



King's Research Portal

DOI:

[10.1097/JCP.0000000000000792](https://doi.org/10.1097/JCP.0000000000000792)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Joy, G., Whiskey, E., Bolstridge, M., Porras-Segovia, A., McDonagh, T. A., Plymen, C. M., & Shergill, S. S. (2017). Hearts and Minds: Real-Life Cardiotoxicity with Clozapine in Psychosis. *Journal of Clinical Psychopharmacology*, 37(6), 708-712. <https://doi.org/10.1097/JCP.0000000000000792>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Journal of Clinical Psychopharmacology

Hearts and minds; real life cardiotoxicity with clozapine in psychosis

--Manuscript Draft--

Manuscript Number:	JCP-D-17-00090R1
Full Title:	Hearts and minds; real life cardiotoxicity with clozapine in psychosis
Article Type:	Original Contribution
Keywords:	Clozapine Cardiomyopathy Myocarditis Cardiotoxicity
Corresponding Author:	George Joy, MBBS MRCP(UK) UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	
Corresponding Author's Secondary Institution:	
First Author:	George Joy, MBBS MRCP(UK)
First Author Secondary Information:	
Order of Authors:	George Joy, MBBS MRCP(UK) Eromona Whiskey, MPharm Mark Bolstridge, MBChB Alex Porras Segovia, MD Theresa A McDonagh, BSc(HONS) MBChB (HONS) MD MRCP Carla M Plymen, BSc(HONS) MCRP(UK) MD(Res) Sukhi S Shergill, BSc MBBS SFHEA PhD FRCPsych
Order of Authors Secondary Information:	
Manuscript Region of Origin:	UNITED KINGDOM
Abstract:	<p>Introduction Schizophrenia has a 1% prevalence in the population; 30% of these patients are treatment refractory. Clozapine is the only drug licensed to treat treatment refractory psychosis, but concerns about potential adverse effects result in only a proportion of eligible patients being treated. While a well documented neutropenia risk is mitigated by routine blood testing, cardiac toxicity is a commonly cited reason to discontinue clozapine treatment. However; there is little data on the real life cardiac outcomes in those receiving clozapine treatment.</p> <p>Methods Retrospective review of electrocardiogram, echocardiogram and clinical outcomes in 39 inpatients with treatment-refractory schizophrenia, treated with clozapine and other anti-psychotic medication, referred for cardiology opinion.</p> <p>Results Commonest reasons for referral were development of left ventricular (LV) impairment or sinus tachycardia with normal LV function. Patients were reviewed by a range of cardiologists, receiving varied interventions. Median LV ejection fraction (EF) in the clozapine group was normal (52%). Serial echocardiograms demonstrated that clozapine treated patients with LV impairment had no change in LVEF over a four month follow up. LVEF did not differ between patients treated with clozapine and other antipsychotics. However; over an 11 year follow-up period, 48% of patients had discontinued clozapine treatment.</p>

Conclusion

This naturalistic study demonstrates that clozapine is not associated with significant cardiac mortality or morbidity. There is a real need for multidisciplinary working between specialist cardiologists and psychiatrists caring for these complex patients to facilitate optimal long-term physical and mental health outcomes.

(a) Complete manuscript title

Hearts and minds; real life cardiotoxicity with clozapine in psychosis

(b) authors' full names, highest academic degrees, and affiliations

Author 1

Dr. George Joy, MBBS MRCP(UK),
King's College Hospital NHS Foundation Trust
Denmark Hill, London, SE5 9RS
Tel: 020 3299 9000

Author 2

Mr. Eromona Whiskey, MPharm
Clinical Lecturer, South London & Maudsley Hospital
Denmark Hill
SE5 8AZ
Tel: 020 3228 6000

Author 3

Dr. Mark Bolstridge MBCHB
South London & Maudsley Hospital
Denmark Hill
SE5 8AZ
Tel: 020 3228 6000

Author 4

Dr. Alejandro Porras-Segovia, MD
Mental Health Service
Granada University Hospital
Granada, Spain

Author 5

Prof. TA McDonagh BSc(HONS) MBChB (HONS) MD MRCP
Cardiology Department, King's College Healthcare NHS Foundation Trust
Denmark Hill
London
SE5 9RS

