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Literature review

Treatment strategies for clozapine-induced sialorrhea in France: A systematic review

Stratégies de traitement de la sialorrhée induite par la clozapine en France : une revue systématique

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ABSTRACT

Background: Clozapine-induced hypersialorrhoea (or hypersalivation) is a common side effect, and at present there is no therapeutic strategy with a validated indication to treat it. The corrective strategies proposed in the scientific literature have varying degrees of validity. As a result, it is important to regularly update the available data and to make proposals that are in line with the specialties available in each country.
Material and methods: A systematic review of the literature respecting PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statements was carried out using the PubMed, Embase and Cochrane databases with the keywords "Clozapine", "induced", "hypersalivation" or "sialorrhea". Only articles dealing with substances marketed in France and written in French or English were selected.
Results: 64 articles were included in this review. The various strategies identified corresponded mainly to treatments with regulatory actions on the cholinergic, noradrenergic and dopaminergic neurotransmission systems. This selection of drug strategies available in France for clozapine-induced hypersalivation identified 17 substances.
Discussion and conclusion: The level of evidence concerning treatments for clozapine-induced hypersialorrhoea remains limited. As a first option, and if clinically feasible (benefit-risk ratio), a cautious, gradual reduction in dosage is preferred. If this fails, local anticholinergic treatment may be initiated and evaluated following pharmaco-practical recommendations based on the drugs available in France and their level of evidence.

RÉSUMÉ

Contexte: L'hypersialorrhée (ou hypersalivation) induite par la clozapine est un effet secondaire fréquent. A l'heure actuelle, il n'existe pas de stratégie thérapeutique avec une indication validée pour traiter cet effet secondaire. Nous proposons dans cet article une revue systématisée des données disponibles dans la littérature et nous proposons une synthèse des strategies thérapeutiques possibles en France.
Matériel et méthodes: Une revue systématique de la littérature respectant les règles PRISMA (*Preferred Reporting Items for Systematic reviews and Meta-Analyses*) a été réalisée à partir des bases de données PubMed, Embase et Cochrane. Seuls les articles traitant de substances commercialisées en France ont été retenus.

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Résultats: 64 articles ont été inclus dans cette revue systématisée. Les différentes stratégies identifiées correspondent principalement à des traitements ayant des actions régulatrices sur les systèmes de neurotransmission cholinergique, noradrénergique et dopaminergique. Cette sélection des stratégies médicamenteuses disponibles en France dans l'hypersalivation induite par la clozapine a permis d'identifier 17 substances et de proposer des algorithmes de prescription pour les praticiens français.
Discussion et conclusion: Le niveau de preuve concernant les traitements de l'hypersialorrhée induite par la clozapine reste limité. En première intention, et si cela est cliniquement possible, une réduction prudente et progressive de la posologie est préférable. En cas d'échec, un traitement anticholinergique local peut être instauré et évalué. En cas d'échec, d'autres stratégies sont possibles mais doivent être strictement évaluées en fonction du rapport bénéfice-risque.

1. Introduction

After sedation, hypersalivation or hypersialorrhoea is one of the most common side effects attributed to clozapine, affecting 30 to 80% of patients [1]. Clozapine-induced hypersalivation (CIH) develops as soon as treatment is initiated [2] and occurs more frequently at night (85% of cases compared with 48% during the day) [3]. A dose-effect relationship is regularly reported [3], but contradictory data [1,3] and most recent studies suggest that there is no association between hypersalivation, posology and plasma levels of clozapine [3,4].

Whatever, CIH can cause significant psychological distress and may also induce sleep disturbance [5]. A recent study found that 92% of patients taking clozapine suffered from CIH (62% daytime, 89% nocturnal, 65% from both), while 30% of patients reported moderate to severe negative impact on their quality of life [5]. In addition, physical complications such as perioral skin irritations and infections, parotitis and inhalation pneumonitis can be caused by these symptoms [6,7]. In a review published in 2015, sialorrhea and constipation were found to be the main causes of death associated with clozapine [8], and encourage us to consider these undesirable effects as a public health priority [9, 10].

Sialorrhea is an unexpected side effect of clozapine. Clozapine is an anticholinergic/antimuscarinic drug, associated with dry mucous membranes. In particular, clozapine has strong α_2 antagonist, M_4 receptor agonist - partial or complete - and M_1, M_2, M_3 and M_5 receptor antagonist activities [11]. Two main theories (muscarinic and α- adrenergic) have been put forward in an attempt to explain CIH, linked to the complex pharmacological profile of the substance, but the exact underlying mechanism remains undetermined [12].

The first theory involves the muscarinic pathway. M_3 and M_4 muscarinic receptors are highly expressed in salivary gland tissue. However, salivary flow, which is mainly under parasympathetic (cholinergic/muscarinic) control, is essentially regulated by the M_3 receptor, a receptor subtype that is also predominant in the salivary glands [12]. Clozapine has both M_4 agonist – hypersialia-inducing – and M_3 antagonist – hyposialia-inducing – activities. It could be more at risk of dry mouth than hypersalivation because of the predominance of M_3 receptors and their predominant involvement in flow regulation. According to this paradox, it has been hypothesized that in certain patients selective or predominant stimulation of M_4 muscarinic receptors in the salivary glands could ultimately lead to hypersialorrhoea [12,13].

The second theory is associated with α-adrenergic receptors. Clozapine is an antagonist of α_1 and α_2 receptors, two subtypes of receptors present on the salivary glands, where their blockade would cause an increase in blood flow, leading to an intensification of salivary flow [12]. Conversely, β-receptor blockade seems to be more associated with hyposalivation [14]. One hypothesis is that blocking α_1 and α_2 receptors leaves only β receptors free for noradrenergic binding. This imbalance in binding would double the increase in salivary volume [12]. In addition, in response to chronic α-receptor blockade, α_1 and α_2 upregulation may occur. Altered receptor density may also be involved in CIH [15].

Other alternative hypotheses have been proposed to explain the efficacy of CIH correctors. Firstly, with drugs that have no cholinergic or adrenergic regulatory action (benzamide derivatives: amisulpride, sulpiride and metoclopramide) and secondly with antidepressants that have no anticholinergic action (moclobemide and bupropion) [16]. The efficacy of these two groups of agents is all the more questionable as they have potentially opposing actions on dopaminergic neurotransmission.

This systematic PRISMA review aims to synthesize current evidence on clozapine-induced hypersalivation, exploring its prevalence, underlying mechanisms, and management strategies to guide French clinical practice.

2. Material and methods

2.1. Search strategy

We conducted a systematic review of the literature respecting PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statements [17]. We used three databases (PubMed, Embase, Cochrane) with Boolean operators and the following MeSH terms: clozapine AND induced AND hypersalivation AND sialorrhea. No restrictions of year or country were used. We conducted this literature search on December 31, 2023. Additionally, the bibliographical references of studies were screened manually to assess whether they incorporate relevant studies to include in the review. We checked on Cochrane database that no systematic review has been done on this subject.

2.2. Inclusion and exclusion

All papers about clozapine-induced hypersalivation were included for screening. The inclusion criteria are: (a) experimental study, (b) studies in French or in English, (c) human subject. The exclusion criteria are: (a) literature review, (b) meta-analysis. In view of the limited data available, we have chosen not to limit our research to randomized, placebo-controlled clinical trials.

2.3. Data extraction

We created a table to extract and highlight information from the included papers. Features like authors, year of publication, type of study, journal of publication, were reported in this table. Duplicate papers were removed, and then we screened titles and abstracts to determine the eligible studies. Secondly, we selected from this list only those references dealing with treatments marketed in France, in order to ultimately propose a decision-making algorithm for use by French practitioners.

3. Results

3.1. Selection of articles for the systematic literature review

We retrieved 352 articles using our search algorithm. After analyzing the title and abstract, we selected 73 eligible articles, including 24

different therapeutic strategies. After analyzing the content of these articles, 64 articles were retained, including 19 strategies available in France, 12 of which were randomized controlled double-blind clinical studies, the remainder being case reports, cohort studies or open-label studies (n = 52). The item selection strategy is available in the Flowchart (Fig. 1). We decided to keep all the articles for the analysis due to the scarcity of published data in the literature.

3.2. CIH treatment strategies

We have organized the results of our literature review by differentiating between the pharmacological strategies used, and by reporting their level of evidence and the data available in the literature. The Table 1 presents all studies included in this literature review. Table 2 presents the detailed characteristics of affinities (Ki in nM) for muscarinic and adrenergic receptors of clozapine and the various agents used to manage clozapine-induced hypersalivation. Affinities values should be interpreted with caution. These values can vary due to numerous factors, including experimental conditions such as the type of solvent used, the pH and temperature of the solution, protein concentration, and the purity and stability of the ligand or receptor. Additionnally, variations in experimental methodologies (e.g., competitive or direct binding assays) and the biological systems employed (e.g., cells, membranes, or isolated receptors) can also influence the results.

3.2.1. Cholinergic modulators

3.2.1.1. Atropine. Atropine is a cholinergic antagonist that acts by binding strongly to muscarinic receptors (M_1 to M_5; not selective for any receptor subtypes) [18]. Peripheral effects include a decrease in the production of salivary secretions. All the studies used the 1% eye drop form (not officially approved in France) sublingually at a dosage of 1 to 2 drops/day. Study reports 10 patients treated initially with atropine 1% drops, after which their treatment was changed to ipratropium spray. The eye drop form was as effective as 1 or 2 sprays per day [19]. Three patients with severe sialorrhea noticed an immediate improvement following the administration of a drop of atropine 1% administered sublingually at bedtime. The patients showed no adverse effects. Another study described 3 patients who had complete resolution of their hypersialorrhoea in 1 week with 1-2 drops of atropine 1% administrated sublingually at bedtime [20]. No systemic anticholinergic effects were reported. This favorable impact improved sleep quality and adherence to clozapine treatment. One patient suffered from xerostomia at a dosage of 3 drops per day. A single study quantitatively measured the sublingual effect of atropine in 21 patients and showed a significant reduction in salivary secretion in the atropine-treated group compared with the placebo group [18].

3.2.1.2. Glycopyrrolate. Glycopyrrolate (or glycopyrronium) is an antimuscarinic drug with a strong affinity for all M_1 to M_4 receptors, but less than atropine and scopolamine, with no selectivity for any of the subtypes [21]. Clinical studies and case reports have shown the efficacy of glycopyrronium on CIH at doses of 1 mg to 6 mg/day, in tablet or

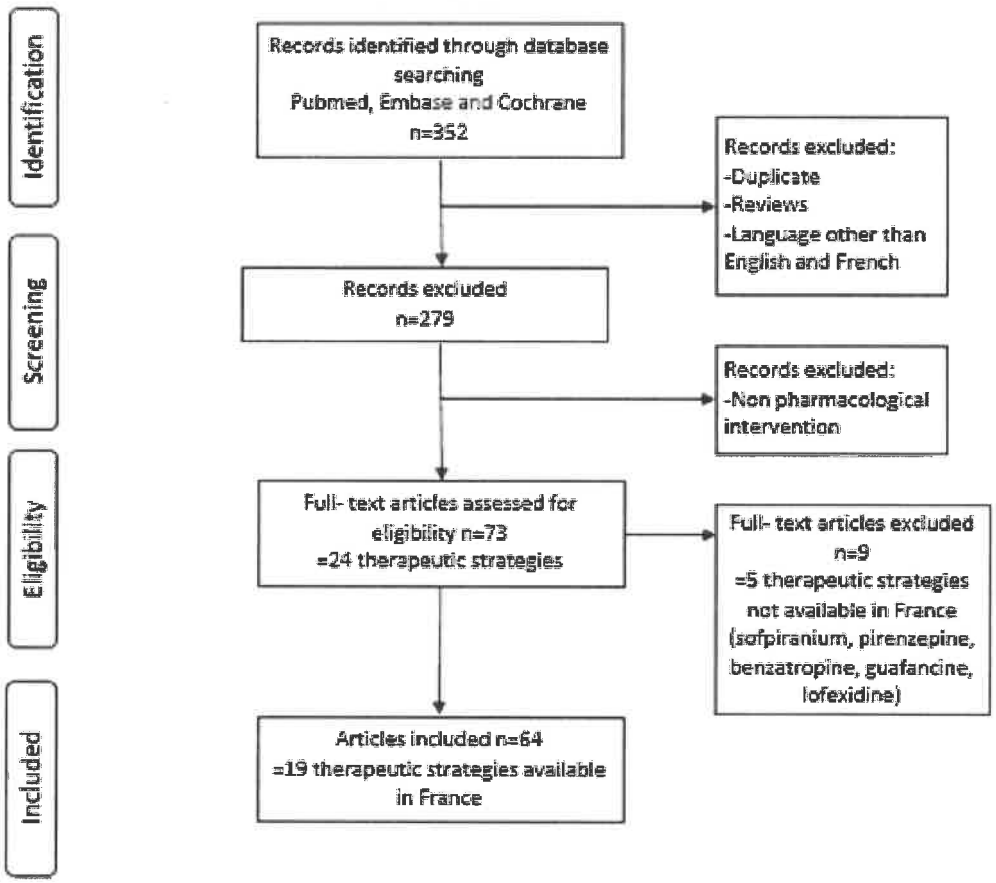

Fig. 1. Flowchart. This flowchart outlines the systematic process used to identify, screen, and include studies in the review. After applying inclusion and exclusion criteria, 64 studies were included in the final qualitative (and/or quantitative) synthesis.

