

The sublingual use of atropine in the treatment of clozapine-induced sialorrhea: A systematic review

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Abstract

Clozapine is considered the golden standard in the treatment of therapy-resistant schizophrenia; however, it associated with bothersome side effects such as sialorrhea. Current evidence suggests that the sublingual use of atropine seems to be safe and effective and could be considered as a first-line treatment of clozapine-induced sialorrhea.

KEY WORDS

atropine, clozapine, sialorrhea, sublingual

1 | INTRODUCTION

There is no doubt that clozapine has taken an important place in the management of treatment-resistant schizophrenia and can even be seen as the golden standard in treatment-resistant schizophrenia.¹⁻³ However, clozapine is associated with a number severe side effects including agranulocytosis, myocarditis, seizures, or sedation. Blood tests are regularly indicated for the determination of leukocytosis and clozapine level. In spite of this, overall mortality in treatment with this drug is lower than with other first- or second-generation antipsychotics.⁴ An irrational fear amongst prescribing psychiatrists seems to play a clinically relevant role in withholding or delaying the initiation of clozapine treatment, unnecessarily prolonging the patients' suffering.⁵

A total of 30% to even 92%^{6,7} of patients taking clozapine are likely to experience an increase in salivation or even excessive salivation or sialorrhea. Despite its occurrence during the day, clozapine-induced sialorrhea (CIS) is usually the most marked and noticeable at night, usually noticeable by the so-called "wet pillow sign".⁸

Both medical and psychosocial adverse effects are associated with sialorrhea. Irritation and maceration can occur at the level of the chin and perioral skin, as well as cheilitis. In

combination with the sedative effect of clozapine, aspiration of the oropharyngeal contents, aspiration pneumonia,⁹ and even suffocation may occur.¹⁰ Chronic sleeping problems can occur because of repetitive throat clearing, clozapine-induced parotitis has also been reported in the past.¹¹ At a psychosocial level, wet clothing and the associated odor, as well as speech difficulties and drooling, can have a stigmatizing effect, leading to reduced self-esteem, social isolation, and ultimately leading to a reduced quality of life.⁸ For instance, more than half of the patients report that CIS has an impact on their quality of life.⁷ These adverse effects may ultimately lead to noncompliance and even discontinuation of clozapine.¹² This is further complicated by the fact that there is no long-acting formula of clozapine available to date.

Validated scales such as the Nocturnal Hypersalivation Rating Scale (NHRS) and the Drooling Severity and Frequency Scale (DSF)⁷ can be used. Objective methods such as the measurement of the diameter of the saliva on a patch on the pillow⁶ or weighing dental cotton rolls¹³ can also be used to quantify the severity of CIS. The Drooling Impact Scale (DIS) is often used in children with developmental problems.¹⁴

Two mechanisms for CIS are suggested: On one hand, the stimulation of the M4 muscarinic receptors and blockade of the $\alpha 2$ receptors by clozapine at the level of the submandibular

salivary glands could explain the increased salivation; on the other hand, reduced laryngeal peristalsis⁸ could contribute to the phenomenon. An association was found between the adrenoceptor alpha 2A gene (ADRA2A) and CIS ($P = .02^{15}$), the $\alpha 2$ receptors also appear to be involved in the swallowing movement-respiratory coordination.¹⁶ A recent article suggests CIS could be linked to M1-receptor agonism by clozapine's metabolite norclozapine, a model derived from the effect pirenzepine being a selective M1-agonist.¹⁷

Atropine is a racemic mixture of d-hyoscyamine and l-hyoscyamine, where the latter is responsible for the most of the physiological effects. It is a competitive antagonist of the muscarinic receptors, thereby inhibiting the effect of acetylcholine, a major neurotransmitter of the parasympathetic nervous system, also innervating the submandibular glands¹⁸ For example, atropine is used to prevent or treat cholinergic effects during operations by excessive vagal stimulation, or to slow down the unwanted muscarinic effects of drugs.¹⁹ Orally administered atropine appears safe and well tolerated up to doses of 0.03mg/ kg. The duration of sublingual atropine is probably close to orally and intramuscularly administered atropine: up to 4 hours.²⁰⁻²² The effect of atropine on sialorrhea can theoretically be explained by its action as a competitive antagonist of acetylcholine on the muscarinic receptors in the salivary glands.