Author 6

Dr. Carla M Plymen BSc(HONS) MCRP(UK) MD(Res)
Cardiology Department, Imperial College Healthcare NHS Trust
Hammersmith Hospital , Du Cane Road, London, W12 0HS
Tel: 020 3313 7382
Fax: 020 3313 1684

Author 7

Prof. Sukhi S Shergill BSc MBBS SFHEA PhD FRCPsych
Professor of Psychiatry & Systems Neuroscience and Honorary Consultant
Psychiatrist

Institute of Psychiatry, Psychology and Neuroscience, King's College London and
Maudsley Hospital London
Denmark Hill
SE5 8AZ
Tel: 020 3228 6000

(c) name and address for correspondence, including fax number, telephone number, and e-mail address

Dr. George Joy
18 Woodcroft Ave.,
Mill Hill,
London
NW7 2AG
Fax. 020 3299 3445
Tel: 07794601143
Email: georgejithinjoy@gmail.com

(d) address for reprints

as above

(e) all sources of support, including pharmaceutical and industry support, that require acknowledgment and relevant disclosures for each author; and

There are no sources of support to declare and no conflicts of interest to declare from any author

(f) a running title of no more than 4 words.

Clozapine cardiotoxicity in real-life

ABSTRACT**Introduction**

Schizophrenia has a 1% prevalence in the population; 30% of these patients are treatment refractory.

Clozapine is the only drug licensed to treat treatment refractory psychosis, but concerns about potential adverse effects result in only a proportion of eligible patients being treated. While a well documented neutropenia risk is mitigated by routine blood testing, cardiac toxicity is a commonly cited reason to discontinue clozapine treatment. However; there is little data on the real life cardiac outcomes in those receiving clozapine treatment.

Methods

Retrospective review of electrocardiogram, echocardiogram and clinical outcomes in 39 inpatients with treatment-refractory schizophrenia, treated with clozapine and other anti-psychotic medication, referred for cardiology opinion.

Results

Commonest reasons for referral were development of left ventricular (LV) impairment or sinus tachycardia with normal LV function. Patients were reviewed by a range of cardiologists, receiving varied interventions.

Median LV ejection fraction (EF) in the clozapine group was normal (52%). Serial echocardiograms demonstrated that clozapine treated patients with LV impairment had no change in LVEF over a four month follow up. LVEF did not differ between patients treated with clozapine and other antipsychotics. However; over an 11 year follow-up period, 48% of patients had discontinued clozapine treatment.

Conclusion

This naturalistic study demonstrates that clozapine is not associated with significant cardiac mortality or morbidity. There is a real need for multidisciplinary working between specialist cardiologists and psychiatrists

caring for these complex patients to facilitate optimal long-term physical and mental health outcomes.

INTRODUCTION

Clozapine is the most effective antipsychotic for treatment resistant schizophrenia, however it is significantly underutilised due to various cardiac side-effects, namely sinus tachycardia, myocarditis and cardiomyopathy [1]. Sinus tachycardia is thought to be a benign process, occurring in 25%, however; myocarditis and cardiomyopathy, whilst carrying a significantly lower incidence, incur significantly elevated mortality [2] [3]. Fears surrounding such potential adverse outcomes are reflected in data which show that 30% of eligible patients were not being offered the clozapine whilst 57% were offered three or more different agents before commencing clozapine [4] [5][6].

The BNF states that clozapine should be used with caution in those with pre-existing cardiac disease and should not be considered in those with severe cardiac compromise [7]: This excludes a significant proportion of patients, given their established cardiac risk factor burden. Further; clozapine is frequently discontinued prematurely at the first sign of either cardiotoxicity or its other well-known side-effect, agranulocytosis. It is clear therefore, that there is considerable difficulty in commencing and maintaining therapy with clozapine, however, there has been no large-scale study of clozapine cardiotoxicity, nor has there been a prospective study of the effects of clozapine in those with established cardiac disease.

Given that clozapine is the only evidence-based treatment licensed in refractory schizophrenia, we sought to review outcomes in the cohort of patients on clozapine referred for cardiac review within our academic health sciences centre. This 'clozapine treated' group was compared to a second group of patients with acute psychosis also referred for cardiac review but whom were taking other antipsychotic agents.

