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SHORT COMMUNICATION

Body weight gain in clozapine-treated patients: Is norclozapine the culprit?

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The antipsychotic drug clozapine is associated with weight gain. The proposed mechanisms include blocking of serotonin (5-$HT_{2a/2c}$), dopamine (D_2) and histamine (H_1) receptors. Clozapine is metabolized by cytochrome P450 1A2 (CYP1A2) to norclozapine, a metabolite with more 5-HT_{2c}-receptor and less H_1 blocking capacity. We hypothesized that norclozapine serum levels correlate with body mass index (BMI), waist circumference and other parameters of the metabolic syndrome. We performed a retrospective cross-sectional study in 39 patients (female $n = 8$ (20.5%), smokers $n = 18$ (46.2%), average age 45.8 ± 9.9 years) of a clozapine outpatient clinic in the Netherlands between 1 January 2017 and 1 July 2020. Norclozapine concentrations correlated with waist circumference ($r = 0.354$, $P = .03$) and hemoglobin A1c (HbA1c) ($r = 0.34$, $P = .03$). In smokers (smoking induces CYP1A2), norclozapine concentrations correlated with waist circumference ($r = 0.723$, $P = .001$), HbA1c ($r = 0.49$, $P = .04$) and BMI ($r = 0.63$, $P = .004$). Elucidating the relationship between norclozapine and adverse effects of clozapine use offers perspectives for interventions and treatment options.

KEYWORDS
body mass index, body weight gain, clozapine, norclozapine, waist circumference

1 | INTRODUCTION

Patients with schizophrenia have a higher prevalence of the metabolic syndrome and higher risk of cardiovascular disease mortality compared to the general population. Being overweight and obese are particular problems in these individuals, especially when second-generation antipsychotics, such as clozapine, are used.[1] The mechanism behind clozapine-induced body weight gain (BWG) has not been elucidated yet, but it is hypothesized that the blocking of serotonin (5-$HT_{2a/2c}$) receptors by clozapine plays an important role.[2]

In addition to the parent drug, drug metabolites should also be considered as a cause for BWG. Clozapine is metabolized by cytochrome P450 1A2 (CYP1A2) to norclozapine, a metabolite with more serotonin (5-HT_{2c}) receptor blocking capacity, more D_2 and D_3 agonistic, and less H_1 receptor blocking capacity than clozapine.[3] Previous studies point towards a more important role for norclozapine than for clozapine in clozapine-associated BWG. Lu et al showed that norclozapine serum levels and not clozapine serum levels were associated with increases in body weight, serum glucose and triglyceride serum levels. They compared two randomly assigned patient groups receiving either clozapine or clozapine with fluvoxamine, a CYP1A2 inhibitor that lowers the norclozapine/clozapine ratio. The patients with fluvoxamine addition had lower norclozapine serum levels and less BWG, body mass index (BMI), glucose and triglyceride serum levels. However, the authors could not rule out a contribution from

The authors confirm that the Principle Investigator for this paper is Dr Koen P. Grootens, MD and that he had direct clinical responsibility for patients.

fluvoxamine itself in the observed results.[4] In a retrospective audit, Lau et al showed that clozapine users who smoke gained significantly more weight in 3 to 12 months compared to nonsmokers (+5.1% versus +1.2%).[5] Polycyclic aromatic hydrocarbons in cigarettes induce CYP1A2 and so advance the formation of norclozapine.[6] Lau et al hypothesized that norclozapine should be the culprit but they had not measured norclozapine serum levels and could not confirm this posited relationship.[5]

More insight into the role of norclozapine in clozapine-associated BWG opens up treatment possibilities and interventions such as the introduction of phenoconversion to lower its formation. To further unravel the mechanism behind clozapine-induced BWG we hypothesized that higher norclozapine serum levels result in higher BMI and larger waist circumference, a parameter of the metabolic syndrome whose correlation with norclozapine serum levels has not been assessed before. The primary aim of this research was to assess the correlations between norclozapine serum levels and BMI and waist circumference. Furthermore, we aimed to acquire more insight into the correlation between norclozapine serum levels and other parameters of the metabolic syndrome, such as triglycerides and high-density lipoprotein (HDL)-cholesterol serum levels. As smoking induces CYP1A2 and hence impacts the metabolization of clozapine and the formation of norclozapine, the outcomes are stratified for smokers and nonsmokers.

What is already known about this subject

- Clozapine use is associated with body weight gain. It is hypothesized that blocking of histamine (H_1), dopamine (D_2) and serotonin (5-$HT_{2a/2c}$) receptors play an important role.

What this study adds

- Serum levels of norclozapine correlate positively and statistically significantly with waist circumference and HbA1c, but not with body mass index (BMI). This is the first time the correlation with waist circumference has been assessed. In smokers norclozapine serum levels correlate with waist circumference, HbA1c and BMI.

