medication practices. This is the first in a series sharing key take-aways from specific investigations.

Death Investigation

Key Findings from a Death Investigation

Sudden Clinical Deterioration: Suspect a Medication Error

ISMP Canada participated in reviewing the unexpected death of an individual who was undergoing rehabilitation in hospital after surgery. More than a week into the hospital stay, the patient began experiencing hypotension, bradycardia, and generalized distress. The patient was transferred to an acute care unit of the same hospital and died later the same day. Initial post-mortem findings suggested that the cause of death was pneumonia; however, the results of toxicology testing, reported several months later, revealed the unexpected presence of verapamil, a medication that had not been prescribed for the patient. In light of this discovery, attention turned to the automated dispensing cabinet (ADC) on the rehabilitation floor. Follow-up investigation of this device indicated that the bin labelled for sustained- release verapamil had been opened and accessed in association with the patient's profile on the morning of the person's death. Unfortunately, no further details relating to the incident were elucidated by the follow-up ADC investigation.

KEY FINDINGS

- The possibility of a medication error was not suspected until the post-mortem toxicology reports were returned, several months after the patient's death. The combination of verapamil found in the patient's body (through post-mortem toxicology testing) and documented access to verapamil from the ADC strongly suggests that verapamil was administered in error and that this drug may have contributed to the observed deterioration in the patient's clinical status.
- Although medication access was linked to the patient's profile, available ADC functionality may not have been fully implemented or optimized. Implementation of error-reducing ADC features can improve safety by restricting health care providers' access to incorrect medications.

RECOMMENDATIONS

- ***Recognize*** that ***a medication error*** could be the cause of a patient's sudden clinical deterioration. The potential for a medication incident may be underappreciated when a differential diagnosis is being developed in this situation.[1]
- ***Optimize ADC functionality*** to reduce the risk for medication errors. Built-in ADC features can restrict access to incorrect medications and can also help in detecting errors more easily through documentation of ADC activity and regular auditing practices.

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The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national not-for-profit organization committed to the advancement of medication safety in all healthcare settings. ISMP Canada's mandate includes analyzing medication incidents, making recommendations for the prevention of harmful medication incidents, and facilitating quality improvement initiatives.

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