METHODS

We undertook a retrospective study of all patients admitted to our national mental health unit and referred, as inpatients, for cardiology review during the past 9 years. This was done via a data-mining search with the

terms 'schizophrenia' 'clozapine', 'antipsychotic', 'cardiomyopathy', 'myocarditis' 'tachycardia' on cardiology clinic letters collated on our electronic system. Patient demographics were recorded, in addition to start and stop dates of clozapine, and dose. Cardiac data at time of review was noted, specifically measurements of echocardiographic (left ventricular ejection fraction) and electrographic indices (QRS duration, QTc interval, heart rate) were recorded. Mortality status (and cause of death) were obtained at time of follow up (date of search).

Results were analysed using student's t-test, Mann-Whitney U, Kruskal Wallis and one-way ANOVA's as necessary. Linear regression analysis was also undertaken to determine correlative data.

RESULTS

Total cohort

During 9 years at our Institution, clozapine was started on 883 inpatients; 27 (0.3%) were referred for cardiology review. A further 12 inpatients on other antipsychotic agents were also referred for cardiology opinion. Mean age for the total cohort was 46 ± 13 years; 31% (12) were female; of those being treated with clozapine, 16 (59%) were referred specifically for tachycardia. Total follow-up time from start of the drug to review of clinic and cardiac data was 10.8 ± 5.8 years.

Clozapine treated patients – whole group

27 patients (69% of the total) referred for review were being treated with clozapine. Mean age at review was 43 ± 12 years and 33% were female (n=9; Table 1). Median left ventricular ejection fraction (LVEF) was 52% (IQR 44-55) and median heart rate (HR) was 98 bpm (IQR 85-114; Table 1).

There was no significant relationship between age and LVEF ($p=0.99$), age and QRS duration ($p=0.16$), age and heart rate ($p=0.73$) or age and QTc interval ($p=0.16$). Further, we found no significant relationship between time on clozapine and LVEF at review ($p=0.85$) or time on clozapine and QRS duration ($p=0.22$).

Clozapine treatment and development of tachycardia

16 patients (59%) being treated with clozapine were referred to cardiology due to the development of a tachycardia. This was a sinus tachycardia in all cases; no arrhythmias were documented at any time point during follow-up in this group. Mean age of this cohort was 44 ± 13 years and 5 were female. LVEF was normal (55% IQR 52-59), as were all electrical intervals (Table 1 below). Mean HR was 103bpm (IQR 94-116; Table 1). There was no significant relationship between time on clozapine and HR ($p=0.15$) or time on clozapine and QTc ($p=0.16$). We also found no significant difference in HR in those with and without symptomatic palpitation ($p=0.49$).

Following review by cardiology, rate controlling medication was started in 44%: Beta-blocker ($n=5$) and ivabradine ($n=2$). However; there was no significant difference in HR in those whom rate controlling medication was started (101 ± 10 bpm) and those in whom it was not (110 ± 14 bpm; $p=0.22$). 40% of symptomatic and 45% of asymptomatic patients were treated.

In total 17 cardiologists were involved in decisions relating to patient management (mean visits 3.75 per patient). At time of follow up 4 patients (25%) had discontinued clozapine, with a time to discontinuation of 28 ± 31 months after review. Reasons for discontinuation were neutropaenia (1), poor compliance (1), patient choice/refusal (2). One patient died in this group and the cause of death was recorded as a suspected suicide.

Clozapine 'Cardiomyopathy' group

Eleven (41%) patients treated with clozapine were referred due to possible development of heart failure/myocarditis or cardiomyopathy. These 11 patients had a median LVEF of 38% (IQR 36-52) at first review; QRSd and QTc were within normal limits 90ms (IQR 88-98) & 431ms (IQR 416-440). There was no significant relationship between time on clozapine and ejection fraction in this group ($r=-0.1$ $p=0.78$).

Follow-up time for this group was 11.6 ± 7 years. During this time 8 patients discontinued clozapine – five diagnosed with myocarditis (only one confirmed with endomyocardial biopsy) and three diagnosed with cardiomyopathy). Three patients died with causes of death as (1) occlusion of descending aorta, (2) subarachnoid haemorrhage, and (3) intestinal pseudo-obstruction (latter two patients were still on clozapine

at time of death). 18 different cardiologists were involved in the management of this patient group; cardiac medication used included: 82% bisoprolol (9), 82% ace inhibitor (9), 27% mineralocorticoid receptor antagonist (3).

