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ORIGINAL RESEARCH ARTICLE

Clozapine-Related Tachycardia: An Analysis of Incidence

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Abstract

Background and objectives Sinus tachycardia commonly occurs at the start of clozapine treatment, often leading to discontinuation owing to perceived adverse cardiovascular effects. However, little evidence exists on its natural course after clozapine initiation. We aimed to determine the frequency and course of clozapine-induced tachycardia over the first month of treatment and to identify possible risk factors

Methods In this cross-sectional study, we serially monitored heart rates (HRs) and other clinical variables of psychiatric inpatients commencing clozapine over the first 28 days. HRs were plotted over time and modelled by explanatory variables, including age group, sex, body mass index (BMI), smoking status and prescribed medications for HR.

Results In total, 123 consecutive inpatients undergoing clozapine titration were assessed daily, with 2901 HR measures collected. After starting clozapine, mean HR increased from 83.7 to 99.5 beats per minute (bpm). Almost all participants (93.5%) had at least one recorded HR > 100 bpm, and 68% had three consecutive days with HR > 100 bpm (being then defined as tachycardic). At least one HR > 120 bpm was recorded in 35.8%, and 8% had persistent HRs > 120 bpm. Tachycardia occurred early during clozapine titration, with a dose response effect at lower doses, which plateaued between 150 and 350 mg daily. Tachycardia spontaneously resolved for some but 44% remained tachycardic at day 28. Female sex was associated with early tachycardia at day 14 ($p = 0.008$) but not at day 28, while age, smoking status, and BMI were not significantly associated with tachycardia.

Conclusions Sinus tachycardia occurred in over two thirds of participants during the first month of clozapine titration. Spontaneous resolution of tachycardia in some suggests watchful monitoring may be appropriate prior to treatment with rate-controlling agents such as β-blockers or ivabradine. Long term follow-up is required to determine the effects of sinus tachycardia on cardiovascular outcomes in patients treated with clozapine.

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Key Points

Sinus tachycardia is a common but poorly studied adverse drug reaction associated with clozapine treatment.

As soon as people start clozapine, their HR increases significantly. Almost all participants (94%) had at least one HR recording above 100 bpm in the first month of clozapine treatment and more than two thirds (68%) had persistent tachycardia.

Tachycardia spontaneously resolved for some, but 44% remained tachycardic by day 28. Spontaneous resolution suggests watchful monitoring may be appropriate over the first month prior to treatment with rate-controlling agents.

1 Introduction

Clozapine is the most effective medication for positive symptoms [1] among one in three people with schizophrenia who are resistant to first-line antipsychotics [2]. However, clozapine is associated with a significant burden of adverse drug reactions (ADRs) [3]. Sinus tachycardia is one of clozapine's most common ADRs, posing a notable challenge, particularly in the early phases of treatment. Tachycardia is commonly defined by a heart rate (HR) exceeding 100 beats per minute (bpm), accompanied by a mean HR of more than 90 bpm within a 24-h period [4]. It has been reported that 33–50% of patients commencing clozapine will experience tachycardia, while over a third of people receiving maintenance treatment have enduring tachycardia [5–8]. While the risk of persistent tachycardia increases with higher clozapine doses, even relatively low doses of 50 mg clozapine induce a significant rise in HR [9]. Risk factors previously hypothesised to increase the likelihood of clozapine-induced tachycardia include younger age, shorter duration of treatment, higher clozapine doses, pre-existing cardiovascular diseases and concurrent use of medications with known cardiac effects, including sodium valproate [6, 7, 10, 11].

Clozapine-induced tachycardia is often conceptualised as a transient and benign phenomenon [12], but it might contribute to cardiac complications and potentially fatal outcomes such as cardiomyopathy and heart failure [13–15] or be a sign of clozapine-induced myocarditis. Tachycardia itself has been shown to be predictive of cardiovascular and all-cause mortality in large population studies [16]. Whether tachycardia is an independent risk factor or a manifestation of underlying sub-clinical pathology has not been determined, though, in general, people with faster HRs have higher morbidity and mortality risks [17].

There is a clear need to better understand the frequency and course of clozapine-induced tachycardia. Much of the extant literature has involved small cohorts with considerable heterogeneity in length of clozapine treatment, methods and timing of HR measurement, lacked pre-clozapine measures and/or has relied on solitary HR measurements, which are prone to bias. Small and predominantly male samples have meant subgroup analyses by demographic factors such as biological sex have been underpowered. In this study, we serially tracked the HRs of over 123 consecutive patients (46 of whom were female) admitted for inpatient psychiatric treatment and who commenced clozapine during their admission. The aim was to determine the frequency and course of clozapine-induced tachycardia over the first month of clozapine treatment and to identify possible risk factors.