Various systemic treatment options are available for CIS (anticholinergic medication, $\alpha 2$ -agonists, scopolamine, pirenzepine, and amisulpride) but are generally of little use because of their limited effectiveness or side effects profile. Reviews of the various treatments claim to date that the sample size is too small or that the studies are of insufficient quality to give clinical practice a clear direction.⁶ Furthermore, several lines of evidence indicate that anticholinergic agents may contribute to cognitive deficits in schizophrenic patients, which are a critical determinant of functional outcome.²³ Other than with clozapine, sialorrhea is also seen to lesser extent with other antipsychotics such as risperidone.²⁴ One systematic review examining the effect of anticholinergic medication for non-clozapine neuroleptic-induced hypersalivation turned out to be an "empty" review as all screened articles were excluded.²⁵ Other medication groups associated with drooling are direct and indirect cholinergic agonists that are used to treat dementia of the Alzheimer type and myasthenia gravis.²⁶

Two patients of the author, who were successfully treated of CIS by the sublingual use of atropine, gave rise to this systematic review. The aim of this systematic review is to gather the existing evidence for the effectiveness of sublingual application of atropine in reducing or resolving of CIS, as well as looking into the safety, side effects, and dosage of sublingually administered atropine. We also looked at the sublingual use of atropine in sialorrhea of other etiology to get a clearer picture on the effectivity, safety, side effects, and dosage.

Limitations

With respect to the treatment of CIS, only case reports and case series were found, implying a major risk of publication bias. Despite the overwhelmingly positive results, a need for randomized clinical trials remains.

Summations

Despite its anecdotal clinical use, a moderate amount of case reports suggest that sublingual atropine is an effective, safe treatment with few side effects in the treatment of CIS.

2 | MATERIALS AND METHODS

Two independent authors searched MEDLINE/PubMed, PsycINFO, EMBASE, and the Cochrane databases, from their respective inception dates until 1 June 2018 without restriction for language, date of publication, and study design, for the keywords "sialorrhea," "hypersalivation," "clozapine" and "atropine." A first search was performed with all three of the aforementioned keywords, a second search was performed with only "sialorrhea" and "atropine," to investigate the sublingual use of atropine in sialorrhea of other etiologies (Figure 1). Articles reporting the effect of local use of atropine in the treatment of CIS and sialorrhea of other etiologies were included. An unpublished case series conducted in our center was also included in the results. The reports were published between 1991 and September 2018.

3 | RESULTS

A total number of 13 articles were found to be eligible for the systematic review. Regarding the local treatment with atropine for CIS, 7 articles were found, no randomized clinical trials, no open label, or retrospective studies were found. The results consisted entirely of case reports and case series (2 and 5 articles respectively, and one unpublished case series in our center). As for the treatment with local atropine in sialorrhea of another etiology, six studies were found, of which only one randomized clinical trial, two pilot studies, one open label study, and two case reports.

3.1 | CIS treated with local atropine

3.1.1 | Case reports

Sharma²⁷ describes a patient that achieved a reduction and ultimately a complete resolution of CIS with the use of two

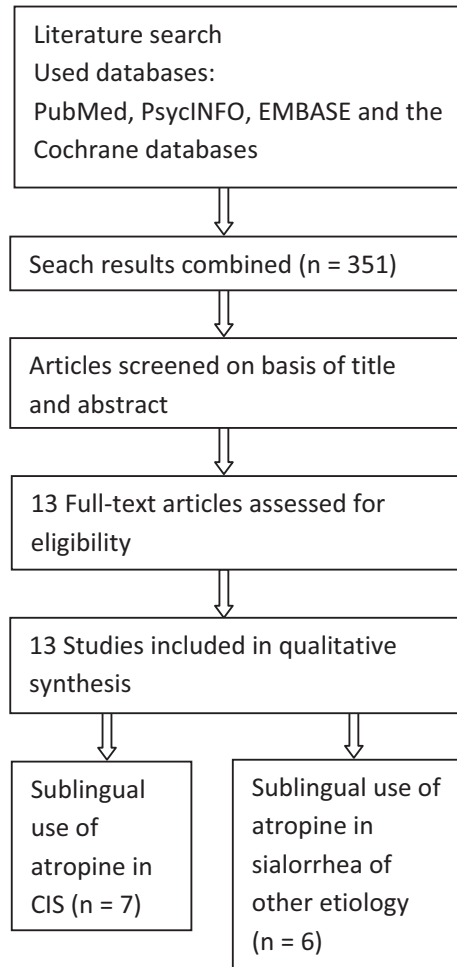


FIGURE 1 Methods of research using PRISMA

drops of atropine 1% twice a day after 2 weeks. She experienced no significant side effects.