Clozapine Group Comparison

There was no significant difference in age ($p=0.49$), gender, QRS duration ($p=0.74$) or QTc interval ($p=0.56$) in those developing a tachycardia or symptoms and signs of heart failure. LVEF was significantly lower in the clozapine 'cardiomyopathy' group (38% vs 55%; $p<0.001$) and HR was significantly higher in the clozapine tachycardia group (103 vs 83bpm; $p=0.002$).

Those with LV impairment tended to be seen earlier than those who developed tachycardia, however; this did not reach statistical significance with a median time to review of 4.7 vs 7.2 years ($p=0.24$). Patients in the former group were far more likely to have clozapine discontinued compared to those in the tachycardia group ($p=0.027$) and clozapine tended to be discontinued sooner after referral in the clozapine cardiomyopathy group compared to the clozapine tachycardia group (median time 0.3 vs 2.3 years $p=0.065$).

Non-clozapine antipsychotic treatment

Twelve patients being treated with an antipsychotic other than clozapine were referred for review during the same time period (Table 2). Average age was 56 ± 9 years and 25% (3) were female. Median HR was 75bpm (IQR 67-96); QRS duration 95ms (IQR 90-117); QTc interval 451ms (IQR 90-117) and LVEF 31% (IQR 27-43).

This cohort was treated with antipsychotic medication for 4.2 (1.6-9.7) years until initial cardiology review. At follow-up, only 8 were being treated with the same antipsychotic; 4 had discontinued their original antipsychotic. Only one of these was secondary to a suspected cardiac side-effect (risperidone); the remainder comprised risperidone ($n=2$) and olanzapine ($n=1$) and these agents were changed for non-cardiac reasons. One patient died in this group with cause of death recorded as heart failure (this patient was on risperidone).

All patients with reduced LVEF were treated with at least 2 prognostic heart failure medications: Diagnoses comprised ischaemic cardiomyopathy (n=4), dilated cardiomyopathy (DCM) secondary to hypertension (n=3), DCM secondary to valvular disease (n=2), DCM related to chemotherapy (n=1) and DCM possibly viral cause (n=1). Sixteen cardiologists managed this group of patients.

Comparison Clozapine vs other antipsychotics: Reduced LVEF

There was a significant difference in age at cardiology review with those on clozapine being younger than those not taking this drug (44 ± 13 vs 56 ± 9 years; $p=0.02$). There was no significant difference between length of time on drug at review between the two groups ($p=0.35$). There was otherwise no significant differences in LVEF, HR, QRS duration or QTc interval between the two groups .

Serial Echocardiogram data in the clozapine cardiomyopathy group and non-clozapine antipsychotics

In total, 7 patients in both groups (14) had serial echocardiograms during their drug treatment. Patients on non-clozapine antipsychotics had echocardiograms over a longer duration of time (28 ± 25 months vs 4 ± 3 months; $p=0.029$) compared to those on clozapine.

There was a non-significant trend towards clozapine having less deterioration in LVEF per month compared to other antipsychotics ($0.8\pm1.4\%$ vs $0.3\pm0.8\%$; $p=0.09$). Patients on non-clozapine antipsychotics were more likely to experience deterioration in ejection fraction during treatment 86% vs 14% $p=0.004$. In the 4 patients on clozapine that did have an echocardiogram before treatment, we find a mild mean LV impairment ($51\pm3\%$) which did not significantly deteriorate post-clozapine treatment (mean $54\pm4\%$; $p=0.18$).

DISCUSSION

Clozapine has been shown to reduce all-cause mortality, homelessness and suicidality in treatment resistant schizophrenia, as compared to other antipsychotics, however anxiety regarding cardiotoxicity significantly limits its use [8]. Our experience appears to contradict many of the concerns regarding its use; this study shows that clozapine is generally very safe, with an absence of any cardiac related mortality during the follow up period, and no evidence that longer duration of treatment correlated with deterioration in cardiac

function, even in those with preceding LV impairment. Despite this, we also show that our cohort had a significant number of patients where clozapine was discontinued.

