

The Effect of Glycopyrrolate on Nocturnal Sialorrhea in Patients Using Clozapine

A Randomized, Crossover, Double-Blind, Placebo-Controlled Trial

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Abstract:

Background: Nocturnal sialorrhea is one of the most frequent adverse events in clozapine treatment. Symptomatic management of sialorrhea usually consists of off-label treatment with anticholinergic agents. The aim of the current study is to evaluate the efficacy and safety of glycopyrrolate in patients using clozapine that experience sialorrhea.

Methods: In a double-blind randomized crossover trial, patients with nocturnal sialorrhea ($n = 32$) were randomized to treatment with glycopyrrolate 1 mg or placebo. This double-blinded phase was followed by an optional open label extension phase with glycopyrrolate 2 mg. Exposure periods consisted of 6 consecutive days and were separated with 1 washout week. The primary outcome was clinical improvement of nocturnal sialorrhea assessed by the Patient Global Impression of Improvement (PGI-I).

Results: The proportion of patients with a clinical improvement according to PGI-I did not significantly differ between 1 mg and placebo (18.8% vs 6.3%, $P = 0.289$); however, in patients using glycopyrrolate 2 mg once daily versus placebo, it did (43.5% vs 6.3%, $P = 0.039$). Glycopyrrolate was not associated with severe adverse events or worsening of cognitive adverse events.

Conclusions: Glycopyrrolate 1 mg was not superior to placebo, whereas 2 mg showed a significant clinical improvement of nocturnal sialorrhea compared with placebo. Glycopyrrolate seemed to be a tolerable anticholinergic agent in the treatment of clozapine-associated sialorrhea.

Key Words: clozapine, sialorrhea, hypersalivation, glycopyrrolate, nocturnal sialorrhea

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Clozapine is the only antipsychotic agent with demonstrated efficacy in patients with refractory schizophrenia and with demonstrated antisuicidal properties.^{1,2} However, its use is hampered by its safety profile, including serious potential life-threatening adverse effects such as agranulocytosis and myocarditis,^{3–5} but also effects impairing tolerability to the drug such as (nocturnal) sialorrhea.⁶ The prevalence of sialorrhea in patients using clozapine is estimated at 30% to 90%, rendering it the

second most common adverse event of clozapine after sedation.^{3,5} Sialorrhea often occurs shortly after initiation of clozapine therapy, and most patients exhibit sialorrhea only during sleep.^{3–6}

The impact of sialorrhea is generally underestimated. It reduces quality of life and can lead to complications including parotitis, mucositis, sleep disorders, and aspiration pneumonia.^{5,7,8} Moreover, sialorrhea can be socially incapacitating and can result in poor medication adherence or even patient-initiated discontinuation of clozapine, potentially leading to severe psychiatric deterioration.⁹

The exact mechanism behind sialorrhea is unknown. It is considered a paradoxical effect because due to the anticholinergic properties of clozapine itself, a reduction of saliva secretion would be more expected. Multiple hypotheses exist to explain this paradoxical effect involving differences in affinity for muscarinic 3 (M3) and muscarinic 4 (M4) receptors. Clozapine tends to have stronger agonistic effects on M4 receptors than antagonistic effects on the M3 receptors, thereby inducing saliva secretion.¹⁰ Moreover, it has been hypothesized that clozapine may reduce the swallowing reflex and thereby contributing to sialorrhea.¹¹

Various anticholinergic agents have been suggested as treatment options for sialorrhea in patients using clozapine; however, their use is hampered by central anticholinergic adverse effects including memory impairment and other cognitive deficits.^{12–14} Glycopyrrolate is an anticholinergic agent with a quaternary ammonium structure, limiting its passage across the blood-brain barrier, thereby greatly reducing the risk for central anticholinergic adverse effects.¹⁵ The effect of glycopyrrolate on sialorrhea has been studied in one randomized controlled trial so far, comparing a fixed oral dosage of 1 mg of glycopyrrolate with 2 mg of biperiden, twice daily.¹⁴ Glycopyrrolate reduced sialorrhea significantly more than biperiden with less effect on cognitive function.¹⁴ However, glycopyrrolate has not been compared with placebo. Furthermore, beneficial effects of glycopyrrolate on sialorrhea have been reported in case reports and case series.^{16–18} In addition, glycopyrrolate has been shown to be effective in treating sialorrhea in patients with Parkinson disease and in children with neurological disorders.^{19–21} However, at present, there are—as far as we know—no published studies comparing glycopyrrolate with placebo on clozapine-associated nocturnal sialorrhea.

