Tachycardia in patients treated with clozapine versus antipsychotic long-acting injections

Björn M. Nilsson, Oscar Edström, Leif Lindström, Petter Wernegren and Robert Bodén

Tachycardia is a known adverse effect during clozapine treatment. However, prevalence reported differs widely between studies and hitherto there are no studies comparing clozapine-treated patients with a similar control group. The present study was carried out to assess the prevalence of tachycardia in patients treated with clozapine and antipsychotic long-acting injections (LAI). Data on heart rate (HR), concomitant medication, and relevant anthropometric and laboratory measurements were collected for all clozapine-treated patients ($n = 174$) in a defined catchment area and compared with data on patients treated with LAI ($n = 87$). In total, 33% of patients on long-term clozapine treatment had tachycardia (HR > 100) compared with 16% in the LAI group ($P < 0.001$). The mean HR was 91 in the clozapine group and 82 in the LAI group ($P < 0.001$). Clozapine dose correlated with HR. The majority of patients with HR more than 100 received no specific treatment for tachycardia. In conclusion, the prevalence of tachycardia was twice as high in patients treated with clozapine as in a similar patient group with severe schizophrenia spectrum disorder. The tachycardia was in many cases clinically unnoticed. Tachycardia during antipsychotic treatment is a common phenomenon that must be monitored for actively and, when noticed, further investigated and treated. ***Int Clin Psychopharmacol*** **32:219–224 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Department of Neuroscience, Psychiatry, Uppsala University

Correspondence to Björn M. Nilsson, MD, PhD, Department of Neuroscience, Psychiatry, Uppsala University, Uppsala SE-75185, Sweden
Tel: +46 76 724 8848/+46 70 614 4489; fax: +46 18 515 810;
e-mails: bjorn.nilsson@neuro.uu.se, bjorn.nilsson@akademiska.se

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Introduction

About one-third of individuals with schizophrenia are considered to be treatment resistant or minimally responsive to conventional antipsychotics (Teo *et al.*, 2013). Treatment resistance may be because of a low sensitivity for antipsychotics or lack of adherence. In the former, clozapine has the best evidence (McEvoy *et al.*, 2006; Leucht *et al.*, 2013), and in the latter, antipsychotic long-acting injections (LAI) are a significant option (Agid *et al.*, 2010). Clozapine has a superior efficacy for psychotic symptoms (Leucht *et al.*, 2013). The substance has also been associated with lower mortality and a lower risk for suicide compared with other antipsychotic agents (Tiihonen *et al.*, 2009; Hayes *et al.*, 2015). In many cases, clozapine implies a treatment that is unchangeable, the patient must remain on clozapine, and the side effects have to be managed (Nielsen *et al.*, 2013). The severe cardiac adverse effects of clozapine include increased risk for myocarditis (Ronaldson *et al.*, 2015), cardiomyopathy (Merrill *et al.*, 2005), and sudden cardiac death (Ray *et al.*, 2009). Long-term cardiovascular health may also be at risk because of the metabolic side effects of clozapine. Weight gain is common and the risk for type II diabetes, hyperlipidemia, and metabolic syndrome is increased (Mitchell *et al.*, 2013).

Clozapine also has positive chronotropic properties. Clozapine-associated tachycardia is often covert, that is, neither the patient nor the caregivers are aware of the problem. Consequently, a significant tachycardia might persist during years without adequate treatment. When noticed, there is safe and uncomplicated treatment for clozapine-associated tachycardia with β-adrenergic blocking agents (Stryjer *et al.*, 2009). The reported prevalence of tachycardia among clozapine-treated patients varies from as low as 3% (Naber *et al.*, 1989), around 25% (Safferman *et al.*, 1991), to a high prevalence of more than 50% (Centorrino *et al.*, 1994). However, these studies have not primarily focused on tachycardia and they are heterogeneous in the number of patients, method, and time of measurement. Tachycardia is mostly reported as a transient phenomenon during clozapine titration (Marinkovic *et al.*, 1994). There are but a few studies that have measured heart rate (HR) in long-term maintenance clozapine treatment and they report different prevalence numbers: from 14 to 58% (Gerlach *et al.*, 1989; Centorrino *et al.*, 1994; Yusufi *et al.*, 2007; Hyde *et al.*, 2015).