Our findings confirm that the cardiotoxic effects related to clozapine tend to fall into two distinct categories: a sinus tachycardia with preserved left ventricular function, and a presentation with impairment of left ventricular function without significant tachycardia. It's heartening that none of those in the tachycardia group developed cardiac disease during the follow up period. Two patients in this group had borderline impaired ejection fraction at review; one had undergone previous cardiothoracic surgery to repair a flail mitral valve leaflet, and the other had suspected ischaemic cardiomyopathy. Neither showed progression of LV impairment and no other patient in this group developed this. Our findings would therefore support the literature that clozapine associated tachycardia is benign, however further prospective study is needed to assess the long-term benefits of masking tachycardia with rate-controlling drugs.

Tachycardia is also a recognized feature, albeit extremely non-specific, of myocarditis. We found that 59% of referrals to the cardiology service with 'tachycardia' were prompted due to a concern of myocarditis in the patient. Our study estimates an average incidence of clozapine myocarditis at 0.11%, less than current estimates of the incidence (0.7-1.2%) [9]. The only definitive method for diagnosis myocarditis is through endomyocardial biopsy, which was only undertaken in one of our patients in the study. The clinical features of myocarditis are wide-ranging and non-specific, however tachycardia does not feature in its diagnostic criteria, and often complicates the initial dose titration of the drug. Ronaldson et al advocated for weekly CRP & troponin monitoring in the first month of starting clozapine. CRP and troponin are both sensitive but non-specific for myocarditis and would be excellent gatekeepers to echocardiography, especially in the first month of dose-titration where myocarditis is most common, however the usefulness of this screening method has not been assessed and does not form part of standard practice [10][11].

We find no significant correlation between duration on clozapine and left ventricular EF suggesting that clozapine does not cause a cumulative detrimental effect on cardiac function as supported by another study

by Chow et al as outlined below [12]. In those patients with LV systolic dysfunction already present at the time of cardiology review, we found no deterioration in cardiac function in the short term whilst remaining on clozapine. Baseline echocardiography is not routinely performed in our patients prior to starting clozapine, thus it is difficult to be sure if LV systolic dysfunction pre-dated - and was thus unrelated to - clozapine use: We should remember that this cohort of patients is at significant risk for other cardiovascular disease.

Other studies might suggest that long-term clozapine use is associated with a small decline in LV systolic function over time. Chow *et al* compared patients with schizophrenia receiving either clozapine (n=100) or taking non-clozapine antipsychotics (n=21) and 20 healthy, untreated, individuals over a 2 year period. They noted a reduced EF of approximately 3.9% in the clozapine group compared with the group taking other antipsychotics, and 6.5% compared to the healthy group [12]. We feel that comparing those with schizophrenia and its incumbent cardiovascular risk profile to healthy individuals is fundamentally flawed and, further; a 4% difference between the groups is well within the established margin of reporting error for LVEF. Another group studied 38 patients on clozapine over a 12 month period and likewise found subclinical LV dysfunction in one third of treated patients with a 5% decline in EF during the course of the study [13]. The authors in this latter group however, ascribe LV dysfunction to an EF of between 50-55%: many cardiologists would feel this is within the normal range and as such it is difficult to interpret the findings of this study. It is also very important to note the major limitation in these studies is that the use of prognostic heart failure medications were not described in the treatment or control groups; this would significantly affect LV function, but also change and recovery of such also [12, 13].

Other retrospective studies namely conducted by Ronaldson et al and Haas et al describes clinical features, biochemical and echo findings of patients diagnosed with clozapine myocarditis. [1][3] Our study is unique in that provides additional insight into the management approaches adopted by clinicians, and a comparison with cardiac outcomes of non-clozapine antipsychotics, something that has not yet been described to our knowledge. Our study also has the longest follow-up period for these patients at 11 years and data was

obtained from the largest psychiatric research centre in Europe.

