



The association between exposure to clozapine, olanzapine, and quetiapine and the outcomes perimyocarditis and heart failure: A population-based cohort study

Eric Clapham^{a,b,*}, Johan Reutfors^b, Marie Linder^b, Lena Brandt^b, Johan Sundström^{c,d}, Robert Bodén^a

^a Department of Medical Sciences, Psychiatry, Uppsala University, Sweden

^b Centre for Pharmacoepidemiology (CPE), Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Sweden

^c Department of Medical Sciences, Clinical Epidemiology, Uppsala University, Sweden

^d The George Institute for Global Health, University of New South Wales, Sydney, Australia

ARTICLE INFO

Keywords:

Antipsychotics
Clozapine
Cardiac adverse events
Myocarditis
Pericarditis
Cardiomyopathy

ABSTRACT

The risk of cardiac adverse events following clozapine use is debated and is unknown for the chemically related and widely used antipsychotics olanzapine and quetiapine. National Swedish registers were used to identify all patients 16–75 years old with antipsychotic dispensations between 2005 and 2018. The short-term outcome was a diagnosis of perimyocarditis (pericarditis and/or myocarditis) within two months of first dispensation, and the long-term outcome was heart failure (including cardiomyopathy) within three years. Cox regressions with time varying exposure were used to estimate hazard rates (HR) and their 95% confidence intervals (CI). A total of 201,045 individuals were included in the cohort. The risk of developing perimyocarditis during clozapine treatment tripled compared to no antipsychotic treatment (HR 3.4, CI 1.6–7.3), although the absolute rate remained comparably low. The long-term risk of heart failure during clozapine treatment was also elevated (HR 1.3, CI 1.1–1.7). Treatment with either or both olanzapine or quetiapine was not associated with an increased relative risk of perimyocarditis, or heart failure compared to no antipsychotic treatment. Clozapine use is therefore associated with a substantially elevated short-term risk of perimyocarditis and an increased risk of heart failure within three years.

1. Introduction

The antipsychotic drug clozapine is the only approved treatment for therapy refractory schizophrenia (Rubio and Kane, 2020) and in this group some 40% of individuals are estimated to respond to clozapine (Siskind et al., 2017). It may also be used in other conditions such as risk of suicide in schizophrenia spectrum disorders, Parkinson's disease psychosis and bipolar disorder (Gammon et al., 2021). However, clozapine has been associated with serious cardiac adverse events such as myocarditis and pericarditis (De Berardis et al., 2018; Kilian et al., 1999; Sahyouni and Hefazi, 2021), typically early on in the treatment course. In the following text, they are jointly referred to as perimyocarditis as the two conditions form a continuum and can be difficult to differentiate in clinical practice (Manda and Baradhi, 2022; Sharif and Dehghani, 2013). Clozapine has also been associated with adverse cardiac events

after longer exposures, including cardiomyopathy and its clinical consequence, heart failure (Kilian et al., 1999; Whiskey et al., 2020).

Perimyocarditis can run a dramatic and sometimes lethal clinical course, and can also lead to subsequent cardiomyopathy and heart failure (Ronaldson, 2017). Why clozapine may lead to perimyocarditis is largely unknown, but the condition typically develops within the first treatment month (Bellissima et al., 2018). Myocarditis after clozapine exposure is often associated with eosinophilic infiltration of the myocardium, which indicates that it may be a type I hypersensitivity reaction (Kilian et al., 1999), or reflect a syndrome of a clozapine-caused hypereosinophilia (Hagg et al., 2001). Myocarditis has been documented as a side effect of clozapine in over 350 case studies since 1980 (Bellissima et al., 2018), while there is only a limited number of case studies involving pericarditis, suggesting it may be overlooked with comorbid myocarditis (Bugge et al., 2016). The reported incidence range for

* Corresponding author at: Department of Medical Sciences, Psychiatry, Uppsala University, Ing 10, vån 3, Uppsala SE-751 85, Sweden.

E-mail address: Eric.Clapham@neuro.uu.se (E. Clapham).