2 Methods

2.1 Participants

All patients initiating clozapine during an inpatient mental health admission to a Queensland tertiary hospital between March 2017 and Nov 2022 were included in the study. Patients followed a fixed clozapine titration protocol [18] for the first 2 weeks, with doses increasing up to 200 mg and flexible titration beyond 200 mg after 2 weeks. The only exclusion criterion was if patients had fewer than 10 days of observations. This was a study of a retrospective de-identified data extract, with a waiver of consent as part of the ethics approval.

2.2 Measures and Outcomes

This was a cross-sectional study examining HR during the first 28 days of clozapine treatment. Demographic data, including age, sex, BMI, smoking status and ethnicity were collected. Physical health measures, including HR and blood pressure (BP), were taken in a seated upright position. Data on HR and BP were collected for 3 days prior to commencing clozapine and then daily across the titration period. A maximum of 28 days of monitoring was conducted. Data on clozapine dose, clozapine plasma level and norclozapine plasma level were recorded against their corresponding days of titration.

2.3 Ethics

The study was approved by the Metro South Human Research Ethics Committee (reference HREC/2020/QMS/60964).

2.4 Statistical Analysis

All analyses were performed using R statistical software [19]. Baseline tachycardia was defined as a participant having a HR > 100 bpm for all 3 days prior to clozapine commencement. Mean baseline HR was calculated using the same measures and was grouped into 10 bpm increments as a categorial variable. Baseline hypertension was defined as systolic BP (SBP) > 140 mmHg for all three pre-clozapine measures. Tachycardia during treatment was determined by having ≥ 3 days consecutive HR > 100 bpm. Participants were considered to be tachycardic at day 14 or day 28 if they had HR > 100 bpm on the day of the timepoint and the 2 preceding days. Change from baseline HR was calculated as a raw value (bpm) and as a percentage change. Change in bpm was converted to a categorical measure (< 10 bpm, 11–20 bpm and > 20 bpm) for days 14 and 28.

Descriptive analysis was performed to characterise the sample cohort with chi-squared testing for comparison of categorical variables, and *t*-test, Wilcoxon–Mann–Whitney or Kruskal–Wallis testing for continuous data, as appropriate to the number of data groups and their distribution. Missing data were handled using available case analysis and presented as number and percentage where relevant. Fisher's exact test was used to determine the odds ratios for tachycardia at day 14 or day 28 of treatment, with exploratory variables including age group, sex, BMI, smoking status and baseline HR group. Haldane–Anscombe correction was used where there were no events in the reference group. Multinominal logistic regression was used to determine the relationship between the above exploratory variables, with change in HR as a categorial variable at day 14 and day 28 as the outcome. Correlation analysis was conducted using Spearman's rank correlation coefficient for non-parametric data. Linear modelling was used to further assess relationships if correlations were identified.

3 Results

During the study period, 123 consecutive inpatients were initiated on clozapine and had data collected for at least 10 days. A total of 2901 HR measures were collected. Participants had a mean age of 36.8 years (standard deviation (SD) 11.7), with 63% being males and 64% being of Caucasian ethnicity. Mean BMI was 30.0 (SD 7.3). In addition, 42% were obese, defined as a BMI > 30 kg/m^2 (see Table 1). In total, 70 participants (57%) remained in hospital for the duration of the study and so had 28 days of data collection. The mean duration of stay was 24 days (SD 8.2).

In terms of titration schedules, 112 participants (91%) were prescribed clozapine according to a standard Australian titration schedule [18], achieving a dose of 200 mg/day at day 14, a further 8 had more rapid titrations, and 3 were titrated more slowly. Eight patients (6.5%) were prescribed β-blockers for tachycardia during the study period. Of these, three were taking medication from day 1 of clozapine initiation, while five commenced β-blockers during titration.

Further data on participant characteristics analysed by their baseline HR are available in the Supplementary File.

For the 3 days prior to clozapine initiation, mean HR was 83.7 bpm (range 62–108), which increased significantly to

