

Clozapine-induced hypersalivation: an estimate of prevalence, severity and impact on quality of life

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Abstract

Objectives: The objective of this study was to evaluate the prevalence and severity of clozapine-induced hypersalivation, and assess the impact hypersalivation has on global functioning.

Methods: Participants attending a dedicated clozapine clinic were invited to undertake a structured interview regarding their experiences of clozapine-induced hypersalivation. Two psychometric instruments to measure hypersalivation, the Nocturnal Hypersalivation Rating Scale and the Drooling Severity and Frequency Scale were used.

Results: Clozapine-induced hypersalivation was experienced by 92% of participants, with nocturnal hypersalivation more prevalent compared to daytime hypersalivation (85% versus 48%). Daytime drooling was severe in 18% of cases and was present on a frequent or constant basis for 20% of individuals. Hypersalivation had at least a moderate impact on the quality of life of 15% of study participants.

Conclusions: Clozapine-induced hypersalivation is the most prevalent adverse effect experienced by patients treated with clozapine and negatively impacts on quality of life, particularly if daytime drooling is present. The development of further strategies to ameliorate this adverse effect is required given the demonstrated lack of success to date in managing this condition.

Keywords: clozapine, drooling, frequency, hypersalivation, incidence, prevalence, quality, life schizophrenia, severity, sialorrhea, sialorrhoea

Introduction

Clozapine has consistently been demonstrated to have the greatest efficacy amongst all antipsychotic agents in the management of psychosis [Asenjo Lobos *et al.* 2010], with beneficial effects for positive symptoms, negative symptoms and cognitive symptoms demonstrated [Burton, 2006]. Clozapine has also been shown to significantly improve patients functioning [Wheeler *et al.* 2009] and quality of life [Kim *et al.* 2006; Lewis *et al.* 2006]. However, its potential for inducing profound neutropenia has predominantly limited its use to treatment-resistant schizophrenia [Crilly, 2007]. Clozapine is also associated with a wide array of more prevalent, albeit predominantly less severe, adverse effects many of which impact on individuals' quality of life. One of the most prevalent of these is hypersalivation, although wide

variance in prevalence rates (30–80%) has been reported [Syed *et al.* 2008]. In addition, hypersalivation has been found to be under-reported to clinicians [Yusufi *et al.* 2007]. Consequently, not only may the rates of clozapine-induced hypersalivation be high, the effect on patient's quality of life may also be under-estimated [Nielsen *et al.* 2010].

Limited data are present pertaining to the severity of hypersalivation experienced by patients treated with clozapine. Existing studies predominantly investigate either the prevalence of numerous adverse effects experienced, of which hypersalivation is one [Syed *et al.* 2008] or investigate salivary flow rates in the context of antipsychotic-induced hypersalivation [Ben-Aryeh *et al.* 1996]. Consequently in this study we wanted to ascertain, through structured interviews, the prevalence

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of hypersalivation at a specialized clozapine clinic. In addition, we wanted to ascertain: (1) the severity of hypersalivation experienced by patients, (2) the impact of hypersalivation on individuals' quality of life, (3) patients perspectives in relation to how hypersalivation ranked amongst other adverse effects experienced, (4) if hypersalivation was associated with treatment dose or plasma levels of clozapine, (5) if any previous management strategies had alleviated this adverse effect and (6) participants' views in relation to their mental health care team's perspective regarding hypersalivation.

Method

Participants

This study was undertaken at a dedicated clozapine clinic in Galway University Hospital, Ireland. Consecutive participants attending for their routine blood tests (full blood count) were invited to participate. Exclusion criteria included individuals <18 years of age, the presence of an intellectual disability (intelligence quotient <70), a diagnosis of dementia and the presence of acute psychosis. Of the 161 individuals attending, 1 individual was excluded due to experiencing acute psychosis and 62 individuals refused to participate. Thus, the study consisted of a sample size of 98 (61%) individuals who provided written informed consent to participate in this study (see Figure 1). Ethical approval was attained from the Galway University Hospital Research Ethics Committee and the study was conducted in accordance with the Helsinki declaration on research ethics.