<https://doi.org/10.1016/j.psychres.2023.115336>

Received 26 April 2023; Received in revised form 28 June 2023; Accepted 6 July 2023

Available online 12 July 2023

0165-1781/© 2023 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

clozapine-associated perimyocarditis is wide: from 0.1% to 5.3% (Sandarsh et al., 2021; Siskind et al., 2020). On the one end, the only population-based register study, based on Danish health registers, found myocarditis, pericarditis and cardiomyopathy to be no more common among clozapine-treated patients than among patients treated with other antipsychotics (Rohde et al., 2018). This is contrasted by the estimated 3% incidence of clozapine-associated perimyocarditis in Australia (Ronaldson et al., 2015; Siskind et al., 2020).

It is unknown whether there is also an increased risk of perimyocarditis with the chemically related, and much used, antipsychotics quetiapine and olanzapine. A recent pharmacovigilance study has detected a signal for both quetiapine and olanzapine use as a probable risk increase for perimyocarditis (De Las Cuevas et al., 2022). There are also several case studies for perimyocarditis, cardiomyopathy, and heart failure in the literature (Bhagal et al., 2018; Hagiwara et al., 2018; Puttegowda et al., 2016; Smolders and Smolders, 2017; Vang et al., 2016; Wassef et al., 2015). However, the previously mentioned Danish population-based study did not observe an increased risk of cardiac adverse events during treatment with olanzapine and quetiapine (Rohde et al., 2018). However, even if the incidence of perimyocarditis and heart failure is low during olanzapine and quetiapine treatment, it may be of clinical importance to identify even a small increase in risk, as these compounds are among the most commonly used antipsychotics (Halfdanarson et al., 2017).

To summarize, the magnitude of the risk for perimyocarditis, cardiomyopathy, and heart failure during clozapine treatment is unknown, and it is uncertain whether there also is a risk with olanzapine and quetiapine. We therefore carried out a population-based cohort study using Swedish national health registers to investigate the risk of adverse cardiac events during exposure to clozapine, olanzapine, quetiapine, and other antipsychotics.

2. Methods

2.1. Data sources

The Swedish National Patient Register (Ludvigsson et al., 2011), the Prescribed Drug Register (Wettermark et al., 2007), the Cause of Death Register (National Board of Health, 2010), and the Total Population Register were used for this study (Ludvigsson et al., 2016). All Swedish residents are assigned a unique personal identification number at birth or upon immigration (Ludvigsson et al., 2009), which were used to link the registers. The Cause of Death Register includes all deaths that occur in Sweden as well as deaths abroad among Swedish residents. The Total Population Register encompasses all legal residents in Sweden and includes information on migration in and out of the country.

The National Patient Register provided information on outcomes and potential confounding factors. The register contains details on diagnoses from inpatient discharge as well as outpatient visits within specialized care. Beginning in 1997, diagnoses are coded according to the International Classification of Disease (ICD) version 10.

The Prescribed Drug Register was used to assess antipsychotic exposure and potential confounding medications. The register contains information on all dispensed drugs at Swedish pharmacies since July 2005, and includes information on Anatomical Therapeutic Chemical (ATC) classification code, quantity, and dates of dispensing. Drugs administered during inpatient care are not recorded in the Prescribed Drug Register.

2.2. Study design and population

This study used a cohort design with time-dependent exposure to antipsychotic medication. The full cohort included Swedish residents 16 to 75 years old, who filled a first prescription for any of the included antipsychotics between January 1, 2006, and December 31, 2018. A schizophrenia cohort was constructed including only individuals aged

up to 55 years with the ICD-10 schizophrenia spectrum diagnoses of schizophrenia, schizoaffective disorder, or unspecified non-organic psychosis (ICD-10 codes F20, F25 or F29) given after July 1, 2005. For purposes of supplementary analyses we considered the full cohort excluding individuals with a schizophrenia spectrum diagnosis. In supplementary analyses we also included the full cohort aged up to 65 years of age. This was intended to exclude late-onset schizophrenia, which may be associated with dementia (Kodesh et al., 2020). Analyses stratified by sex were also conducted.