Table 1 Participant characteristics

DEMOGRAPHIC FEATURES	
Age (years)	
Mean (SD)	36.8 (11.7)
Median [min, max]	36.0 [18.0, 76.0]
Sex	
Female, *n* (%)	46 (37.4%)
Male, *n* (%)	77 (62.6%)
BMI (kg/m^2)	
Mean (SD)	30.0 (7.27)
Median [min, max]	28.7 [16.6, 54.7]
Missing, *n* (%)	3 (2.4%)
BMI > 30 kg/m^2, *n* (%)	51 (41.5%)
Missing BMI data, *n* (%)	3 (2.4%)
Ethnicity	
African, *n* (%)	6 (4.9%)
Asian, *n* (%)	14 (11.4%)
Caucasian, *n* (%)	79 (64.2%)
Indian, *n* (%)	1 (0.8%)
Indigenous (Aboriginal), *n* (%)	9 (7.3%)
Pacific Islander, *n* (%)	1 (0.8%)
Māori, *n* (%)	2 (1.6%)
Indigenous (Torres Strait Islander), *n* (%)	1 (0.8%)
Missing ethnicity data, *n* (%)	11 (8.9%)
BASELINE OBSERVATIONS	
Baseline tachycardia	
Present, *n* (%)	4 (3.3%)
Absent, *n* (%)	119 (96.7%)
Hypertension	
Present, *n* (%)	3 (2.4%)
Absent, *n* (%)	120 (97.6%)
Current smoker	
Yes, *n* (%)	69 (56.1%)
No, *n* (%)	54 (43.9%)
Cigarettes per day (*n*) for smokers	
Mean (SD)	19.1 (7.92)
Median [min, max]	20.0 [10.0, 40.0]
Days of follow up	
Mean (SD)	24.1 (5.18)
Median [min, max]	28.0 [11.0, 28.0]

BMI body mass index (mg/kg^2), *SD* standard deviation

91.6 bpm after the first 3 days of clozapine treatment ($p < 0.001$). Only 3% of patients had tachycardia prior to starting clozapine. Throughout the first 4 weeks of clozapine treatment, HR measurements averaged 99.5 bpm (range 56–158 bpm). Generally, patients' HRs started rising in the first week of clozapine titration and then plateaued in the second week (Fig. 1). HR increased most for participants with lower baseline HRs (Fig. 2a, b). Further data on changes in HR at day 14 and day 28 by baseline HR group are available in the Supplementary File.

Most participants ($n = 115$, 93.5%) had at least one recorded HR > 100 bpm during the first 4 weeks of treatment, and 44 (35.8%) had at least one HR recording exceeding 120 bpm. In total, 84 (68.3%) met the criteria for tachycardia, with at least 3 consecutive days with HRs > 100 bpm recorded (of whom 10 (8%) had HR recordings persistently exceeding 120 bpm).

Five participants developed myocarditis and stopped clozapine; four of these participants presented with fever, while the remaining participant had new electrocardiogram (ECG) abnormalities. All these participants had tachycardia > 100 bpm but only one had a HR > 120 bpm. Clozapine was stopped following confirmation of elevated cardiac enzymes in all five patients.

There was evidence of a possible dose–exposure–response effect with HR rising as clozapine dose increased up to 150 mg, but the dose-HR curve flattened between 150–350 mg (Fig. 3), and overall, there was no correlation (Spearman's rho = 0.079, $p = 0.28$). HRs appeared higher in those receiving more than 350 mg of clozapine, but these estimates were less precise owing to the smaller number of participants prescribed higher doses. Clozapine serum level demonstrated a linear trend towards positive correlation (Spearman's rho = 0.21, $p = 0.0038$); however, this may have been influenced by outliers with gross elevated clozapine levels (Supplementary File). Linear modelling of the relationship between clozapine level and HR yielded an R^2 of 0.05, indicating that that level alone is a poor predictor of HR. There was no demonstrated correlation between clozapine/norclozapine