The objective of this study was to determine the effect of oral glycopyrrolate on nocturnal sialorrhea compared with placebo in psychiatric patients treated with clozapine.

METHODS

Study Design

This study was designed as a multicenter, randomized, double-blind, placebo-controlled crossover trial with an extended open label phase. The double-blind phase consisted of baseline

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measurements and 2 intervention weeks separated by a 1-week washout period (Fig. 1).

During the intervention, each participant was randomly assigned to receive either once daily glycopyrrolate 1 mg before bedtime or placebo before bedtime. Randomization was performed by computer-generated random allocations at the clinical trial support unit of the Department of Clinical Pharmacy at the University Medical Center Utrecht. Allocation concealment was ensured through the use of sequentially numbered, opaque, sealed envelopes.

Both investigators and patients were blinded to the sequence of interventions during the double-blind phase. Participants were instructed to take the study medication for 6 consecutive days during intervention. Participants who tolerated the medication in the intervention weeks (defined as no worsening of adverse events compared with baseline) and who were willing to participate in the open label extension phase, were instructed to take 2 mg glycopyrrolate (unblinded) once daily for 6 consecutive days after 1 washout week.

After each week, during the weekly consultation, questionnaires were completed by the participants in the presence of the researcher (total of 6 times).

At the end of follow-up, the treating physician discussed with the patient the possibility of continuing the use of glycopyrrolate. The physician took into account in this discussion whether the patient had experienced any benefit from the glycopyrrolate and whether the patient tolerated glycopyrrolate during the study, including the open label phase.

Inclusion and Exclusion Criteria

Patients using clozapine for at least 30 days in the same dose and who were experiencing nocturnal sialorrhea were eligible to participate.

Inclusion criteria were as follows 1) having a diagnosis meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria of a psychiatric disorder; 2) using clozapine in a dosage that had remained unchanged for at least 30 days before inclusion; 3) aged between 18 and 65 years; 4) having nocturnal sialorrhea defined as a score ≥ 2 on the Patient Global Impression of Severity (PGI-S) scale; 5) having no change in dosages of comedication potentially influencing salivary flow (clonidine, sulpiride, and moclobemide) for 1 month before inclusion; 6) able to answer questionnaires during a weekly consultation with the researcher; and 7) willing and, according to the treating physician, able to give informed consent.

Exclusion criteria were as follows: 1) known hypersensitivity to glycopyrrolate, sorbic acid, or saccharine sodium; 2) a comorbidity associated with sialorrhea (eg, Parkinson disease, cerebral palsy); 3) having the following comorbidities: inadequately treated constipation, urine retention, and bladder obstruction; 4) concomitant use of anticholinergic agents: tricyclic antidepressants or anticholinergics (atropine, ipratropium bromide, trihexyphenidyl, biperiden, scopolamine, and oxybutynin); 5) concomitant use of medications that potentially interact with glycopyrrolate (potassium chloride slow-release tablets, digoxin, and corticosteroids); 6) pregnancy or lactation; 7) a history of myasthenia gravis, cardiac arrhythmia, symptomatic coronary insufficiency, glaucoma, pylorus stenosis, paralytic ileus, prostate hypertrophy, and renal failure; 8) inability to autonomous intake of medication; and 9) an abnormal electrocardiogram.

At baseline, blood was drawn, and an electrocardiogram was recorded to assess participant eligibility. Medication dispensing data from the community pharmacy and patient records from the

general practitioner were collected. All participants had to give written informed consent to participate before study inclusion.

