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CASE REPORT



## Tropicamide ophthalmic solution reduces clozapine-induced sialorrhea: a case report

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### ABSTRACT

Clozapine-induced sialorrhea (CIS) is a common, treatment-limiting, and stigmatizing side effect. All systemic agents that are used for CIS may increase clozapine side effects such as blood pressure changes, constipation, or arrhythmias or may have a negative impact on cognition. Sublingual application of antimuscarinic medications might be a low side effect option for treatment of CIS. Our aim is to propose an off-label treatment option of tropicamide ophthalmic solution given orally via sublingual route for CIS and stimulate further examination. A 33-year-old male inpatient with schizophrenia had been on clozapine 800 mg and amisulpride 600 mg per day. His drooling was occasional and severe as drool dripped off his chin during the day and night. Tropicamide 1% (1 mg/ml) ophthalmic solution was applied orally via sublingual route 1–2 drops at each side of his mouth before going to bed as monotherapy for CIS. Wet area over the pillow, Visual Analogue Scale (VAS), Nocturnal Hypersalivation Rating Scale, the MOS 36-Item Short-Form Health Survey (SF-36), Udvalg for Kliniske Undersøgelser Side Effect Rating Scale, the Scale for the Assessment of Negative Symptoms, and the Scale for the Assessment of Positive Symptoms were administered at baseline visit and at one-week intervals. No side effects were observed. On VAS, the patient rated his sialorrhea 5/7 at baseline, 4/7 after one 1 drop, and 3/7 after 2 drops. Nocturnal hypersalivation yielded score 4 before tropicamide was initiated. After 1 drop of tropicamide at each side of the mouth, the score was 3 and after 2 drops at each side, it was 2. Tropicamide ophthalmic solution might present as a low side effect, off-label option for treatment of CIS. The promising effect should be examined by randomized controlled trials to translate this into clinical practice.

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Clozapine; drooling; hypersalivation; sialorrhea; treatment; tropicamide

## Introduction

Clozapine-induced sialorrhea (CIS) is a common side effect occurring in 30% of clozapine-treated patients [1]. The underlying mechanism is not fully understood. The pathophysiology of CIS may be related to the effect of clozapine on muscarinic M4 receptor agonism and adrenergic alpha-2 antagonism [2]. CIS is thought to be related to a disturbance of deglutition and not merely an increase in salivary flow rate [3]. Most of the patients complain nocturnal sialorrhea which may also be a result of disruptions of the circadian rhythm [2]. Despite clozapine's documented effectiveness, CIS can be treatment-limiting, as patients are unable to tolerate drooling that is stigmatizing during the day and impairs sleeping at night. It may also be a risk factor for aspiration pneumonia, which has been observed in clozapine-treated patients [4].

The treatment options suggested in CIS are glycopyrrolate, biperiden [5], amisulpride augmentation [6], scopolamine (hyoscine) butylbromide [7], and low-dose amitriptyline [8]. In a recent study,

metoclopramide was found effective and safe in CIS [9]. All systemic agents that are used for sialorrhea may increase clozapine's side effects such as blood pressure changes, constipation, and arrhythmias or may have a negative impact on cognition [5]. There are case reports suggesting the potential use of sublingual atropine [10–14] in CIS. However, potential problems surrounding the sublingual use of atropine were also highlighted owing to long half-life, systemic side effects, and its high absorption rate from the mucous membranes and readily crossing the blood–brain barrier [15]. On the other hand, tropicamide is a short-acting muscarinic receptor antagonist with a plasma half-life of 30 min. It has a relatively high selectivity for the M4 receptor subtype [16]. Ophthalmic preparations of tropicamide are usually used to dilate the pupil and relax the lens so that eye examinations can be carried out thoroughly.

Also, sialorrhea is debilitating and frequent in Parkinson's disease (PD) and related to reduced oromotor control and autonomic dysfunction. A pilot study testing intraoral tropicamide films for the relief of

sialorrhea in PD patients has suggested a potentially useful reducing effect compared to placebo [17]. In the Lloret et al.'s pilot study intraoral use of tropicamide had no adverse effects. They concluded that it was a possible treatment for sialorrhea in PD. However, we could not locate a single study exploring the use of tropicamide ophthalmic drops for CIS treatment.

There are no general accepted guidelines to treat CIS and all systemic agents that are used for sialorrhea might also increase clozapine side effects. Therefore, we decided to administer a local agent tropicamide, which was shown to have a low side effect profile in animals when given orally via sublingual route [18]. Here, we present a case with occasional severe drooling to whom we administered tropicamide ophthalmic solution sublingually as an off-label, low side effect option.

### Case presentation

We present a 33-year-old male inpatient who had a psychotic disorder for a duration of 12 years with schizophrenia diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [19]. He had been on clozapine 800 mg and amisulpride 600 mg per day. His drooling was occasional and severe as drool dripped off his chin while talking on the phone but it worsened at night. Informed consent was obtained from the patient for off-label use of tropicamide, as well as conducting assessments for publication of the following case report.