Table 1
Summary of studies reporting treatment of clozapine-induced hypersalivation.

Dose, galenic	Design	Measurement	Results	References
Cholinergic modulators				
Atropine 1%				
1 drop sublingually at bedtime + 1 drop in a glass of water at the bedside	CS N = 3	Not specified	Immediate relief and lasted through-out the night	[86]
1–2 drops 1% solution sublingually daily in the morning	CR N = 1	Not specified	Resolution of the hypersalivation persisting throughout the day	[87]
1 drop sublingually at bedtime	CS N = 10	Not specified	Beneficial effect but atropine was short acting, necessitated repeat dosing because of rebound sialorrhea	[19]
2 drops sublingually b.i.d	CR N = 1	Not specified	Decrease in hypersalivation within 2 weeks and after complete resolution	[88]
1 drop/d up to t.i.d + hyoscine 300 µg at bedtime	CR N = 1	Not specified	Instantaneous relief and allowed increase in the clozapine	[89]
Not specified	Survey N = 13	7 points scale for experience of nocturnal salivation, daytime salivation and side effects	Improvement of nocturnal and daytime salivation	[90]
1–2 drops at night sublingually	CS N = 3	Not specified	Improvement in sialorrhea within one week of treatment initiation. Adverse events: dry mouth (3 drops), resolved after decreasing the dose to 1-2 drops	[20]
1–3 drops/day sublingually (0.56 mg)	DB, RCT N = 23	-TNHS -CGI	1% atropine drops (1.7 mg) can be just as effective as amitriptyline tablets (29.08 mg)	[91]
1–2 drops at night sublingually	CS N = 2	Not specified	Almost immediate resolution	[92]
2 drops at bedtime sublingually (600 µg)	Multicenter DB, RCT N = 10	Cotton rolls and cotton wool pads used to measure the change in the saliva	Sublingual atropine reduced the saliva secretion significantly more than the placebo A significant decrease in standing pulse rate was recorded in the participants in the atropine group	[18]
0.6 or 1.2 mg atropine solution sublingually or 0.6 mg oral tablet	CO, randomized N = 7	Secretion saliva	Sublingual and oral atropine are effective in reducing the saliva secretion at a lower plasma concentration after sublingual administration, with a dose-dependent effect.	[93]
Glycopyrrolate				
0.5–2 mg b.i.d	CR N = 1	DRS	Reduction in 2 days, and after 2 weeks significant decrease Adverse effect: constipation at 2 mg b.i.d	[94]
2–4 mg b.i.d	CS, OL N = 3	Staff observation	Efficacy of glycopyrrolate in the treatment of CIS in 3 adolescents Adverse effects: constipation, dry mouth	[22]
1 mg b.i.d	DB, CO, randomized N = 13	-DRS -MMSE	Significant reduction on the DRS No significant changes in cognitive function	[7]
1–2 mg b.i.d or t.i.d	CS N = 4	DSFS	Effective in alleviating symptoms in ¾ patients	[23]
1 mg at bedtime	CR N = 1	wet surface of pillow in cm	After few weeks, reduction of 5 cm diameter No adverse event	[24]
1 mg/d for 6 days 2 mg/d for 6 days (OL)	DB, CO RCT N = 32 OL N = 23	-NHRS -PGI-S -MSQ	A significant mean difference in NHRS score was observed	[25]
1 mg b.id or t.i.d	RCT N = 29	-retention rate -DRS	Overall retention rate was 76%	[26]
4 mg/d	CR N = 1	Not specified	Reduction but the patient received tDCS sessions at the same time	[27]
Scopolamine				
Transdermal patch 1 mg/72 h behind the ear	CS N = 4	Not specified	Effective in patients suffering severe hypersalivation	[95]
Transdermal patch 1.5 mg/72 h	CR N = 1	Not specified	Sialorrhea resolved entirely within hours with a benefit persisted for many months	[28]

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Table 1 (*continued*)

Dose, galenic	Design	Measurement	Results	References
Per os 30–60 mg daily	CS N = 5	-VAS -FRS -DSS -DFS	Any significant differences for VAS and FRS The patients' DSS and DFS scores differed significantly between the baseline and week 4 1 patient developed abdominal air pockets (60 mg/day)	[29]
5% ointment 0.1 g (rice grain-sized) to both of postauricular skin areas at bedtime	CR N = 1	NHRS	First minimal reduction, Sialorrhea improved after the ointment dose was doubled After 6 days NHRS = 0 (absent)	[96]
Ointment was applied in the morning	DB CO randomized N = 20	- Measurement of saliva with cotton roll-based -VAS	No significant reduction in saliva production	[97]
Per os 0.3 mg	DB CO randomized N = 11	-TNHS -masse of the pillowcase -anxiety -depression and quality of life	Beneficial effect of scopolamine	[30]
Per os 0.3 mg twice or three times daily	RCT N = 5	-retention rate -DRS	Overall retention rate was 76%	[26]
Ipratropium Bromide nasal spray				
0.03% 1 spray at bedtime	CS N = 10	NHRS	Improvement in 8/10 patients Minor side effects (dry nostrils)	[32]
0.03% 2 sprays sublingually at bedtime or 0.06% 3 times/d	CS N = 9	Self report	2 patients had no response	[33]
0.03% 2 sprays sublingually at bedtime	DB RCT CO Randomized N = 20	-TNHS -VAS-S -VAS-D	No difference	[31]
0.03% 2 sprays one or twice a day	CS N = 10	Not specified	Improvement in all patients	[19]
Trihexyphenidyl				
5–15 mg/d at bedtime	OL N = 14	NHRS	Effective in 11/14 patients	[34]
5 mg at bedtime	CS N = 2	Not specified	No impact in hypersalivation	[98]
6 mg in divided doses	CR N = 1	Not specified	Marked reduction No side effects	[99]
2 mg at bedtime	CR N = 1	-Wet area of pillow -DFS -DSS	Complete resolution of sialorrhea	[100]
Amitriptyline				
75–100 mg/d	CS N = 4	Not specified	Reduced or disappearing of hypersalivation	[101]

Table 1 (*continued*)

Dose, galenic	Design	Measurement	Results	References
25 mg at bedtime	CR N = 1	Not specified	Marked reduction of nocturnal sialorrhea, with disappearance of daytime sialorrhea.	[35]
10 mg/d	CR N = 1	Not specified	Rapid and complete resolution of sialorrhea after 3 days	[36]
25 mg/d at night	RCT N = 23	-TNHS -CGI	Amitriptyline (29.08 mg daily, oral) as effective as 1% atropine drops (1.7 mg)	[91]
20–30 mg/d at bedtime	CS N = 4	Subjective reports	Rapid resolution of both nighttime and daytime hypersalivation No side effects	[37]
Oxybutynine				
5 mg twice a day	CR N = 1	DSS	Significant reduction of the sialorrhea within 24 hours No adverse events	[38]
Biperiden				
6 mg/d	CR N = 1	Not specified	Sweating and sialorrhea caused by clozapine treatment were eliminated by treatment with biperiden	[102]
2 mg twice a day	DB CO randomized N = 13	-DRS -MMSE	-DRS scores were significantly lower with glycopyrrolate treatment than with biperiden -No significant differences in MMSE scores in patients treated with glycopyrrolate -Significant reduction in MMSE scores in patients treated with biperiden	[7]
Tropicamide				
1% ophthalmic solution 1–2 drops sublingually to each side of the mouth at bedtime	CR N = 1	-Wet area over the pillow, -VAS -NHRS -SF-36 -UKU -SANS -SAPS	Reduction of the hypersalivation	[40]
Noradrenergic modulators				
Clonidine				
Patch 0.1 mg-0.2 mg once a week	CS N = 4	Not specified	In 2 patients marked and sustained response 1 patient developed tolerance 1 patient did not respond	[15]

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Table 1 (*continued*)

Dose, galenic	Design	Measurement	Results	References
50 µg-100 µg at bedtime	Open label naturalistic case series N = 12	-Approximate visual estimate of the diameter of wet area over pillow -subjective response: none or minimal, somewhat or partial, and good.	Most of the patients reported a decrease in sialorrhea without any adverse events 1 patient: did not respond 8 patients: partial response 3 patients: good response Limit: self report	[41]
0.05 mg twice a day	CR N = 1	The bottle of saliva and wet pillow were observed by staff	Clonidine was used to mitigate sialorrhea but was associated with thrombocytopenia that resolved upon discontinuation	[103]
Terazosin				
2 mg at night	OL, non-randomized, retrospective N = 15	Chart review	Response in 93% patients (100% when combined with benzatropine)	[104]
1–2 mg at night	CR N = 1	Not specified	In combination with benzatropine 2 mg at night. After 3 months the parotid gland swelling was completely gone	[42]
Dopaminergic mudulators				
Amisulpride				
600 mg/d	CR N = 1	Not specified	In combination with pirenzepine 150 mg/d	[50]
400 mg/d	DB CO RCT N = 20	NHRS	NHRS indices were considerably lower with amisulpride Tolerability and safety of the amisulpride–clozapine Combination was good, in that there were no severe extrapyramidal-motor side-effects Prolactin levels increased in 95%of the patients (two-fold higher in women) resulting in a high risk for adverse effects associated with hyperprolactinemia	[43]
100 mg/d in divided doses	CR N = 1	Not specified	Improvement in sialorrhea after one week	[99]
50 mg/d	CR N = 1	Not specified	Significant improvement in both daytime and nighttime sialorrhea after 3 months of adding amisulpride	[105]

Table 1 (*continued*)