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Altogether, it is difficult to draw conclusions on how common clozapine-associated tachycardia is.

The aims of the present study were as follows: (a) to obtain the prevalence of tachycardia in all clozapine-treated patients in a defined catchment area, (b) to compare HR and tachycardia prevalence with a similar population with a severe disorder, patients treated with LAI, (c) to investigate possible dosing effects on tachycardia, and (d) to estimate how many patients receive adequate treatment for persistent tachycardia.

Patients and methods

Study populations

The study was approved by the regional ethics review board in Uppsala, Sweden. Treatment-resistant patients were defined in the present study as either being treated with clozapine or treated with LAI. Data were collected from all patients on clozapine treatment in the main catchment area of Uppsala County and from all patients receiving LAI in the outpatient clinic for psychotic disorders at Uppsala University Hospital serving 847 patients at the time of the study. The clozapine group included all patients on clozapine irrespective of diagnosis and concomitant medication (including LAI) during the study period. The LAI group was treated with depot injections of perphenazine (28%), zuclopenthixole (25%), haloperidol (15%), flupenthixole (13%), paliperidone (9%), risperidone (5%), fluphenazine (2%), olanzapine (1%), and aripiprazole (1%).

Data collection

This is a cross-sectional study on data collected from the patient's case files during April 2013–September 2014. Background data consist of demographic characteristics, concomitant medication including β-adrenergic blocking agents, and routine measurements of hemoglobin (Hb) and thyroid-stimulating hormone. Clozapine medication was expressed with the actual clozapine dose in mg/day, whereas antipsychotic medication in the LAI group was expressed as chlorpromazine equivalents/day (CPZ) at the time of HR measurement. The median clozapine dose 300 mg/day in the study is thus equipotent to 450 mg CPZ (Gardner *et al.*, 2010). The main outcome measure was HR during rest. If several measures were available, the most recent HR was chosen. HR values collected during fever, seizures, intoxication, or pain were excluded. HR was measured using an automatic blood pressure and pulse monitor (Omron M6W; Omron Healthcare, Kyoto, Japan), in a few cases manually in the radial artery, or with ECG. To investigate the possible influence of clozapine dose on HR, a separate analysis was carried out with patients on a low dose and a high dose, with the median dose (300 mg clozapine/day) as the cut-off. Further, the proportion of patients with treatment for tachycardia was investigated.

Definition of parameters

Tachycardia is defined as HR of at least 100 bpm. However, several patients in this population were already treated with β-blocking medication for the indication tachycardia. To minimize the risk of misclassification and to obtain a true prevalence measure, these patients were included in the analysis as having tachycardia, irrespective of recorded HR. Further, there were patients on β-blockers for the indication hypertension. Stryjer *et al.* (2009) reported that β-blockers (atenolol and propranolol) decrease the HR with a mean of 16.45 bpm in clozapine-associated tachycardia. According to this finding, we have chosen to include patients with β-blockers for other indications, as having tachycardia, if HR was at least 85. This is an operational definition not established in the literature; therefore, an additional analysis was carried out with the exclusion of these patients.

