

Reducing clozapine-induced hypersalivation

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Hypersalivation is a well-documented side effect of clozapine that may affect nearly 30% of patients who take this medication.¹ Because clozapine has anticholinergic properties that are expected to reduce secretions, hypersalivation is considered a paradoxical effect. This paradox can be explained by examining clozapine's actions at the molecular level.

Clozapine has antagonistic activity at many types of receptors, including D1 to D5 dopaminergic, α 1 and α 2 adrenergic, serotonergic, histaminergic, and M1, M2, M3, and M5 cholinergic.² By contrast, clozapine's activity at M4 cholinergic receptors is agonistic. The combination of clozapine's antagonist activity at α 2 adrenergic receptors and agonist activity at muscarinic M4 receptors results in hypersalivation.³ Clozapine also increases pooling of saliva in the mouth by diminishing esophageal motility, which gives the appearance of hypersalivation as a result of reduced saliva clearance through normal swallowing.⁴

Practical lifestyle changes

Excessive saliva secretion and pooling can be reduced by practical behavioral and/or pharmacologic interventions. Patients who chew gum during the day will increase their swallowing unconsciously⁵;

recommend sugarless gum to help avoid tooth decay and gum disease. If hypersalivation is particularly bothersome at night, patients may find it useful to cover their pillows with an absorbent towel.

Pharmacologic treatments

Pharmacologic interventions rely on counteracting clozapine's secretion-inducing effects by opposing M4 agonism, α 2 antagonism, or both. Antimuscarinic medications such as benztropine, trihexyphenidyl, amitriptyline, or pirenzepine often are used to reduce hypersalivation,⁶ although 1 systematic review concluded further evidence is needed to support the effectiveness of this approach.⁷ The α 2 antagonism can be opposed by using the α 2 agonist clonidine, which can be administered as a weekly transdermal patch of 0.1 to 0.2 mg.⁸ In 1 retrospective study, the cholinergic and adrenergic mechanisms of hypersalivation were addressed by combining benztropine (2 mg/d in a divided dose) with the α 1 antagonist terazosin (2 mg/d). This combination reduced hypersalivation significantly in all patients after 12 weeks, exceeding the efficacy of either benztropine or terazosin administered alone.⁹

Hypersalivation is an inconvenient, potentially embarrassing aspect of clozapine treatment that can cause avoidable distress. One or more of these suggestions

Antimuscarinic medications and chewing gum can help prevent excess saliva from disrupting a patient's life

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may help control an adverse effect that could diminish patient satisfaction and undermine treatment compliance.

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Introduction by

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