Dose, galenic	Design	Measurement	Results	References
50 mg-150 mg/d j	CR N = 1	-DFS -DSS -Area of wet surface over the pillow	Significant improvement in daytime sialorrhea Minimal improvement in nocturnal sialorrhea Adverse effects: constipation	[51]
400 mg/d	OL, CS N = 53	NHRS	Effective in reducing CIH in 74% patients with a better NHRS In 1 patient CIH worsened	[44]
50 mg–100 mg/d	CS N = 5	Five-point Likert improvement scale	Drastic improvement in daytime and nocturnal CIH with very low dose of amisulpride	[106]
50 mg/d	CR N = 1	-NHRS -PBRS -HDRS	After 4 weeks, reduction of CIH	[107]
Sulpiride				
150-300 mg/d	CS N = 15	NHRS	Significant reduction in sialorrhea	[54]
2 × 50 mg–150 mg twice a day	CR N = 1	-NHRS -DSFS	14-day period without hypersalivation but hypersalivation reappeared as a side effect despite regularly taking Sulpiride	[108]
Metoclopramide				
10–30 mg/d	DB, RCT N = 30	-DSS -NHRS	22 subjects (66.7%) treated with metoclopramide reported significant decline or total disappearance No adverse effects	[55]
20 mg/d	Retrospective, observational cohort study N = 14	Continuation of treatment	5 patients continued treatment with a mean duration of 27 months, and 1 patient continued until transfer with duration of 3 months. 8 patients discontinued treatment after a mean duration of 8 months 5 patients reported adverse effects (4 patients experienced tremors and one patient reported nausea)	[109]
Other correcting agents				
Moclobemide				

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Table 1 (*continued*)

Dose, galenic	Design	Measurement	Results	References
150–300 mg/d	OL, CS N = 14	NHRS	Two thirds of the subjects have demonstrated a beneficial effect after the addition of moclobemide One third of them have been nonresponders None of the patients had any adverse effects	[60]
300 mg/d	OL, CS N = 53	NHRS	83% demonstrated some kind of improvement Any adverse events	[44]
Bupropion				
100-150 mg/d	CR N = 1	Not specified	Dramatic reduction in daytime CIH however, excessive salivation was still present when the patient was asleep	[62]
N-Acetylcysteine				
1200–2400 mg/d	CS N = 5	VAS	After four weeks of follow-up, the severity of sialorrhea decreased significantly with NAC augmentation. No significant side effects	[64]
Botulinum toxin A				
150 IU once into parotid glands bilaterally	CR N = 1	Not specified	Hypersalivation was markedly reduced after 2 weeks and remained unchanged during a 12-week follow-up period without adverse events	[68]
50 IU (5 IU at 3 sites into each parotid gland and 5 IU at 2 sites into each submandibular gland)	CS N = 2	-DRS -DSS -DFS	Significant reduction in sialorrhea in both subjects, and a follow-up assessment at 8 weeks found occasional drooling in case 1 and no drooling in case 2	[70]
Botulinum toxin B				
2500 units BTX (500 units into each parotid gland and 250 units into each submandibular gland)	DB, RCT N = 9	-DSS -DFS	Improvement of sialorrhea in patients treated and reduction of sialorrhea lasted for 8 to 16 weeks after a single injection No patient reported any side effects	[69]
1000 IU in each parotid gland and 250 IU in each submandibular gland	CR N = 1	Not specified	Decrease in hypersalivation within 24 hours and complete resolution by 72 hours Benefits continue at 2 months after treatment	[71]
Add-on antipsychotic for decrease clozapine dose				
Quetiapine Protocol: diminution of 25% of daily clozapine dose to be substituted by quetiapine with a ratio of exactly clozapine 1 mg to quetiapine 2 mg	R Non-blind Non-randomized N = 312	Not specified	All patients experienced elimination of hypersalivation with clozapine-quetiapine combination therapy and addition of benzatropine or terazosin.	[77]

CO: crossover; CR: case report; CS: case series; DB: double blind; OL: open-label; R: retrospective; RCT: randomized control trial; VAS: Visual Analog Scale; NHRS: Nocturnal Hypersalivation Rating Scale; DRS: Drooling rating scale; MMSE: Mini Mental State Examination; DSFS: drooling Severity and Frequency Scale; PGI: Patient Global Impression of improvement; MSQ: Medication Satisfaction Question; FRS: Face rating scale; DSS: Drooling Severity scale; TNHS: Toronto Nocturnal Hypersalivation Scale; DFS: Drooling frequency scale; PANSS: Positive and Negative Syndrome Scale; CGI: Clinical global impression scale; SAS: Simpson-Angus Scale; ESRS: Extrapyramidal Symptom Rating Scale; MSAS: Maniac State Assessment; SF-36: the short form of health survey; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; UKU: Udvalg for Kliniske Undersøgelser.

oral solution form, with few adverse effects [7,22–27]. One study compared glycopyrronium with biperiden and found better results in the glycopyrrolate group with a significantly lower drooling rating scale (DRS) score. However, these favorable results cannot be transposed in French clinical practice due to the unsuitable dosage (inhaled form) or excessive cost (oral solution) of the drugs.

3.2.1.3. Scopolamine. Scopolamine is a non-selective muscarinic receptor antagonist with an affinity ≤ 1 nM for M_3 and M_4 receptors. Only one study has shown the efficacy of scopolamine in patch form (1.5 mg every 72 hours) with very rapid resolution of CIH [28]. Oral scopolamine has been tested in very different dose ranges, from 0.3 mg/d to 30–60 mg/d [26,29,30]. Treatment was effective in all three studies, but one patient reported potentially dose-dependent abdominal air-pouch-like digestive disturbances at a dose of 60 mg/d [29]. To date, there are no data supporting the use of scopolamine at a 1 mg/72 h dose, in accordance with the galenic formulation available in France.

3.2.1.4. Ipratropium. Ipratropium is a muscarinic antagonist with a very high affinity (≤ 1 nM) for M_1, M_3 and M_4 receptors. These favorable pharmacological properties – very low risk of central effects and marked antisecretory effects in the context of hypersecretion – seem to justify its assessment in CIH [31]. Ipratropium 0.03% was used to treat CIH in a 6-month study of 10 patients receiving intranasal treatment [32]. The Nocturnal Hypersalivation Rating Scale (NHRS), showed that 8 out of 10 patients had an initial improvement that lasted through to 6 months' follow-up. Another study was conducted over 6 months on 10 patients who received 1–2 sprays/day of sublingual ipratropium 0.03% with very good results [19]. After 6 months, all 10 patients had reduced or completely resolved their CIH. Positive results were also described in a study of 9 patients who received 0.03% sublingual ipratropium 2 to 3 times a day, with the dose increased to 0.06% up to 3 times a day for patients who had not been relieved [33]. A partial to complete response without adverse effects was reported in 77% of patients. In 2009, a randomized, double-blind,

Table 2
Affinities (Ki in nM) for muscarinic and adrenergic receptors for clozapine and the various correctors of clozapine-induced hypersalivation.

Ki [nM]	M_1	M_2	M_3	M_4	M_5
Clozapine [11]	1.4–31	14–204	7–109	6–29	5–94
Cholinergic correctors of CIH					
Atropine [11]	0.20–1.1	0.63–1.5	0.1–1.1	0.3–1	0.21–1.7
Glycopyrrolate [21]	9.76	9.19	8.73	9.90	ND
Scopolamine [11]	1.1	0.44–2.0	0.44	0.80	2.07
Ipratropium [11]	0.49	1.5	0.51	0.66	1.7
Trihexyphenidyl [11]	1.6	7	6.4	2.6	15.9
Amitriptyline [11]	11–14.7	11.8	12.8–39	7.2	15.7–24
Oxybutynine [11,110]	0.66–5.9[b]	13–14[b]	0.72–5.3[b]	0.54	74
Biperiden [11,111]	0.54[b]	10.71[b]	1.86[b]	1.70–2.04[c]	4,4
Tolterodine [112,113]	3.0–8.1[b]	3.8–9.8[b]	3.4–17[b]	5–13[b]	3.4–21[b]
Tropicamide [11]	66.1[b]	50.1[b]	38.01[b]	3.47	ND
Ki [nM]	α_{1A}	α_{1B}	α_{2A}	α_{2B}	α_{2C}
Clozapine [11]	1.62	7	24–142	27	2.9–34
Noradrenergic correctors of CIH					
Clonidine [11]	**316.23**	**316.23**	**35.48–61.69**	**69.18–309**	**134.89–501.2**
Terazosin [11,114] (*S-terazosin*)[a]	1.82-6.3	0.8-2.5	729[b]	3.5[b]	46.4[b]

In bold: agonist actions. ND: non-determined; NB: The values were preferably taken from the "PDSP Ki Database" site (https://pdsp.unc.edu/databases/kidb.php) [11] and when the data were incomplete on this website they were completed by the references indicated in the table. These values are averages that may evolve with scientific advancements, and that the table provides indicative ranges and trends rather than absolute values.

[a] S-terazosin shows higher affinities for α-noradrenergic receptors compared to R-terazosin.

[b] data for rodents.

[c] data for rabbit + chick.

placebo-controlled trial was conducted in 20 patients [31]. Patients received 2 doses of sublingual ipratropium 0.03% at bedtime and efficacy was assessed using the Toronto Nocturnal Hypersalivation Scale (TNHS). The results showed no difference between the ipratropium and placebo groups. In 2001, another study showed that the use of sublingual atropine 1% was as effective as 2 doses of sublingual ipratropium 0.03% spray per day [19].

3.2.1.5. Trihexyphenidyl. Trihexyphenidyl is a non-selective muscarinic receptor antagonist which binds with greater affinity to the M_1 and M_4 subtypes. A study on 14 patients showed a 44% reduction in the NHRS score in patients treated with trihexyphenidyl at a dose ranging from 5 to 15 mg/d [34].

3.2.1.6. Amitriptyline. Amitriptyline is a tricyclic antidepressant whose antimuscarinic activity appears to have effects on CIH. Amitriptyline has antagonistic effects on all muscarinic receptors M_1 to M_5 with comparable affinities, but a slightly higher affinity for M_4. Retrieved studies consist of clinical case reports with variable doses ranging from 10 mg to 100 mg/day. In all cases, amitriptyline appears to be effective, but the method used to assess the reduction or remission of CIH is not explained [35–37].

3.2.1.7. Oxybutynin. Oxybutynin blocks all muscarinic receptor subtypes with high affinity, except M5, and with an affinity ≤ 1 nM for M_1, M_3 and M_4 receptors. A single clinical case describes a limited effect of oxybutynin used at a dose of 5 mg 2x/d in combination with 6 mg risperidone and 1.5 mg benzatropine to limit CIH [38].

3.2.1.8. Biperiden. Biperiden has a high affinity, mainly for muscarinic M_1, M_3 and M_4 receptors. A randomized study comparing biperiden with glycopyrrolate showed that glycopyrrolate 2 mg/d was more effective than biperiden at a dose of 4 mg/d [7].

3.2.1.9. Tropicamide. Tropicamide is a short-acting muscarinic receptor antagonist. It has a relatively high selectivity for the M_4 receptor subtype [39]. One case report showed that tropicamide was effective with 1 or 2 drops at each side of the mouth with no adverse effect [40].

3.2.2. Noradrenergic modulators

3.2.2.1. Clonidine. Clonidine is a centrally acting antihypertensive molecule with partial agonism at central α_2 receptors. By acting on presynaptic α_2 receptors, clonidine reduces plasma levels of noradrenaline, resulting in less stimulation of β-receptors, likely to reduce salivation [11]. In a case series of 12 patients treated with oral clonidine for 4 weeks, doses ranged from 0.05 to 0.1 mg/day [41]. Response was defined as a reduction of at least 5 cm in the diameter of the surface of the wet pillow. Subjective response was also reported by patients. Eleven patients had a partial or good response. Clonidine was well tolerated. The main disadvantages of clonidine stem from its potential additive effect on the hypotensive and sedative effects of clozapine, as well as its frequent depressogenic risk (depression is contraindicated with the use of clonidine).

