261 - References

References

Schizophrenia and related psychoses CHAPTER 1 Clozapine rechallenge following severe constipation Some patients have been successfully rechallenged following severe cases of CIGH, but this process does not come without risk. Prophylactic measures should be used for those with a history of CIGH or who are deemed high risk of developing CIGH. Minimise the use of other constipating drugs and ensure other modifiable risk factors are addressed (fibre and fluid intake, exercise). Conventional laxatives should be started in regular and adequate doses to prevent constipation from developing. A number of more experimental options are available. Prescribers must familiarise themselves with the literature (at the very least by reading the SPC) before using any of these treatments and involvement of gastrointestinal specialists is encouraged. Orlistat, a drug used to aid weight loss, is also known to have a laxative effect, particularly when a high-fat diet is consumed. It was reported as being successfully used for three patients with severe constipation associated with opioid use (hypomotility- induced constipation).41 A small, randomised placebo controlled study of orlistat for clozapine-induced constipation found a favourable difference at study endpoint (week 16) for the prevalence of constipation, diarrhoea and normal stools for orlistat compared with placebo,42 although 47 of the 54 participants required conventional laxatives. Orlistat is known to reduce the absorption of some drugs from the GI tract. It is therefore important to monitor plasma clozapine levels if starting treatment with orlistat. Bethanechol, a cholinergic agonist, was effective at 30mg/day in reducing the amount of laxatives and enemas required to maintain regular bowel movements for a patient diagnosed with clozapine-related CIGH.43 Another case report described use in a patient with a gastrostomy, where up to 200mg/day bethanechol was given to reduce dilation of the bowel.44 Bethanechol should only ever be initiated after other options have failed and in consultation with a gastroenterologist.43 Prucalopride is a 5HT4 agonist which increases gut motility and is licensed for chronic constipation where laxatives have failed to provide adequate relief. Case reports of successful use for clozapine-induced constipation have been described,45,46 and superior efficacy to lactulose for this indication was demonstrated in an open-label study.47 Linaclotide (licensed in the UK for constipation in irritable bowel syndrome) and plecanatide (available in the USA for chronic idiopathic constipation) are oral guanylate cyclase C agonists. Neither has any published data to date supporting use in antipsychotic-induced constipation, beyond a single case report for linaclotide.44 Key message ■ ■Prevent clozapine-related constipation by aggressive use of stimulant laxatives. References

1. Shirazi A, et al. Prevalence and predictors of clozapine-associated constipation: a systematic review and meta-analysis. Int J Mol Sci 2016; 17:863.

2. Hibbard KR, et al. Fatalities associated with clozapine-related constipation and bowel obstruction: a literature review and two case reports. Psychosomatics 2009; 50:416–419.
3. Rege S, et al. Life-threatening constipation associated with clozapine. Australas Psychiatry 2008; 16:216–219.
4. De Hert M, et al. Second-generation antipsychotics and constipation: a review of the literature. Eur Psychiatry 2011; 26:34–44.
5. Meltzer HY, et al. Effects of antipsychotic drugs on serotonin receptors. Pharmacol Rev 1991; 43:587–604.