Individuals were excluded if they had a diagnosis of perimyocarditis, cardiomyopathy or, for the long-term outcome, heart failure (ICD-10 diagnoses are given in Supplementary Table 1) prior to filling a first prescription of an antipsychotic. Individuals were also excluded if they had been prescribed an antipsychotic medication during a wash-out period between July 1 and December 31, 2005. This means that an individual who was first included in the cohort on January 1, 2006, had at least six months of non-prescription, while subsequently included individuals had a longer such period. The intention was to exclude prevalent users as far as possible while not sacrificing too much of the available data set.

The initial prescription of an antipsychotic medication when an individual is included in the cohort, is referred to as the 'index prescription'. Individuals who had been discharged from psychiatric inpatient care, lasting more than 14 days and ending less than 30 days prior to filling the index prescription, were excluded. This was done to exclude recent hospitalizations that could have involved medication changes, since register data on inpatient medications are not available in Sweden. Individuals were censored when they reached the age of 75 years (or 55 for the sub-cohort), emigrated, or died (right censoring). Individuals were also censored in the absence of outcome after two months (for perimyocarditis) or three years (for heart failure). These time limits have been used previously (Rohde et al., 2018) and it is believed that the three-year cut off is sufficient for heart failure to develop without substantially diluting the outcome with other causes beyond clozapine treatment.

Once an individual had experienced the outcome under study, that individual was no longer included in the cohort. The time dependent design means that an individual could switch antipsychotic exposure. Individuals who had been censored due to absence of outcome could be re-included if they had been prescribed a new antipsychotic, given that they still fulfilled the inclusion criteria. The two outcomes were studied in separate models.

The number of psychiatric hospitalizations since July 1, 2005 was assessed at the time of the index prescription to represent the individual's history of inpatient treatment.

2.3. Exposure

Exposures were divided into the following groups: antipsychotic medication including clozapine, antipsychotic medication including either or both olanzapine and quetiapine but not clozapine; antipsychotic medication not including clozapine, olanzapine, or quetiapine; and unexposed to antipsychotic medication. During periods of psychiatric inpatient care individuals were assigned to a separate exposure group, unknown inpatient medication (UIM). Individuals were assigned an unexposed group after the last prescription was completed, but individuals who later filled a prescription for an included antipsychotic medication were reassigned to an exposed group. Exposure was aggregated not least to limit the number of separate groups and increase statistical power. However, in supplementary analyses, exposure to clozapine without olanzapine or quetiapine as well as olanzapine and quetiapine separated were also analyzed.

All antipsychotic medications were included unless there was a specific reason not to do so, and therefore oral antipsychotics which are predominantly used as sedatives or antiemetics, as well as short acting injectable antipsychotics, were not included as index prescriptions. ATC

codes for excluded antipsychotics are given in Supplementary Table 3.

Exposure time was constructed using a semi-manual approach based on package size and prescription information in text format. Exposure time was counted from the day the prescription was filled. When no dosage information was available on the prescription, it was assumed that the individual was prescribed the most common dose (mode) in the data set. For long acting injectables, the time between injections was derived from the prescription or, when not available, assumed to be equal to the manufacturer's recommendation. When the manufacturer had more than one recommended interval, the empirically most frequently occurring interval was used, based on the prescriptions where information was available. In order to allow for some inconsistency in prescription filling without generating separate exposure episodes (Nielsen et al., 2008), the estimated prescription duration was extended by 25% (grace period); any previous remaining grace period was cancelled when a new prescription was filled.

Since antipsychotic treatment during outpatient care just before hospitalization may have led to adverse cardiac outcomes being diagnosed during the subsequent hospitalization, episodes of unknown inpatient medications were reassigned to the preceding antipsychotic exposure episode, if any, in supplementary analyses.

2.4. Outcomes

The short-term outcome was a diagnosis of perimyocarditis (pericarditis and/or myocarditis) within two months. The long-term outcome was heart failure, including cardiomyopathy within three years, as the clinically relevant consequence of cardiomyopathy is heart failure. Henceforth, heart failure is defined to include cardiomyopathy. In addition to heart failure, we also analyzed the more specific outcome of cardiomyopathy in supplementary analyses.

For outpatients, the date of visit to the clinic was used, while for inpatients the date of discharge was used as the date of onset of the outcome. ICD-10 codes corresponding to the outcomes of perimyocarditis and heart failure are listed with descriptions in Supplementary Table 1.