3.2.2.2. Terazosin. Terazosin is an alpha blocker which binds mainly to peripheral α_{1A} adrenergic receptors. Similarly, to clozapine, this binding could reinforce α_{1A} blockade and promote α_2 stimulation, leading to a benefit similar to that of clonidine. In this single descriptive study available, terazosin at a dose of 2 mg/day was used as a 3rd line treatment after failure of scopolamine and partial efficacy of benzatropine 2 mg at bedtime, leading to a terazosin and benzatropine combination [42]. Three months after the introduction of this combination, the parotid gland had returned to normal size (it being understood that swelling of this gland is observed in cases of CIH) [42]. Similarly, to clonidine, terazosin should be used with caution because of its potentiating effect on orthostatic hypotension, which clozapine may itself generate.

3.2.3. Dopaminergic modulators

3.2.3.1. Amisulpride. Amisulpride is an antipsychotic of the benzamide class. Its pharmacodynamic profile is characterized by a selective and predominant affinity for dopamine D_2 and D_3 receptors [43]. The benefits of amisulpride in CIH are based on the pharmacological rationale observed with sulpiride, transposed to amisulpride due to the close pharmacochemical relationship between the both substances. Several studies have reported the use of amisulpride to control CIH. In the single randomized controlled trial published, the authors observed an improvement in NHRS score at a dose of 400 mg/d in 20 patients over 3 weeks [43]. NHRS score had decreased by the end of the 2nd week of treatment. Amisulpride also improved the PANSS (Positive and Negative Syndrome Scale) score.

There are wide differences in the dosages used in the literature, with amisulpride doses ranging from 50 to 400 mg/d. The 6 available case studies report an improvement in CIH with few or no adverse effects. In another open-label study in 2 phases, compared amisulpride to moclobemide for 2 weeks, the NHRS score improved with amisulpride at a dose of 400 mg/d, with complete disappearance of hypersalivation in one patient [44]. However, amisulpride appeared less effective than moclobemide; with a lower response rate (74% versus 84% of patients respectively) [44].

Given both its overall efficacy (as with clozapine, on both positive and negative symptoms) [45,46] and its pharmacological profile (strong D_2 blockade, unlike clozapine), amisulpride has long been considered as an interesting candidate for combination with clozapine in cases of resistance to clozapine monotherapy [47–49]. Amisulpride in CIH could therefore also be considered a beneficial strategy for the treatment of schizophrenia: first in patients who only partially respond to clozapine [47–49]; and secondly, in order to reduce the dose of clozapine [50]. This strategy implicitly validates the idea of a dose-related CIH. In a clinical case, a patient was stabilized on 800 mg/d of clozapine with hypersalivation which could only be effectively reduced, while maintaining clinical efficacy, by combining it with amisulpride at 600 mg/d, reducing the clozapine dose by half [50]. This strategy appears to validate the benefit of using amisulpride to limit the dosage of clozapine, although treatment with pirenzepine, an anticholinergic agent which corrects CIH, had to be maintained.

It should be remembered that high doses of amisulpride are associated with adverse effects such as hyperprolactinemia and extrapyramidal syndrome. Pending further studies to validate an effective dose for CIH, it is recommended to start with the lowest dose of 50 mg/d and to increase it if no response is observed after one week [51]. Although the strategy of combining clozapine and amisulpride to optimize efficacy seems straightforward, evidence is lacking to support is use in correcting CIH.

3.2.3.2. Sulpiride. Sulpiride is a benzamide-type antipsychotic. Like amisulpride, it exerts its action mainly through its binding to D_2 and D_3 receptors. As it also has a non-anticholinergic and non-adrenolytic properties, the hypothesis of its action on saliva secretion would parallel its peripheral action in reducing gastric secretion, which has long been identified [52,53], while a central regulatory component in these antisecretory effects is also considered [52]. An open-label study of 18 patients was conducted to test the effect of sulpiride at doses of 150 to 300 mg/d for 21 days: efficacy was assessed using the NHRS scale; after 7 days, 12 patients had an improvement in CIH and 6 patients had a significant reduction [54].

3.2.3.3. Metoclopramide. Metoclopramide is defined as a "hidden neuroleptic", due to its dopamine antagonist properties [55]. It is also a benzamide derivative. It prevents vomiting by blocking chemoreceptors in the chemoreceptor trigger zone. In a randomized double-blind study versus placebo for 3 weeks in 58 patients treated with clozapine and presenting with CIH, patients who did not respond to the initial dose of 10 mg/d could be increased to 30 mg/d and were assessed using the NHRS and DSS scores [55]. Twenty subjects treated with metoclopramide showed a significant reduction or total disappearance of CIH, compared with 8 patients treated with placebo. The precise mechanism of action of the benefit of metoclopramide in CIH has not yet been identified. One hypothesis is that it inhibits the relaxation of gastric smooth muscle produced by dopamine, thereby improving the cholinergic responses of gastrointestinal smooth muscle [56]. Ultimately, this action is accompanied by stimulation of gastric motility, increasing the efficiency of gastric emptying and possibly limiting gastric hypersecretion due to stagnation [56,57]. This favorable effect appears to be similar to that described by the anti-secretory dynamics observed with sulpiride.

3.2.4. Other correcting agents

3.2.4.1. Moclobemide. Moclobemide is a benzamide-type antidepressant which acts as a reversible inhibitor of type A monoamine oxidase (MAO), inducing an increase in cerebral monoaminergic mediators (mainly noradrenaline and serotonin) [58]. The peripheral nervous system is inhibited at the preganglionic level by the increase in noradrenaline, resulting in a reduction in salivation. While clozapine-induced antagonism of α1 and α2 receptors is likely to induce hypersalivation, stimulation of the same receptors by a noradrenergic boost seems likely to counteract it.

Nevertheless, in the case of moclobemide, the increase in serotonin levels is the most pronounced compared with the other monoamines [59]. The induction of dry mouth by serotonin reuptake inhibitors (SRIs) is a known phenomenon and demonstrates in particular that the anticholinergic/antimuscarinic action is not the only cause of iatrogenic xerostomia. Interestingly to note, on the basis of a recent meta-analysis, while SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin and noradrenaline reuptake inhibitors) are all associated with an increased risk of dry mouth, SNRIs present a significantly higher risk than SSRIs [58]. These data could argue for an impact intensified by the combined pro-serotoninergic and noradrenergic effects, in terms of induction of hyposialia, as with moclobemide [58].

The doses between 150 and 300 mg/day led to rapid improvement in most of the patients included (from the 4th day of treatment in one of the available studies [60]). To assess the effect of moclobemide compared with another drug, a 6-week study was conducted in which this antidepressant at 300 mg/d was compared with amisulpride 400 mg/d in 53 patients [44]. Following randomization, patients were treated with each drug for 2 weeks, with a 2-week treatment-free period between the two treatments. Reduction in CIH was assessed using the NHRS score, and the results showed that both treatments were effective, with 84% of patients improving with moclobemide and 74% with amisulpride. Both studies showed that moclobemide was well tolerated.

3.2.4.2. Bupropion. Bupropion is a selective norepinephrine and dopamine reuptake inhibitor. The effect of noradrenergic stimulation of α_1/α_2 receptors could be the main contributor of the correction of CIH. A single case in the literature reports a beneficial effect of bupropion at a dose of 150 mg after a series of failures of different molecules (6 in total), but with a limited effect because it is ineffective at night [61]. It should be noted that the authors suggest a reduction in CIH by dopaminergic regulation: bupropion could reduce hypersalivation by normalizing the swallowing reflex abnormalities observed in central hypodopaminergic conditions such as Parkinson's disease [62]. However, the possibility of applying hypodopaminergia in CIH seems to be contradicted by 2 facts: firstly, the low dopaminergic blocking potential of clozapine. Secondly, parkinsonian hypodopaminergia, or hypodopaminergia related to antipsychotics, seems to be more related to a motor impact with swallowing defects [63]. All in all, these data argue more in favor of noradrenergic rather than dopaminergic regulation of CIH by bupropion.

3.2.4.3. N-acetylcysteine. N-acetylcysteine (NAC) is a mucolytic-type mucomodifier which promotes expectoration. A single case report shows a beneficial effect in 5 patients, all of whom improved after 4 weeks of treatment at a dose of 1200 mg, 1 to 2 times daily [64]. One study suggests an antioxidant role for NAC in protecting the parotid glands against oxidative damage [65]. The improvement in CIH could therefore be due to an antioxidant effect of NAC treatment, although no studies support the relationship between clozapine, sialorrhea and oxidative stress [64]. Nevertheless, the benefit of NAC remains of great potential interest for increasing overall tolerance to clozapine by reducing oxidative stress [66].

3.2.4.4. Botulinic toxin. Botulinic toxin has more recently been investigated in CIH for targeted use in the salivary glands. Injection of toxin (serotype A and B) blocks the peripheral release of acetylcholine in the salivary glands. Its regulatory action in CIH would therefore involve local and global antimuscaniric effects due to lack of stimulation [67].

Available studies show that injection of botulinum toxin at varying doses into the salivary glands (parotid and/or submandibular) is effective and very rapid [68–71]. The effect on the CIH lasts several months after the injection without adverse effects. However, this invasive

method, with a potential risk of jaw dislocation [67], remains reserved for forms resistant to all other alternatives, with an indication made by a specialist in otolaryngology (in accordance with the product monograph).

4. Discussion

This systematic literature review is the first presenting an overview of 19 available treatments in France. Despite these limitations, it is necessary to constantly update the knowledge about these treatments in order to guide medical clinical practice. We present below the summary elements on the pharmacological rationale of the different strategies for correcting CIH (See Table 3 for the synthesis of molecules approved for use in France, as well as the contraindications associated with these treatments).

4.1. Anticholinergic correctors

Clozapine exhibits activities as both an M_4 agonist–promoting hypersialia–and an M_3 antagonist–promoting hyposialia. Based on the hypothesis of a predominant stimulation of M_4 muscarinic receptors in the salivary glands to explain the emergence of CIH [12,13,72], the corrective action of proposed strategies (atropine, glycopyrronium, scopolamine, ipratropium, trihexyphenidyl, amitriptyline, oxybutynin, biperiden) seems to be able to rely on the antagonistic action for the M_3 and M_4 receptors of these treatments. These all actually have affinities greater than those of clozapine for these same receptors (norclozapine, the main metabolite, pharmacologically active, has affinities all lower than that of clozapine for muscarinic receptors). In fact, by binding more than clozapine to these receptors, these treatments will tend to intensify the lever of hyposialia (by M_3 antagonism) and to correct the lever of hypersalivation (by M_4 antagonism), explaining the character potential corrector.

4.2. Noradrenergic correctors

Clozapine has a very strong affinity for α_{1A} receptors, strong for α_{1B} and α_{2C} receptors and more moderate for α_{2A} and α_{2B} receptors. The antagonism of α_1 and α_2 receptors would go in the direction of hypersalivation, in the same way as the stimulation of β receptors. From the perspective of double α_1 and α_2 blockade, overstimulation of β receptors would therefore contribute to the exacerbation of hypersalivation, already induced by α_1/α_2 blockade. In this sense, the beneficial action of clonidine could be explained by a reduction in α-noradrenergic blockade with α_2 stimulation. While the beneficial action of terazosin could be explained by the fact that a selective and intensified blockade of α_1 receptors, already blocked by clozapine, could promote α_2 fixation and limit the impact of hypersalivation. It should be noted that the noradrenergic strategy appears less well explained with regard to affinities than the anticholinergic theory mentioned previously. The binding affinity of clonidine and terazosin appears to be comparable to lower than that of clozapine, respectively for the α_2 (α_{2A} and α_{2B}) and α_{1A} receptors.

4.3. Dopaminergic correctors

Although the action of D_2 receptor blockers, derived from benzamide, such as sulpiride, amisulpride and metoclopramide, is incompletely understood, their benefit appears to be linked to the pharmacological effects described with sulpiride and metoclopramide and based on a negative regulation of gastric secretory activity. This effect also seems to be similar to what is observed with gastric antisecretory treatments (H_2 antagonists and proton pump inhibitors) which can induce dry mouth [73].