Structured interview and measures

Demographic data collected included gender, age, employment, and marital and domiciliary status. Clinical data included diagnosis, time on clozapine (in years), clozapine dose and most recent clozapine plasma level at the time of interview. We utilized two psychometric instruments to measure hypersalivation, the Nocturnal Hypersalivation Rating Scale (NHRS) [Spivak *et al.* 1997] and the Drooling Severity and Frequency Scale (DSFS) [Rashnoo and Daniel, 2015]. The NHRS is a validated five-item scale utilized to ascertain the severity of nocturnal salivation. Scores range from no nocturnal hypersalivation to being awoken at least three times per night due to hypersalivation [Spivak *et al.* 1997]. Due to the anticipated number of participants

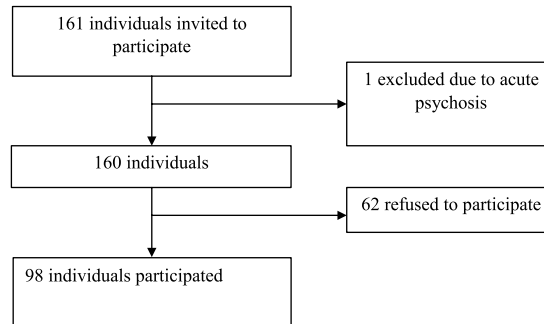


Figure 1. Flow diagram.

that might score '1' (patient has saliva on pillow in the morning) but who were not awoken because of this, we also enquired if participants had to change their pillow more frequently or had to cover their pillow with a towel due to hypersalivation [Bai *et al.* 2001]. The DSFS a validated instrument to assess the severity of daytime drooling [Rashnoo and Daniel, 2015]. Drooling severity is graded on a five-point scale with scores ranging from no drooling to profuse drooling, where drool drips off the body onto objects and furniture. Drooling frequency is assessed on a four-point scale from no drooling to constant drooling. The two scores are then summed together to give the drooling severity and frequency score.

Impact of hypersalivation on quality of life was measured on a five-point scale ranging from 'no impact' on quality of life to 'single biggest problem' in life. In addition, participants were directly asked about the presence of 16 additional side effects (see Table 3), and asked to rank the side effects experienced depending on their impact on quality of life to a maximum of 3. This could include side effects other than the 16 listed. Participants who were currently experiencing hypersalivation were also asked if they perceived that their treating team was aware of the impact that hypersalivation had on their quality of life. All interviews were conducted by one researcher who was not involved in patients' clinical care (all patients were fully aware of this).

Statistical analysis was performed using the Statistical Package for Social Sciences 21.0 for Windows (SPSS Inc., IBM, New York, USA). We utilized the Student's *t*-test for parametric data and the Chi-square test for nonparametric categorical data where appropriate. The Spearman's rank correlation coefficient (nonparametric) was used to

determine the correlations between quality of life and indices of hypersalivation severity.

Results

Demographic and clinical data

Demographic and clinical data are described in Table 1. Of note, 70 individuals (71.4%) were male and the mean age of participants was 41.4 years ($SD = 12.1$). The most common relationship status was single (80.6%), with most participants either living alone (25.2%) or with siblings or parents (39.8%) and the most common socioeconomic class (SEC) was SEC V (60.2%). All individuals had either a DSM-5 diagnosis of treatment-resistant schizophrenia (90.8%) or schizoaffective disorder (9.2%). Clozapine was augmented with additional antipsychotic agents in 33 individuals (33.7%), with aripiprazole or amisulpride employed in all but 7 individuals. Clozapine treatment was also augmented with mood-stabilizing agents (21.4%) and antidepressants (18.4%). Treatments to ameliorate hypersalivation had been employed in 17 individuals (17.3%) with three of these participants noting a modest benefit, which was independently corroborated by medical and clozapine nursing staff.

