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Clozapine-induced gastrointestinal hypomotility

Schizophrenia and related psychoses CHAPTER 1 Clozapine-induced gastrointestinal hypomotility Constipation is a common adverse effect of clozapine treatment with a prevalence of more than 30%, three times that seen with other antipsychotics.1 The mechanism of action is not completely understood but is thought to be a combination of the drug's anticholinergic2,3 and antihistaminergic properties,4 which are further complicated by antagonism at 5-HT3 receptors.2,3,5 In addition, clozapine-induced sedation can result in a sedentary lifestyle,4 which is itself a risk factor for constipation. Clozapine causes constipation by slowing transit time through the gut. Mean transit times are four times longer than normal and 80% of patients taking clozapine show reduced transit time.6 Clozapine-induced GI hypomotility (CIGH) is a much greater risk to life than clozapine- related agranulocytosis.4 When constipation is severe, the case fatality rate is around 20–30%.4,7–9 One long-term study10 found an incidence of 37/10,000 cases of severe hypomotility and 7/10,000 constipation-related deaths. Case fatality was 18%. Enhanced monitoring and effective treatment of CIGH are clearly needed to reduce the likelihood of constipation-related fatality. A GI history and abdominal examination are recommended prior to starting treatment and, if the patient is constipated, clozapine should not be initiated until this has resolved.8 CIGH is most severe during the first 4 months of treatment,8 but may occur at any time. Adopting the Rome III criteria11 at routine FBCs might be a successful strategy to combat preventable deaths due to CIGH, but even this does not guarantee identification of hypomotility.12 A study that examined the diagnostic accuracy of constipation screening found self-reporting to have a sensitivity of just 18%. Adding the Rome criteria improved this to 50%, but this means half of cases were still missed.13 Opinions differ on the relationship between clozapine dose and constipation, and between clozapine plasma level and constipation.8,14,15 However, most studies report that deaths that have occurred as a result of CIGH have higher than average daily doses.8,9,16 Older age, male sex and higher daily doses have been proposed as possible risk factors for death based on case series review16 and pharmacovigilance database studies (Box 1.4).9 Box 1.4 Risk factors for developing clozapine-induced constipation8,17–20 ■ ■Increasing age ■ ■Female sex ■ ■Anticholinergic medication ■ ■Higher clozapine dose/plasma concentration ■ ■Hypercalcaemia ■ ■GI disease ■ ■Obesity ■ ■Diaphoresis ■ ■Low-fibre diet ■ ■Poor bowel habit ■ ■Dehydration (exacerbated by hypersalivation) ■ ■Diabetes ■

■Hypothyroidism ■ ■Parkinson’s disease ■ ■Multiple sclerosis

Revision #1
Created 2026-01-04 20:13:30 UTC by Omar Ayman
Updated 2026-01-04 20:13:30 UTC by Omar Ayman