Our experience is that the short to medium term outcome during therapy with clozapine is acceptable with no observable deterioration in LV function. Any potential decline in cardiac function with clozapine needs to be balanced against the beneficial effects of the drug on patients with treatment-resistant schizophrenia, which carries its own considerable morbidity and mortality. Effective prognostic medical therapy of LV dysfunction would be hoped to support the ongoing use of clozapine: This is something that facilitates ongoing cancer therapy with a similar agent that causes LV dysfunction, trastuzumab [14]. For this reason, the authors advocate for referral and ongoing follow-up of these patients in specialist heart failure units.

During the 9 years data was collected, 883 patients in total were started on clozapine in our Trust, approximating to 100 initiations per year. Despite this volume, there are no national clinical guidelines for the monitoring of cardiotoxicity in patients receiving clozapine; a starting point might be adopting those already in place for anti-cancer drugs; such as the afore-mentioned trastuzumab, used in breast cancer. Here, baseline echocardiograms are done followed by further studies at 4 and 8 months and on completion of treatment [14].

Our study found 18 different cardiologists involved in the management of these patients, with wide ranging clinical decisions based on the preference and expertise of the individual cardiologist, the vast majority of whom were not heart failure specialists. There is a wealth of data to support the fact that any patient with LV dysfunction has less mortality under a specialist [15] and as such we propose that a dedicated team (including a heart failure specialist) should manage these patients facilitating early review and ongoing dialogue with psychiatrists to enable continuation of clozapine and prevention of premature (unnecessary) discontinuation of it. Of the significant number of patients who had clozapine discontinued, it is entirely possible that some of them might have been advised to continue had their care been under specialist joint supervision and had there been structured guidelines in place. The lack of a cohesive coordinated approach to care in our study is emphasized by the finding that the group of patients receiving heart rate control drugs compared to those that did not had

no significant difference in heart rate nor symptoms nor outcome.

Tendency to increased cardiac mortality in patients with schizophrenia is attributable at least in part to the adverse metabolic effects of antipsychotics, including weight gain, dyslipidaemia and diabetes [16]. However, one of the largest population studies to date, the Fin11 trial, demonstrates that clozapine reduces all-cause mortality as compared to other anti-psychotics [8]. Of course, the better treated their mental health is the better treated the cardiac problems tend to be. The majority of antipsychotics in common use have been associated with cardiotoxicity to varying degrees as described by Coulter et al, with the highest incidence attributed to clozapine use [17]. However a bias must be conferred to the fact that clozapine cardiotoxicity is much better described than cardiotoxicity associated with other antipsychotics. This bias is observed in our cohort of patients on non-clozapine antipsychotics where only one patient had cardiac side-effect mentioned as a contributing factor to their impaired cardiac function, in contrast to clozapine where this was considered the culprit in all patients, despite very similar cardiac risk factor profiles.

Conclusions:

Clozapine use is relatively safe with very acceptable short and medium term data. Misconceptions and lack of specialist knowledge drive early termination of its use and fears regarding what are often benign side effects. We advocate for the promotion of joint working between heart failure and psychiatric teams in multidisciplinary fashion.

Limitations

Although we are the largest mental health unit in the UK, the sample size presented here is relatively small. It is possible that this reflects the low, but true, incidence of clozapine cardiotoxicity however it is also possible that patients may have been missed due to referral to the emergency department instead of cardiology specifically. This is unlikely however, as such patients would be expected to have been subsequently picked up by the cardiologists. It is also possible that sub-acute incidences of myocarditis were missed – however we feel that this reflects the nature of myocarditis in that many healthy individuals will never present to medical

services either. In our unit we undertake CRP and troponin measurements on starting clozapine so it is unlikely that even subacute cases were missed however.