Clozapine-induced hypersalivation

Hypersalivation was experienced by 90 individuals (91.8%) (Table 2), with 83 individuals (84.7%) experiencing nocturnal hypersalivation and 47 individuals (48.0%) experiencing daytime drooling at the time the study was conducted. Of those individuals with nocturnal hypersalivation, 31 individuals (31.6%) were awoken from sleep. A total of 50% of individuals with nocturnal hypersalivation who were not awoken (mild on NHRS) changed their pillow frequently or used a towel at night due to significant drooling. In relation to daytime drooling, 20 individuals (20.4%) experienced either frequent or constant drooling and 18 individuals (18.4%) experienced drool dripping onto their clothes or objects.

A total of 13 individuals (15.3%) suffering from clozapine-induced hypersalivation at the time of the study believed it had at least a moderate impact on their quality of life (see Table 2). Modest correlations were noted between total

Table 1. Demographic and clinical characteristics.

Variable	n (%)
Gender	
Male	70 (71.4%)
Female	28 (28.6%)
Employment status	
3rd level education	8 (8.2)
Employed	26 (26.5)
Unemployed	64 (65.3)
Relationship status	
Single	79 (80.6)
In a relationship	4 (4.1)
Married	12 (12.2)
Divorced / separated	3 (3.1)
Living arrangements	
Alone	25 (25.2)
With parents or siblings	39 (39.8)
With partner or spouse	13 (13.3)
In supported accommodation*	21 (21.4)
Socioeconomic class	
I or II	10 (10.2)
III	21 (21.4)
IV	8 (8.2)
V	59 (60.2)
Diagnosis	
Schizophrenia	89 (90.8)
Schizoaffective disorder	9 (9.2)
Additional antipsychotic agents	
Amisulpride	12 (12.2)
Aripiprazole	14 (14.3)
Olanzapine	3 (3.1)
Risperidone	1 (1.0)
Haloperidol	1 (1.0)
Flupenthixol decanoate	1 (1.0)
Zuclopenthixol decanoate	1 (1.0)
None	65 (66.3)
Mood stabiliser medications**	
Sodium valproate	12 (12.2)
Lamotrigine	6 (6.1)
Lithium	5 (5.1)
None	77 (78.6)
Antidepressants	
Yes	18 (18.4)
No	80 (81.6)
Treatments utilized to reduce hypersalivation	
Hyoscine hydrobromide	13 (13.3)
Scopolamine patch	2 (2.0)
Pirenzepine	1 (1.0)
Procyclidine	1 (1.0)
None	81 (82.7)
	Mean (SD), range
Age	41.4 (12.1), 18–83
Clozapine treatment	
Dose (mg/day)	354.1 (159.4), 75–925
Serum level	0.41 (0.24), 0.1–1.4
Duration of treatment (years)	7.3 (6.7), 0.2–21.5
*Accommodation provided by mental health or homeless services.	
**Two participants were on two mood-stabilizing medications.	

Table 2. Clozapine-induced hypersalivation.

Measure of hypersalivation	<i>n</i> (%)
Presence of hypersalivation	
Yes	90 (91.8)
No	8 (8.2)
NHRS	
Absent	15 (15.3)
Minimal (saliva on pillow)	52 (53.1)
Mild (wakes patient once per night)	15 (15.3)
Moderate (wakes patient twice per night)	9 (9.2)
Severe (wakes patient three times or more)	7 (7.1)
DSFS: drooling severity	
Nil	51 (52)
Mild drooling (wets lips)	16 (16.3)
Moderate drooling (drool reaches lips and chin)	13 (13.3)
Severe drooling (drool drips onto clothing)	15 (15.3)
Profuse drooling (drool drips onto furniture or objects)	3 (3.1)
DSFS: drooling frequency	
No drooling	51 (52)
Occasional drooling	27 (27.6)
Frequent drooling	11 (11.2)
Constant drooling	9 (9.2)
Impact of hypersalivation on quality of life	
No effect	36 (42.4)
Minor effect	33 (38.8)
Moderate effect	7 (8.2)
Major effect	5 (5.9)
Profound effect (greatest difficulty in life at present)	1 (1.2)
Perceived awareness of hypersalivation by treating team*	
Fully aware	52 (61.2)
Underestimated or minimal awareness	8 (9.4)
Totally unaware	13 (15.3)

DSFS, Drooling Severity and Frequency Scale; NHRS, Nocturnal Hypersalivation Rating Scale.
*Some participants chose not to answer this question (*n* = 17).