Tropicamide 1% (1 mg/ml) ophthalmic solution was initiated as 2 drops (total dose 0.1 ml) orally before going to bed as monotherapy for CIS. Administration was 1 drop to each side of mouth between the cheek and the lower gum initially and then the dose was increased to 2 drops at each side after one week to achieve a total dose of 0.2 ml per day. The wet area over the pillow, Visual Analogue Scale (VAS), Nocturnal Hypersalivation Rating Scale (NHRS), the short form of health survey (SF-36), Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale, the Scale for the Assessment of Negative Symptoms (SANS), and the Scale for the Assessment of Positive Symptoms (SAPS) were administered at baseline visit and at one-week intervals. VAS was used to score the magnitude of salivation and was anchored at "0" on the left side and "7" on the right. NHRS is a validated single-item 5-point self-report scale for measuring the degree of nocturnal salivation which a respondent experiences. It consists of the five points: 0, absent; 1, minimal (signs of saliva on the pillow in the morning); 2, mild (hypersalivation wakes the patient once during the night); 3, moderate (hypersalivation wakes the patient twice during the night); and 4, severe (hypersalivation wakes the patient at least thrice during the night) [20]. The SANS and the SAPS were developed by Andreasen [21,22] and have been extensively used

to evaluate the positive and negative symptoms in schizophrenia. The SANS consists of 5 subscales and 25 items while the SAPS includes 4 subscales and 34 items. Clinicians score items from 0 to 5 using information obtained from the patient, the family and the hospital records. Erkoç et al. reported the Turkish version of both scales to be valid and reliable [23,24]. The 36-item Short-Form Health Survey (SF-36) is a patient-reported survey of patient health designed for use in clinical practice and research, health policy evaluations, and general population surveys. This multidimensional instrument was developed in 1992 by Ware and Sherbourne. The evaluation of the results was done by attributing scores to each question, which were then transformed into a scale ranging from 0 to 100, where 0 corresponds to the worst quality of life and 100 to the best [25]. The Turkish version of the SF-36 has been validated by Kocyigit et al. [26]. UKU Side Effect Rating Scale is a clinician-rated (observer) scale. It was developed to provide a comprehensive side effect rating scale with well-defined and operationalized items to assess the side effects of psychopharmacological medications [27].

During the follow-up of seven weeks, no side effects were observed associated with tropicamide. On VAS, the patient rated sialorrhea 5/7 at baseline, 4/7 during the first week with 1 drop of tropicamide at each side of the mouth and 3/7 after 2 drops at each side. Assessment of sialorrhea at night according to NHRS yielded score 4 before tropicamide was initiated. After 1 drop of tropicamide at each side of the mouth (total dose 0.1 ml per day), the score was 3 (moderate) and after 2 drops at each side (total dose of 0.2 ml per day), it was 2 (mild). There was no change in SF-36. After one month of follow-up, amisulpride had been slowly tapered down and stopped and aripiprazole was started and gradually increased up to 30 mg per day. SAPS score was reduced after switching to aripiprazole. However, SANS scores did not change. The wet area over the pillow was also measured during each rating. Measured outcomes did not change throughout the time with the same dose of tropicamide. There was a two-week break in the prescription of tropicamide solution due to availability issues. One day after tropicamide solution discontinued, sialorrhea recurred at the pre-initiation severity. After re-initiation of tropicamide drops, relief was observed.

### Discussion

Sublingual application of tropicamide ophthalmic solution provided relief on CIS in this patient with schizophrenia whose drooling was occasional and severe. One of the explanations to CIS is the agonistic effect of clozapine on M4 receptor 2. Tropicamide has a relatively high selectivity for the M4 receptor subtype. Therefore, the effect of tropicamide on reducing CIS seems to be a

result of M4 receptor agonistic activity. There are no general accepted guidelines and none of the treatments is FDA-approved for CIS. Therefore, trying safe and tolerable off-label interventions may be reasonable. Besides systemic agents, tropicamide when given orally via sublingual route may be a low side effect options for treating CIS.

There was a switch from amisulpride to aripiprazole during the treatment to achieve better clinical outcomes. Regarding the effect of amisulpride on salivation, there are contradictory results in the current literature. A study on humans reported that low-dose amisulpride was effective to reduce CIS4; on the other hand, animal studies suggested no effect on salivation [28]. We did not observe any change in the subjective rating of the patient on VAS during cross-titration of amisulpride and aripiprazole. Also, tropicamide does not have interactions with either aripiprazole or amisulpride.

The findings reported in this case report should be considered in light of certain limitations. First, this is not a clinical study therefore not enough to inform clinical practice. Second, although the patient and the nurses were trained, the fact that the patient frequently turned the pillow upside down or displaced it made the measurements of the wet area over the pillow difficult. This is a limitation of most of the published studies exploring CIS [29]. The VAS essentially is clearly a highly subjective measure and has been of the most value when looking at change within individuals as it was done in our case. To the best of our knowledge, this is the first case report suggesting the potential off-label use of tropicamide ophthalmic drops sublingually for CIS. Patients with schizophrenia are facing a severe burden of CIS, while there are no general accepted guidelines to treat it. Therefore, another significance is the potential to stimulate further investigation on the treatment of CIS with local agents. Atropine is another antimuscarinic agent that was suggested in case reports to be effective in treating CIS when given orally via sublingual route [10–14]. However, it has long half-life, systemic side effects, high absorption rate from the mucous membranes, and readily crosses the blood–brain barrier [15]. Tropicamide may be preferable owing to its shorter half-life and less systemic side effect profile when given orally via sublingual route [30]. We also want to highlight that in our case, tropicamide was administered by psychiatry nurses to an inpatient; we do not advise to prescribe it to an outpatient due to the important side effects such as hallucinogenic effect when not adherent to the suggested amount and the route of administration [31]. Therefore, education is needed for healthcare team members on the appropriate use, potential risks, and benefits of this off-label agent to provide the best possible care for patients.

## Conclusions

There are no general accepted guidelines for treating CIS. Tropicamide ophthalmic solution may be a low side effect, off-label option for treating CIS in inpatients with schizophrenia. Healthcare team members should get education regarding the appropriate use of the agent. The promising effect should be explored with long-term randomized controlled trials to inform clinical practice.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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