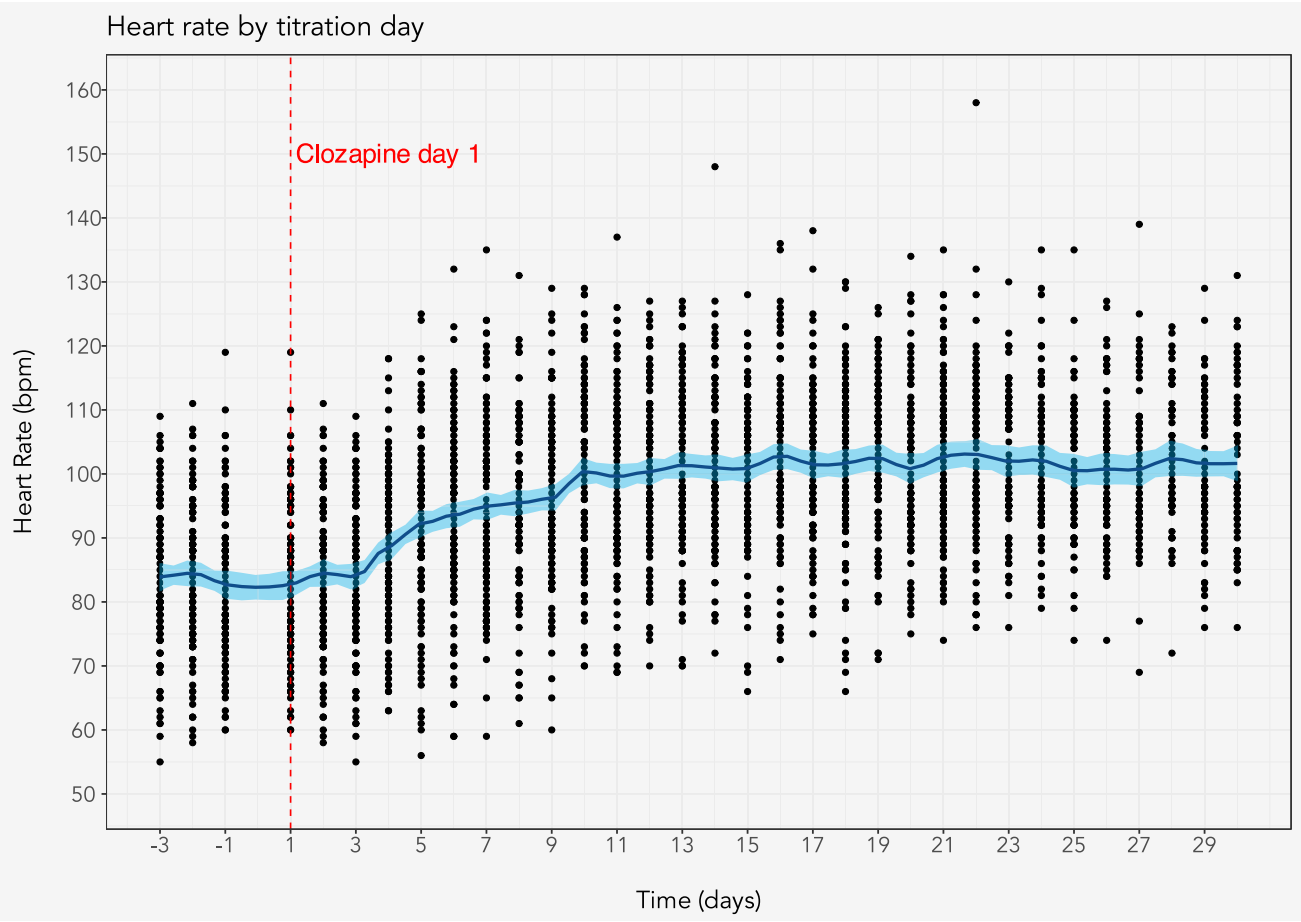

Fig. 1 Heart rate (HR) by time on clozapine. The first 3 days of HR measures were taken prior to commencing clozapine. HR increases almost immediately on commencement of titration and plateaus after approximately 1 week; blue line = Loess smoothed mean HR for entire cohort; blue shading = standard error

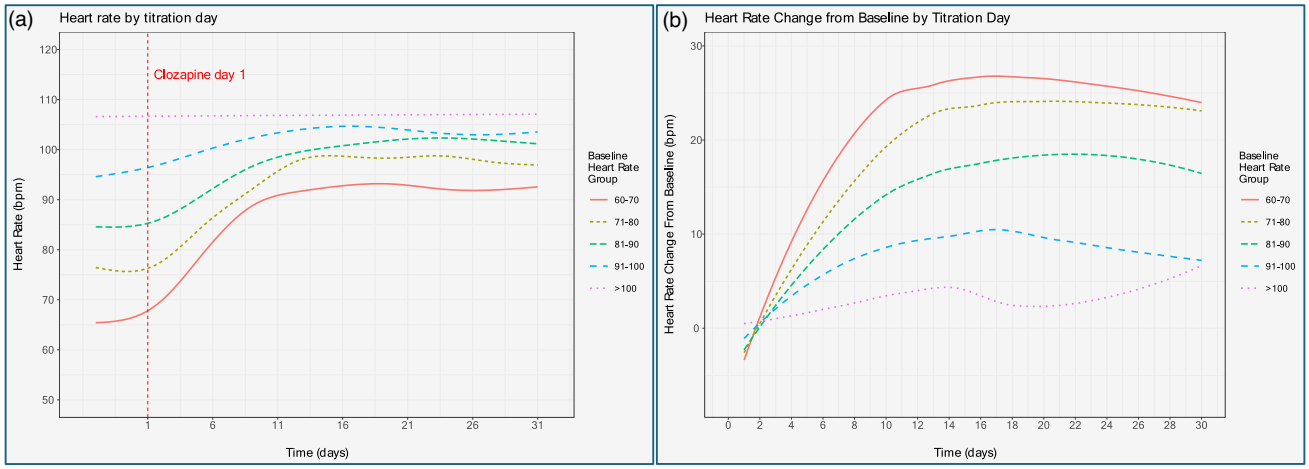

Fig. 2 **a** Heart rate (HR) by clozapine titration day, grouped by baseline HR group. The graph demonstrates that most participants had an increase in HR across titration, stabilising at around day 11. **b** Heart rate (HR) change from baseline, grouped by baseline HR group in beats per minute (bpm), demonstrates that change in HR is most pronounced in the participants with lower baseline HR