Statistical analysis

To test for normality, the quotient skewness/SEM was used. Non-normally distributed parameters are presented as median and inter quartile range and normally distributed parameters are presented as mean and SD. Continuous and normally distributed parameters were compared using Student's *t*-tests and non-normally distributed variables were compared using the Mann–Whitney *U*-test. Nominal or ordinal variables were investigated using the χ^2-test. Pearson's correlation coefficient and Spearman's ρ were performed in the correlation analyses of HR, clozapine dose, and age. For the analysis of concomitant antipsychotic medication, the patients were assigned to three different groups: (a) treatment with only clozapine, (b) treatment with clozapine and other antipsychotic agent, and (c) treatment with LAI. For these purposes, analysis of variance with subsequent Bonferroni tests and Kruskal–Wallis tests were used. *P*-values below 0.05 were considered statistically significant. The statistical analyses were carried out using SPSS, version 21.0, IBM Corp., Armonk, New York, USA.

Results

The study groups

The total number of clozapine-treated patients in the catchment area was 174. The number on LAI was 87. Table 1 shows the characteristics of the study groups.

Heart rate and tachycardia prevalence

Recorded HR was missing during the study period for 10 patients in the clozapine group and four patients in the LAI group. Table 2 shows resting HR in the two groups. The clozapine group had a significantly higher mean HR than the LAI group. To control for possible confounding, a second analysis was carried out with the exclusion of patients on concomitant stimulant or β-blocking medication. In this analysis, patients on clozapine still had significantly higher HR.

Table 1 Characteristics of patients treated with clozapine or antipsychotic long-acting injections

	Clozapine ($n=174$)	LAI ($n=87$)[a]
Age [mean (SD)]	46 (13)	54 (12)*
Sex male/female (%)	60/40	49/51
Smokers (%)	27	49[b,**]
Diagnosis		
Schizophrenia (%)	75	59**
Schizoaffective disorder (%)	16	18
Bipolar disorder (%)	2	10**
Psychotic disorder (%)	5	7
Other (%)	2	6
Duration of illness [median (IQR)] (year)	22 (17)	24 (20)
Antipsychotic medication [median (IQR)] (mg/day)	300 (200)	280 (233)[c]
Duration of present medication [median (IQR)] (year)	12 (15)	4 (6)***
Concomitant antipsychotic treatment (%)		
Aripiprazole	21	3**
Risperidone	8	2
Zuclopenthixol	9	3
Other[d]	16	14
β-Blocking agents (%)	20	8**
Anticholinergics (%)[e]	32	44
Lithium (%)	3	6
Thyroid hormones (%)	7	9
Systolic blood pressure [median (IQR)] (mmHg)	130 (20)	135 (29)***
Diastolic blood pressure [mean (SD)] (mmHg)	83 (10)	85 (12)
BMI [median (IQR)] (kg/m^2)	28.8 (7.6)	29.0 (8.4)
Hemoglobin [mean (SD)] (g/l)	144 (13)	149 (13)*
TSH [median (IQR)] (mIU/l)	2.01 (1.55)	1.99 (1.83)

IQR, inter quartile range; LAI, long-acting injections; TSH, thyroid-stimulating hormone.
[a]The LAI group was treated with depot injections of perphenazine (28%), zuclopenthixole (25%), haloperidol (15%), flupenthixole (13%), paliperidone (9%), risperidone (5%), fluphenazine (2%), olanzapine (1%), and aripiprazole (1%).
[b]Data on smoking were missing in 21 patients in the clozapine group and in 12 patients in the LAI group.
[c]Dose in the LAI group is expressed as chlorpromazine equivalents mg/day.
[d]Other antipsychotics include haloperidol, quetiapine, olanzapine, flupenthixole, levomepromazine, amisulpiride, and perphenazine.
[e]Anticholinergics include; biperiden, trihexylphenidyl, hyoscamine, methylscopolamine, butylscopolamine
*$P<0.05$, unpaired *t*-test.
**$P<0.05$, χ^2-test.
***$P<0.05$, Mann–Whitney *U*-test.

