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Clozapine-induced hypersalivation: the association between quantification, perceived burden and treatment satisfaction reported by patients

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We read with great interest the recent *Therapeutic Advances in Psychopharmacology* article by Maher and colleagues entitled 'Clozapine-induced hypersalivation: an estimate of prevalence, severity and impact on quality of life'.[1] The authors evaluated the prevalence of clozapine-induced hypersalivation (CIH) in a population of psychiatric patients in a specialized clozapine clinic. In addition, they assessed and quantified the severity of CIH, using the Nocturnal Hypersalivation Rating Scale (NHRS) and the Drooling Severity and Frequency Scale, and its impact on global functioning. They reported that CIH was the most prevalent adverse effect negatively impacting the quality of life in patients treated with clozapine.

The NHRS is a validated five-item scale used to determine patient-reported hypersalivation. Owing to their subjective nature, individual differences exist in patient-reported treatment satisfaction and perceived burden of hypersalivation. With regard to the extent to which changes in NHRS score affect patients' perceived burden and treatment satisfaction, we here report an association between NHRS and, firstly, the Patient Global Impression of Severity (PGI-S) five-point scale (regarding CIH specifically), which has similar anchors for scoring as the Clinical Global Impression-Severity scale, and, secondly, the Medication Satisfaction Questionnaire (MSQ) seven-point scale among patients experiencing CIH before and after treatment with the anticholinergic agent glycopyrrolate.

We included 32 psychiatric patients experiencing nocturnal CIH in a double-blind crossover study (EudraCT number: 2012-002299-15) and investigated the association between NHRS score, perceived burden of CIH (PGI-S), and participants' satisfaction (MSQ) with clozapine treatment, comparing before intervention (baseline) and after intervention with glycopyrrolate 1 mg and 2 mg.[2] Thus, further to the study of Maher and colleagues[1] we investigated the effect of treatment of CIH on severity and perceived burden within patients.

All participants ($n = 32$) received glycopyrrolate 1 mg once daily for 6 days consecutively. This treatment was followed by a washout week and eventually by an optional open-label treatment with glycopyrrolate 2 mg once daily ($n = 23$) for 6 days consecutively. Only patients who were willing to continue and who met the eligibility criteria participated in the open-label treatment. We calculated Spearman's rank correlation coefficients to assess the association between the different patient-reported outcome scales.

A decrease in NHRS score after intervention with glycopyrrolate 1 mg once daily was significantly associated with a decrease in PGI-S score (r_s (30) = 0.747, $p < 0.001$), but with a nonsignificant change in MSQ score (r_s (30) = −0.165, $p = 0.366$). A decrease in NHRS score after intervention with glycopyrrolate 2 mg once daily was not significantly associated with a change in either PGI-S (r_s (21) = 0.264, $p = 0.224$) or MSQ (r_s (21) = 0.052, $p = 0.814$) score. This indicates that clozapine users perceived a decreased burden of CIH, reflected by a decrease in PGI-S, when the NHRS score decreased. However, further decrease in NHRS score did not lead to a coherent decrease in PGI-S, as

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Table 1. Patient-reported outcome parameters and associations.

	Baseline (*n* = 32)	1 mg (*n* = 32)	Δ1 mg – baseline (*n* = 32)	2 mg (*n* = 23)	Δ2 mg – baseline (*n* = 23)
NHRS, median (IQR)	3 (2)	2 (3)	0 (1)	1 (1)	−1 (1)
PGI-S median (IQR)	3 (2)	3 (1)	0 (2)	2 (1)	−1 (1)
MSQ median (IQR)	5 (2)	6 (1)	0 (0)	6 (3)	0 (1)
NHRS *versus* PGI-S, r_s (*p* value)	0.347 (0.051)	0.616 (< 0.001)	0,747 (< 0.001)	0.687 (< 0.001)	0.264 (0.224)
NHRS *versus* MSQ, r_s (*p* value)	0.179 (0.326)	0.268 (0.139)	−0.165 (0.366)	0.223 (0.306)	0.052 (0.814)

IQR, interquartile range; MSQ, Medication Satisfaction Questionnaire; NHRS, Nocturnal Hypersalivation Rating Scale; PGI-S, Patient Global Impression of Severity; r_s, Spearman's rank correlation coefficient.

observed after intervention with glycopyrrolate 2 mg. Satisfaction towards clozapine therapy (MSQ) was not influenced by any intervention.

This could at least partly be explained by the patient selection in our study, as individuals who were already receiving clozapine treatment were very satisfied with clozapine therapy at baseline, despite experiencing CIH (Table 1). This is consistent with findings from a study in which clozapine users reported benefit of treatment and had the intention to continue taking clozapine, despite the presence of CIH.[3] Thus, high satisfaction towards treatment and improved quality of life are likely to promote adherence to clozapine, thereby improving long-term treatment outcomes. Also, subjective experiences of clozapine treatment reported by patients are found to be a useful component of outcome measures.[3] In addition, owing to the selection criteria for the optional open-label treatment (glycopyrrolate 2 mg), the outcomes of this intervention in our study may have been influenced by selection bias.

Overall, given these findings, we suggest that patient-reported quantification of hypersalivation should be placed into perspective with patients' perceived burden of hypersalivation and treatment satisfaction. That is, not all patients tend to respond in the same manner regarding the perception of disease burden and treatment satisfaction in the context of decreased NHRS scores.

In addition, an interesting question arises with regard to whether MSQ score is significantly affected by a decrease in NHRS score specifically in clozapine-naïve patients who are starting clozapine therapy, as these individuals are not yet used to the drug. In this respect, routine use of patients' perceived burden and treatment satisfaction scales in the evaluation of hypersalivation in clinical practice, as suggested by Maher and colleagues[1] would provide insights into this topic.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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