DSFS score ($r = 0.38$, $p < 0.001$), drooling frequency ($r = 0.38$, $p < 0.001$), drooling severity ($r = 0.39$, $p < 0.001$) and NHRS score ($r = 0.21$, $p = 0.06$) and impact on quality of life. Two individuals had previously experienced hypersalivation with antipsychotic medications and this became even more severe with clozapine treatment. The presence of hypersalivation was not significantly correlated with duration of treatment ($r = -0.41$, $p = 0.70$), clozapine dose ($r = 0.12$, $p = 0.27$) or plasma level of clozapine ($r = -0.11$, $p = 0.34$). The presence or severity of hypersalivation was not affected by treatment with additional antipsychotic ($r = -0.04$, $p = 0.73$) or other psychotropic agents ($r = -0.14$, $p = 0.20$).

A majority of participants believed their treating clinician or clozapine nurse had a good awareness of their experience of hypersalivation (71.2%).

Other adverse effects

A mean of 4.6 (SD = 2.9) adverse effects were experienced by participants, with particularly high rates of clozapine-induced drowsiness (62.2%), fatigue (56.1%) and weight gain (48.0%) noted (Table 3). Hypersalivation was ranked as the most significant adverse effect by 7.1% of participants and was ranked as one of the three most significant adverse effects by 24 participants (24.5%). Clozapine-induced drowsiness

Table 3. Adverse effects experienced.

	Adverse effects		
	Experienced <i>n</i> (%)	Most significant <i>n</i> (%)	One of 3 most significant <i>n</i> (%)
Clozapine-induced side-effects			
Hypersalivation	90 (91.8)	7 (7.1)	24 (24.5)
Drowsiness	61 (62.2)	13 (13.3)	30 (30.6)
Fatigue	55 (56.1)	11 (11.2)	23 (23.5)
Weight gain	47 (48.0)	13 (13.3)	26 (26.5)
Gastrointestinal upset	31 (31.6)	6 (6.1)	14 (14.3)
Dizziness	29 (29.6)	3 (3.1)	9 (9.2)
Restless legs	22 (22.4)	2 (2.0)	6 (6.1)
Urinary incontinence or retention	20 (20.4)	1 (1.0)	5 (5.1)
Tachycardia	17 (17.3)	2 (2.0)	3 (3.1)
Tremor	15 (15.3)	1 (1.0)	3 (3.1)
Rigidity	14 (14.3)	0 (0.0)	1 (1.0)
Agitation	11 (11.2)	2 (2.0)	4 (4.1)
Headache	10 (10.2)	1 (1.0)	4 (4.1)
Hypertension	8 (8.2)	0 (0.0)	1 (1.0)
Seizures	7 (7.1)	2 (2.0)	2 (2.0)
Skin reactions	7 (7.1)	0 (0.0)	0 (0.0)
Other*	7 (7.1)	2 (2.0)	7 (7.1)

*Included sexual dysfunction, insomnia, dysphagia, reduced appetite or abnormal taste in mouth.

(13.3%), weight gain (13.3%) and fatigue (11.2%) were the most significant adverse effects reported by participants.

Discussion

Our principle finding in this study is a very high rate (92%) of hypersalivation secondary to treatment with clozapine. This finding is consistent with some studies [Qurashi *et al.* 2015; Essali *et al.* 2009] but higher than several other previous studies [Davydov and Botts, 2000; Syed *et al.* 2008]. In contrast to some of these studies, we utilized two validated instruments to measure rates of hypersalivation. Previous estimates of lower rates might be due to nonreporting by patients who were not questioned directly about this adverse effect [Yusifi *et al.* 2007].