Table 2 Resting heart rate in patients on clozapine versus antipsychotic long-acting injections

	Clozapine ($n=164$)[a]	LAI ($n=83$)[a]	*P*-value
HR [mean (SD)] (bpm)	91 (13)	82 (15)	<0.001*
HR without chronotropics [mean (SD)]	92 (14)[b]	84 (14)[b]	<0.001*
Tachycardia (%)	33	16	<0.01**
Subtachycardia HR ≥90 (%)	59	24	<0.001**

HR, heart rate; LAI, long-acting injections.
[a]Data on HR were missing in 10 of the total number of clozapine-treated patients in the catchment area ($n=174$) and in four of the 87 LAI patients.
[b]$n=138$ versus $n=76$ when patients with positive or negative chronotropics (stimulants and β-blockers) were excluded.
*Unpaired *t*-test.
**χ^2-Test.

The prevalence of tachycardia differed significantly between the two groups, with 33% in the clozapine group versus 16%. Post-hoc analysis with the patients on β-blockers for hypertension and HR of at least 85 excluded showed a proportion of 28% with tachycardia in the clozapine group compared with 16% in the LAI group ($P<0.05$). In a separate analysis, the proportion of patients with subtachycardia (HR ≥90) was 59% of the clozapine-treated patients and 24% of the LAI-treated patients. Of the patients with tachycardia, 39% received treatment with HR-lowering agents.

A separate analysis of the patients diagnosed with schizophrenia was also carried out and yielded a mean HR 92±14 in the clozapine group versus mean 83±16 in the LAI group ($P=0.001$).

Correlations

HR correlated with clozapine dose in mg/day ($r=0.33$, $P<0.001$). There was no correlation between CPZ equivalents/day and HR in the LAI group. When clozapine-treated patients were divided into low-dose (<300 mg/day) ($n=54$) and high-dose groups (≥300 mg/day) ($n=120$), the mean HR was 87 versus 95 bpm ($P<0.001$) and tachycardia 20 versus 46% ($P<0.001$), respectively. There was no correlation between the Hb value and HR in the study groups. Age correlated weakly with HR in the clozapine group ($r=-0.23$, $P<0.01$), but not in the LAI group.

Concomitant antipsychotic medication

Analysis of variance, followed by Bonferroni post-hoc test failed to show any effect of concomitant antipsychotic medication on HR in clozapine-treated patients. The clozapine-only group ($n=79$) showed a mean HR 90±14 and in the clozapine + concomitant antipsychotic group, the mean HR was 91±13 compared with a mean HR of 82±15 in the LAI controls. The corresponding figures for tachycardia were 34% in the clozapine monotherapy group, 32% in the clozapine + antipsychotics group, and 16% in the LAI group. Patients with add-on aripiprazole treatment were significantly more common in the clozapine group ($n=36$). To exclude a possible confounding effect on HR, these 36 patients were analyzed separately. The mean HR was 92 and the proportion tachycardia 32% in patients with add-on aripiprazole, numbers that are almost identical to the whole clozapine-treated population (Table 2).

Discussion

The main finding of the study was a tachycardia prevalence of 33% in clozapine-treated patients. Clozapine treated patients also had higher resting HR and double the prevalence of tachycardia compared with patients treated with LAI. Further, in clozapine-treated patients, HR showed a positive correlation with clozapine dose. The strengths of the present study are as follows: (a) the inclusion of all clozapine-treated patients in a geographically defined catchment area. The prevalence measure is based on 164 patients of an entire population of all 174 clozapine-treated patients. The minor attrition

should not interfere with the generalizability of the results. (b) Possible confounders relevant for HR, such as smoking, β-blockers, or add-on antipsychotics, were taken into account. (c) To our knowledge, clozapine-associated tachycardia has not been studied previously in comparison with a similar treatment-resistant control group treated with LAI. (d) The study focused on HR in long-term clozapine maintenance treatment (median 12 years). Most previous studies report data from the clozapine titration phase.

