SAFETY ALERT

SERIOUS HARM ASSOCIATED WITH FAILURE TO ADJUST CLOZAPINE DOSING

We have received Pennsylvania Patient Safety Reporting System (PA-PSRS) reports of serious harm associated with a failure to adjust dosing upon reinitiation of clozapine therapy. Clozapine is an atypical antipsychotic approved for the treatment of treatment-resistant schizophrenia. Despite its clinical effectiveness, it is used as a last-line therapy and has risk evaluation and mitigation strategy (REMS) requirements because it can cause a number of serious and potentially fatal adverse effects such as agranulocytosis. Additionally, clozapine requires dose adjustments when used concomitantly with several categories of medications, such as CYP inducers and inhibitors, anticholinergic drugs, and drugs that cause QT interval prolongation.

In patients who have discontinued clozapine for two or more days, the manufacturer recommends the therapy be reinitiated at 12.5 milligrams once daily or twice daily to reduce the risk of hypotension, bradycardia, and syncope. Cases of severe cardiovascular effects have been documented in patients whose doses were not titrated appropriately after an interruption in therapy.

Action Items

- Design and implement effective "hard stops" and alerts in the electronic health record (EHR) to notify any new starts, last date taken, and interruption of therapy for more than two days.

- Document in the EHR any changes that are made to the medication therapy, including the rationale.

- Record the details of medication administration in the medication administration record (MAR) and not solely in the text of the progress notes.

- Ensure medication reconciliation includes date last taken.

- Verify the enrollment of the patient in REMS to avoid a disruption in therapy.

- Educate the multidisciplinary healthcare team on the prescribing and safety information of clozapine, including strategies to detect early signs of adverse effects. Ensure that drug information and institution-specific guidelines, if available, are easily accessible to the healthcare team.

- Ensure periodic review of high-alert medications or medications that require REMS by the pharmacy and therapeutics (P&T) committee. Review should include verification that alerts or hard stops within the EHR function as intended and an analysis of the frequency at which they are triggered.

- Enhance drug-checking software and clinical decision support within the EHR. Review and streamline