Comley et al²⁸ reported one patient with schizophrenia that showed a complete resolution of the sialorrhea that was bothersome mainly during the day that after the use of 1 or 2 eye drops of sublingual atropine 1%. They did not mention any side effects.

Finally, Mustapha²⁹ published a report on one patient who, despite hyoscine, continued to suffer from severe CIS, which had ceased with 1-3 drops of sublingual atropine 1%, allowing the clozapine levels to be adjusted. However, the CIS did not return after discontinuation of atropine, meaning it could have been a temporary side effect, besides the fact that the treatment was in combination with hyoscine.

3.1.2 | Case series

Tessier et al³⁰ mention ten patients treated with atropine eye drops that were switched to a nasal spray (ipratropium bromide 0.03%, structurally related to atropine). This form is

described as being equally effective at a frequency of 1 to 2 sprays per day. The greater simplicity of use and the longer duration of action were described as an advantage, but a bothersome taste was noted as a possible drawback.

Antonello et al³¹ discuss three patients with severe sialorrhea in his case series, that had an immediate improvement with the administration of one drop of atropine 1% administered sublingually at bedtime. The patients experienced no side effects. They used a “top-up method” in which one drop was dissolved in glass of water to counter a possible recurrence of salivation during night.

Furthermore, Santana³² describes three patients where a complete resolution of the sialorrhea could be observed within 1 week with 1 to 2 drops per night of sublingually administered atropine 1%. This also led to improvements in sleep quality, adherence to clozapine, and no systemic anticholinergic effects were reported. One patient suffered from xerostomia at a dosage of three drops per night.

Leung³³ describes three patients with a complicated treatment of CIS with sublingual atropine: One disorganized patient emptied the whole bottle, one patient no longer had sialorrhea when stopping atropine after 2 months, and a patient was accidentally given the product in his eye, which impaired his vision during five days.

3.1.3 | Own case reports

In our center, we treated two patients with schizophrenia being treated with clozapine that with 1 or 2 sublingually administered atropine eye drops 1% at night showed an almost immediate complete resolution of their nocturnal salivation and showed no side effects.

3.2 | Sialorrhea of other etiology treated with sublingual atropine

3.2.1 | Case reports

A case report³⁴ describes sialorrhea in a patient with severe head trauma who was treated with atropine drops, with a 50% reduction of secretion, intraoral, and oropharyngeal accumulation of saliva and had negligible side effects. The exact dose way of measuring the sialorrhea and the exact nature of side effects could not be found.

Another case report from Rapoport et al³⁵ describing a child admitted in palliative care with metachromatic leukodystrophy showed that one atropine drop 0.5% sublingually (0.25 mg every 6 hours) had a beneficial effect within 15-30 minutes, the need of aspiration was greatly reduced and the oxygen saturation improved. The cardiac monitor showed no significant tachycardia, no other anticholinergic side effects were reported.

3.2.2 | Open label trial

Dias³⁶ investigated 25 children with cerebral palsy, with a statistically significant improvement (measured with the Drooling Impact Scale) before and after treatment with atropine. This was administered sublingually at a concentration of 0.5% 3× a day (with 6 hours interval). There was a low frequency of side effects compared with other anticholinergics.

3.2.3 | Pilot studies

A pilot study of Hyson³⁷ describing 6 Parkinson's patients and one patient with progressive supranuclear palsy showed a subjective and objective statistically significant reduction in salivation with atropine administered sublingually, measured on a Likert scale (from 1 to 5) and by weighing dental cotton wool rolls. One patient developed a delirium but could also be explained by a concurrent bladder infection; two patients experienced an increase of hallucinations but had concealed the fact that they had those before the start of the study (as this was an exclusion criterion).

Another pilot study about children with sialorrhea (n = 11³⁸) with various underlying disorders (including cerebral palsy, epilepsy, and autism) showed a significant reduction in salivation after sublingual administration of atropine eye drops 1-2× a day, by weighing dental cotton wool rolls and measurement on a visual analogue scale or VAS with the parents). No irreversible adverse reactions were noted, xerostomia occurred in 3 children and some parents reported difficulties with the administration.

