Clozapine Dosing for Treatment-resistant Schizophrenia

Clozapine Initiation and Dose Titration

- Start at 12.5 mg orally at night, then 2 times daily after 2-3 days. Titrate up by 12.5 to 50 mg daily every 2-3 days in divided doses as tolerated to a target dose of 300 to 450 mg daily.[1] Due to sedation, evening doses may be higher than morning doses during the titration phase.
- Once at target dose, further dose adjustment should not exceed 50 mg daily and no more frequently than twice weekly based on response, tolerability, and clozapine blood levels (do not exceed 900 mg daily).[1]
- Adverse events are most common during the initial dose titration phase. A slow dose titration reduces the initial risk of adverse effects (see Clozapine Monitoring for guidance on monitoring for adverse effects). Risk for some adverse effects, like constipation and seizures, are also dose dependent.[1,2]
- Taper down the dosage of the failed antipsychotic when clozapine is initiated.
    - One cross-taper approach is to keep the dose of the failed antipsychotic constant during the first week of clozapine treatment, and then to gradually reduce the dose by about 25% per week.[2] Adjust the cross-taper based on tolerability and the ability to increase clozapine to a therapeutic dose.
- Consider patient-specific factors that may impact dosing (see examples in Table 1).[1,2]
    - Caution: patients who smoke tobacco or who drink a lot of caffeinated beverages may experience changes in clozapine effectiveness or tolerability if they suddenly change their daily consumption habit.
- Once a maintenance dose is achieved and the patient is stable, once-daily dosing is as tolerable as twice daily dosing.[3-5]

Table 1. Examples of Patient-specific Factors that Influence Clozapine Blood Levels (adapted from Correll, et al.).[2]

Elevate Clozapine Blood Levels	***Reduce*** Clozapine Blood Levels
May require *lower* dosing or temporary discontinuation during severe infection	May require *higher* dosing or discontinuation of interacting medication
• Female sex (estrogen) • Older age • Asian or Native American ancestry • Obesity • Inflammation from severe infection (monitor levels and adjust accordingly) • High caffeine use • Concurrent valproic acid • Low CYP1A2 expression • Strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin)	• Environmental smoke exposure • Concurrent phenytoin, phenobarbital and topiramate >400 mg/day (induces CYP1A2) • Strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, St. John's wort, rifampin)

Clozapine Blood Levels (Therapeutic Drug Monitoring):

Monitoring clozapine levels is recommended initially to provide feedback for dosing and confirmation of adherence.[6] However, routinely obtaining levels may not be necessary if the patient is tolerating and responding to clozapine.

- Trough clozapine levels should be measured on at least two occasions separated by at least 1 week at a stable dose of clozapine.[6]
- Clozapine levels assessed at original target doses can guide future dose titration since each patient's metabolism can vary (see examples in Table 1).[7]
- The minimum trough clozapine level associated with a typical therapeutic response is around 350 ng/mL. Levels above 600 ng/mL are associated with higher risk for dose-dependent adverse events like seizures.[6]
- Target the lowest effective clozapine level when therapeutic drug monitoring is used.
- Some patients may only respond at higher clozapine levels (higher than 600 ng/mL), which may warrant use of prophylactic anticonvulsant therapy.[2]

Clozapine Trial Duration

Unless clozapine therapy is not tolerated:

- Patients should continue clozapine at therapeutic doses (confirmed by blood levels) for at least 3 months before evaluating response.[6]
- For patients with strong negative symptoms, aggression, or who are at high risk of suicide, a minimum trial duration of at least 16 weeks is recommended before evaluating response.[2]

Measuring Clinical Response

- After at least 3 months at therapeutic doses, use a standardized symptom-rating scale, such as the 30-item Positive and Negative Symptom Scale (PANSS), or a standardized brief psychiatric rating scale, such as the 6-item PANSS-6 to determine response.[2]

Reinitiation of Therapy

Reinitiation of treatment after even a brief interruption in therapy requires a dosage reduction to minimize the risk for hypotension, bradycardia and syncope.[8]

- If 1 day of clozapine is missed: Resume clozapine at 40% to 50% of the previous total daily dose. If the dose is tolerated, it may be titrated faster than initially.
- If 2 days of clozapine are missed: Resume clozapine at about 25% of the previous total daily dose. If the dose is tolerated, it may be titrated faster than initially.
- If more than 2 days of clozapine are missed: Reinitiate therapy at 12.5 mg once or twice daily. If the dose is tolerated, it may be titrated faster than initially.

Discontinuing Clozapine:

When the decision to discontinue clozapine is not based on an emergency, the clozapine dosage should be tapered over at least 6 months, with cross-titration to an alternative antipsychotic chosen based on history of response and tolerability.[2]

References:

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