Table 3
Specialties that can be used in CIH in France and their contraindications.

INN	Trade names	Galenic presentations	Recorded contraindications from the ANSM monographs (French Medicines Agency)
Atropine	Atropine Faure® NR	Ophthalmic solution 1% single dose container 0.4 mL (one drop = 250 µg of atropine)	- Patients with known or suspected angle-closure glaucoma - Breastfeeding - Children under 12 years old
	Atropine Alcon®	Ophthalmic solution 1% 10 mL bottle (one drop = 310 µg of atropine)	
Glycopyrrolate or glycopyrronium	Seebri breezhaler®	Inhalation powder (capsule) (one dose = 44 µg glycopyrronium)	
	Sialanar® NR	Oral solution 320 µg/mL Commercialization 2023, approval for the symptomatic treatment of severe sialorrhea in children aged 3 years and older and adolescents with chronic neurological disorders	- Pregnancy and breastfeeding - Glaucoma - Urinary retention - Severe renal insufficiency - History of intestinal obstruction, ulcerative colitis, paralytic ileus, pyloric stenosis and myasthenia gravis - Concomitant treatment with oral solid potassium chloride and anticholinergics
Scopolamine	Scopoderm® NR	Transdermal patch 1 mg/72 h	- Risk of angle-closure glaucoma - Risk of urinary retention due to urethroprostatic disorders - Child under 15 years old
Ipratropium	Atrovent®[b]	Nasal spray 0.03% (one spray = 21 µg of ipratropium)	Infectious rhinitis
Trihexyphenidyl	Artane®	Tablet 2 & 5 mg 0.4% oral solution	- Risk of angle-closure glaucoma - Risk of urinary retention due to urethroprostatic disorders - Decompensated heart disease - Patients with a wheat allergy (other than coeliac disease) (for immediate-release tablet forms)
	Parkinane®	Extended release capsule 2 & 5 mg	

(continued on next page)

Table 3 (*continued*)

INN	Trade names	Galenic presentations	Recorded contraindications from the ANSM monographs (French Medicines Agency)
Amitriptyline	Laroxyl®	Tablet 25 & 50 mg Oral solution 40 mg/mL	- Recent myocardial infarction - Heart block or cardiac rhythm disorder and coronary insufficiency - Concomitant treatment with MAOIs (monoamine oxidase inhibitors) - Severe liver disease - Children under 6 years old
Oxybutynine	Ditropan® Oxybutynine®	Scored tablet 5 mg	- Risk of urinary retention due to urethroprostatic disorders - Intestinal obstruction - Toxic megacolon - Intestinal atony, paralytic ileus - Severe ulcerative colitis - Myasthenia gravis - Angle-closure or shallow chamber glaucoma
Biperiden	Akineton®	Extended release tablet 4 mg	- High sensitivity to anticholinergics - Risk of angle-closure glaucoma - Risk of urinary retention due to urethroprostatic disorders - Decompensated heart disease - Child under 15 years old
Tolterodine	Detrusitol®	Tablet 2 mg	
Tropicamide	Mydriaticum®[b]	Ophthalmic solution 0.5% 10 mL bottle (1 drop = 150 µg of tropicamide) Ophthalmic solution 2 mg single dose container 0.4 mL (1 drop = 150 µg of tropicamide)	- Risk of angle-closure glaucoma
Clonidine	Catapressan®	Scored tablet 0.15 mg	- Severe bradyarrhythmia due to sinus node disease or second or third degree atrioventricular block - Depressive disorder
Terazosin	Dysalfa®[b] Hytrine®[b]	Tablet 1 & 5 mg	- History of orthostatic hypotension

Table 3 (*continued*)

INN	Trade names	Galenic presentations	Recorded contraindications from the ANSM monographs (French Medicines Agency)
Amisulpride	Amisulpride® Solian®	Scored tablet 100, 200, 400 mg Oral solution 100 mg/mL	- Concomitant prolactin-dependent tumors - Pheochromocytoma - Children and adolescents under 15 years - Breastfeeding - Association with levodopa - Association with torsadogenic drugs (except tolerance rule)[a]
Sulpiride	Dogmatil® Sulpiride®	Capsule 50 mg Scored tablet 200 mg Oral solution 0.5 g/100 mL	- Prolactin-dependent tumors, - Pheochromocytoma, known or suspected, - Association with: dopaminergics other than Parkinson's* and torsadogens (except tolerance rule)[a] - Acute porphyria
Metoclopramide	Primperan® Metoclopramide®	Scored tablet 10 mg Oral solution 0.1%	- When stimulation of gastrointestinal motility presents a danger: gastrointestinal hemorrhage, mechanical obstruction or digestive perforation - Known or suspected pheochromocytoma, due to the risk of episodes of severe hypertension - Known history of tardive dyskinesia with neuroleptics or metoclopramide - Epilepsy - Parkinson - In association with levodopa or dopaminergic agonists - Known history of methemoglobinemia with metoclopramide or NADH cytochrome-b5 reductase deficiency. - Child under one year old
	Prokinyl®	Extended release capsule 15 mg	
Moclobemide	Moclamine®	Scored tablet 150 mg	- Acute confusional states - Children under 15 years old - Breastfeeding. - Association with drugs-related risk of hypertensive crises or serotonin syndrome[a]

(*continued on next page*)

Table 3 (*continued*)

INN	Trade names	Galenic presentations	Recorded contraindications from the ANSM monographs (French Medicines Agency)
Bupropion	Zyban® NR	Extended release tablet 150 mg	- Progressive convulsive disorder or any history of convulsions - Central nervous system tumor -Initiation or continuation of alcohol withdrawal or any other medication whose discontinuation carries a risk of convulsions (in particular benzodiazepines and related drugs) - Diagnosis or history of bulimia or anorexia nervosa -Severe hepatic cirrhosis -Association with MAOIs -Diagnosis or history of bipolar disorder (risk of mania) -Patients already treated with another medication with bupropion, the incidence of convulsions being dose-dependent and to avoid overdoses.
N-acetylcysteine	Acetylcysteine®, Exomuc® Fluimucil®, Mucomyst® NR	Powder for oral solution (sachet) 200 mg	-Children under 2 years old
	Acetylcysteine® NR	Effervescent tablet 200 mg	
	Exomuc® Fluimucil® NR	Powder for oral solution (sachet) 600 mg	
		Sugared tablets for oral solution 600 mg	
	Mucodrill® NR	Effervescent tablet 600 mg without sugar	
	Fluimucil® NR	Oral solution 2% without sugar	
Botulinum toxin A	Alluzience® Azzalure® Bocouture® Botox® Dysport® Letybo® Vistabel® Xeomin® NR	200 U/mL injectable solution 125 U injectable solution 50 & 100 U injectable solution 50 & 100 & 200 U injectable solution 300 & 500 U injectable solution 50 U injectable solution 50 & 100 U injectable solution 50 & 100 & 200 U injectable solution	- Myasthenia gravis - Infection at the injection site
			Contraindications common to all the above substances: hypersensitivity to the active substance or to one of the excipients

NR: not reimbursed medicines in France; INN: International Nonproprietary Name.

[a] See details in the ANSM monographs.

[b] Additional contraindications to substances related to the active ingredient (see details in the ANSM monographs).

4.4. Other correctors

The benefit of moclobemide and bupropion is based on uncertain pharmacology in CIH. Their serotoninergic and noradrenergic action for moclobemide and noradrenergic action for bupropion are probably the main levers of this action [61]. Although moclobemide benefits from an evaluation on a relatively large number of patients (compared to other treatments evaluated in CIH), it is not evaluated within the framework of a randomized controlled trial. Furthermore, doubt persists about the benefit and specificity of action of these treatments compared to other antidepressants also likely to induce dry mouth (like SSRIs or SNRIs) [58]. The improvement of CIH through antioxidant action also deserves to be further validated by carrying out randomized controlled trials and could be evaluated in the context of the overall improvement in tolerance to clozapine.

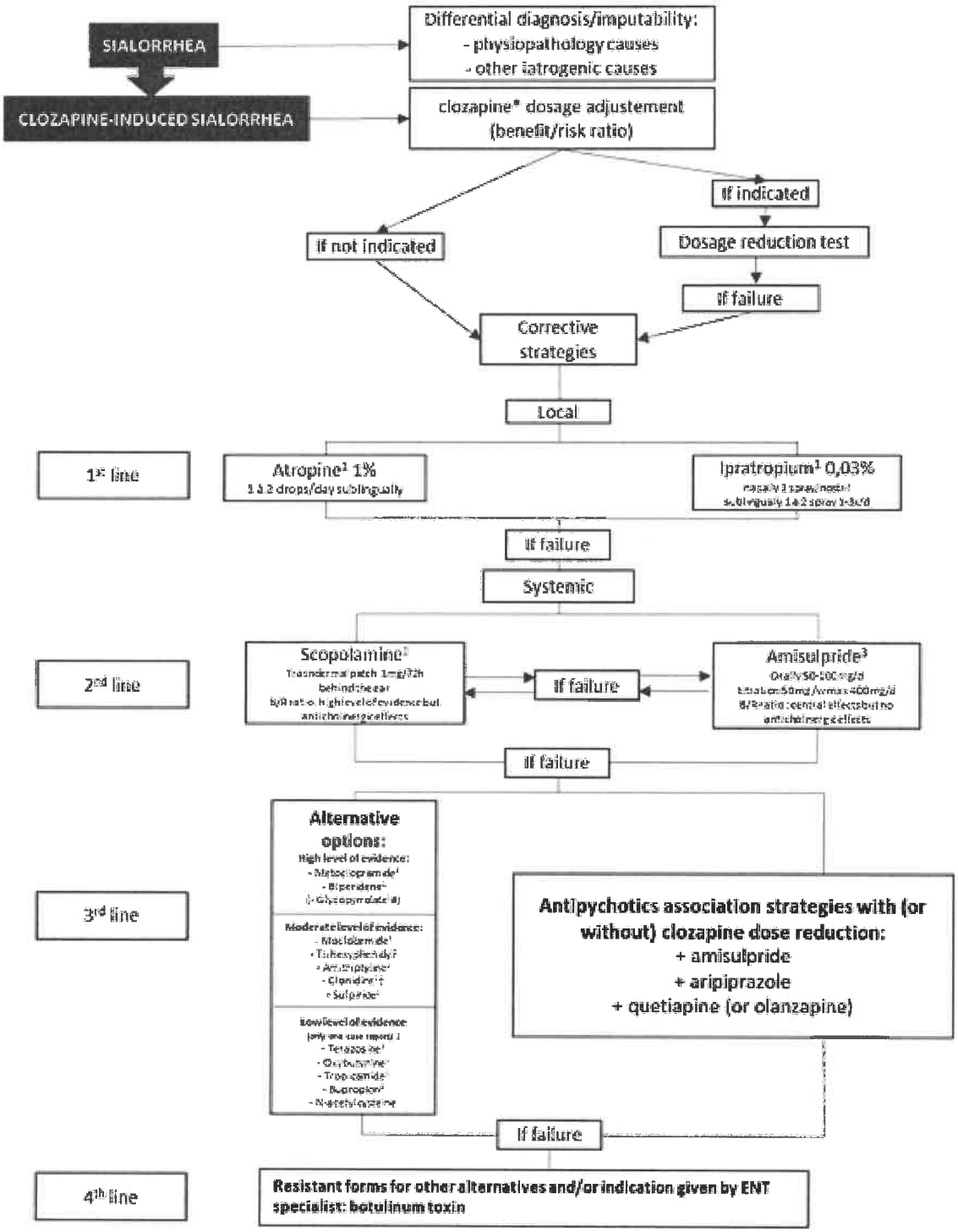
4.5. Add-on antipsychotic

Although the possibility of a dose-effect relationship is regularly evoked, the data in the literature generally contradict this hypothesis (1,3–5). This adaptation would nevertheless appear appropriate in a benefit-risk ratio, and if CIH seems to have appeared following a recent increase in dosage, after sufficient initial tolerance. However, as clozapine is used for resistant schizophrenia, the severity of the pathology does not always allow for treatment reduction without threatening the patient's psychological stability. In this context, an antipsychotic combination strategy is conceivable. The general principle in most cases is to use the maximum tolerated dose of clozapine (which does not generate hypersalivation) and to add an antipsychotic treatment with complementary pharmacology. The most rational option may be using a combination of clozapine and amisulpride [44]. Amisulpride has been identified as a corrective agent for hypersalivation and as a potential adjunct to clozapine in highly resistant situations [47–49,74]. As amisulpride is a corrective agent for CIH, it may also be considered to maintain a constant dose of clozapine, especially if a previous attempt to reduce the dose was associated with less psychological stability. An alternative consists of a combination of clozapine and aripiprazole, whose benefit was presumed before being validated by extensive cohort results [48,75,76]. Associations with others MARTAs (multi-acting receptor targeted antipsychotics, such as clozapine) are also conceivable, as with quetiapine and olanzapine [77].