The sinus tachycardia observed during clozapine treatment is often explained by the strong anticholinergic properties of the substance (Buckley and Sanders, 2000; Chengappa *et al.*, 2000; Agelink *et al.*, 2001). A possible contributing factor may also be that clozapine increases norepinephrine in plasma (Breier, 1994). The tachycardia should thus be considered a type A adverse reaction because of a primary pharmacodynamic influence, and also as dose dependent and reversible. We did find an association between dose and HR, but another study in a smaller sample could not establish such a relationship (Centorrino *et al.*, 1994). There are few studies on HR comparing clozapine and other antipsychotics, but clozapine appears to increase HR to a greater extent (Agelink *et al.*, 2001, Cohen *et al.*, 2001). In a recent study on left ventricular dysfunction, the mean HR was reported to be 93 ± 12 in clozapine-treated patients compared with 79 ± 11 in a control group with other antipsychotic medication (Chow *et al.*, 2014). These figures are very similar to the results in our study (mean 91 ± 13 vs. 82 ± 15). In premarketing studies on clozapine in the USA, tachycardia was found in 25% of the patients and it was noted that the tachycardia will persist in many cases (Safferman *et al.*, 1991).

Also, in our LAI group, 16% had HR above 100. A contributing factor may be concomitant anticholinergic medication (44%) because of extrapyramidal side effects in this group. Besides anticholinergic drug effects, severe psychiatric illness may imply autonomic dysfunction in itself. Bar *et al.* (2005) reported that unmedicated patients with schizophrenia have higher HR than healthy controls because of lower parasympathetic tonus.

High resting HR irrespective of the origin is associated with increased mortality in the normal population and also subtachycardia with HR more than 90 is reported to increase the risk of mortality three-fold (Jensen *et al.*, 2013). The question arises as to whether this is the case also during clozapine treatment, particularly as patients with treatment resistant disorder are vulnerable and at high risk for metabolic complications (Mitchell *et al.*, 2013). Clozapine also increases the risk for myocarditis, cardiomyopathy, and sudden cardiac death (Merrill *et al.*, 2005; Ray *et al.*, 2009). Further, tachycardia may be the first recognizable symptom in myocarditis or pericarditis, and might possibly also predict malignant arrhythmias such as ventricular tachycardia and sudden death (Stryjer *et al.*, 2009). Long-term clozapine treatment has also been associated with asymptomatic left ventricular dysfunction (Chow *et al.*, 2014). However, there are epidemiological findings, reporting both overall lower mortality and lower cardiovascular mortality in clozapine treatment (Tiihonen *et al.*, 2009; Hayes *et al.*, 2015). At present, there are no available data on a possible relationship between clozapine-associated tachycardia and mortality. In our study, only 39% of patients with tachycardia received β-blocking therapy. This figure shows that tachycardia is easily overlooked in the everyday clinical work. We propose that these patients should be investigated by ECG and persistent tachycardia should be treated. A recent Cochrane review on pharmacological intervention for clozapine-induced sinus tachycardia showed a lack of controlled studies and was thus unable to confidently inform clinical practice (Lally *et al.*, 2016). Nevertheless, the addition of β-blockers has long been an effective clinical alternative for the treatment of clozapine-associated tachycardia (Stryjer *et al.*, 2009). According to our own experience, β-blockers for example, low doses of bisoprolol, are well tolerated and β-block add-on may also offer symptomatic relief in patients who are aware of and suffer from tachycardia. However, clozapine often causes orthostatic reactions and in the case of hypotension or orthostatism, ivabradine may be a better option (Lally *et al.*, 2014). A liberal use of Therapeutic Drug Monitoring with controls of serum clozapine levels is strongly recommended as our data suggest a dose–response relationship for tachycardia.

