Summary
Managing the Nonhematological Adverse Effects of Clozapine

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Psychopharmacology Institute
Introduction

• Seizures, benign fever, tachycardia, constipation and metabolic issues should never be reasons for discontinuing clozapine.
• Given the absence of viable alternatives to clozapine, every effort must be made to manage these conditions.

Managing Sialorrhea

• Sialorrhea presents social and medical consequences (e.g. aspiration).
• Orally applied medications (atropine 1% drops or ipratropium 0.06% spray) are preferred as they do not increase constipation risk
• Consider trying low dose terazosin before using glycopyrrolate if the orally applied medications are not effective

Managing Constipation

• Bulk agents can make constipation worse and should be avoided
• After docusate, the next agent to add is PEG-3350, and if needed a stimulant (and lastly) lubiprostone

Managing Orthostasis

• Management strategies for orthostasis:
  • Use standard or slower dose titration, and lowest effective dose based on clinical response and plasma levels
  • Encourage adequate fluid intake, may add NaCl if possible
  • Minimize use of concurrent alfa 1-adrenergic antagonists and benzodiazepines
  • If patient remains symptomatic:
    • Volume expansion with 9-fludrocortisone

Managing Fever

• Fever is not uncommon, is usually benign, and should never be a reason to permanently stop clozapine
• Clozapine can be held for 24 hours to evaluate causes (e.g. infection, myocarditis)

Managing Tachycardia

• In patients without orthostasis, tachycardia should be managed with low dose atenolol
• One should not base decisions on QTc prolongation if the Bazett formula is used
Myocarditis and Cardiomyopathy

- Myocarditis is relatively rare, only occurs in the first 1-6 weeks of therapy, and can be diagnosed based on elevated serum troponin I/T values in > 90% of cases
- Whether to stop clozapine in cases of dilated cardiomyopathy is a complex clinical decision that should involve the patient, family, and possibly an ethicist

Metabolic Effects

- Consider routine use of metformin given the abundant safety data, and the high rates of weight gain and insulin resistance
  - Starting doses should be low to minimize risk of diarrhea
  - Strongly encourage vigorous physical activity as it has physical and CNS benefits

Sedation

- Use plasma levels to guide treatment and to minimize exposure to excessively high levels
- Modafinil might not work very well, but appears safe at doses up to 300 mg/d

Seizures

- Seizures are never a reason to discontinue clozapine
- Divalproex is the anticonvulsant of choice

Conclusions

- Clozapine is the only antipsychotic with proven efficacy for treatment-resistant schizophrenia
- With a little effort, clinicians can become adept at managing the adverse effects of clozapine
- Management of common adverse effects is critical to keeping patients on clozapine, especially where there are usually no other therapeutic alternatives