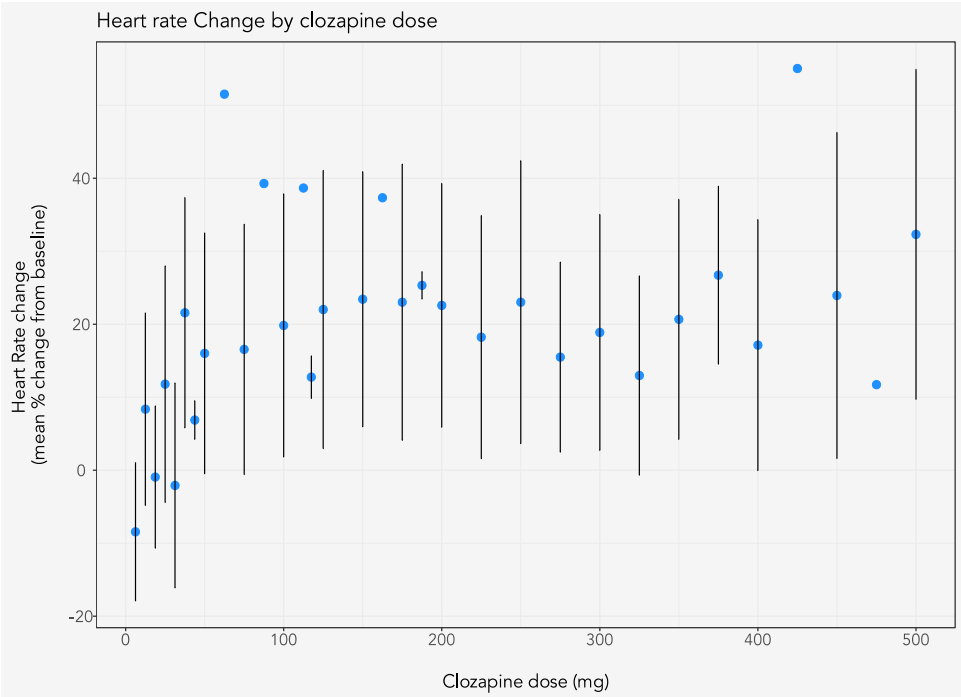

Fig. 3 Heart rate (HR) change from baseline by clozapine dose. Blue dot represents the mean percentage change from baseline at that dose. No significant correlation shown between heart HR and clozapine dose (Spearman's rho = 0.079, $p = 0.28$). Early change in HR at commencement of clozapine aligns with the exposure relationship seen in Fig. 1

ratio and HR during titration (Spearman's rho = 0.0085, $p = 0.90$).

Ethnicity, smoking status and BMI were not significantly associated with tachycardia (Table 2). Younger age and female sex were both associated with higher risk of tachycardia at day 14, but these associations were no longer statistically significant at day 28. Likewise, a higher baseline HR was associated with increased risk of tachycardia at day 14, but not at day 28.

Being tachycardic at day 14 was a strong predictor of being tachycardic at day 28 (odds ratio (OR) 11.28; 95% confidence interval (CI) 3.53–45.78). Multinominal logistic regression, with change in HR at day 14 and day 28 as a categorical variable, revealed that having a higher baseline HR was associated with lower change in HR at day 14, but this relationship was no longer present at day 28 (Table 3). Tachycardia at day 14 was associated with increased likelihood of HR change of 11–20 bpm (estimate

Table 2 Odds ratios for tachycardia according to demographic and clinical risks*

	Odds ratio (OR)	95% CI	*P*-value**
	Day 14		
Age			
> 30 years	Reference	Reference	Reference
< 30 years	2.27	1.01–5.55	0.050
Sex			
Female sex	Reference	Reference	Reference
Male sex	0.34	0.14–0.76	0.008
Ethnicity—other than Caucasian	2.20	0.91–5.85	0.089
Current smoker	1.22	0.57–2.59	0.59
BMI > 30	0.66	0.31–1.40	0.28
Baseline HR group			
61–70 bpm	Reference	Reference	Reference
71–80 bpm	2.56	0.58–12.68	0.22
81–90 bpm	4.29	0.99–22.66	0.031
91–100 bpm	19.38	3.30–163.55	< 0.0001
> 100 bpm	No non-events		
	Day 28		
Age			
> 30 years	Reference	Reference	Reference
< 30 years	1.59	0.50–4.54	0.44
Sex			
Female sex	Reference	Reference	Reference
Male sex	0.74	0.28–1.95	0.55
Ethnicity—other than Caucasian	0.49	0.15–1.50	0.27
Current smoker	0.74	0.28–1.95	0.55
BMI > 30	0.74	0.28–1.95	0.55
Baseline HR Group			
61–70 bpm	Reference	Reference	Reference
71–80 bpm	5.62	0.51–305.46	0.18
81–90 bpm	5.23	0.50–275.10	0.19
91–100 bpm	4.66	0.43–250.06	0.20
> 100 bpm	8.44	0.25–814.53	0.18
Tachycardia at day 14	11.28	3.53–45.78	< 0.0001

