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Clinical correlates of sialorrhea in clozapine patients

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Abstract
Objective: Sialorrhea occurs more frequently in patients on clozapine than in those on other antipsychotics and has an adverse impact on the quality of life. We evaluated clinical correlates of sialorrhea.
Method: 79 patients with schizophrenia (54 males, 25 females; mean age 43.3 years, SD=12.7) from an urban clozapine clinic participated. Their total daily 24 hour dose of clozapine ranged from 100 to 650mg with the average at 341.8, SD=133.1). The part administered at nighttime ranged from 25 to 600mg, with the average at 258.7, SD=106.7.
Results: The scores on Nocturnal Hypersalivation Rating Scale (NHRS) ranged from 0 to 4 with the average at 1.7, SD=1.2. The symptom was absent in 17.7%, minimal in 36.7%, mild in 15.2%, moderate in 21.5%, and severe in 8.9% of patients. The intensity of sialorrhea was not significantly correlated to the daily clozapine dose, or its nighttime part, or duration of clozapine treatment, age, and gender. The presence of concurrent other antipsychotics slightly increased the NHRS scores (r=.37) and the presence of antihypertensive medication slightly reduced these sialorrhea scores (r=-.25).
Discussion and Conclusions: About a half of the patients reported mild to severe nocturnal hypersalivation, but its intensity seems unrelated to the clozapine dose or to its nighttime administration. No gender or age differences in hypersalivation were found. Concurrent use of other antipsychotics could lightly intensify the sialorrhea.

Keywords: clinical, sialorrhea, clozapine, frequently, participated

1. Introduction

Sialorrhea occurs more frequently in patients on clozapine than in those on other antipsychotics [1]. It is the most salient adverse effect of clozapine and has an adverse impact on the patient's quality of life [2]. Some complications such as aspiration pneumonia have been reported [3]. In some cases, patients reported drowning in their own saliva, or waking up from a sound sleep choking, and severely impaired sleep due to fear of choking, and also some related noncompliance with clozapine treatment as a result [4].
However, despite sialorrhea, most patients usually remain satisfied with clozapine treatment [5].
Our study examines correlates of sialhorrhea in clozapine therapy, i.e., the relationship of measures of sialorrhea to dose of clozapine, duration of clozapine treatment, and other clinical variables.

2. Method

The participants were 79 patients (54 men, 25 women) in an urban clozapine clinic in London, UK. All were diagnosed with schizophrenia. On the average, they were treated with clozapine already for 102.9 months. The duration of clozapine treatment ranged from 2 years to over 11 years. The descriptive data with respect to total daily dose per 24 hours as well as separately for the nighttime dose are listed in Table 1.

Table 1: Descriptive statistics

	N	Minimum	Maximum	Mean	SD
Duration of clozapine therapy in months	79	24	141	103.5	38.4
Clozapine dose (mg) per day (24 hours)	79	100	650	341.8	133.2
Nighttime clozapine dose (mg)	78	25	600	258.7	106.7
Age in years	79	20	79	43.3	12.7
Salivation measure (NHRS)	79	0	4	1.7	1.2

Salivation was measured via Nocturnal Hypersalivation Rating Scale (NHRS) developed by Spivak's team. [6]. The NHRS is scored as follows: 0 = no nocturnal hypersalivation, 1 =
minimal (saliva on pillow), 2 = mild (wakes patient once per night), 3 = moderate (wakes patient twice per night), and 4 = severe (wakes patient three times or more).

Twenty-two of the 79 patients were concurrently on other antipsychotics such as aripiprazole and Risperidone, 16 were concurrently on antidepressants (SSRIs: sertraline and citalopram), 18 on mood stabilisers (mainly valproate, carbamazzpine, or lamotrigine), and 11 on antihypertensive medication. The numbers within each specific medication brand would be too small to calculate correlations to the

dose of clozapine and the same if true about medications for diabetes (7 patients) or for cholesterol (9 patients): the correlations could not be meaningfully generalized due to small size of such subgroups within a larger category.