2 | METHODS

2.1 | Design and study population

We conducted an observational, retrospective cross-sectional study to assess the correlation between norclozapine serum levels and BMI, waist circumference and other parameters of the metabolic syndrome (triglycerides, HDL-cholesterol, fasting glucose and HbA1c serum levels) stratified for smokers and nonsmokers. The study population consisted of patients visiting a specialised clozapine outpatient clinic from the Reinier van Arkel Mental Health Institute, Hertogenbosch, the Netherlands. For this study we included information of the last registered outpatient clinic visit with data on norclozapine serum levels and the metabolic parameters between 1 January 2017 and 1 July 2020. All patients visiting this clozapine outpatient clinic were eligible. Inclusion criteria were 18 years or older, valid measurements of norclozapine serum levels above the detection limit, and measurement of BW and waist circumference within 1 month prior to or after measurement of the norclozapine and clozapine serum levels. For the other parameters of the metabolic syndrome the time interval was set at 3 months prior to or after measurement of the serum drug levels. In case parameters were measured several times within the interval, the measurement nearest to the drug level measurement were included. In addition, patients were stratified into smokers and nonsmokers.

The study was approved by the local Medical Research Ethics Committee of the Reinier van Arkel Academy, Hertogenbosch and received a waiver for the Dutch Medical Research Involving Human Subjects Act.

2.2 | Sample size calculation

We calculated the sample size with an expected $r = 0.5$ based on a type I error rate (α, two tailed) of 0.05, a type II error rate (β) of 0.20 and previously found correlation coefficients for norclozapine serum levels and BWG varying between $r = 0.16$ and $r = 0.89$.[7] Based on this calculation the study population should preferably comprise at least 29 patients.

2.3 | Outcomes

For all eligible patients the following data were collected: gender (F/M), age (years), height (m), body weight (kg), smoking (yes/no/unknown), norclozapine and clozapine serum levels (μg/L), waist circumference (m) and other parameters of the metabolic syndrome triglycerides (mmol/L), HDL-cholesterol (mmol/L), fasting glucose (mmol/L) and HbA1c serum levels (mmol/mol). BMI was calculated with body weight (kg) and height (m) (weight [kg]/height $[m]^2$).

2.4 | Determinant

Serum levels of norclozapine (μg/L) and clozapine (μg/L) were determined by high-performance liquid chromatography with ultraviolet detection (Hitatchi). The intra-assay and inter-assay coefficients of variation were < 10% for clozapine and norclozapine. The lower limit

of detection was 45 μg/L for clozapine and 55 μg/L for norclozapine. The serum levels of triglycerides (mmol/L), HDL-cholesterol (mmol/L), fasting glucose (mmol/L) and HbA1c (mmol/mol) were measured by Advia Chemistry XPT (Siemens) according to routine laboratory practice.

2.5 | Data analysis

Patient characteristics are presented as mean with standard deviation (SD), median with range or frequency with percentage where appropriate and are stratified for smoking behaviour and gender. The Pearson correlation coefficient was assessed for norclozapine, clozapine and the ratio norclozapine/clozapine serum levels (μg/L) and BMI (kg/m^2), waist circumference (m) and the other selected parameters of the metabolic syndrome (triglycerides [mmol/L], HbA1c [mmol/mol], and HDL-cholesterol serum levels [mmol/L]) using IBM SPSS Statistics version 22. Furthermore, the Pearson correlation coefficients for norclozapine and clozapine serum levels and the parameters of the metabolic syndrome were calculated separately for smokers and nonsmokers using IBM SPSS Statistics version 22. A *P* value of less than .05 was considered statistically significant. No corrections for multiple tests were applied, as there were underlying hypotheses for stratification in smokers and nonsmokers.

3 | RESULTS

During the study period the clozapine outpatient clinic comprised 44 patients. Five patients did not meet the inclusion criteria: two patients had norclozapine serum levels below the detection limit of 55 μg/L, one patient had no body weight (BW) measurement within the set time interval, one patient had no waist circumference measured within the set time interval and one patient refused blood tests. Therefore, the study population comprised 39 patients (female $n = 8$, 20.5%) aged from 22 to 62 years (mean ± SD 45.8 ± 9.8 years). The characteristics of the 39 included patients are summarized in Table 1. None of the patients were "underweight" (BMI lower than 18.5 kg/m^2). The BMI of 13 patients (33.3%) was "normal" (18.5-24.9 kg/m^2), the BMI of 18 patients (46.2%) was categorized as "overweight" (25.0-29.9 kg/m^2), the BMI of seven patients (17.9%) was categorized as "obese" (higher than 30.0-39.9 kg/m^2) and one patient (2.6%) was categorized as morbid obese (higher than 40.0 kg/m^2). Seven out of eight females (87.5%) had a waist circumference over 0.88 m and 17 out of 31 males (54.8%) had a waist circumference over 1.02 m.