Setting

Recruitment took place between April 2013 and June 2015 at the University Medical Center Utrecht, an academic teaching hospital in the center of The Netherlands, with annually approximately 28,000 clinical, 15,000 day-care hospitalizations, and 334,000 outpatient visits, and at the Mental Health Services North-Holland North, Heerhugowaard (a mental health-care institute located in North Holland, covering a population of 225,000 inhabitants). This study was approved by the Medical Ethical Committee at the University Medical Center Utrecht. All study procedures were carried out in accordance with the Declaration of Helsinki and standards of Good Clinical Practice. The study was registered at www.clinicaltrialsregister.eu (EudraCT number: 2012-002299-15).

Interventions

During the double-blind phase, the intervention consisted of 5 mL (1 mg) glycopyrrolate oral solution of 0.2 mg/mL or 5 mL placebo approximately within 1 hour before bedtime during consecutive 6 days. Based on previous studies with glycopyrrolate on sialorrhea, a 1-mg dose each dose point was considered an effective and tolerable dose.²⁰

The trial medication was prepared by the Department of Clinical Pharmacy of the University Medical Center Utrecht and dispensed by the clinical pharmacy department of the University Medical Center Utrecht and Medical Center Alkmaar.

The placebo oral solution consisted of the same compounds as the glycopyrrolate oral solution with the exception of the active substance glycopyrronium bromide. The other components were kept in the placebo to ensure similarity in taste and appearance. To assure blinding of investigators, both placebo and verum were provided with identical opaque plastic droplet bottles. During the open label phase, intervention involved the intake of 10 mL (2 mg) glycopyrrolate oral solution of 0.2 mg/mL during 6 consecutive days.

Outcomes

The primary outcome was clinical improvement of nocturnal sialorrhea measured by the 7-point Patient Global Impression of Improvement (PGI-I) scale.

Clinically significant improvement was defined as a score 1 ("very much better") or 2 ("much better") on the PGI-I scale (Table 1). In addition, the PGI-S, the Nocturnal Hypersalivation Rating Scale (NHRS), and the Medication Satisfaction Questionnaire (MSQ) (Table 1) were used to determine the severity of nocturnal sialorrhea, the extent of occurrence of nocturnal sialorrhea, and the participants' satisfaction with clozapine as treatment of participant's psychiatric disorder, respectively. During the study period of 6 weeks, these patient-reported outcomes were collected by the researcher each week during the weekly visit.

Furthermore, participants were asked to identify their treatment preference at the end of the double-blinded phase and also at the end of the open label phase. In terms of patient safety monitoring, blood was also drawn in the last week of inclusion and occurrence of possible side effects, and especially, constipation was evaluated with questionnaires during the weekly visit by the researcher. Occurrence or worsening of constipation was monitored extensively using specific constipation assessment questionnaires during the weekly visits as clozapine is also related to increased incidence of constipation, consequently enhancing the risk of an ileus.