BMI body mass index (mg/kg^2), *bpm* beats per minute, *CI* confidence interval, *HR* heart rate

*Haldane–Anscombe correction applied to reference group

**Fisher's Exact Test

= 2.82, standard error = 1.93, *p*-value = 0.048) and > 20 bpm (estimate = 4.78, standard error = 1.95, *p*-value = 0.015) at day 28. Smoking was also associated with an increased likelihood of a bigger increase in HR at day 28: 11–20 bpm (estimate = 2.82, standard error = 1.34, *p*-value = 0.040) and > 20 bpm (estimate = 2.92, standard error = 1.36, *p*-value = 0.032).

Subgroup analysis on participants who remained in hospital over the entire study period ($n = 70$), and thus had 28 days of HR measurements, is shown in Table 3. In total, 59% had tachycardia at day 14, and by the end of 4 weeks, 44% had tachycardia (Table 4).

4 Discussion

This study examined the incidence of clozapine-induced tachycardia in people commencing clozapine through daily monitoring of HR over the first month of clozapine treatment. Almost all our participants (93.5%) had at least one recorded HR > 100 bpm, and two thirds had at least 3 consecutive days with HRs above 100 bpm recorded. In addition, 44 (35.8%) had at least one HR recording exceeding 120 bpm, and about 8% had persistent recordings exceeding 120 bpm. Participants with lower baseline HR had greater increases in HR during clozapine

Table 3 Multinominal logistic regression, with change in HR as a dependent variable; HR change of ≤ 10 bpm was the reference outcome

Day 14 HR change group									
11–20 bpm	Estimate	Std. error	*Z* value	*P*-value	> 20 bpm	Estimate	Std. error	*Z* value	*P*-value
(Intercept)	1.29	1.32	0.98	0.33	(Intercept)	2.29	1.21	1.89	0.06
Age < 30 years	0.08	0.59	0.14	0.89	Age < 30 years	− 0.14	0.63	− 0.23	0.82
Male sex	− 1.00	0.63	− 1.59	0.11	Male sex	− 0.66	0.69	− 0.96	0.34
Ethnicity other than Caucasian	− 0.29	0.66	− 0.44	0.66	Ethnicity other than Caucasian	− 0.33	0.72	− 0.45	0.65
Current smoker	− 0.45	0.65	− 0.69	0.49	Current smoker	0.30	0.67	0.44	0.66
BMI > 30	− 0.59	0.59	− 1.00	0.32	BMI > 30	− 0.78	0.62	− 1.27	0.21
Baseline HR group					Baseline HR group				
61–70 bpm	Reference				61–70 bpm	Reference			
71–80 bpm	1.78	1.29	1.39	0.17	71–80 bpm	0.87	1.09	0.79	0.43
81–90 bpm	− 0.42	1.15	− 0.37	0.71	81–90 bpm	− 1.84	0.95	− 1.93	0.054
91–100 bpm	− 0.95	1.21	− 0.79	0.43	91–100 bpm	− 4.75	1.41	− 3.36	0.00078
> 100 bpm	− 1.21	1.57	− 0.77	0.44	> 100 bpm	− 17.95	1131.10	NA	NA
Day 28 HR change group									
11–20 bpm	Estimate	Std. Error	*Z* Value	*P*-value	> 20 bpm	Estimate	Std. Error	*Z* Value	*P*-value
(Intercept)	− 0.24	2520.35	0.00	1.00	(Intercept)	17.30	1688.53	NA	NA
Age < 30 years	− 1.10	1.03	− 1.06	0.29	Age < 30 years	− 1.54	1.07	− 1.44	0.15
Male sex	− 0.09	1.03	− 0.08	0.93	Male sex	1.24	1.07	1.16	0.25
Ethnicity other than Caucasian	0.31	1.13	0.28	0.78	Ethnicity other than Caucasian	0.71	1.16	0.61	0.54
Current Smoker	2.82	1.34	2.11	0.040	Current Smoker	2.92	1.36	2.15	0.032
BMI > 30	0.70	0.88	0.79	0.43	BMI > 30	0.36	0.96	0.38	0.71
Baseline HR group					Baseline HR group				
61–70 bpm	Reference				61–70 bpm	Reference			
71–80 bpm	0.92	2520.35	0	1.00	71–80 bpm	− 17.72	1688.53	− 0.01	0.99
81–90 bpm	− 2.19	2520.35	− 0.001	1.00	81–90 bpm	− 20.78	1688.53	− 0.012	0.99
91–100 bpm	− 7.66	2520.35	− 0.003	1.00	91–100 bpm	− 26.73	1688.53	− 0.016	0.99
> 100 bpm	− 5.83	2520.35	− 0.002	1.00	> 100 bpm	− 41.42	2732.04	NA	NA
Tachycardia on day 14	3.81	1.93	1.98	0.048	Tachycardia on day 14	4.78	1.95	2.45	0.015

BMI body mass index (mg/kg^2), *bpm* beats per minute, *HR* heart rate

titration, though this did not increase the risk of tachycardia. Neither age, ethnicity nor BMI predicted the risk of tachycardia by day 14 or day 28. Younger age (< 30 years) and female sex increased the risk of tachycardia by day 14, but there was no risk difference by day 28. Cigarette smoking was associated with higher change in HR at day 28, suggesting that smoking may contribute to some of the effect seen.

