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PATIENT SAFETY NETWORK

Delayed Clozapine Prescription in an Elderly Man With Dementia

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The Case

An 86-year-old man with neurodegenerative dementia, epilepsy, type 2 diabetes, and hypertension was admitted for agitation and suicidal ideation. Psychiatry was consulted and recommended initiation of clozapine at a dose of 12.5 mg daily. Because of the drug's risks for adverse effects, clozapine must be prescribed and dispensed in accordance with Food and Drug Administration regulations, which mandate a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers. The clozapine REMS program requires both prescribers and patients to be registered in an online database, in which laboratory monitoring results are regularly reported.

The REMS-registered psychiatry attending entered the initial order (12.5 mg) per hospital protocol. However, during the hospitalization, the medicine intern, who was not registered with the REMS program, titrated the dose to 25 mg daily. The intern was able to modify the dose in the hospital without any alerts because he was not writing a new order or prescription (which would have required REMS registration). Moreover, despite having had no experience with or education about REMS, the intern also wrote the discharge prescription because he was unaware that he was ineligible to prescribe clozapine.

Upon receipt of the prescription, the outpatient pharmacist checked the REMS registry and noted the medicine intern was not a registered prescriber. He contacted the attending psychiatrist, who then wrote a new prescription. However, the patient's family was unable to pick up the prescription for 3 days. During this gap in therapy, the patient experienced recurrence of paranoia and required readmission to the hospital for worsening psychiatric symptoms.

The Commentary

by Candy Tsourounis, PharmD, and Katayoon Kathy Ghomeshi, PharmD

The Food and Drug Administration (FDA) has identified certain medications that need special attention to ensure that the benefits of therapy outweigh the risks associated with medication use. For these medications, a Risk Evaluation and Mitigation Strategy (REMS) program may apply. The purpose of REMS is to reduce the occurrence or severity of serious known risks. The REMS program is designed to inform the health care team, including the patient, about particular strategies that can reduce the likelihood of the therapy to cause harm.(1)

The FDA may require a REMS program if the agency deems that the FDA-approved labeling and prescribing information is inadequate to ensure that the benefits outweigh the risks of using the drug. Once the FDA determines that a drug warrants a REMS program, it works with the drug manufacturer to approve the REMS.(2) The specific details and requirements of a REMS program vary from medication to medication. REMS information can be found in a variety of places, including the drug manufacturer website and tertiary drug information resources. The FDA also has a website that lists all current REMS drugs, and FDA-approved prescribing information can provide details about specific REMS.(3)

Over time, REMS requirements can change. Some medications may not have REMS programs when first released on the market but may be deemed to require one later, after the FDA and the health care community gain more experience with the medication. In other cases, REMS requirements may change or be removed. A key point to consider is that the REMS program is not designed to mitigate all adverse drug events. Rather, it is focused on preventing, monitoring, and/or managing very specific and serious risks—to inform, educate, and reinforce actions that will reduce the frequency or severity of the associated harm.(1)

Under REMS, risk may be reduced by providing patient- or health care–directed communication or by requiring particular activities or clinical interventions.(4) Patient communication is often facilitated through the use of a Medication Guide, a handout provided to the patient at the time of prescription medication dispensing. The communication may be targeted to providers, pharmacists, nurses, and other professionals who are part of the health care team. Required activities may include mandatory certifications and agreement to complete risk mitigation activities or documentation of safe use conditions before the medication is dispensed (e.g., laboratory test reporting).(4) These examples are commonly referred to as Elements to Assure Safe Use (ETASU).

Once a REMS designation is required for a given medication, clinical decision support can be embedded into the electronic health record (EHR) to help systematize the REMS program requirements (Figure). For example, if a medication requires a prescriber or patient to be enrolled in a REMS program, it can be incorporated as drug-specific ordering information, as well as include specific questions asking whether the provider and/or patient is registered. Order instructions, order questions, displaying relevant laboratory results, and formulary restrictions (e.g., restricted to psychiatry, etc.) are some of the strategies that could be helpful and will be discussed in further detail below.