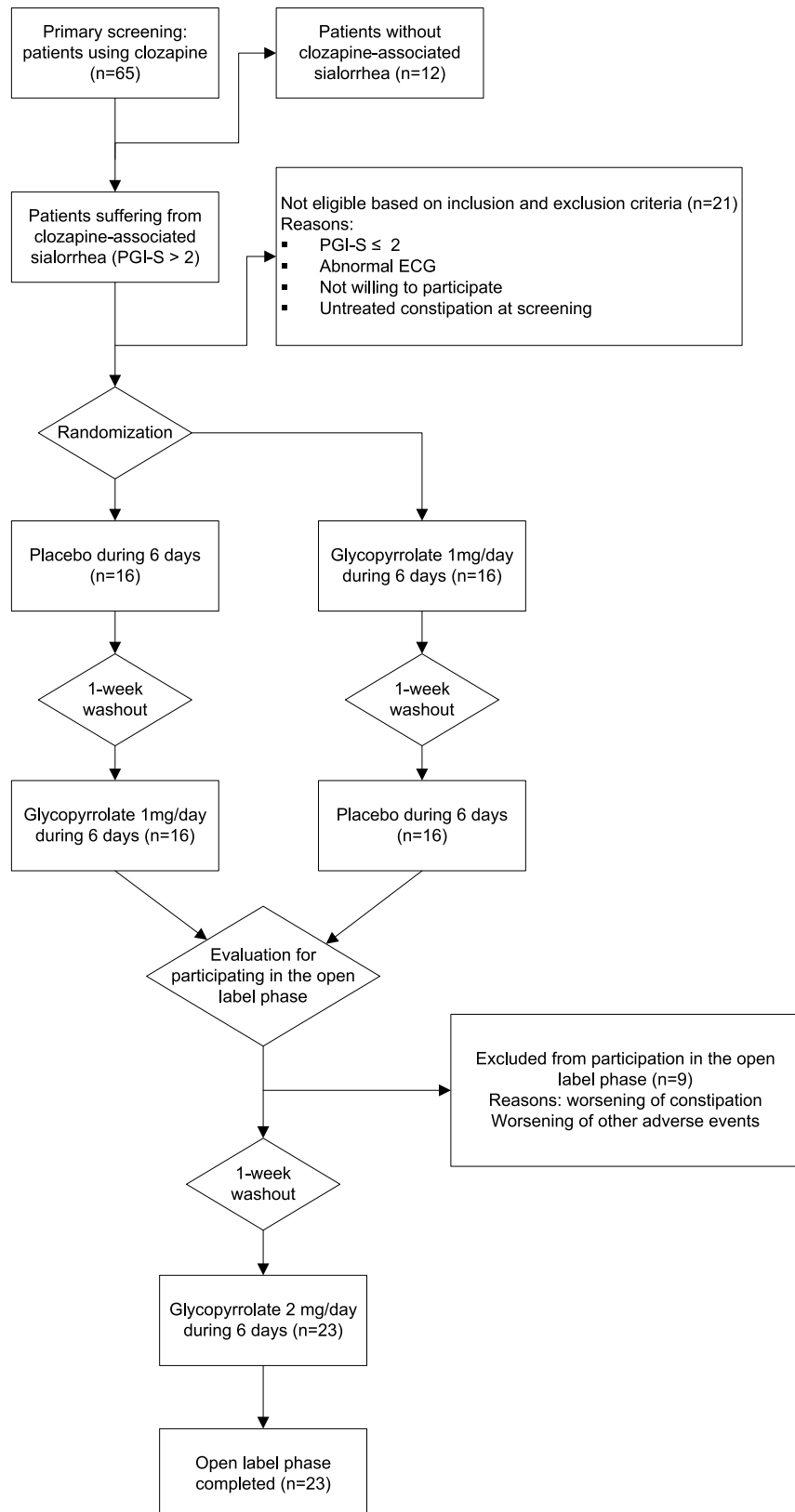


FIGURE 1. Flow chart of the patient inclusion and exclusion. The flow chart displays the distribution of patients throughout the study, including the double-blinded phase and the extended open label phase. PGI-S indicates Patient Global Impression of Severity; ECG, electrocardiography.

TABLE 1. Outcome Measures

Scale	Question	Score	Description
PGI-I	Check the one number that best describes how the symptoms of your nocturnal sialorrhea are now, compared with how they were before you began taking medication in this study.	1	Very much improved
		2	Much improved
		3	Minimally improved
		4	No change
		5	Minimally worse
		6	Much worse
		7	Very much worse
PGI-S	Check the one number that best describes the severity of impact concerning your nocturnal sialorrhea.	1	No problems with nocturnal sialorrhea
		2	A little affected
		3	Quite much affected
		4	Much affected
		5	Very much affected
MSQ	How satisfied or dissatisfied are you, in general, with clozapine as treatment of your mental disorder at this moment?	1	Extremely dissatisfied
		2	Very dissatisfied
		3	Dissatisfied
		4	Somewhat satisfied
		5	Satisfied
		6	Very satisfied
		7	Extremely satisfied
NHRS	Check the one number that best describes the severity of symptoms of nocturnal sialorrhea.	0	Absent
		1	Minimal: minor signs of saliva on the pillow in the morning
		2	Mild: major signs of saliva on the pillow in the morning
		3	Moderate: sialorrhea wakes the patient up once during the night
		4	Moderate/severe: sialorrhea wakes the patient up twice during the night
		5	Severe: sialorrhea wakes the patient up at least 3 times during the night