3.3 | Randomized clinical trials

De Simone³⁹ performed an RCT in 22 palliative care patients with cancer of the upper gastrointestinal tract, in a prospective randomized placebo-controlled cross-over trial. However, the study failed to confirm the effectiveness of atropine sublingually (two drops or 0.5 mg every 6 hours) over placebo in this population. In spite of this, the participants showed improvements on all outcome measures (including sialorrhea). Given the limited sample size, the heterogeneous response and inaccurate measurement (only VAS was used to measure the salivation), the results of this RCT should not be considered as definitive.³³

4 | DISCUSSION

A total of 24 patients with CIS were reported, of whom 21 responded favorably to sublingually administered atropine, including two patients who were successfully treated at our center. Leung³³ is the first to mention possible complications of the treatment that occurred in three of his patients. A total of 67 patients with sialorrhea of other etiology treated with

atropine locally were studied so far with generally a favorable outcome, including one RCT reporting on 22 patients in palliative care.

The fact that the suggested treatment with atropine is administered locally can be seen as an important benefit of this treatment. Although it could have a potentially additive anticholinergic effect due to systemic resorption of clozapine, no reporting of symptoms pointing in this direction has been made yet, even in case of an accidental overdosing.³³ This is important given the fact that patients may already experience anticholinergic side effects such as constipation, urinary retention, cardiac arrhythmias due to the use of clozapine and may also have cognitive problems due to their disease,⁴⁰ which could on its turn increase due to systemic therapy against the sialorrhea.²³ Cardiac monitoring in one palliative child treated with a single drop of atropine 0.5% administered sublingually showed no significant tachycardia.³⁵ The method is cheap, has a fast onset of action, with in some cases even effect after 15 to 30 minutes.³⁵ A nasal spray with ipratropium bromide would have the additional advantage of being more user-friendly and having a longer duration of action.³⁰ Stroup⁴¹ suggests anticholinergic drops (ipratropium bromide or atropine) as a second-line treatment, after trying sugarless gum during the day or a towel over the pillow at night.

Possible side effects in the reviewed literature are the occurrence of xerostomia at higher dosages: with one patient with CIS this occurred with three drops³² and in 3 out of 11 children studied by Norderyd³⁸ taking only 1 to 2 doses per day. The unpleasant taste and at times, the too short duration of action with reoccurrence of salivation in the early morning, which on its turn can be managed by the "top-up method".³¹ Some patients experience difficulty in administering the drops in a correct amount.³⁶

Some safety concerns include the fact that more disorganized patients or distracted staff members have been reported to accidentally administer the drops in the eyes of the patient, an accidental overdose (as with any product) is also possible.³³ Some parents of children with sialorrhea treated with atropine sublingually experienced some difficulties in administering it.³⁸ Accidental overdoses seem to be more easy with eyedrops than with nose sprays³⁰

The posology of atropine eye drops 1% in CIS usually limited 1 to 2 drops 1 to 2× a day. In sialorrhea of other etiology, a more frequent administration with 1 to 2 drops every 6 hours, which seems to make sense in the light of the pharmacokinetics of atropine²⁰⁻²²

From the case reports and case series (n = 24) reviewed, the authors conclude the sublingual administration of atropine appears to be a simple, effective, safe, and promising treatment for CIS, although Leung³³ reminds us to be mindful of accidental overdosing and ocular administration. To date, 67 patients with sialorrhea from another etiology were treated with atropine

effectively, with the exception of one methodologically weaker RCT, and with few side effects. Despite a lack of randomized controlled studies to clearly inform clinical practice, the reviewed articles suggest that sublingual atropine in the management of CIS is a useful intervention. A recent paper published by Stroup⁴¹ even suggested it as a second-line treatment, after trying sugarless gum and a towel over the pillow.

There are several limitations in the literature published up to this date. So far, only case reports and case series have been published on the local treatment with atropine for CIS. The primary outcome measure is not recorded in an accurate way despite the availability of subjective and objective measurement instruments such as the NHRS, the DSFS, the DIS or the diameter of the salivary fluid, a patch on the pillow,^{6,7} or weighing intra-orally placed dental rolls.¹³ Furthermore, with the exception of one case series, little attention is paid to the systematic questioning of symptoms that may indicate systemic absorption of atropine. Besides, due to the fact that only case reports and case series have been published, the risk of publication bias or placebo effect cannot be overlooked. Moreover, comparative efficacy of sublingual atropine to the existing treatments for CIS cannot be evaluated. Suggestions for further research include performing large-scaled controlled studies with adequate measuring instruments including dental rolls and systematic evaluation of symptoms indicating systemic absorption of atropine, to have a better view on this promising treatment of CIS.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Thomas VAN DER POORTEN: involved in reviewing of literature and contributed with own case reports. Marc DE HERT: reviewed the literature and reviewed and advised on research.

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