The clozapine REMS was developed to reduce the likelihood of patients experiencing severe neutropenia from the medication, which may lead to serious or fatal infections.(5) The REMS outlines the requirements for prescribers and pharmacies who are eligible to prescribe and dispense clozapine. The REMS requirements for health care team members entails enrolling in the REMS program, reviewing education designed for providers, and successfully completing a knowledge assessment. The clozapine REMS was

first issued in 2015, and it was last updated in early 2019 to allow prescribers and pharmacies to prescribe and dispense clozapine for inpatient use if the patient is already registered with REMS.(6) A summary of current clozapine's Elements to Assure Safe Use can be found on the FDA website.(3,6)

In this case, the patient experienced an adverse drug event, not from the risks that were managed through the REMS, but from missing his treatment due to administrative delays in obtaining the medication as a result of the REMS program. This delay suggests a systems etiology, and a review of medication systems will help identify possible causes of this error.(7) Using this approach, it appears that critical drug information was missing when the medical resident went to modify the clozapine order and prescribe it for discharge. Presumably, the medication order screen did not specify the requirement that dose changes and discharge prescriptions needed to be written by a REMS-authorized prescriber. Lack of staff education also contributed, as the provider who modified the dose and the inpatient pharmacist who reviewed the order did not recognize these missing requirements. There was also a lack of quality control or independent check system for this high-risk drug.

Another approach to reviewing this medication error is to evaluate applicable steps in the medication-use process listed in Table 1. At the time of this case, clozapine dose modifications could only be performed by a REMS-authorized provider. With the recent update to the clozapine REMS, inpatient dose modifications no longer require REMS-authorized providers to adjust therapy, thus mitigating the initial error. The delayed medication error could have been prevented if the clinical decision support was designed to inform the prescriber that upon discharge, any outpatient prescriptions would require REMS-authorized providers to prescribe clozapine. The clinical decision support should incorporate a final check that assures that a REMS-authorized provider has written the discharge medication order. A pharmacist reviewing discharge medication orders can also support this safety check. Routine REMS program updates and education could have also helped to prevent this error.

The goal is to prevent medication errors from occurring, make errors detectable if they occur, and mitigate harm if the medication reaches the patient. The most important way to reduce risk is to perform a comprehensive review of the medication safety systems for clozapine or for other medications with REMS programs. Table 2 lists several safety systems that can be considered.(8) Some of the strategies focus on individuals, and others focus on systems. It is important to layer several different strategies for more robust safety planning.

Take-Home Points

- Risk Evaluation and Mitigation Strategy (REMS) programs are designed to mitigate serious, known medication safety risks.
- Lack of knowledge and compliance with REMS requirements can lead to medication errors.
- Designing and implementing comprehensive safety systems, including those embedded in clinical decision support systems, can help prevent medication errors.