TABLE 1 Patient characteristics

n = 39	
Female	8 (20.5%)
Age (mean years ± SD)	45.8 ± 9.9
Smokers	18 (46.2%)
Diagnosis	
Schizophrenia	16 (41.0%)
Therapy resistance schizophrenia	16 (41.0%)
Schizophrenia affective disorder	6 (15.4%)
Bipolar disease type 1	1 (2.6%)
Mean norclozapine serum level (μg/L) (± SD)	232.3 ± 130.1
Female (n = 8)	248.3 ± 123.2
Male (n = 31)	228.1 ± 133.4
Smokers (n = 18)	241.2 ± 155.4
Nonsmokers (n = 21)	224.7 ± 107.2
Mean clozapine serum level (μg/L) (± SD)	340.7 ± 182.4
Female (n = 8)	452.1 ± 225.6
Male (n = 31)	311.9 ± 161.6
Smokers (n = 18)	326.9 ± 190.6
Nonsmokers (n = 21)	352.4 ± 179.0
Mean ratio norclozapine/clozapine serum level (μg/L) (± SD)	0.76 ± 0.38
Female (n = 8)	0.60 ± 0.26
Male (n = 31)	0.80 ± 0.40
Smokers (n = 18)	0.86 ± 0.46
Nonsmokers (n = 21)	0.68 ± 0.27
Mean body mass index (kg/m^2)	27.8 ± 5.5
Female (n = 8)	29.8 ± 8.2
Male (n = 31)	27.3 ± 4.6
Smokers (n = 18)	27.7 ± 4.9
Nonsmokers (n = 21)	27.9 ± 6.0
Mean waist circumference (m)	105.1 ± 13.3
Female (n = 8)	1.07 ± 0.17
Male (n = 31)	1.05 ± 0.13
Smokers (n = 18)	1.05 ± 0.13
Nonsmokers (n = 21)	1.06 ± 0.14
Mean triglycerides (mmol/L)	2.0 ± 1.4
Mean HDL-cholesterol (mmol/L)	1.3 ± 0.4
Mean fasting blood glucose (mmol/L), one unknown	6.0 ± 1.8
Mean HbA1c (mmol/mol)	37.9 ± 12.6

3.1 | Correlation of norclozapine and clozapine serum levels with BMI and waist circumference

The Pearson correlation coefficients for norclozapine and clozapine serum levels and parameters of the metabolic syndrome are summarized in Table 2. When taking all patients together, norclozapine serum levels correlated with waist circumference ($r = 0.354$, $P = .03$; Figure 1), but did not correlate with BMI ($r = 0.282$, $P = .08$). After stratification for smoking behaviour, smokers showed a positive and significant correlation between norclozapine serum levels and BMI ($r = 0.63$, $P = .005$) and the correlation with waist circumference was stronger ($r = 0.723$, $P = .001$). In

TABLE 2 Pearson correlation coefficients of norclozapine and clozapine serum levels and parameters of the metabolic syndrome

n = 39	Correlation coefficients norclozapine serum levels (μg/L)			Correlation coefficients clozapine serum levels (μg/L)			Correlation coefficients ratio norclozapine/clozapine serum levels (μg/L)		
Parameters of the metabolic syndrome	All patients	Smokers (n = 18)	Nonsmokers (n = 21)	All patients	Smokers (n = 18)	Nonsmokers (n = 21)	All patients	Smokers (n = 18)	Nonsmokers (n = 21)
Body mass index (kg/m^2)	r = 0.282 (P = .08)	**r = 0.627 (P < .01)**	r = −0.035 (P = .88)	r = 0.039 (P = .82)	r = 0.318 (P = .20)	r = −0.167 (P = .47)	r = 0.240 (P = .140)	r = 0.439 (P = .068)	r = 0.068 (P = .769)
Waist circumference (cm)	**r = 0.354 (P = .03)**	**r = 0.723 (P < .01)**	r = −0.043 (P = .85)	r = 0.099 (P = .55)	r = 0.289 (P = .24)	r = −0.065 (P = .78)	r = 0.220 (P = .178)	**r = 0.488 (P = .04)**	r = −0.078 (P = .738)
Triglycerides (mmol/L)	r = 0.058 (P = .72)	r = 0.221 (P = .38)	r = −0.130 (P = .57)	r = −0.098 (P = .55)	r = −.042 (P = .87)	r = −0.133 (P = .57)	r = 0.069 (P = .678)	r = 0.196 (P = .436)	r = −0.136 (P = .558)
HDL-cholesterol (mmol/L)	r = −0.219 (P = .18)	r = −0.411 (P = .09)	r = −0.049 (P = .83)	r = 0.117 (P = .48)	r = −0.143 (P = .57)	r = 0.271 (P = .24)	r = −0.338 (P = .035)	r = −0.374 (P = .126)	r = −0.268 (P = .240)
Fasting glucose (mmol/L)	r = 0.093 (P = .58)	r = 0.098 (P = .71)	r = 0.101 (P = .66)	r = 0.082 (P = .62)	r = 0.033 (P = .90)	r = 0.120 (P = .60)	r = −0.012 (P = .945)	r = 0.080 (P = .760)	r = −0.108 (P = .642)
HbA1c (mmol/mol)	**r = 0.340 (P = .03)**	**r = 0.493 (P = .04)**	r = 0.122 (P = .60)	r = 0.054 (P = .75)	r = −0.182 (P = .47)	r = 0.311 (P = .17)	r = 0.275 (P = .090)	**r = 0.645 (P = .004)**	r = −0.339 (P = .133)