We calculated the Pearson correlations of the salivation measure to daily total dose of clozapine as per 24 hours, nighttime dose of clozapine, duration of clozapine treatment, age, gender, presence or absence of other antipsychotics, antidepressants, mood stabilizers, and antihypertensive medication.

With respect to treatment of sialorrhea, 19 patients were managed with the medications listed in the Table 2.

Table 2: Hypersalivations medications

	Frequency	Percent within the 79 patients
Atropine eye drops 1% (off license)	1	1.3
Hyoscine (supplied by GP)	1	1.3
Hyoscine 300mcg - 3 times a day	1	1.3
Hyoscine 300mcg - BD	1	1.3
Hyoscine 300mcg BD	2	2.5
Hyoscine 300mcg ON	3	3.8
Orphenadrine 50mg BD	1	1.3
Tribenzhexol 10mg - ON	1	1.3
Tribenzhexol 5mg OD prn	1	1.3
Tribenzhexol 5mg - BD	1	1.3
Tribenzhexol 5mg - OD	1	1.3
Tribenzhexol 5mg BD	3	3.8
Tribenzhexol 5mg OD	1	1.3
Tribenzhexol 5mg OM	1	1.3

As shown in Table 2, most commonly prescribed in this group of patients were Tribenzhexol (9 patients) and Hyoscine (8 patients). These subgroups are also too small for comparisons of these two medications.

3. Results

The scores on Nocturnal Hypersalivation Rating Scale (NHRS) ranged from 0 to 4 with the average at 1.7, SD=1.2. The symptom was absent in 17.7%, minimal in 36.7%, mild in 15.2%, moderate in 21.5%, and severe in 8.9% of patients.

The extent of sialorrhea was not significantly correlated with daily (24 hour) total dose of clozapine, nighttime dose of clozapine, duration of clozapine treatment, age, gender, presence or absence of other antidepressants, and mood stabilizers: all these correlations were at $p > .05$ (1-tailed).

Being concurrently on other antipsychotics significantly increased the intensity of sialorrhea ($r=37$, $p=.001$, 2-tailed). Patients on antihypertensive medication reported less sialorrhea ($r=-.25$, $p=.028$, 2-tailed).

In this group of patients, those treated with salivation reducing medications still experienced slightly higher levels of sialorrhea ($r=.22$, $p=.025$, 1-tailed), see also proportions in Table 3.

Table 3: NHRS scores in patients treated versus untreated for salivation

	Salivation measure (NHRS)				
	absent	minimal	mild	moderate	severe
No medication for salivation (N=60)	23.3%	35.0%	16.7%	16.7%	8.3%
On medication for salivation (N=19)	0.0%	42.1%	10.5%	36.8%	10.5%
All patients (N=79)	17.7%	36.7%	15.2%	21.5%	8.9%

4. Discussion

The correlations involving concurrent use of other antipsychotics in addition to clozapine and especially the correlation involving antihypertensive medication are significant along statistical criteria, but the underlying relationships are somewhat weak for clinical predictions in individual cases, and this is probably especially true with respect to the potential of antihypertensive medication to reduce hypersalivation. Nevertheless, some caution is needed in adding other antipsychotics to clozapine as it may not only somewhat increase the sialorrhea, but it may also generate other adverse side-effects.

The particular contribution of the present study lies in demonstrating statistically that, in general and within the usual therapeutic ranges, the daily dose size of clozapine or its nighttime dose size are unrelated to intensity of hypersalivation. The duration of clozapine treatment, patient's age, and gender also do not change the intensity of sialorrhea.

5. Conclusions

About a half of the patients reported mild to severe nocturnal hypersalivation, but its intensity seems unrelated to the clozapine dose or to its nighttime administration. No gender or age differences in hypersalivation were found. Concurrent use of other antipsychotics could lightly intensify the sialorrhea.

6. References

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