4.6. Algorithm for managing hypersalivation under clozapine in France

The production of good practice recommendations on CIH involves a dual challenge aimed at identifying substances: 1) benefiting from the best level of evidence in terms of benefit-risk ratio; 2) marketed in France; 3) with a dosage form compatible with the demonstration of

their effectiveness in this indication. On the basis of our systematic review of the literature in line with the aforementioned criteria and relying on the elements of discussion previously stated, we propose a decision-making algorithm for the treatment of CIH for French psychiatry (Fig. 2).



[1]Anticholinergics agents, [2]Noradrenergics agents, [3]Dopaminergics agents, [4]Anti-depressants agents
*contradictory data on the dosage reduction benefit and on the pharmacologic therapeutic monitoring (plasma concentrations of clozapine contro)
B/R ratio : benefit/risk ratio
level of evidence could come under the 1st or 2nd line, but there is no adapted medicine in the french pharmacopoeia or excessive pharmacoeconomics impact in this indication
† benefit/risk ratio checkto validate the use : frequent depressing risk + increased risk of clozapine-induced hypotension/sedation

Fig. 2. Strategies for correction of clozapine-induced hypersialorrhea (CIH).

Our first strategy is to consider the iatrogenic causality of hypersalivation (certain pathophysiological conditions may induce it) [78] and the selective involvement of clozapine (other treatments may be involved, such as other antipsychotics or benzodiazepines) [78,79], and without recourse to a corrective strategy of adjunctive therapy, to consider the possibility of reducing the dosage of clozapine, in accordance with benefit-risk ratio (see above). As previously mentioned, reducing the dose may be appropriate if CIH emerges following a recent dose increase, after an initial period of tolerance.

In terms of corrective options, we propose first-line strategies that meet the following criteria: (i) sufficient level of evidence in the literature, (ii) a local action and (iii) availability of drugs reimbursed in France. The preferred strategies are atropine 1% in eye drops for sublingual use and ipratropium 0.03% in nasal spray for nasal or sublingual use. These options are supported by strong evidence in the literature (see Table 1). Among these, atropine has the highest level of evidence, as demonstrated by recent studies, reviews and meta-analyses [80–82]. Local treatments to manage CIH appear particularly relevant in terms of benefit-risk ratio for patients with treatment-resistant schizophrenia, for whom it is preferable to avoid systemic treatments as first-line option. To the best of our knowledge, localized use (e.g., sublingual) minimizes the contraindications associated with systemic treatments such as certain anticholinergics or D_2 blockers (benzamides) (see Table 3). Moreover, corrective strategies-particularly those with the strongest level of evidence- are primarily anticholinergic drugs. However, systemic effects of M_1 antagonist can exacerbate clozapine's impact, notably increasing the risk of constipation. The consequences of clozapine-induced constipation can be severe [83], making it highly preferable to avoid increasing the anticholinergic load as part of a first-line treatment strastegy.

In the second-line treatment, systemic action strategies may become appropriate. Scopolamine has been evaluated in three randomized controlled trials, while amisulpride has been assessed in only one (see Table 1). Prioritizing scopolamine can be considered in cases of partial response to first-line strategies. However, this treatment carries potential risks associated with its anticholinergic effects: at the peripheral level, it may cause constipation, and at the central level, it may increase the risk of cognitive impairments or worsen existing ones, as well as potentiate the sedative effects of clozapine. Additionnaly, scopolamine is not reimbursed in France. Amisulpride may be preferred in the second-line option in cases of complete non-response to first-line strategies, offering an alternative pharmacological mechanism. As a potent D_2 receptor antagonist, amisulpride carries risks of extrapyramidal syndromes, hyperprolactinemia and sedation, particularly with at higher doses. Nevertheless, amisulpride is reimbursed in France and may facilitate a reduction in the clozapine dose (see below). The benefit-risk ratio of each 2nd-line strategy must therefore be evaluated in relation to the patient's clinical profile. Given the difference in pharmacology, it seems reasonable, in the event of failure of one strategy, to consider trying the other as an alternative before switching to a 3rd line approach.

For 3rd-line treatments, biperiden, an anticholinergic, and metoclopramide, a benzamide D_2 antagonist, appear as potential alternatives (see Table 1). These are systemic agents with action profiles comparable to those of scopolamine and amisulpride, respectively. Both strategies are reimbursed in France, and metoclopramide has a solid level of evidence in recent literature on CIH [84,85]. Other 3rd-line options have lower levels of evidence (see Table 1). Among these, clonidine, with its alternative pharmacology (noradrenergic action), is challenging to use due to its risk of depressogenic effects. Tropicamide, an M_4 antagonist, is mentioned in a case report by Kilic et al. [40] and in a chart review [81] (published after the target dates for this systematic review). The relevance of this treatment will need to be further assessed in the years to come. N-acetylcysteine demonstrates a very good tolerance profile (no psychic adverse effects) and could be considered in combination with other agents potentially before progressing to the 3rd line treatments.

In addition to corrective strategies, a third-line option could involve considering a combination of antipsychotics (see Table 1) as previously discussed. This approach might represent a mixed strategy: (i) a corrective and supplementary agent for activity, such as amisulpride (with or without a reduction in clozapine dosage), or (ii) a supplementary agent without an identified corrective effect (although olanzapine exhibits moderate M_4 antagonist activity), such as aripiprazole, quetipiane or olanzapine (accompanied by a reduction in the dose of clozapine). While there is currently very limited data supporting the use of antipsychotic combinations for CIH [50], evaluating their efficacy appears highly relevant when compared to the other options [75].

The 4th line option involving botulinum toxin is considered in cases where all other pharmacological strategies ahev failed. The relevance of this option should be assessed by an ENT specialist. Among the limitations of our work, it is worth noting that the methodology of our systematic review, which was based on a limited number of databases, may not have identified potential treatments for CIH. Nevertheless, this approach appears to have been effective in identifying the treatments available in France.

5. Conclusion

In this systematic review on corrective treatments for CIH, we identified 19 substances and presented their level of evidence by focusing selectively on drugs available in France. The data collected led to the proposal of a decision-making algorithm for the management of CIH for French clinical psychiatry. The data currently available in the literature on CIH offer a misleading picture. The number of CIH corrective substances evaluated and potentially interesting is substantial, but the assessments are generally insufficient due to the low number of randomized controlled trials proposed. Regular updates of these treatment algorithms and available molecules are necessary to strengthen the management of these frequent and potentially harmful adverse effects for patients.

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Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] Bird A.M, Smith T.L, Walton A.E. Current treatment strategies for clozapine-induced sialorrhea. Ann Pharmacother 2011;45:667–75. https://doi.org/10.1345/aph.1P761.
[2] Syed R, Au K, Cahill C, et al. Pharmacological interventions for clozapine-induced hypersalivation. The Cochrane Collaboration. Cochrane Database Syst Rev. Chichester, UK: John Wiley & Sons, Ltd; 2008. https://doi.org/10.1002/14651858.CD005579.pub2. CD005579pub2.
[3] Maher S, Cunningham A, O'Callaghan N, et al. Clozapine-induced hypersalivation: an estimate of prevalence, severity and impact on quality of life. Ther Adv Psychopharmacol 2016;6:178–84. https://doi.org/10.1177/2045125316641019.
[4] Skokou M, Karavia E.A, Drakou Z, et al. Adverse drug reactions in relation to clozapine plasma levels: a systematic review. Pharm Basel Switz 2022;15:817. https://doi.org/10.3390/ph15070817.
[5] Sanagustin D, Martin-Subero M, Hogg B, et al. Prevalence of clozapine-induced sialorrhea and its effect on quality of life. Psychopharmacology (Berl) 2023;240:203–11. https://doi.org/10.1007/s00213-022-06294-3.
[6] Iqbal M.M, Rahman A, Husain Z, et al. Clozapine: a clinical review of adverse effects and management. Ann Clin Psychiatry 2003;15:33–48. https://doi.org/