Swedish routine monitoring related to cardiac adverse events of patients initiating treatment follows the recommendations of the European Medicines Agency (EMA, 2002). This includes, for instance, a physical examination, an ECG in many cases, the advice that tachycardia following treatment initiation should be interpreted as a possible sign of myocarditis, and gradual dose titration.

2.5. Confounding

There is evidence of an association between psychotic conditions such as schizophrenia and substance use disorders (Khokhar et al., 2018), HIV (Bauer-Staeb et al., 2017; Liang et al., 2020) and inflammatory diseases (Cullen et al., 2019). Cardiovascular disease is over-represented in schizophrenia (Ringgen et al., 2014). This indicates that these conditions are not only associated with the outcome but are true confounders. Hyperthyroidism is associated with the outcome, but the association with exposure is more tentative (Scorza et al., 2011), although it may be considered a potential cofounder. Polypharmacy, prescription of a long acting injectable, and psychiatric comorbidity reflects disease severity and may modify the risk of the outcomes. To illustrate covariates relevant as confounders for the outcomes, directed acyclic graphs were drawn (Supplementary Figures 1–2).

In the fully adjusted analyses, the included confounders were: sex; age; somatic conditions and medications known to increase the risk of perimyocarditis, cardiomyopathy, and heart failure; presence of polypharmacy defined as more than one prescribed antipsychotic; prescription of a long acting injectable; psychiatric diagnosis, by ICD-10 main category. The somatic conditions and medications that were controlled for are given in Supplementary Table 2.

2.6. Statistical analysis

For categorical variables, descriptive statistics were given as numbers and proportions, while means and standard deviations were provided for continuous variables. Main analyses used time dependent Cox regressions (Zhang et al., 2018). Antipsychotic exposure was the only time dependent variable. As an additional measure, the proportional hazards assumption was tested by inspection of log-log plots (Supplementary Figs. 3, 4), although this is not strictly applicable for the counting process approach. Control for confounding was implemented using categorical variables; except for age, which was included as a continuous variable representing age as the logarithm of whole years. The confounders were updated if a previously censored individual was re-included following resumed antipsychotic use. Hazard rates were computed using episodes with no antipsychotic exposure as the reference group. Variances were computed using the robust sandwich estimator (Binder, 1992; Kauermann and Carroll, 2001), to take into account that each individual may contribute to several exposure periods. As a sensitivity analysis, we also estimated a Fine-Gray model with death as a competing risk. All statistical analyses were performed using SAS 9.4.

2.7. Ethics

The study was approved by the regional ethical review board in Stockholm (ref. nr. 2017/1236–31/2).

3. Results

A total of 201,045 individuals were included in the full cohort and were prescribed at least one of the included antipsychotics from January 1, 2006, to December 30, 2018 (Fig. 1 and Table 1). The mean age was 43.5 years (52.8% women). Most individuals were on antipsychotic monotherapy (84.5%), and most had a history of less than five episodes of psychiatric hospitalizations (96.3%). A mood disorder was the most common psychiatric condition (47.7%), closely followed by neurotic, stress-related, or somatoform disorders (46.0%).

Within the full cohort, 15,238 fulfilled diagnostic and age criteria necessary to be included in the schizophrenia cohort. The mean age was 37.7 years (41.4% women). Just over a third were on antipsychotic monotherapy (36.7%) and most had less than five episodes of psychiatric hospitalization (89.1%).

Of those who initiated clozapine treatment in the full cohort, 9 out of 5493 individuals (0.16%), developed perimyocarditis within two months and the incidence rate was 1.93 per 1000 person-years (Table 2). A lower incidence rate of 0.35 per 1000 person-years was found for those exposed to olanzapine and/or quetiapine. Compared to no antipsychotic treatment, the risk of developing perimyocarditis while on clozapine treatment was tripled in the full cohort (aHR 3.4; 95% confidence interval [CI] 1.6–7.3) and was five times higher in the schizophrenia cohort (aHR 5.4; CI 1.2–24.1). However, exposure to olanzapine and/or quetiapine was not associated with perimyocarditis in either the full cohort (aHR 0.8; CI 0.4–1.3) or the schizophrenia cohort (aHR 1.6; CI 0.4–7.6). Belonging to the exposure group UIM was associated with an elevated risk of perimyocarditis in the schizophrenia cohort only (aHR 17.1; CI 1.5–197.1), but this was based on only 3 outcome events.