Sample Size

Sample size calculation was based on the McNemar test with an expected clinically significant improvement in nocturnal sialorrhea severity in 15% of the placebo intervention and 45% in the treatment group during the double-blind phase, according to previous studies on glycopyrrolate in sialorrhea other than in patients on clozapine, using an alpha of 0.05 with 80% power. Taking into account 34% discordant pairs with positive efficacy results of glycopyrrolate–negative efficacy results of placebo and 4% discordant pairs with negative efficacy results of glycopyrrolate–positive efficacy results placebo, a total of 32 participants had to finish the double-blind phase, involving the intake of 1 mg/d glycopyrrolate oral solution or placebo oral solution after 6 days.

Data Analysis

The proportions of participants with a clinical improvement according to PGI-I were compared with the McNemar test. The PGI-I, PGI-S, NHRS, and MSQ scores between the interventions were compared using Wilcoxon matched-pairs signed rank tests.

Although not expected because of the washout period based on the elimination half-life of glycopyrrolate, potential carryover effects were evaluated by comparing the efficacy outcome parameters at the end of washout with the baseline efficacy outcome parameters using the Wilcoxon matched-pairs signed rank test. All data analyses were performed using SPSS for Windows version

21.0 (IBM, Chicago, IL). An alpha level of 0.05 was considered statistically significant for all performed statistical tests.

RESULTS

A total of 32 participants were included and finished the double-blind phase (Table 2). Nine participants did not enter the open label phase because of meeting the exclusion criteria for the open label phase including (worsening) constipation and abrupt smoking cessation (Fig. 1). Indications for clozapine therapy were schizophrenia, schizoaffective disorder, psychotic disorder, and bipolar I disorder (Table 2). The median duration of clozapine therapy at baseline was 83 months.

During the double-blind phase, no carryover effects (washout week 1 vs baseline) were seen in all efficacy outcome parameters including PGI-I, PGI-S, NHRS, and MSQ, whereas during the open label phase (washout week 2 vs baseline), a significant mean difference in NHRS score was observed (mean difference, -0.43 [-0.83 to -0.44], $P = 0.038$).

Two patients (6.3%) experienced a clinically relevant improvement on placebo, whereas 6 patients (18.8%) on glycopyrrolate 1 mg according to PGI-I (RR = 3.0 [0.65–13.76], $P = 0.289$). Neither of the secondary outcome parameters (PGI-S, NHRS, and MSQ) did significantly differ.

A statistically significant higher proportion of patients reported a clinical improvement on PGI-I during the open label phase on glycopyrrolate 2 mg compared with placebo: 43.5% versus 6.3% (RR = 6.96 [1.23–20.36], $P = 0.039$) (Table 3).

TABLE 2. Patient Characteristics at Baseline

	Double-Blinded (n = 32)	Double-Blinded and Open Label (n = 23)
Male, n (%)	21 (65.6)	13 (56.5)
Age in yr, mean (SD)	38.9 (11.2)	39.2 (12.1)
Weight in kg, mean (SD)	82.4 (16.9)	80.7 (17.2)
Smoking n (%)	9 (28.1)	5 (21.7)
Alcohol consumption in alcohol units per week, median (IQR)	0 (4)	0 (4)
Use of recreational drugs, n (%)	4 (12.5)	3 (13.0)
Clozapine dose in mg/d, median (IQR)	250 (200)	250 (100)
Duration of clozapine therapy in months, mean (SD)	89.9 (63.2)	85.7 (68.4)
Indication of clozapine therapy		
Schizophrenia, n (%)	23 (71.9)	
Schizoaffective disorder bipolar type, n (%)	4 (12.5)	
Psychotic disorder not otherwise specified, n (%)	3 (9.4)	
Bipolar I disorder, n (%)	2 (6.3)	
Heart rate in bpm, mean (SD)	90.9 (10.0)	91.0 (10.5)
Systolic blood pressure in mmHg, mean (SD)	123.5 (12.6)	124.8 (12.9)
Diastolic blood pressure in mmHg, mean (SD)	84.1 (11.5)	85.2 (12.4)
Sodium serum level in mmol/L, median (IQR)	139 (2)	139 (2)
Potassium serum level in mmol/L, mean (SD)	4.1 (0.3)	4.1 (0.3)
Creatinine serum level in μ mol/L, mean (SD)	79.6 (14.2)	78.4 (15.9)