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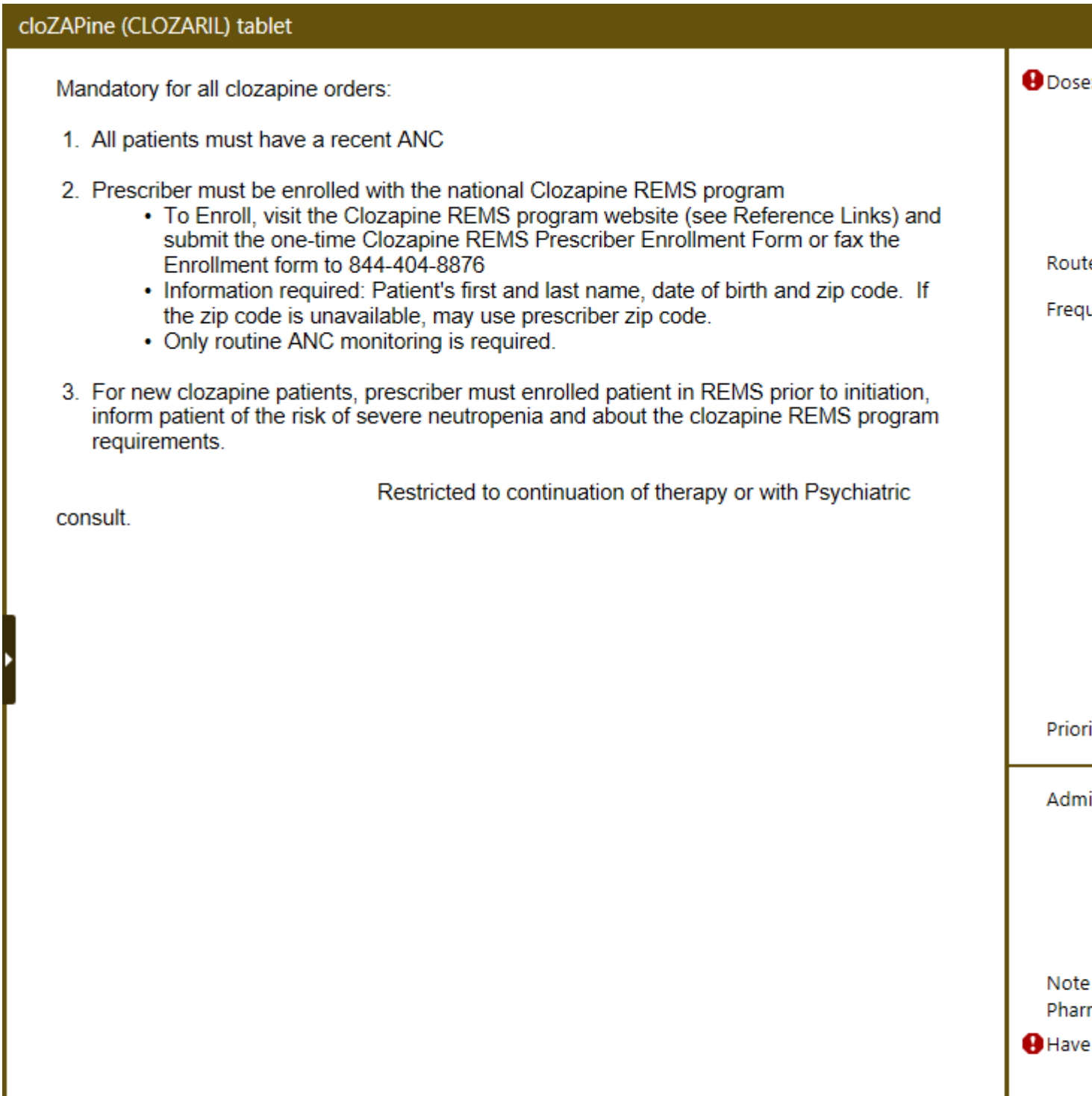
Figure

Figure. Example of Clinical Decision Support for REMS-Requiring Medication in Electronic Health Record.



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Tables

Table 1. Medication Error Assessment Based on Applicable Steps in the Medication Use Process.

Steps in the Medication Use Process	Assessment
Planning	Does the hospital have a formulary restriction for clozapine, or other similar REMS drugs that may need to be prescribed by specialized or certified providers?
Procurement	Does the medication have any special procurement requirements, such as only being accessible via specialty pharmacies?
Storage	Is the medication readily accessible for use without the oversight of pharmacy dispensing?
Prescribing	Is the provider aware of any restrictions in the ability to prescribe this medication or safety requirements for prescribing this medication?
Order Review	Is the pharmacist reviewing the order aware of the REMS criteria, in terms of assessing the patient's eligibility for the medication, the provider's certification/training, and the medication order?
Monitoring	Are appropriate monitoring steps being taken for lab assessments as well as registration in the REMS program?

Table 2. Safety Systems to Improve Medication Safety.(8)

Education/Information	Delivering educational presentations at grand rounds, in-services, and accessible drug information resources
Rules and Policies	Adopting a policy to oversee how REMS requirements are assessed and implemented
Checklists and Double-Check Systems	Instituting a process for necessary lab draws, prospective pharmacist review
Standardization and Protocols	Incorporating formulary restrictions to limit patients or providers who are deemed ineligible
Automation and Computerization	Integrating clinical decision support into computerized prescriber order entry systems
Forcing Functions and Fail-Safes	Including transitions of care and medication reconciliation pharmacists for safety and efficacy review of discharge medications

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