Tachycardia appeared early in the titration, with a dose response effect at lower clozapine doses that plateaued around 150 mg daily. In total, 59% percent had tachycardia at day 14, but this resolved for some, and by the end of 4 weeks, 44% had tachycardia.

4.1 The Findings in the Context of Prior Studies

Our findings align with previous research that shows that clozapine-induced tachycardia is common when starting clozapine, and it persists in many patients [5–8, 20]. Tachycardia has been reported as the third most common adverse drug reaction cited as a reason for clozapine discontinuation (after sedation and neutropenia) [21], but it is often overlooked by treating clinicians [6].

Risk factors previously suggested to increase the likelihood of clozapine-induced tachycardia include younger age, higher clozapine doses and concurrent use of medications with known cardiac effects [6, 7, 10, 11]. The current

Table 4 Tachycardia amongst participants with both day 14 and day 28 measurements ($n = 70$)

	Day 14		Day 28	
	Tachycardic	Not tachycardic	Tachycardic	Not tachycardic
All participants who remained in hospital for at least 28 days ($n = 70$)	**Total = 41 (59%)** F = 23 (74%) M = 18 (46%)	**Total = 29 (41%)** F = 8 (26%) M = 21 (54%)	**Total = 31 (44%)** F = 15 (48%) M = 16 (41%)	**Total = 39 (56%)** F = 16 (52%)) M = 23 (59%)
If tachycardic at day 14 ($n = 41$)	**Total = 41** F = 23 M = 18 HR>120bpm: Total = 3 (7.3%)	–	**Total = 27 (66%)** F = 14 (61%) M = 13 (72%) HR>120bpm: Total = 1 (3.7%)	**Total = 14 (34%)** F = 9 (39%) M = 5 (27%)
If not tachycardic at day 14 ($n = 29$)	–	**Total = 29** F = 8 M = 21	**Total = 4 (14%)** F = 1 (12.5%) M = 3 (14%) HR > 120 bpm: Total = 0	**Total = 25 (86%)** F = 7 (87.5%) M = 18 (86%)

HR heart rate, *F* female, *M* male

Tachycardia defined as having ≥ 3 days consecutive HR > 100 bpm

findings showed a more complex association with clozapine dose with an initial dose-response effect which plateaued at 150 mg. Tachycardia was associated with younger age at day 14; this association was not significant at day 28, although this may have been a question of power. Our findings also identified people who smoked as experiencing a greater increase in their HR in terms of bpm increase. It was also interesting that those with the lowest baseline HRs had the greatest average increases in bpm—this has not been studied before, and it warrants further attention.

4.2 Strengths and Limitations

There has been little research on clozapine-induced tachycardia. The strengths of this study included the large sample size and sequential daily measuring of HR in a systematic and consistent fashion. We adopted a relatively conservative definition of tachycardia in which participants required persistently elevated HRs > 100 bpm over 3 days to meet the criteria to increase sensitivity and avoid being biased by outlier measurements.

In terms of limitations, data were only collected during the period of hospital admission, with patients with earlier discharge having shorter duration of total data collection. The small number of people on non-standard clozapine titration schedules and on β-blockers meant meaningful analyses by these variables was not possible. We also did not know if patients were being exposed to clozapine for the first time or if they were undergoing a re-trial. Clozapine levels were not routinely collected during the first 2 weeks of titration, and as such we were not able to adequately explore the early relationship between clozapine levels and tachycardia. We did not have information on other medications, aside from medications that regulated HR. The recordings of baseline HR were taken 3 days before starting clozapine during the participant's hospital admission. Given that they are likely to have been experiencing acute psychosis and associated stress, it is quite possible their HRs were elevated above their normal resting rates. Lastly, this study only considered the first month of clozapine treatment. Further research is required to look at longer term clozapine treatment.