The study has some limitations. In Sweden, clozapine is licensed only for treatment-resistant schizophrenia disorder (TRD). None of the depot antipsychotics is currently licensed for TRD. Accordingly, LAI may be used in TRD but also in patients with poor compliance for oral medication, and this difference between the groups is a limitation. There were slight differences in the age and distribution of diagnoses between the groups that may confound the results. However, the more obvious difference in the duration of present medication may not be of such importance as the figures 12 versus 4 years suggest. These data just report the median time of the last medication and clozapine is mostly a medication that patients remain on, whereas patients on LAI may have changed medication several times or have had many preceding years on different oral prescriptions. In this respect, the similar duration of illness between the groups is important. The majority of data were collected from regular visits in the outpatient clinic by the means of an automatic HR and blood pressure monitor, but manual pulse measurement was also performed in some cases, as well as ECGs. HR measurements were performed by trained healthcare staff. As the study was cross-sectional, our data could not clarify whether the tachycardia observed was persistent. Patients on clozapine also had lower Hb: 144 ± 13 versus 149 ± 13 g/l. These values are within the normal clinical range and the difference

should not have a major influence on HR. No correlation was found between Hb and HR in either of the study groups. There were also more concomitant antipsychotic medications in the clozapine group, particularly with aripiprazole. A separate analysis of aripiprazole add-on patients still showed the same HR and frequency of tachycardia as in clozapine monotherapy. However, the numbers of patients on concomitant medication were small, restricting the possibilities for subgroup analysis, and data should be interpreted with caution. Further, clozapine patients had lower systolic blood pressure. Systolic pressure is a product of cardiac output and peripheral resistance, whereas cardiac output implies both stroke volume and HR. Under normal circumstances, peripheral systolic blood pressure tends to show a positive association with HR. The slightly lower systolic pressure in the clozapine group may not easily explain the higher HR. Another limitation is the lack of data on clozapine concentration in serum. Recorded doses provide a rough estimate of the serum level, but the metabolism of clozapine is dependent on several external factors. The study could not control quantitatively for smoking or coffee consumption. Both are positive chronotropic agents and they both have a strong influence on CYP1A2 activity and clozapine metabolism (van der Weide *et al.*, 2003). Taken together, the correlation analysis of dose and HR should be interpreted with caution. As there were fewer smokers in the clozapine group, the higher HR in clozapine-treated patients could not be explained by the positive chronotropic effects of smoking.

Our definition of tachycardia as HR of at least 85 in patients already on β-blockers for hypertension was supported by the findings of Stryjer *et al.* (2009). Accordingly, this is not an arbitrary definition, but still lacks considerable evidence in the literature. However, the estimated prevalence of tachycardia in our clozapine-treated sample would have led to a type 2 error if these patients with β-blockers had been excluded. To evaluate how large an impact these patients had on the prevalence estimate, calculations were performed with antihypertensive β-blocking therapy excluded. This diminished the tachycardia prevalence to 28%. We considered the inclusion of these patients also to be essential and that 33% is a more valid estimate of tachycardia prevalence.

Conclusion

Tachycardia after long-term treatment was found in one-third of the clozapine-treated patients, and a minority of these received treatment for tachycardia. As the prevalence data are based on all patients with clozapine treatment in a defined catchment area with minimal attrition, they should also be generalizable to other similar clozapine-treated populations. In addition, the study found a significant higher HR in clozapine-treated patients compared with LAI-treated patients. Tachycardia is thus a prevalent phenomenon in this patient group. Further cohort studies are needed to determine whether the observed tachycardia is persistent. Our data were recorded after long-term treatment. They may thus be suggestive of a clozapine-associated tachycardia that will remain after years and years of treatment and continue to affect the patients' cardiovascular health. This is important as effective and safe treatment for tachycardia is available. From a clinical perspective, increased HR in patients with severe psychiatric illness is often unnoticed. Routines for regular monitoring of HR during clozapine treatment may not exist or have a low compliance. Treatment-resistant schizophrenia is a serious disorder and termination of clozapine treatment is seldom possible. Thus, tachycardia, when noticed, should be further investigated with ECG and Therapeutic Drug Monitoring and - if still persistent - treated.

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Conflicts of interest

There are no conflicts of interest.

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