Of those who initiated clozapine treatment in the full cohort, 87 out of 5486 individuals (1.6%), developed heart failure within three years, and the incidence rate was 5.05 per 1000 person-years (Table 3). The incidence rate for heart failure in the full cohort was 3.26 per 1000 person-years within three years of initiating treatment with olanzapine and/or quetiapine. Compared to no antipsychotic treatment, the risk of heart failure was elevated for clozapine in the full cohort (aHR 1.3; CI 1.1–1.7) but not in the schizophrenia cohort (aHR 1.1; CI 0.6–1.8). Exposure to olanzapine and/or quetiapine was not associated with a higher risk of heart failure, compared to no antipsychotic treatment,

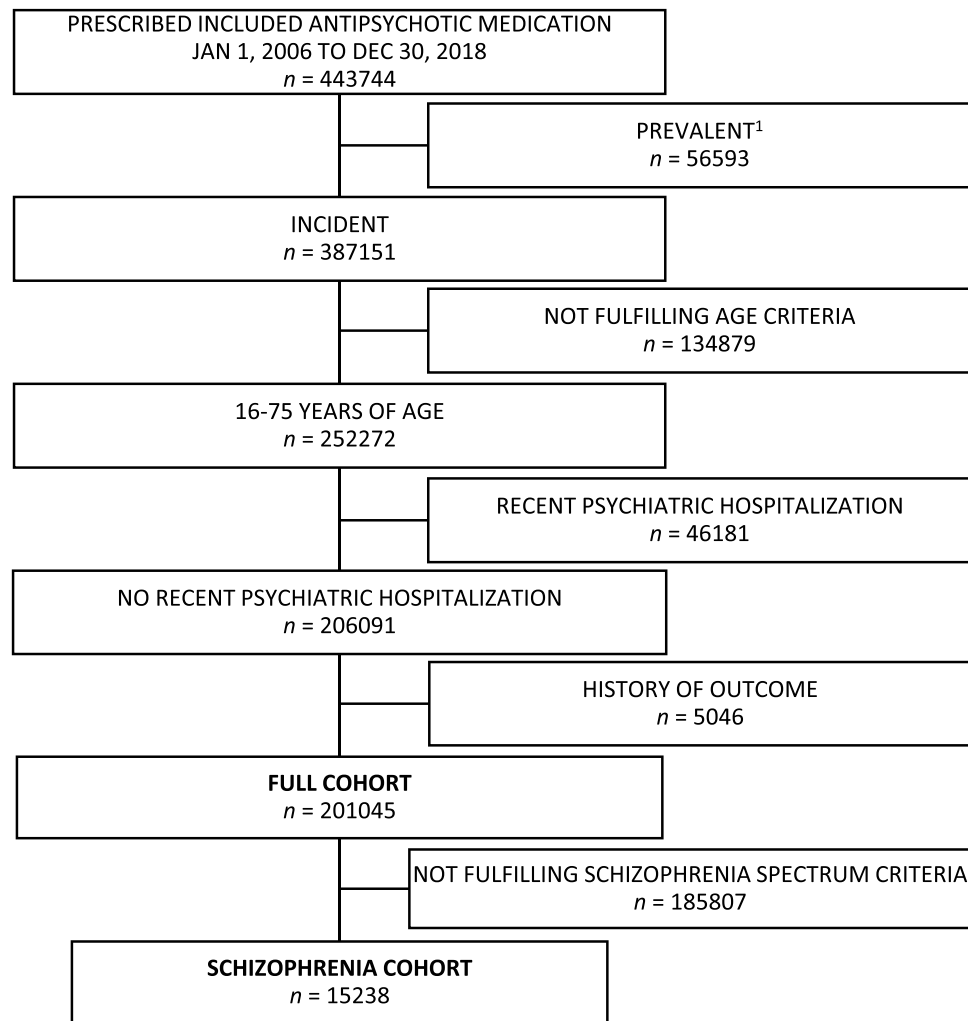


Fig. 1. Flowchart for cohort inclusion.