4.3 Hypothesised Mechanisms of Clozapine-Induced Tachycardia

The mechanisms whereby clozapine induces tachycardia appear multifactorial and have not been fully elucidated. Hypotheses include clozapine's action on the autonomic nervous system, particularly the cholinergic and adrenergic pathways. Muscarinic receptor antagonism may reduce vagal tone, resulting in increased HR. Clozapine may enhance sympathetic activity, leading to elevated levels of norepinephrine and subsequently tachycardia [22]. Moreover, clozapine's affinity for various receptors, including histamine and serotonin receptors may be contributory to tachycardia through indirect mechanisms involving alterations in neurotransmitter release and modulation of cardiac ion channels. In the longer term, the metabolic side effects of clozapine, such as weight gain and insulin resistance, might also indirectly contribute to cardiovascular issues, including tachycardia [23].

4.4 Clinical Presentation, Risk Factors and Implications

In clinical practice, approaches to monitoring and treating clozapine-induced tachycardia are variable, meaning that it often goes undetected and untreated. Our data show that tachycardia is very common during clozapine initiation, and regular cardiovascular monitoring is recommended, particularly during the early stages of treatment. Given tachycardia > 100 bpm self-resolved in one third of patients by 4 weeks, watchful monitoring may be warranted over the first month of treatment. However, patients with systemic symptoms, including raised BP or persistent tachycardia > 120 bpm may require early treatment. Slower dose titration and adjustment may help mitigate the initial onset of tachycardia [24].

Tachycardia is commonly asymptomatic but may present with shortness of breath, palpitations or chest discomfort. Tachycardia may be an early sign of myocarditis or cardiomyopathy, so serious underlying cardiotoxicity should be ruled out [23]. Persistent tachycardia exceeding 120 bpm or a change in HR of more than 30 bpm from baseline have been identified as risk markers for myocarditis, specifically during clozapine titration [25]. While cardiovascular events, notably myocarditis or cardiomyopathy, require clozapine discontinuation, isolated tachycardia (provided myocarditis is ruled out) should not precipitate discontinuation but rather should be appropriately managed [26].

In terms of pharmacological interventions, a 2016 systematic review found no eligible randomised trials for clozapine-induced tachycardia [23], but some lower quality evidence exists. For example, Stryjer et al. found that β-blockers decreased the mean HR of 20 people with clozapine-associated tachycardia by 16.5 bpm, with 85% no longer meeting criteria for tachycardia [27]. There are further case reports/series of persistent tachycardia being successfully treated with β-blockers [10, 28] and clozapine dose reduction [24, 28].

Despite the limited published evidence, the use of cardiac-specific β-blockers was supported to treat clozapine-induced tachycardia in a Delphi study of international psychosis experts [29]. Cardio-selective β-blockers such as atenolol should be trialled first line, starting at 12.5 mg daily and titrated to the lowest effective dose, up to a maximum of 100 mg daily [3]. Bisoprolol has been recommended over atenolol by some authors, as its higher β-1 selectivity may confer a lower impact on glucose metabolism, making it preferable for patients at risk of diabetes [30].

Ivabradine is a suitable second-line option [31], which can be commenced at 5 mg twice daily and increased to 7.5 mg twice daily after 2–4 weeks if necessary [3]. Ivabradine specifically inhibits the I_f channel in the sinoatrial node. Unlike β-blockers, ivabradine reduces HR without affecting blood pressure or myocardial contractility, making it a potentially safer option for patients with cardiovascular comorbidities [28]. However, more robust clinical trials are needed to establish its efficacy and safety profile in this context.

Non-pharmacological strategies include ensuring adequate fluid intake, avoiding excessive caffeine or nicotine, and monitoring for other contributing factors such as fever or dehydration. Considering that many people treated with clozapine also suffer from increased cardiovascular risk related to smoking and metabolic side effects [32, 33], it is important to actively manage additional cardiometabolic risks.

Future research should focus on well-designed RCTs to evaluate both pharmacological and non-pharmacological interventions. In addition, exploring genetic and biomarker-based predictors of tachycardia risk could help tailor individualized treatment strategies, improving patient outcomes and minimising adverse effects.

5 Conclusions

Sinus tachycardia is a common clozapine adverse effect, occurring in 68% of participants during the first month of clozapine titration. While tachycardia resolved in one third of patients, it was still present for 44% of those initiated on clozapine after 4 weeks of treatment. The long-term implications of tachycardia are unclear, but it potentially predisposes to cardiovascular mortality or signifies clozapine myocarditis. Careful and ongoing monitoring is required. The end of the first month of clozapine initiation may be an appropriate time to consider treatment for persistent tachycardia. Long-term follow-up is required to determine the effects of sinus tachycardia on cardiovascular outcomes in patients treated with clozapine.

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Declarations

Availability of Data and Materials The dataset is available from the corresponding author on request and with appropriate ethics approval.

Code Availability Not applicable.

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Metro South Human Research Ethics Committee - HREC/2020/QMS/60964.

Consent to Participate This was a study of a retrospective de-identified data extract, with a waiver of consent as part of the ethics approval.

Consent to Publish Not applicable.

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