REFERENCES

- [1] Ronaldson KJ, Fitzgerald PB, Taylor J et al, A new monitoring protocol for clozapine- induced myocarditis based on an analysis of 75 cases and 94 controls, Aust N Z J Psychiatry 2011 Jun; 45(6): 458-65
- [2] Alawami M, Wasywich C, Cicovic et al, A systematic review of clozapine induced cardiomyopathy, Int J Cardiol 2014, 176 , (2) , 315 – 320
- [3] Haas SJ, Hill R, Krum H, Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. Drug Saf. 2007;30(1):47-57.
- [4] Cooper S, Crawford M, Dicks S, et al. Report of the second round of the National Audit of Schizophrenia (NAS2) 2014
- [5] Mistry H, Osborn D, Underuse of clozapine in treatment-resistant schizophrenia, Adv Psychiatr Treat 2011, 17, 250–255
- [6] Tungaraza TE, Farooq S. Clozapine prescribing in the UK: views and experience of consultant psychiatrists. Ther Adv Psychopharmacology. 2015;5(2):88-96.
- [7] Joint Formulary Committee, 2017. Clozapine. In: JOINT FORMULARY COMMITTEE. British National Formulary [online]. London: BMJ Group and Pharmaceutical Press. Available from: https://www.medicinescomplete.com/mc/bnf/current/PHP2273-clozapine.htm?q=clozapine&t=search&ss=text&tot=12&p=1#_hit accessed 4th July 2017
- [8] Tiihonen J, Lonnqvist J, Wahlbeck K et al, 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study), Lancet. 2009 Aug 22;374(9690):620-7
- [9] Layland JJ, Liew D, Prior DL, Clozapine-induced cardiotoxicity: a clinical update, Med J Aust 2009; 190 (4): 190-19

- [10] Caforio AL1, Pankuweit S, Arbustini E, Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, *Eur Heart J*. 2013 Sep;34(33):2636-48
- [11] Goitein O, Sabag A, Koperstein Rafi et al, Role of C reactive protein in evaluating the extent of myocardial inflammation in acute myocarditis, *J Cardiovasc Magn Reson* 201517(Suppl 1):291
- [12] Chow V, Yeoh T, Ng AC, Asymptomatic left ventricular dysfunction with long-term clozapine treatment for schizophrenia: a multicentre cross-sectional cohort study, *Open Heart*. 2014 Feb 26;1-10(1)
- [13] Rostagno C1, Domenichetti S, Gensini GF. Does a subclinical cardiotoxic effect of clozapine exist? Results from a follow-up pilot study, *Cardiovasc Hematol Agents Med Chem*. 2012 Jun;10(2):148-53
- [14] Scottish Intercollegiate Guidelines Network (SIGN), Treatment of primary breast cancer. Edinburgh: SIGN; 2013, (SIGN publication no. 134
- [15] Mitchell P, Marle D, Donkor A et al, National Heart Failure Audit April 2013-March 2014, published October 2015
- [16] Raedler TJ, Cardiovascular aspects of antipsychotics. *Curr Opin Psychiatry*. 2010 Nov;23(6):574-81
- [17] Coulter DM1, Bate A, Meyboom RH et al, Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study, *BMJ*. 2001 May 19;322(7296):1207-9.

	Other Antipsychotics group (n=12)	Clozapine 'Cardiomyopathy' group (n=11)	Clozapine 'Tachycardia' group (n=16)	Clozapine Total group (n=27)	p value*	Whole group (n=39)
Age, years	56 ±9 (p=0.02)**	44 ± 13	40 ± 13	43 ± 12	0.49	46+/-13
Gender (% female)	3 (25%)	4 (36%)	5 (31%)	9 (33%)	-/-	12 (31%)
Time on drug at review, median (IQR) years	4.2 (1.6-9.7) p=0.35**	4.7 (0.3-7.3)	7.2 (1.3-10)	4.8 (0.8-8.5)	0.24	4.8 (0.8-8.5)
Heart rate Median (IQR) bpm	75 (67-96) p= 0.63**	83 (76-90)	103 (94-116)	98 (85-114)	0.002*	92 (79-106)
QRS duration Median (IQR) ms	95 (90-117) p=0.09**	90 (88-98)	90 (85-96)	90 (86-96)	0.74	90 (88-99)
QTc interval Median (IQR) ms	451 (422-502) p = 0.14**	431 (416-440)	432 (418-453)	434 (418-458)	0.56	437 (418-460)
LVEF Median (IQR) %	31 (27-43) p=0.26**	38 (36-52)	55 (52-59)	52 (44-55)	<0.001*	46 (36-55)
Clozapine discontinued	-	8 (73%)	4 (25%)	13 (48%)	0.027*	

Table 1: Demographics, cardiac variables and p-values. *denotes comparison between the clozapine cardiomyopathy and tachycardia groups. **denotes comparison between clozapine cardiomyopathy and other antipsychotics group