One potential reason for participants to not report hypersalivation may relate to participants not perceiving this adverse effect as having the greatest impact on their quality of life. A total of 29% of individuals in this study believed their clinicians were either partially or fully unaware of this adverse effect. Although less frequently reported in this study, drowsiness, fatigue and weight gain

were rated as having a greater impact on quality of life. While hypersalivation (nocturnal and daytime) impacted on quality of life in this study, only daytime drooling demonstrated statistical significance in this regard. This finding is in contrast to a recent study [Qurashi *et al.* 2015] where nocturnal hypersalivation was also found to impact statistically on quality of life. However, unlike Qurashi and colleagues [Qurashi *et al.* 2015] who undertook a comparison of clozapine-induced hypersalivation compared to previous antipsychotic-induced hypersalivation; we undertook no such comparison, as hypersalivation has consistently been reported as more prevalent secondary to clozapine than other antipsychotic agents [Asenjo Lobos, 2010]. Indeed, only two participants stated that this was a significant adverse effect for them previously with other psychotropic agents. Our study was also based in a different setting (general adult service *versus* a forensic service) and included a larger cohort of patients.

Hypersalivation is a paradoxical side effect of clozapine given its potent anticholinergic effects. Although several proposed mechanisms exist, management strategies based on such mechanisms have demonstrated minimal efficacy to

date. Proposed mechanisms include clozapine agonism at the M4 muscarinic receptor [Zorn *et al.* 1994], alpha-2 antagonism [Corrigan *et al.* 1995] unopposed beta adrenoceptors activity secondary to alpha-1 and alpha-2 antagonism [Rogers and Shamkro, 2000] and decreased laryngeal peristalsis [Praharaj *et al.* 2006]. Pharmacotherapeutic strategies employed based on these mechanisms include the use of antimuscarinic agent, scopolamine [Takeuchi *et al.* 2015], pirenzepine [Rogers and Shramko, 2000] and atropine [Chu *et al.* 2015], alpha-2 agonists such as clonidine [Praharaj *et al.* 2005; Praharaj *et al.* 2006] and a variety of other agents including minocycline [Qurashi *et al.* 2014], amisulpride [Krein *et al.* 2006] and botulinum toxin [Kahl *et al.* 2004]. Reviews of all available treatments to date have largely concluded that sample sizes are too small or of insufficient study quality to clearly inform or change clinical practice [Rogers and Shramko, 2000; Sockalingam *et al.* 2007; Syed *et al.* 2008]. In this study, only three participants demonstrated any benefit with such treatment, with this effect only modest in nature. No association was ascertained between hypersalivation and either dose or plasma level of clozapine. Thus, dose alteration or augmentation of clozapine with other agents may not be strategies that confer a significant benefit for this adverse effect, albeit this study was not longitudinal in design and thus caution is required with such an interpretation.

There are a number of limitations with this study. First, the assessor was not blinded to current patient management; however, he was not involved in the clinical management of any patient which was made explicit to participants. Second, a relatively large sample (37.3%) refused to engage with this study; however no statistical difference in diagnosis, treatment or other demographic or clinical factors were noted between the groups. Third, approximately one-third of participants were on additional antipsychotic agents with other participants treated additionally with mood-stabilizing or antidepressant agents. However, no difference in the rates or severity of hypersalivation was identified between individuals attaining clozapine monotherapy and those attaining prescribed psychotropic agents.

Conclusion

Clozapine-induced hypersalivation is the most prevalent adverse effect suffered by patients treated with clozapine with daytime drooling, in

particular negatively impacting on patients' quality of life. We believe, based on the findings of this study that the NHRS and DSS should be employed routinely for the measurement of hypersalivation for patients treated with clozapine. In addition, information regarding the effect of hypersalivation on patients' quality of life should be attained. The development of further strategies to ameliorate hypersalivation would be welcomed given the lack of effective treatment strategies to date. Such strategies may be associated with improved quality of life and increased levels of treatment adherence.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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