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Pharmacologic Interventions for the Treatment of Clozapine-Induced Hypersalivation

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CADTH

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Key Messages

- Five randomized controlled trials were identified regarding the clinical effectiveness of pharmacologic interventions for the treatment of clozapine-induced hypersalivation.
- No evidence-based guidelines were identified regarding the use of pharmacologic interventions for the treatment of clozapine-induced hypersalivation.

Research Questions

1. What is the clinical effectiveness of pharmacologic interventions for the treatment of clozapine-induced hypersalivation?
2. What are the evidence-based guidelines regarding the use of pharmacologic interventions for the treatment of clozapine-induced hypersalivation?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were clozapine, hypersalivation, and pharmacologic interventions. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2016 and November 3, 2021. Internet links were provided, where available.

Selection Criteria

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. Open-access, full-text versions of evidence-based guidelines were reviewed when abstracts were not available.

Results

Five randomized controlled trials[1-5] were identified regarding the clinical effectiveness of pharmacologic interventions for the treatment of clozapine-induced hypersalivation. No evidence-based guidelines were identified regarding the use of pharmacologic interventions for the treatment of clozapine-induced hypersalivation. Additionally, no health technology assessments, systematic reviews, and non-randomized studies were identified.

Table 1: Selection Criteria

Criteria	Description
Population	People with clozapine-induced hypersalivation
Intervention	Pharmacologic interventions (e.g., amisulpride, benzhexol, botulinum toxin, clonidine, glycopyrrolate, hyoscine, pirenzepine, propantheline, sulpride)
Comparator	Q1: Alternative pharmacologic interventions, supportive treatment, no treatment, placebo Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., quality of life, symptom severity, safety [e.g., adverse events]) Q2: Recommendations regarding best practices (e.g., appropriate patient populations or clinical settings, recommended treatment strategies, strategies to mitigate harms, adverse events, and misuse)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

References

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

1. Mubaslat O, Lambert T. The effect of sublingual atropine sulfate on clozapine-induced hypersalivation: a multicentre, randomised placebo-controlled trial. *Psychopharmacology.* 2020 Oct;237(10):2905-2915. PubMed
2. Segev A, Evans A, Hodsoll J, et al. Hyoscine for clozapine-induced hypersalivation: a double-blind, randomized, placebo-controlled cross-over trial. *Int Clin Psychopharmacol*. 2019 03;34(2):101-107. PubMed
3. Sheikhmoonesi F, Zarghami M, Hendoi N, Azari P, Cherati JY, Rezapour M. Comparing the impact of atropine drops and amitriptyline tablets in treatment of clozapine-induced sialorrhea: a randomized double-blind placebo controlled clinical trial. *Acta Medica Iranica*. 2018 24 Dec;56(12):757-763.
4. Man WH, Colen-de Koning JC, Schulte PF, et al. The effect of glycopyrrolate on nocturnal sialorrhea in patients using clozapine: a randomized, crossover, double-blind, placebo-controlled trial. *J Clin Psychopharmacol*. 2017 Apr;37(2):155-161. PubMed
5. Kreinin A, Miodownik C, Mirkin V, et al. Double-blind, randomized, placebo-controlled trial of metoclopramide for hypersalivation associated with clozapine. *J Clin Psychopharmacol.* 2016 Jun;36(3):200-205. PubMed

Non-Randomized Studies

No literature identified.

Guidelines and Recommendations

No literature identified.

Appendix 1: References of Potential Interest

Systematic Review and Meta-Analyses

Not Specific to Clozapine-Induced Hypersalivation

6. Dashtipour K, Bhidayasiri R, Chen JJ, Jabbari B, Lew M, Torres-Russotto D. RimabotulinumtoxinB in sialorrhea: systematic review of clinical trials. *J Clin Mov Disord.* 2017; 4:9. PubMed

Unclear Comparator

7. Chen SY, Ravindran G, Zhang Q, Kisely S, Siskind D. Treatment strategies for clozapine-induced sialorrhea: a systematic review and meta-analysis. *CNS Drugs.* 03 2019; 33(3): 225-238. PubMed

Methods Not Specified

8. Van der Poorten T, De Hert M. The sublingual use of atropine in the treatment of clozapine-induced sialorrhea: a systematic review. *Clin Case Rep*. 2019 Nov;7(11):2108-2113. PubMed

Randomized Controlled Trials

Not Specific to Clozapine-Induced Hypersalivation

9. Isaacson SH, Ondo W, Jackson CE, et al. Safety and efficacy of rimabotulinumtoxinb for treatment of sialorrhea in adults: a randomized clinical trial. *JAMA Neurol*. 2020 04 01;77(4):461-469. PubMed

Alternative Comparator

10. Takeuchi I, Hanya M, Uno J, Fujita K, Kamei H. Effectiveness of the repeated administration of scopolamine ointment on clozapine-induced hypersalivation in patients with treatment-resistant schizophrenia: a preliminary study. *Asia Pac Psychiatry.* 2017 Dec;9(4). PubMed

Non-Randomized Studies

Not Specific to Clozapine-Induced Hypersalivation

11. Toulemonde P, Maltezeanu A, Broucqsault H, Fayoux P. Tolerance of salivary gland botulinum toxin A injection under local anesthesia for the treatment of sialorrhea in children: an observational study. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2021 Jun 30;30:30. PubMed

12. Abboud WA, Nadel S, Hassin-Baer S, Arad A, Dobriyan A, Yahalom R. Ultrasound-guided botulinum toxin injections into the salivary glands for the treatment of drooling. *Isr Med Assoc J.* 2019 Feb;21(2):116-119. PubMed

13. Taib BG, Williams SP, Sood S, Ung K, Nixon PP, Sharma R. Treatment of sialorrhoea with repeated ultrasound-guided injections of botulinum toxin A into the parotid and submandibular glands. *Br J Oral Maxillofac Surg*. 2019 06;57(5):442-448. PubMed

14. Shariat-Madar B, Chun RH, Sulman CG, Conley SF. Safety of ultrasound-guided botulinum toxin injections for sialorrhea as performed by pediatric otolaryngologists. *Otolaryngol Head Neck Surg.* 2016 05;154(5):924-927. PubMed

Not Specific to Pharmacological Treatment

15. Weitzman RE, Kawai K, Nuss R, Hughes A. A 10-year retrospective review of botulinum toxin injections and surgical management of sialorrhea. *Cureus.* 2020 May 01;12(5):e7916. PubMed

Additional References

16. Vova JA, Green MM, Brandenburg JE, et al. A Consensus statement on the use of botulinum toxin in pediatric patients. *Pm R* 2021 Sep 23;23:23. PubMed

17. Gupta S, Khastgir U, Croft M, Roshny S. Management of clozapine-induced sialorrhoea. *BJPsych Advances.* 2020 01 Mar;26(2):106-10.

18. Appendix 16 – clozapine-related hypersalivation. V03-Apr 19 (*PPT-PGN-05 – safe prescribing of clozapine – (NTW(C) 38 - policy on pharmacological therapies).* Northumberland (GB):Northumberland, Tyne and Wear NHS Foundation Trust; 2019. https://www.cntw.nhs.uk/content/uploads/2019/04/PPT-PGN-05-App16-Clozapine-related-hypersalivation-V03-Apr-19.pdf Accessed 2021 Nov 5.

19. Haastrup MB, Henriksen DP, Christensen MMH. Drug-induced sialorrhoea. *Adverse Drug React Bull.* 2018 01 Dec;313(1):1211-1214.