 6. Every-Palmer S, et al. Clozapine-treated patients have marked gastrointestinal hypomotility, the probable basis of life--threatening gastrointestinal complications: a cross sectional study. EBioMedicine 2016; 5:125–134. 7. Cohen D, et al. Beyond white blood cell monitoring: screening in the initial phase of clozapine therapy. J Clin Psychiatry 2012; 73:1307–1312. 8. Palmer SE, et al. Life-threatening clozapine--induced gastrointestinal hypomotility: an analysis of 102 cases. J Clin Psychiatry 2008; 69:759–768. 9. Handley SA, et al. Clozapine-induced gastrointestinal hypomotility: presenting features and outcomes, UK pharmacovigilance reports, 1992–2017. Br J Psychiatry 2022; 220:355–363. 10. Every-Palmer S, et al. Clozapine-induced gastrointestinal hypomotility: a 22-year bi-national pharmacovigilance study of serious or fatal 'slow gut' reactions, and comparison with international drug safety advice. CNS Drugs 2017; 31:699–709. 11. Rome Foundation. Rome IV Disorders and Criteria. 2021 (last accessed October 2024). https://theromefoundation.org. 12. Every-Palmer S, et al. Pharmacological treatment for antipsychotic-related constipation. Cochrane Database Syst Rev 2017; 1:CD011128. 13. Every-Palmer S, et al. Constipation screening in people taking clozapine: a diagnostic accuracy study. Schizophr Res 2020; 220:179–186. 14. Chengappa KN, et al. Anticholinergic differences among patients receiving standard clinical doses of olanzapine or clozapine. J Clin Psychopharmacol 2000; 20:311–316. 15. Vella-Brincat J, et al. Clozapine-induced gastrointestinal hypomotility. Australas Psychiatry 2011; 19:450–451. 16. West S, et al. Clozapine induced gastrointestinal hypomotility: a potentially life threatening adverse event: a review of the literature. Gen Hosp Psychiatry 2017; 46:32–37. 17. Nielsen J, et al. Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? J Clin Psychiatry 2013; 74:603–613; quiz 613. 18. Nielsen J, et al. Risk factors for ileus in patients with schizophrenia. Schizophr Bull 2012; 38:592–598. 19. Longmore M, et al. Oxford Handbook of Clinical Medicine. Oxford: Oxford University Press; 2010. 20. ZTAS. Zaponex Fact Sheet – Constipation. 2023 (last accessed February 2025); https://www.ztas.com/PDF/FS_Constipation_jan2023.pdf. 21. Hayes G, et al. Clozapine-induced constipation. Am J Psychiatry 1995; 152:298. 22. Muller-Lissner SA. Effect of wheat bran on weight of stool and gastrointestinal transit time: a meta analysis. Br Med J 1988; 296:615–617. 23. Harvey RF, et al. Effects of increased dietary fibre on intestinal transit. Lancet 1973; 1:1278–1280. 24. National Prescribing Centre. The management of constipation. Med Rec Bulletin 2011; 21:1–8. 25. NHS. Exercise. Physical activity guidelines for adults aged 19 to 64. 2024 (last accessed October 2024); https://www.nhs.uk/live-well/ exercise. 26. Fitzsimons J, et al. A review of clozapine safety. Expert Opin Drug Saf 2005; 4:731–744. 27. Young CR, et al. Management of the adverse effects of clozapine. Schizophr Bull 1998; 24:381–390. 28. Every-Palmer S, et al. The Porirua protocol in the treatment of clozapine-induced gastrointestinal hypomotility and constipation: a pre- and post--treatment study. CNS Drugs 2017; 31:75–85. 29. Swegle JM, et al. Management of common opioid--induced adverse effects. Am Fam Physician 2006; 74:1347–1354. 30. Voderholzer WA, et al. Clinical response to dietary fiber treatment of chronic constipation. Am J Gastroenterol 1997; 92:95–98. 31.

Brandt LJ, et al. Systematic review on the management of chronic constipation in North America. Am J Gastroenterol 2005; 100 Suppl 1:S5–S21. 32. Esteve Pharmaceuticals (formerly Intrapharm Laboratories). Summary of Product Characteristics. Lactulose 10g / 15ml oral solution sachets. 2023 (last accessed October 2024); https://www.medicines.org.uk/emc/medicine/25597. 33. Partanen JJ, et al. High burden of ileus and pneumonia in clozapine-treated individuals with schizophrenia: a Finnish 25-year follow-up register study. Am J Psychiatry 2024; 181:879–892. 34. Leong QM, et al. Necrotising colitis related to clozapine? A rare but life threatening side effect. World J Emerg Surg 2007; 2:21. 35. Townsend G, et al. Case report: rapidly fatal bowel ischaemia on clozapine treatment. BMC Psychiatry 2006; 6:43. 36. Karmacharya R, et al. Clozapine-induced eosinophilic colitis. Am J Psychiatry 2005; 162:1386–1387. 37. Erickson B, et al. Clozapine--associated postoperative ileus: case report and review of the literature. Arch Gen Psychiatry 1995; 52:508–509. 38. Schwartz BJ, et al. A case report of clozapine-induced gastric outlet obstruction. Am J Psychiatry 1993; 150:1563. 39. Drew L, et al. Clozapine and constipation: a serious issue. Aust N Z J Psychiatry 1997; 31:149. 40. Ikai S, et al. Reintroduction of clozapine after perforation of the large intestine: a case report and review of the literature. Ann Pharmacother 2013; 47:e31. 41. Guarino AH. Treatment of intractable constipation with orlistat: a report of three cases. Pain Med 2005; 6:327–328. 42. Chukhin E, et al. In a randomized placebo-controlled add-on study orlistat significantly reduced clozapine-induced constipation. Int Clin Psychopharmacol 2013; 28:67–70. 43. Poetter CE, et al. Treatment of clozapine-induced constipation with bethanechol. J Clin Psychopharmacol 2013; 33:713–714. 44. Tomulescu S, et al. Managing recurrent clozapine-induced constipation in a patient with resistant schizophrenia. Case Rep Psychiatry 2021; 2021:9649334. 45. Thomas N, et al. Prucalopride in clozapine-induced constipation. Aust N Z J Psychiatry 2018; 52:804. 46. Hui KO. Prucalopride for the treatment of clozapine induced constipation: a case report. Juniper Online J Case Stud 2018; 6:555683. 47. Damodaran I, et al. An open-label, head to head comparison study between prucalopride and lactulose for clozapine induced constipation in patients with treatment resistant schizophrenia. Healthcare (Basel) 2020; 8:533.

Revision #1
Created 2026-01-04 20:13:32 UTC by Omar Ayman
Updated 2026-01-04 20:13:32 UTC by Omar Ayman