10.3109/10401230309085668.
[7] Liang C.-S, Ho P.-S, Shen L.-J, et al. Comparison of the efficacy and impact on cognition of glycopyrrolate and biperiden for clozapine-induced sialorrhea in schizophrenic patients: a randomized, double-blind, crossover study. Schizophr Res 2010;119:138–44. https://doi.org/10.1016/j.schres.2010.02.1060.
[8] Mustafa F.A, Burke J.G, Abukmeil S.S, et al. Schizophrenia past clozapine: reasons for clozapine discontinuation, mortality, and alternative antipsychotic prescribing. Pharmacopsychiatry 2015;48:11–4. https://doi.org/10.1055/s-0034-1394397.
[9] Saenger R.C, Finch T.H, Francois D. Aspiration pneumonia due to clozapine-induced sialorrhea. Clin Schizophr Relat Psychoses 2016;9:170–2. https://doi.org/10.3371/CSRP.SAFI. 061213.
[10] Nielsen J, Foldager L, Meyer J.M. Increased use of antibiotics in patients treated with clozapine. Eur Neuropsychopharmacol 2009;19:483–6. https://doi.org/10.1016/j.euroneuro.2009.03.002.
[11] Roth BL, Driscol J. "PDSP Ki Database". Psychoactive Drug Screening Program (PDSP). University of North Carolina at Chapel Hill and the United States National Institute of Mental Health. n.d.
[12] Praharaj S.K, Arora M, Gandotra S. Clozapine-induced sialorrhea: pathophysiology and management strategies. Psychopharmacology (Berl) 2006; 185:265–73. https://doi.org/10.1007/s00213-005-0248-4.
[13] Bai Y.-M, Lin C.-C, Chen J.-Y, et al. Therapeutic effect of pirenzepine for clozapine-induced hypersalivation: a randomized, double-blind, placebo-controlled, cross-over study. J Clin Psychopharmacol 2001;21:608–11. https://doi.org/10.1097/00004714-200112000-00012.
[14] Wang X, Serrano Martinez P, Terpstra J.H, et al. (-Adrenergic signaling induces Notch-mediated salivary gland progenitor cell control. Stem Cell Rep 2021;16: 2813–24. https://doi.org/10.1016/j.stemcr.2021.09.015.
[15] Grabowski J. Clonidine treatment of clozapine-induced hypersalivation. J Clin Psychopharmacol 1992;12:69–70.
[16] Cuvelier E, Gressier B, Fovet T, et al. Prise en charge de l'hypersialorrhée iatrogène: revue de la littérature et recommandations pratiques. L'Encéphale 2022;48:700–11. https://doi.org/10.1016/j.encep.2022.03.013.
[17] Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9 https://doi.org/10.7326/0003-4819-151-4-200908180-00135. [W64].
[18] Mubaslat O, Lambert T. The effect of sublingual atropine sulfate on clozapine-induced hypersalivation: a multicentre, randomised placebo-controlled trial. Psychopharmacology (Berl) 2020;237:2905–15. https://doi.org/10.1007/s00213-020-05627-4.
[19] Tessier P, Antonello C. Clozapine and sialorrhea: update. J Psychiatry Neurosci JPN 2001;26:253.
[20] Matos Santana T.E, Capurso N.A, Ranganathan M, et al. Sublingual atropine in the treatment of clozapine-induced sialorrhea. Schizophr Res 2017;182:144–5. https://doi.org/10.1016/j.schres.2016.10.039.
[21] Mori N, Buchwald P, Wu W.M, et al. Pharmacological effects of some newly developed soft anticholinergics and a receptor-binding QSAR study. Pharm 2006; 61:148–53.
[22] Robb A.S, Lee R.H, Cooper E.B, et al. Glycopyrrolate for treatment of clozapine-induced sialorrhea in three adolescents. J Child Adolesc Psychopharmacol 2008; 18:99–107. https://doi.org/10.1089/cap.2007.0037.
[23] Blissit K.T, Tillery E, Latham C, et al. Glycopyrrolate for treatment of clozapine-induced sialorrhea in adults. Am J Health Syst Pharm 2014;71:1282–7. https://doi.org/10.2146/ajhp130636.
[24] Praharaj S.K, Munoli R.N, Sharma P.S.V.N. Low-dose glycopyrrolate for clozapine-associated sialorrhea. J Clin Psychopharmacol 2014;34:392. https://doi.org/10.1097/JCP.0000000000000102.
[25] Man W.H, Colen–de Koning J.C.A, Schulte P.F.J, 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; 37:155–61. https://doi.org/10.1097/JCP.0000000000000657.
[26] Qurashi I, Chu S, Drake R, et al. Glycopyrrolate in comparison to hyoscine hydrobromide and placebo in the treatment of hypersalivation induced by clozapine (GOTHIC1): a feasibility study. Pilot Feasibility Stud 2019;5:79. https://doi.org/10.1186/s40814-019-0462-1.
[27] Astha, Tekkalaki B. Cessation of clozapine-induced severe hypersalivation along with improvement of residual persistent auditory hallucinations by tDCS in a patient of chronic schizophrenia - A case report. Indian J Psychiatry 2022;64: 110. https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_552_21.
[28] Gaftanyuk O, Trestman R.L. Scolpolamine patch for clozapine-induced sialorrhea. Psychiatr Serv Wash DC 2004;55:318. https://doi.org/10.1176/appi.ps.55.3.318.
[29] Takeuchi I, Suzuki T, Kishi T, et al. Effect of scopolamine butylbromide on clozapine-induced hypersalivation in schizophrenic patients: a case series. Clin Psychopharmacol Neurosci 2015;13:109–12. https://doi.org/10.9758/cpn.2015.13.1.109.
[30] 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;34:101–7. https://doi.org/10.1097/YIC.0000000000000251.
[31] Sockalingam S, Shammi C, Remington G. Treatment of clozapine-induced hypersalivation with ipratropium bromide: a randomized, double-blind, placebo-controlled crossover study. J Clin Psychiatry 2009;70:1114–9. https://doi.org/10.4088/JCP.08m04495.
[32] Calderon J, Rubin E, Sobota W.L. Potential use of ipatropium bromide for the treatment of clozapine-induced hypersalivation: a preliminary report. Int Clin Psychopharmacol 2000;15:49–52. https://doi.org/10.1097/00004850-200015010-00008.
[33] Freudenreich O, Beebe M, Goff D.C. Clozapine-induced sialorrhea treated with sublingual ipratropium spray: a case series. J Clin Psychopharmacol 2004;24: 98–100. https://doi.org/10.1097/01.jcp.0000106228.36344.2e.
[34] Spivak B, Adlersberg S, Rosen L, et al. Trihexyphenidyl treatment of clozapine-induced hypersalivation. Int Clin Psychopharmacol 1997;12:213–5. https://doi.org/10.1097/00004850-199707000-00005.
[35] Praharaj S.K, Arora M. Amitriptyline for clozapine-induced nocturnal enuresis and sialorrhoea. Br J Clin Pharmacol 2007;63:128–9. https://doi.org/10.1111/j.1365-2125.2006.02748.x.
[36] Sinha S, Simlai J, Praharaj K.S. Very low dose amitriptyline for clozapine-associated sialorrhea. Curr Drug Saf 2016;11:262–3. https://doi.org/10.2174/1574886311666160426130252.
[37] Cereda G, Boscutti A, Lazzaretti M, et al. Amitriptyline for clozapine-induced hypersalivation: a case series. Schizophr Res 2022;243:110–1. https://doi.org/10.1016/j.schres.2022.02.035.
[38] Leung J.G, Puri N.V, Jacobson M.J. Immediate-release oxybutynin for the treatment of clozapine-induced sialorrhea. Ann Pharmacother 2011;45:1160. https://doi.org/10.1345/aph.1Q270.
[39] Lazareno S, Buckley N.J, Roberts F.F. Characterization of muscarinic M4 binding sites in rabbit lung, chicken heart, and NG108-15 cells. Mol Pharmacol 1990;38:805–15.
[40] Kilic O, Ozturk M, Ata Gozcelioglu E. Tropicamide ophthalmic solution reduces clozapine-induced sialorrhea: a case report. Psychiatry Clin Psychopharmacol 2017;27:431–4. https://doi.org/10.1080/24750573.2017.1347601.
[41] Praharaj S.K, Verma P, Roy D, et al. Is clonidine useful for treatment of clozapine-induced sialorrhea? J Psychopharmacol (Oxf) 2005;19:426–8. https://doi.org/10.1177/0269881105053311.
[42] Immadisetty V, Agrawal P. A successful treatment strategy for clozapine-induced parotid swelling: a clinical case and systematic review. Ther Adv Psychopharmacol 2012;2:235–9. https://doi.org/10.1177/2045125312455187.
[43] Kreinin A, Novitski D, Weizman A. Amisulpride treatment of clozapine-induced hypersalivation in schizophrenia patients: a randomized, double-blind, placebo-controlled cross-over study. Int Clin Psychopharmacol 2006;21:99–103. https://doi.org/10.1097/01.yic.0000188216.92408.69.
[44] Kreinin A, Miodownik C, Sokolik S, et al. Amisulpride versus moclobemide in treatment of clozapine-induced hypersalivation. World J Biol Psychiatry 2011;12: 620–6. https://doi.org/10.3109/15622975.2010.527370.
[45] Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. The Lancet 2013;382:951–62. https://doi.org/10.1016/S0140-6736(13)60733-3.
[46] Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. The Lancet 2019;394:939–51. https://doi.org/10.1016/S0140-6736(19)31135-3.
[47] Zink M, Knopf U, Henn F.A, et al. Combination of clozapine and amisulpride in treatment-resistant schizophrenia--case reports and review of the literature. Pharmacopsychiatry 2004;37:26–31. https://doi.org/10.1055/s-2004-815471.
[48] Porcelli S, Balzarro B, Serretti A. Clozapine resistance: augmentation strategies. Eur Neuropsychopharmacol 2012;22:165–82. https://doi.org/10.1016/j.euroneuro.2011.08.005.
[49] Barber S, Olotu U, Corsi M, et al. Clozapine combined with different antipsychotic drugs for treatment-resistant schizophrenia. Cochrane Database Syst Rev 2017;3:CD006324. https://doi.org/10.1002/14651858.CD006324.pub3.
[50] Croissant B, Hermann D, Olbrich R. Reduction of side effects by combining clozapine with amisulpride: case report and short review of clozapine-induced hypersalivation. Pharmacopsychiatry 2005;38:38–9. https://doi.org/10.1055/s-2005-837771.
[51] Praharaj S.K, Ray P, Gandotra S. Amisulpride improved debilitating clozapine-induced sialorrhea. Am J Ther 2011;18:e84–5. https://doi.org/10.1097/MJT.0b013e3181c84bbd.
[52] Desai J.K, Parmar N.S. Gastric and duodenal anti-ulcer activity of sulpiride, a dopamine D2 receptor antagonist, in rats. Agents Actions 1994;42:149–53. https://doi.org/10.1007/BF01983482.
[53] Lam S.K, Lai C.L. Inhibition of sulpiride on the cephalic phase of gastric acid and gastrin secretion in duodenal ulcer patients. Scand J Gastroenterol 1976;11: 27–31.
[54] Kreinin A, Epshtein S, Sheinkman A, et al. Sulpiride addition for the treatment of clozapine-induced hypersalivation: preliminary study. Isr J Psychiatry Relat Sci 2005;42:61–3.
[55] 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;36:200–5. https://doi.org/10.1097/JCP.0000000000000493.
[56] Miodownik C, Kreinin A, Lerner P.P, et al. Treatment of clozapine-associated sialorrhea: the role of benzamide derivatives. J Clin Psychopharmacol 2023;43: 171–7. https://doi.org/10.1097/JCP.0000000000001655.
[57] Hatlebakk J.G, Berstad A. Pharmacokinetic optimisation in the treatment of gastro-oesophageal reflux disease. Clin Pharmacokinet 1996;31:386–406. https://doi.org/10.2165/00003088-199631050-00005.
[58] Cappetta K, Beyer C, Johnson J.A, et al. Meta-analysis: Risk of dry mouth with second generation antidepressants. Prog Neuropsychopharmacol Biol Psychiatry 2018;84:282–93. https://doi.org/10.1016/j.pnpbp.2017.12.012.