The Pearson correlation coefficients that correlate significantly are presented in bold.

FIGURE 1 Scatterplot for norclozapine serum levels (μg/L) versus waist circumference (cm) stratified for smokers and nonsmokers

addition, the ratio norclozapine/clozapine serum levels correlated positively and significantly with waist circumference in smokers (r = 0.488, P = .04).

3.2 | Correlation of norclozapine and clozapine serum levels with other parameters of the metabolic syndrome

Norclozapine serum levels correlated positively and significantly with HbA1c (r = 0.34, P = .03). In smokers norclozapine serum levels correlated more strongly with HbA1c (r = 0.49, P = .04).

4 | DISCUSSION

This is one of the first studies addressing the relation between the clozapine metabolite norclozapine and BWG in patients with schizophrenia. We hypothesized that higher norclozapine serum levels result in higher BMI and larger waist circumference.

In our study population, norclozapine serum levels correlated with waist circumference but not with BMI. Waist circumference is considered a valuable predictor for metabolic syndrome and found to be the single best anthropometric surrogate for predicting insulin resistance in nondiabetic clozapine users.[8,9] This is the first study assessing the correlation between norclozapine serum levels and waist circumference and so it provides a first estimate of this relationship. Norclozapine serum levels did not correlate with assessed parameters of the metabolic syndrome except HbA1c.

After stratifying for smoking behaviour, norclozapine serum levels correlated with waist circumference, HbA1c and BMI in smokers but not in nonsmokers. Smoking induces CYP1A2 and enhances the formation of norclozapine. Lau et al showed that smoking induces more BWG and hypothesized that the formation of norclozapine should be the culprit.[5] Other studies showed the reverse and found that norclozapine serum levels correlated best with BWG ($r = 0.89$, $P = .046$) in a very small sample of nonsmokers.[7] The positive and significant correlation between the norclozapine/clozapine serum level ratio and waist circumference in smokers points to a possible relationship between CYP1A2, norclozapine serum levels, smoking and parameters of the metabolic syndrome. Although the exact relationships are not completely clarified, most studies, including ours, shows a better correlation between norclozapine serum levels and parameters of the metabolic syndrome than for clozapine serum levels and these parameters.[4,5,7]

The limitations of our study are the cross-sectional design, the rather small sample size and risk factors of clozapine-associated BWG that were not taken into account in our analysis. The cross-sectional design does not allow for establishing causal relationships. However, that was not the aim of our study and is suggested for follow-up research. The number of patients in our study is rather small but even this small sample shows that norclozapine serum levels correlate with important parameters of the metabolic syndrome. Furthermore, in our analysis we did not include known risk factors of BWG in clozapine users, such as low baseline BMI, female gender and negative symptoms. Although this information was obtainable, further stratification would not provide any conclusions due to the small number of patients.

Although this study illuminates the relationship between norclozapine serum levels and BWG only slightly, the correlation with waist circumference is of clinical relevance as it justifies more attention for high norclozapine serum levels in daily practice. Even though additional studies will be needed to confirm this relationship, researching the impact of interventions to decrease the formation of norclozapine, such as smoking cessation and CYP1A2 inhibition, on waist circumference is now conceivable. Further efforts in unravelling the mechanism of clozapine-induced body weight gain are important for clinical practice as clozapine is the most effective drug for treatment-resistant schizophrenia and adherence despite weight gain is a major challenge for patients.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[10]

COMPETING INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, N.T.J., H.J.D., R.J.vM., E.P.vP., K.P.G. Data curation, N.T.J., A.J., E.L.G. Methodology, N.T.J., H.J.D., R.J.vM., E.P.vP., K.P.G. Writing – original draft, N.T.J., H.J.D., R.J.vM., E.P.vP., K.P.G. Writing – review & editing, N.T.J., H.J.D., R.J.vM., A.J., E.L.G., E.P.vP., K.P.G.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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