Significant lower scores on PGI-I (mean difference, -1.04 [-1.52 to -0.57], $P = 0.001$), PGI-S (mean difference, -1.26 [-1.83 to -0.70], $P = 0.001$), and NHRS (mean difference, -1.13 [-1.61 to -0.65], $P = 0.001$) were observed in glycopyrrolate 2 mg compared with placebo. Compared with placebo, a significantly higher proportion of participants were willing to continue with glycopyrrolate 1 mg once daily and 2 mg once daily (Table 2).

When comparing glycopyrrolate 2 mg with 1 mg once daily, significant lower PGI-I (mean difference, -0.70 [-1.18 to -0.17], $P = 0.017$), PGI-S (mean difference, -0.96 [-1.43 to -0.52], $P = 0.002$), and NHRS (mean difference, -0.87 [-1.26 to -0.43], $P = 0.004$) scores were found in the 2 mg dosage.

Adverse events of glycopyrrolate, in terms of worsening of baseline events, were mild/moderate and included diaphoresis (4.3%–9.4%), orthostatic hypotension (0%–9.4%), xerostomia (6.3%–8.7%), erectile dysfunction (0%–4.8%), shortened sleep (4.3%–6.3%), headache (0%–6.3%), nervousness (3.1%–4.3%), palpitations (0%–3.1%), and photosensitivity (0%–3.1%). No worsening of cognitive adverse events was observed in the glycopyrrolate intervention groups (Table 4).

DISCUSSION

Principal Findings

Glycopyrrolate 1 mg did not show a significantly higher proportions of participants with a clinical improvement according to

PGI-I (RR = 3 [$P = 0.289$]) compared with placebo, as was defined as our primary outcome, presumably because of the low sample size of this study. Nevertheless, a significant higher proportion of participants indicated to wish to continue using glycopyrrolate 1 mg in comparison to placebo.

Glycopyrrolate 2 mg compared with placebo once daily seemed to be more effective in improving nocturnal sialorrhea based on decreases in all efficacy parameters except for MSQ. This suggests effectiveness in reducing clozapine-associated nocturnal sialorrhea in psychiatric patients of glycopyrrolate, if dosed high enough. During intervention with glycopyrrolate 2 mg, clinical improvement of clozapine-associated sialorrhea was found 7 times more frequent than with placebo. This is in line with a significant decrease in severity of symptoms (NHRS) and impact (PGI-S). Distinctively, the MSQ score did not differ significantly after glycopyrrolate intervention. This could be explained by an already high rate of satisfaction toward clozapine therapy at baseline (mean MSQ baseline score = 5.31 [data not shown]).

However, a significant carryover effect was found on the NHRS during the open label phase (washout week 2 vs baseline), indicating a potential overestimation of lower NHRS scores in glycopyrrolate 2 mg.

Both dosing glycopyrrolate 1 and 2 mg once daily did not result in an increase in adverse events compared with placebo and therefore seems to be a tolerable and safe dose in treating nocturnal sialorrhea.

As expected, no worsening of cognitive adverse events was observed during the interventions. This is in accordance with the beneficial pharmacological property of glycopyrrolate in not being able to cross the blood-brain barrier.¹⁵ Reported adverse events during glycopyrrolate intervention were mild and transient. Most of these adverse events were pharmacologically explained as they were related to the anticholinergic effects of glycopyrrolate.