[59] Nair N.P, Ahmed S.K, Kin N.M. Biochemistry and pharmacology of reversible inhibitors of MAO-A agents: focus on moclobemide. J Psychiatry Neurosci JPN 1993;18:214–25.
[60] Kreinin A, Miodownik C, Libov I, et al. Moclobemide treatment of clozapine-induced hypersalivation: pilot open study. Clin Neuropharmacol 2009;32:151–3. https://doi.org/10.1097/WNF.0b013e31818f1111.
[61] Chew M.L, Mulsant B.H, Pollock B.G, et al. Anticholinergic activity of 107 medications commonly used by older adults: anticholinergic activity of medication. J Am Geriatr Soc 2008;56:1333–41. https://doi.org/10.1111/j.1532-5415.2008.01737.x.
[62] Stern R.G, Bellucci D, Cursi-Vogel N, et al. Clozapine-induced sialorrhea alleviated by bupropion — A case report. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:1578–80. https://doi.org/10.1016/j.pnpbp.2009.09.014.
[63] Mito Y, Yabe I, Yaguchi H, et al. Relationships of drooling with motor symptoms and dopamine transporter imaging in drug-naïve Parkinson's disease. Clin Neurol Neurosurg 2020;195:105951. https://doi.org/10.1016/j.clineuro.2020.105951.
[64] Uzun Ö, Bolu A, Çelik C. Effect of N-acetylcysteine on clozapine-induced sialorrhea in schizophrenic patients: a case series. Int Clin Psychopharmacol 2019. https://doi.org/10.1097/YIC.0000000000000297. Publish Ahead of Print.
[65] Żukowski P, Maciejczyk M, Matczuk J, et al. Effect of N-acetylcysteine on antioxidant defense, oxidative modification, and salivary gland function in a rat model of insulin resistance. Oxid Med Cell Longev 2018;2018:1–11. https://doi.org/10.1155/2018/6581970.
[66] Chrétien B, Fedrizzi S, Lelong-Boulouard V, et al. Could N-acetylcysteine improve the safety of clozapine? Hum Psychopharmacol 2021;36:e2769. https://doi.org/10.1002/hup.2769.
[67] Tan E.K, Lo Y.L, Seah A, et al. Recurrent jaw dislocation after botulinum toxin treatment for sialorrhoea in amyotrophic lateral sclerosis. J Neurol Sci 2001;190:95–7. https://doi.org/10.1016/s0022-510x(01)00565-2.
[68] Kahl K.G, Hagenah J, Zapf S, et al. Botulinum toxin as an effective treatment of clozapine-induced hypersalivation. Psychopharmacology (Berl) 2004;173:229–30. https://doi.org/10.1007/s00213-004-1803-0.
[69] Steinlechner S, Klein C, Moser A, et al. Botulinum toxin B as an effective and safe treatment for neuroleptic-induced sialorrhea. Psychopharmacology (Berl) 2010;207:593–7. https://doi.org/10.1007/s00213-009-1689-y.
[70] Verma R, Anand K.S. Botulinum toxin: a novel therapy for clozapine-induced sialorrhoea. Psychopharmacology (Berl) 2018;235:369–71. https://doi.org/10.1007/s00213-017-4795-2.
[71] Moss L. Early use of botulinum neurotoxin treatment for clozapine-induced sialorrhea. J Acad Consult-Liaison Psychiatry 2021;62:663–4. https://doi.org/10.1016/j.jaclp.2021.05.002.
[72] Zorn S.H, Jones S.B, Ward K.M, et al. Clozapine is a potent and selective muscarinic M4 receptor agonist. Eur J Pharmacol 1994;269:R1–2. https://doi.org/10.1016/0922-4106(94)90047-7.
[73] Scully Cbe C. Drug effects on salivary glands: dry mouth: drug effects on salivary glands: dry mouth. Oral Dis 2003;9:165–76. https://doi.org/10.1034/j.1601-0825.2003.03967.x.
[74] Munro J, Matthiasson P, Osborne S, et al. Amisulpride augmentation of clozapine: an open non-randomized study in patients with schizophrenia partially responsive to clozapine. Acta Psychiatr Scand 2004;110:292–8. https://doi.org/10.1111/j.1600-0447.2004.00356.x.
[75] Tiihonen J, Taipale H, Mehtälä J, et al. Association of antipsychotic polypharmacy vs monotherapy with psychiatric rehospitalization among adults with schizophrenia. JAMA Psychiatry 2019;76:499–507. https://doi.org/10.1001/jamapsychiatry.2018.4320.
[76] Lähteenvuo M, Tiihonen J. Antipsychotic polypharmacy for the management of schizophrenia: evidence and recommendations. Drugs 2021;81:1273–84. https://doi.org/10.1007/s40265-021-01556-4.
[77] Reinstein M.J, Sonnenberg J.G, Mohan S.C, et al. Use of quetiapine to manage patients who experienced adverse effects with clozapine. Clin Drug Investig 2003;23:63–7. https://doi.org/10.2165/00044011-200323010-00008.
[78] Miranda-Rius J, Brunet-Llobet L, Lahor-Soler E, et al. Salivary secretory disorders, inducing drugs, and clinical management. Int J Med Sci 2015;12:811–24. https://doi.org/10.7150/ijms.12912.
[79] Halder A, Ravindran N.P, Nagda P, et al. Review of psychotropic agents associated with sialorrhoea, except clozapine. Indian J Psychol Med 2023;45:14–8. https://doi.org/10.1177/02537176211025789.
[80] Yellepeddi V.K, Race J.A, McFarland M.M, et al. Effectiveness of atropine in managing sialorrhea: a systematic review and meta-analysis. Int J Clin Pharmacol Ther 2024;62:267–77. https://doi.org/10.5414/CP204538.
[81] Mutlu E, Özçelik Eroğlu E, Coşkun FÖ, et al. A systematic chart review of pharmacological interventions in patients with clozapine-induced hypersalivation. Schizophr Res 2023 https://doi.org/10.1016/j.schres.2023.08.004. [S0920996423002621].
[82] 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;7:2108–13. https://doi.org/10.1002/ccr3.2431.
[83] Bulot V, Lemogne C, Nebot N, et al. Systematic prevention of severe constipation induced by antipsychotic agents: A quasi-experimental study. Eur Neuropsychopharmacol 2016;26:1690–1. https://doi.org/10.1016/j.euroneuro.2016.08.004.
[84] Fornaro M, Caiazza C, Solini N, et al. Pharmacological interventions for antipsychotic-related sialorrhea: a systematic review and network meta-analysis of randomized trials. Mol Psychiatry 2023;28:3648–60. https://doi.org/10.1038/s41380-023-02266-x.
[85] Chen S.-Y, Ravindran G, Zhang Q, et al. Treatment strategies for clozapine-induced sialorrhea: a systematic review and meta-analysis. CNS Drugs 2019;33:225–38. https://doi.org/10.1007/s40263-019-00612-8.
[86] Antonello C, Tessier P. Clozapine and sialorrhea: a new intervention for this bothersome and potentially dangerous side effect. J Psychiatry Neurosci JPN 1999;24:250.
[87] Comley C, Galletly C, Ash D. Use of atropine eye drops for clozapine induced hypersalivation. Aust N Z J Psychiatry 2000;34:1033–4. https://doi.org/10.1177/000486740003400102.
[88] Sharma A, Ramaswamy S, Dahl E, et al. Intraoral application of atropine sulfate ophthalmic solution for clozapine-induced sialorrhea. Ann Pharmacother 2004;38:1538. https://doi.org/10.1345/aph.1E077.
[89] Mustafa F. Sublingual atropine for the treatment of severe and hyoscine-resistant clozapine-induced sialorrhea. Afr J Psychiatry 2013;16:236–42. https://doi.org/10.4314/ajpsy.v16i4.32.
[90] Chu S, Qurashi I, Campbell N, et al. A natural study of the efficacy of replacement medications for the treatment of clozapine-induced hypersalivation. Ther Adv Psychopharmacol 2016;6:147–8. https://doi.org/10.1177/2045125315591926.
[91] Sheikhmoonesi F, Zarghami M, Hendoie N, et al. Comparing the impact of atropine drops and amitriptyline tablets in treatment of clozapine-induced sialorrhea: a randomized double-blind placebo controlled clinical trial. Acta Med Iran 2018;757–63.
[92] 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;7:2108–13. https://doi.org/10.1002/ccr3.2431.
[93] Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, et al. Pharmacokinetics and effects on saliva flow of sublingual and oral atropine in clozapine-treated and healthy adults: an interventional cross-over study. Psychiatry Clin Psychopharmacol 2022;32:17–27. https://doi.org/10.5152/pcp.2022.21221.
[94] Duggal H.S. Glycopyrrolate for clozapine-induced sialorrhea. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1546–7. https://doi.org/10.1016/j.pnpbp.2007.06.013.
[95] McKane J.P, Hall C, Akram G. Hyoscine patches in clozapine-induced hypersalivation. Psychiatr Bull 2001;25:277. https://doi.org/10.1192/pb.25.7.277-c.
[96] Goto T, Kato M, Matsumura Y, et al. Scopolamine ointment for clozapine-associated sialorrhea: a case report. J Clin Psychopharmacol 2017;37:106–7. https://doi.org/10.1097/JCP.0000000000000613.
[97] Takeuchi I, Hanya M, Uno J, et al. Effectiveness of the repeated administration of scopolamine ointment on clozapine-induced hypersalivation in patients with treatment-resistant schizophrenia: a preliminary study: Treatment of clozapine-induced hypersalivation. Asia-Pac Psychiatry 2017;9:e12269. https://doi.org/10.1111/appy.12269.
[98] Poyurovsky M, Modai I, Weizman A. Trihexyphenidyl as a possible therapeutic option in clozapine-induced nocturnal enuresis. Int Clin Psychopharmacol 1996;11:61–3. https://doi.org/10.1097/00004850-199603000-00010.
[99] Aggarwal A, Garg A, Jiloha R.C. Trihexyphenidyl (benzhexol) in clozapine-induced nocturnal enuresis and sialorrhea. Indian J Med Sci 2009;63:470–1.
[100] Praharaj S.K, Sarkhel S, Khanande R.V, et al. Complete resolution of clozapine-induced sialorrhea with low dose trihexyphenidyl. Psychopharmacol Bull 2010;43:73–5.
[101] Copp P.J, Lament R, Tennent T.G. Amitriptyline in clozapine-induced sialorrhoea. Br J Psychiatry J Ment Sci 1991;159:166. https://doi.org/10.1192/bjp.159.1.166a.
[102] Richardson C, Kelly D.L, Conley R.R. Biperiden for excessive sweating from clozapine. Am J Psychiatry 2001;158 https://doi.org/10.1176/appi.ajp.158.8.1329-a. [1329-a-1330].
[103] Leung J.G, Kutzke J.L, Morgan R.J, et al. Thrombocytopenia associated with clonidine in a case of clozapine-induced sialorrhea. Ment Health Clin 2020;10:34–7. https://doi.org/10.9740/mhc.2020.01.034.
[104] Reinstein M.J, Sirotovskaya L.A, Chasanov M.A, et al. Comparative efficacy and tolerability of benzatropine and terazosin in the treatment of hypersalivation secondary to clozapine. Clin Drug Investig 1999;17:97–102. https://doi.org/10.2165/00044011-199917020-00003.
[105] Praharaj S.K, Sarkar S, Sinha V.K. Amisulpride treatment for clozapine-induced sialorrhea. J Clin Psychopharmacol 2009;29:189–90. https://doi.org/10.1097/JCP.0b013e318199f264.
[106] Kulkarni R.R. Low-dose amisulpride for debilitating clozapine-induced sialorrhea: case series and review of literature. Indian J Psychol Med 2015;37:446–8. https://doi.org/10.4103/0253-7176.168592.
[107] Bogorni F, Moreira F.F, Pimentel E.M, et al. Amisulpride augmentation for clozapine-refractory positive symptoms: additional benefit in reducing hypersialorrhea. Case Rep Psychiatry 2015;2015:1–2. https://doi.org/10.1155/2015/408179.
[108] Prljača E, Bećirović E, Hasanović M, et al. Clozapine-induced hypersalivation treated with sulpiride-is it a solution? Psychiatr Danub 2021;33:1230–2.
[109] Livermore C, White H, Bailey L, et al. A retrospective case notes review of the effectiveness and tolerability of metoclopramide in the treatment of clozapine-induced hypersalivation (CIH). BMC Psychiatry 2022;22:277. https://doi.org/10.1186/s12888-022-03940-0.
[110] Moriya H, Takagi Y, Nakanishi T, et al. Affinity profiles of various muscarinic antagonists for cloned human muscarinic acetylcholine receptor (mAChR) subtypes and mAChRs in rat heart and submandibular gland. Life Sci 1999;64:2351–8. https://doi.org/10.1016/s0024-3205(99)00188-5.
[111] Bacanak M. Muscarinic M1 and M2 receptors, fasting and seizure development

in animals. Clin Exp Health Sci 2018.
[112] McNamara A, Pulido-Rios M.T, Sweazey S, et al. Pharmacological properties of TD-6301, a novel bladder selective muscarinic receptor antagonist. Eur J Pharmacol 2009;605:145–52. https://doi.org/10.1016/j.ejphar.2008.12.043.
[113] Nilvebrant L, Andersson K.-E, Gillberg P.-G, et al. Tolterodine–a new bladder-selective antimuscarinic agent. Eur J Pharmacol 1997;327:195–207. https://doi.org/10.1016/S0014-2999(97)89661-6.
[114] Hancock A.A, Buckner S.A, Ireland L.M, et al. Actions of terazosin and its enantiomers at subtypes of α- and α2-Adrenoceptors *in vitro*. J Recept Signal Transduct 1995;15:863–85. https://doi.org/10.3109/10799899509049862.