Clozapine: Talking about risks, benefits, and alternatives with patients

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Clozapine is a life-saving medication for many patients with schizophrenia, including those who have a schizophrenia spectrum disorder with suicidality or treatment-resistant disease, but clinicians' discomfort with managing its risk profile has led to it being underutilized. Clinicians who are prepared to discuss the risks and benefits of clozapine—and alternatives, including no treatment—with patients may encounter less reluctance when they recommend a time-limited trial of the drug.

Risks

Clinicians need to be aware of both 1) serious adverse effects that can occur when clozapine needs to be interrupted or discontinued (***Table, page 66***)[1] and 2) common side effects associated with continued use that can be managed without stopping the drug.[2] Common side effects that patients may experience as treatment is initiated include sedation, orthostatic hypotension, constipation, drooling, tachycardia, and metabolic side effects such as weight gain, diabetes, and hyperlipidemia, which are problematic in the long term.

Reassure patients that frequent monitoring of metabolic metrics (including baseline HbA_{1C}, lipid panel, waist circumference, and body mass index, as well as weight monitoring at each visit and metabolic laboratory monitoring every 3 to 6 months thereafter) should be expected, along with early intervention (eg, adding metformin) as appropriate. Constipation is common and can lead to serious, large bowel ileus. Ask about drooling, which can be treated by reducing the dosage or adding glycopyrrolate.

Extrapyramidal symptoms (EPS) including parkinsonism, dystonia, akathisia are uncommon (clozapine was the first "atypical" antipsychotic for this reason), but neuroleptic malignant syndrome (NMS) can occur. Although tardive dyskinesia (TD) is a small risk, clozapine will improve established TD in many patients once they are switched to clozapine. Blood dyscrasias include granulocytopenia and the rare risk of agranulocytosis which are monitored by means of a prescribing registry. Myocarditis and pancreatitis are likely idiosyncratic immune-related side effects that are unique to clozapine among antipsychotics. Other dangerous side effects include a dosage-related risk of seizure, severe hyperglycemia, and diabetic ketoacidosis.

Benefits

Clozapine is FDA-approved for treatment-resistant schizophrenia and for schizophrenia spectrum disorders with recurrent suicidality. Clozapine can be the best antipsychotic for patients who are sensitive to EPS and for those with TD. Antipsychotic efficacy often can be determined in a 2 to 3 month time-limited trial, although, in practice, you might need to wait 6 to 12 months to observe how well clozapine's benefits have accrued.

Alternatives

Not using the most effective antipsychotic, or using no antipsychotic when one is indicated, often results in unstable psychiatric illness, which increases the risk of adverse outcomes (eg, suicide, accidents). Unstable psychiatric disease also complicates treatment of medical problems. An 11-year

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Disclosures
The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clozapine has a low discontinuation rate, suggesting patients perceive its risk-benefit ratio favorably

Table

Clozapine's dangerous side effects and how to manage them

FDA black-box warnings appear in bold type

Side effect	Incidence; comments	Recommendations
Agranulocytosis	0.8%; highest risk in the first 6 months, necessitating weekly CBC monitoring	Discontinuation, no rechallenge for true agranulocytosis; consider the possibility of benign ethnic neutropenia and stable granulocytopenia instead
Seizures	≤5% with clozapine >600 mg/d (dose-related)	Clinical management (therapeutic drug level monitoring; adding an anticonvulsant such as divalproex, gabapentin, lamotrigine in high-risk situations [eg, seizure history])
Myocarditis or cardiomyopathy, QTc > 500 ms	Rare, 0.02% to 0.2%; myocarditis risk peaks at Week 4 of treatment	Discontinuation, generally no rechallenge
Orthostatic hypotension with syncope or cardiorespiratory arrest	9%, 6%, and <1%, respectively	Clinical management (avoid dehydration; use drug titration, behavioral modification; only judicious use of benzodiazepines)
Increased mortality in older patients with dementia-related psychosis	1.6- to 1.7-fold increased risk for all cause mortality (antipsychotic class warning)	Judicious use, titration
NMS	0.02% to 3% for all neuroleptic agents; can present with less prominent rigidity than typical NMS with clozapine	Discontinuation, no absolute contraindication to rechallenge, but recurrence in as many as 30% of affected people
Diabetic ketoacidosis	<1%; usually seen in patients who are predisposed to the condition	Discontinuation and medical management; no absolute contraindication to rechallenge
Ileus	<1%; preceded by severe constipation	Discontinuation and clinical management (laxatives, minimize anticholinergic burden) with potential rechallenge
Pancreatitis	<1%	Discontinuation and medical management; no absolute contraindication to rechallenge
Venous thromboembolism	<1%; but 3-fold higher risk	Discontinuation and medical management; consider rechallenge, as long as appropriate monitoring and prophylaxis are provided

CBC: complete blood count; NMS: neuroleptic malignant syndrome

Source: Reference 1

follow-up study in Finland of patients with schizophrenia showed a lower all-cause mortality with clozapine than with other antipsychotics, all of which collectively were associated with lower mortality compared with no antipsychotic use.[3] Clozapine also is associated with the lowest discontinuation rate of any antipsychotic, which suggests that patients perceive its risk-benefit ratio favorably. Last, patients who might benefit from clozapine, but do not receive it, often will receive polypharmacy, which poses its own risks.

References

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