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Clozapine-induced hypersalivation

258 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Clozapine-induced hypersalivation Clozapine is well known to be causally associated with hypersalivation (sialorrhoea):1 excess salivary pooling in the mouth and drooling, particularly at night. Hypersalivation is dose-2 and plasma concentration-related3 but some degree of excess salvation may be seen in the vast majority of patients.4 Clinical observation suggests that hypersalivation reduces in severity somewhat over time (usually several months) but normally persists to some extent. Clozapine-induced hypersalivation is socially embarrassing and discomfiting, has a negative impact on quality of life4 and is often a reason for patients stopping clozapine treatment.5 Further, hypersalivation has been implicated as a contributory factor in the development of aspiration pneumonia and so is potentially life-threatening.6–10 Effective treatment is a matter of some urgency. The pharmacological basis of clozapine-related hypersalivation remains unclear.11 Suggested mechanisms include muscarinic M4 agonism, adrenergic α2 antagonism, and inhibition of the swallowing reflex.12,13 The last of these is supported by trials which suggest that saliva production is not increased in patients treated with clozapine,14,15 although at least one study has observed marked increases in salivary flow in the first 3 weeks of treatment.16 Whatever the mechanism, medications that reduce saliva production might be expected to diminish the severity of clozapine-induced sialorrhoea. However, there are no medications licensed for this condition and many of the relevant published studies have limitations that preclude any confident treatment recommendations.17 A 2023 network analysis of RCTs testing a range of pharmacological interventions for clozapine- induced sialorrhoea in adults18 yielded ‘low confidence’ findings of efficacy, ranking metoclopramide highest, and decreasing through cyproheptadine, sulpiride, propantheline, diphenhydramine, benzhexol, doxepin, amisulpride, chlorpheniramine, to amitriptyline and atropine. Overall, the evidence, such as it is, seems to favour antimuscarinic agents, such as propantheline and diphenhydramine.19,20 Use of antimuscarinic agents should take account of the risk of compounding clozapine’s liability for serious, potentially life-threatening, gastrointestinal hypomotility.21,22 Topical antimuscarinic treatment might be preferred. Several topical agents have been shown to be effective and a small RCT of sofpironium bromide gel in 2023 produced encouraging results.23 In 2024, another small RCT24 found topical atropine to be more

effective than amitriptyline and ipratropium bromide nasal spray. Metoclopramide and other benzamide compounds are probably second-line treatments.25 Table 1.57 describes pharmacological treatments that have been examined. Non- drug treatments may be used if appropriate – these include chewing gum during the day, elevating pillows and placing a towel on the pillow to prevent soaking.11 Nonetheless, problematic hypersalivation should not be considered an inevitable consequence of clozapine use and strenuous efforts should be made to minimise its severity.

Schizophrenia and related psychoses CHAPTER 1 Table 1.57 Clozapine-related hypersalivation – summary. Treatment Comments Amisulpride 100–400mg/day20,26,27 Supported by a positive RCT compared with placebo, one other in which it was compared with moclobemide and numerous case studies.28–32 May allow dose reduction of clozapine. Amitriptyline 25–100 mg/day33–36 Limited literature support. Adverse effects may be troublesome. Worsens constipation. Atropine given sublingually37–41 or as solution (1mg/10mL) used as a mouthwash Limited literature support and the benefit–risk balance is uncertain, although case reports suggest that it may be a relatively effective and tolerable treatment for some patients in clinical practice41,42 and a 2024 RCT yielded positive findings.24 But one meta-analysis18 failed to find atropine superior to placebo for nocturnal sialorrhoea. Problems with administration have been reported.43 Benzhexol (trihexyphenidyl) 5–15mg/day44 Small, open study suggests useful activity. Used in some centres but may impair cognitive function. Lower doses (2mg) may be effective.45 Benztropine 2mg/day

- terazosin 2mg/day46 Combination shown to be better than either drug alone. Terazosin is an α1 antagonist so may cause hypotension. Botulinum toxin47–50 (Botox) bilateral parotid gland injections (150IU into each gland) Effective in treating sialorrhoea associated with neurological disorders. Six cases of successful treatment of clozapine--related hypersalivation in the literature. Widely used in some US centres. Slow onset of effect. Some botulinum preparations are formally licensed for chronic sialorrhoea caused by neurological conditions in adults. Bupropion 100–150mg/day51 Single case report. May lower seizure threshold. Chlorphenamine20 Antihistamine and relatively weak antimuscarinic. One high-quality study. Clonidine 0.1–0.2mg patch weekly or 0.1mg orally at night52,53 α2 partial agonist. Limited literature support. May exacerbate psychosis, depression and cause hypotension. Diphenhydramine19,20 Antihistamine and potent antimuscarinic. Few high-quality studies. Glycopyrrolate 0.5–4mg bd54–59 One RCT showed glycopyrrolate to be more effective than biperiden without worsening cognitive function while another found significant clinical improvement of ‘nocturnal sialorrhoea’ with 2mg a day, compared with placebo. May worsen constipation. Guanfacine 1mg/day60 α2 agonist. Single case report. May cause hypotension. Hyoscine 0.3mg tablet sucked or chewed up to three times daily or 1.5mg/72 hr patch61–64 Hyoscine hydrobromide is a peripheral and central anticholinergic that is commonly prescribed for clozapine-induced hypersalivation,59 but in the UK is an unlicensed use.65 There is one double-blind RCT.53 May cause cognitive impairment, drowsiness and worsen constipation. Ipratropium nasal spray (0.03% or 0.06%) given sublingually up to two sprays three times a day of the 0.06% or intranasally, one spray into each nostril daily of the 0.03%66,67 Limited literature support. The only placebo-controlled RCT conducted was negative.68 Lofexidine 0.2 mg twice daily69 α2 agonist. Very few data. May exacerbate psychosis, depression and cause hypotension. (Continued)

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