Implications of These Findings With Reference to Other Studies

To date, no drug is registered for the treatment of sialorrhea in patients on clozapine, although pharmacotherapeutic agents

TABLE 3. Efficacy Outcome Measures

	Placebo (n = 32)	1 mg (n = 32)	2 mg (n = 23)
Proportion of patients with a clinical significant improvement based on PGI-I score, n (%)	2 (6.3)	6 (18.8)	10 (43.5)*
PGI-I score, median (IQR)	4 (1)	3 (1)	3 (1)*
PGI-S score, median (IQR)	3 (1)	3 (1)	2 (1)*
NHRS score, median (IQR)	2.5 (2)	2 (3)	1 (1)*
MSQ score, median (IQR)	5.5 (2)	6 (1)	6 (3)
Proportion of patients willing to continue treatment (%)	6 (18.8)	19 (59.4)*	16 (69.6)*
Patient preference during double-blinded phase [†] (n = 32)	2 (6.3%)	15 (46.9%)*	—
Patient preference during open label phase [†] (n = 23)	0 (0.0%)	5 (21.7%)	13 (56.5%)*

* $P < 0.05$ compared with placebo as reference.

[†]Participants who have not indicated a patient preference intervention are not shown.

TABLE 4. Adverse Events

	Baseline (n = 32) Frequency (%)	Placebo (n = 32) Frequency (%) of Worsening/Improvement*	1 mg (n = 32) Frequency (%) of Worsening/Improvement*	2 mg (n = 23) Frequency (%) of Worsening/Improvement*
Cognitive adverse event				
Concentration problems	87.5	0.0/6.3	0.0/6.3	0.0/4.3
Asthenia	84.4	0.0/3.1	0.0/6.3	0.0/4.3
Drowsiness	84.4	0.0/3.1	0.0/6.3	0.0/4.3
Memory impairment	75.0	3.1/3.1	0.0/6.3	0.0/0.0
Accommodation disturbances	25.0	0.0/0.0	0.0/0.0	0.0/0.0
Other central adverse events				
Nervousness	62.5	6.3/6.3	3.1/3.1	4.3/4.3
Prolonged night sleep	78.1	0.0/3.1	0.0/3.1	0.0/0.0
Shortened sleep	18.8	3.1/0.0	6.3/0.0	4.3/0.0
More dreams during night sleep	53.1	3.1/3.1	0.0/9.4	0.0/4.3
Headache	15.6	6.3/3.1	6.3/3.1	0.0/0.0
Dizziness				
Peripheral anticholinergic adverse events				
Xerostomia	37.5	6.3/0.0	6.3/6.3	8.7/4.3
Constipation	50.0	0.0/6.3	0.0/6.3	0.0/4.3
Miction disorders	31.3	0.0/0.0	0.0/0.0	0.0/0.0
Palpitations	25.0	3.1/0.0	3.1/0.0	0.0/0.0
Decreased diaphoresis	15.6	0.0/6.3	0.0/3.1	0.0/0.0
Vaginal dryness	18.2	0.0 [†] /0.0 [†]	0.0 [†] /0.0 [†]	0.0 [†] /0.0 [†]
Blurred vision	28.1	0.0/0.0	0.0/0.0	0.0/0.0
Skin dryness	18.8	0.0/0.0	0.0/0.0	0.0/0.0
Other adverse event				
Nausea and vomiting	34.4	3.1/3.1	0.0/6.3	0.0/0.0
Diarrhea	25.0	0.0/3.1	0.0/3.1	0.0/0.0
Polyuria and polydipsia	50.0	0.0/0.0	0.0/0.0	0.0/0.0
Orthostatic hypotension	71.9	6.3/0.0	9.4/0.0	0.0/0.0
Diaphoresis	50.0	6.3/0.0	9.4/0.0	4.3/0.0
Skin rash	18.8	0.0/0.0	0.0/0.0	0.0/0.0
Pruritis	15.6	0.0/0.0	0.0/0.0	0.0/0.0
Photosensitivity	12.5	0.0/3.1	3.1/3.1	0.0/3.1
Erectile dysfunction	23.8	0.0 [§] /6.3 [§]	4.8 [§] /0.0 [§]	0.0 /0.0
Impaired taste	6.3	3.1/3.1	0.0/3.1	0.0/0.0
Flushing	15.6	0.0/0.0	0.0/0.0	0.0/0.0

*Compared with baseline.

[†]Variable only applicable to women (n = 11).

[‡]Variable only applicable to women (n = 10).

[§]Variable only applicable to men (n = 21).

^{||}Variable only applicable to men (n = 13).

have been studied in various studies and are being used in daily practice.^{9,22}

The use of glycopyrrolate has been evaluated before in a small study and in a number of case reports. In a randomized double-blind, crossover study, glycopyrrolate was compared with biperiden. Glycopyrrolate was given in a dose of 1 mg twice daily and seemed to be an effective agent displaying less impact on cognitive function.¹⁴ Furthermore, in a case study, 3 patients with sialorrhea were treated with glycopyrrolate (4–8 mg) and showed improvement, whereas glycopyrrolate was generally well tolerated.¹⁷ Moreover, in a randomized clinical trial involving patients with Parkinson disease–associated sialorrhea, glycopyrrolate 1 mg 3 times daily has also been shown to be effective.²⁰

Despite these findings supporting these potential beneficial features of glycopyrrolate in sialorrhea, no randomized clinical trial has ever been conducted to determine the effects of glycopyrrolate compared with placebo on nocturnal sialorrhea in patients on clozapine specifically.

Limitations

A limitation of the study is the glycopyrrolate dose. Dose selection is important for obtaining the optimal balance between efficacy and safety. Based on previous studies and case reports involving the use of glycopyrrolate against sialorrhea, we focused on patient safety by choosing a fairly low/normal dose of

glycopyrrolate. The 1 mg dose showed a numerically lower PGI-I, but this was not statistically significant, probably because of power problems or the fairly low dose of glycopyrrolate. Nevertheless, at the end of the double-blind phase, significantly more participants wished to continue with glycopyrrolate 1 mg compared with placebo. It may be clinically advisable to start treatment of clozapine-associated sialorrhea with 1 mg glycopyrrolate before bedtime and double the dose in nonresponders because this dose was more efficacious than placebo and 1 mg glycopyrrolate. However, it should be noted that we did not compare glycopyrrolate 2 mg with placebo in a randomized double-blinded setting, our efficacy outcome measures in the open label phase should thus be interpreted with caution. Future studies should focus on intervention of glycopyrrolate with higher doses of glycopyrrolate in terms of optimizing efficacy.

Furthermore, there is a lack of objectively quantifiable outcome parameters for sialorrhea. Although our outcome rating scales were validated or were based on the validated Clinical Global Impressions scales, these were not outcome parameters that are fully objective. Because of the setting of the study, it was practically not possible to quantify sialorrhea, for example, by measuring the amount of saliva secretion. Moreover, we were interested in outcome scores from the patients' perspective, and therefore, we chose for the more subjective patient-reported outcome scores including PGI-I and PGI-S scales.

It should be noted that our study was not powered to detect differences in adverse events, nor did we perform an objective assessment of cognition. In this respect, our observations are based on observations from the patients themselves and are not conclusive. They are important as they reflect the perception by the patients themselves.

Our study evaluated the effects of glycopyrrolate on nocturnal sialorrhea. Although occurrence of sialorrhea is prominent during the night in patients on clozapine, many patients also experience sialorrhea during the daytime. Future studies should evaluate what dose regimen of glycopyrrolate would be optimal to treat sialorrhea during the night and the daytime.

CONCLUSIONS

Our results indicate that oral glycopyrrolate 1 mg once daily is not more effective than placebo in the treatment of clozapine-associated sialorrhea. Glycopyrrolate 2 mg taken once daily during open label follow-up in patients tolerating 1 mg glycopyrrolate may however be effective in treating clozapine-associated sialorrhea. We detected no cognitive adverse events, and moreover, glycopyrrolate was shown to be well tolerated. The effect of 2 mg glycopyrrolate should be evaluated in a double-blind manner to establish whether 2 mg could be effective to treat sialorrhea in patients on clozapine.

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AUTHOR DISCLOSURE INFORMATION

Wai Hong Man and Jantine C.A. Colen-de Koning contributed equally to this work.

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