¹ Individuals were considered prevalent users if prescribed an antipsychotic medication during a wash-out period between July 1 and December 31, 2005.

either in the full cohort (aHR 1.0; CI 0.9–1.1) or in the schizophrenia cohort (aHR 0.8; CI 0.5–1.3).

The incidence rates of cardiomyopathy alone in the full cohort were 0.46 and 0.36 per 1000 person-years for exposure involving treatment with clozapine and olanzapine and/or quetiapine, respectively (Supplementary Table S4). No significant risk of cardiomyopathy was detected for either clozapine or olanzapine and/or quetiapine in any of the cohorts.

In sensitivity analyses, UIM periods were also reclassified to the nearest previous exposure (Supplementary Tables S5 and S6). Compared to no antipsychotic treatment, the risk of developing perimyocarditis while on clozapine treatment was then quadrupled both in the full cohort (aHR 4.3; CI 1.8–10.3) and in the schizophrenia cohort (aHR 3.8; CI 0.7–20.0) but was only statistically significant in the former case. Treatment with olanzapine and/or quetiapine entailed no higher risk of perimyocarditis. Compared to no antipsychotic treatment, the risk of heart failure was elevated for clozapine in the full cohort (aHR 1.4; CI 1.1–1.7), but not in the schizophrenia cohort (aHR 1.1; CI 0.6–1.8), compared to no antipsychotic treatment. Olanzapine and/or quetiapine was not associated with a higher risk of heart failure.

Further supplementary analyses were also conducted. In particular, the full cohort with age restricted to at most 65 years was analyzed (Supplementary Table S7 and S8). For clozapine compared to no antipsychotic treatment, we found similar risks for both perimyocarditis (aHR 3.00; CI 1.32–6.86) and heart failure (aHR 1.20; CI 0.88–1.62)

compared to the main analyses, but the result for heart failure was no longer statistically significant. Results for olanzapine and/or quetiapine were not statistically significant.

All analyses are adjusted for sex. However, additional sex stratified analyses were also conducted (Supplementary Table S9–S12). A higher risk of perimyocarditis was found for men on clozapine compared to no antipsychotic treatment in the full cohort (aHR 6.35, CI 2.76–14.63) and the schizophrenia spectrum cohort (aHR 7.14, 1.33–38.28). There were no cases of perimyocarditis among women within the defined exposure period of 60 days. For men, the risk of heart failure during treatment with clozapine compared to no antipsychotic treatment was similar as in the main analysis but not statistically significant in either the full cohort or the schizophrenia spectrum cohort. For women, the relative risk increase was significant in both the full cohort (aHR 1.55, CI 1.07–2.23) and the schizophrenia spectrum cohort. Results for olanzapine and/or quetiapine were not statistically significant.

Further, in the full cohort using a Fine-Gray model to consider competing risk of all-cause mortality during follow-up (Supplementary Table S13 and S14), risk of perimyocarditis but not heart failure remained significant for clozapine, compared to no antipsychotic treatment. In the full cohort excluding individuals with schizophrenia spectrum disorders (Supplementary Table S15 and S16), the risk of perimyocarditis and heart failure remained significant.

Exposure to clozapine excluding concurrent olanzapine and quetiapine was also studied (Supplementary Table S17 and S18). Similar

Table 1
Baseline cohort characteristics at inclusion.

Variable	Full cohort N (%)	Schizophrenia cohort N (%)
Total	201,045 (100.0)	15,238 (100.0)
Sex		
Male	94,906 (47.2)	8937 (58.6)
Female	106,139 (52.8)	6301 (41.4)
Age		
Mean age in years (standard deviation)	43.5 (16.9)	37.7 (10.7)
Age groups (years)		
16–25	37,336 (18.6)	2587 (17.0)
26–35	38,601 (19.2)	3864 (25.4)
36–45	36,070 (17.9)	4367 (28.7)
46–55	34,048 (16.9)	4420 (29.0)
56–65	26,926 (13.4)	N/A
66–75	28,064 (14.0)	N/A
Number of other antipsychotics		
0	169,829 (84.5)	5595 (36.7)
1–4	30,933 (15.4)	9449 (62.0)
≥5	283 (0.1)	194 (1.3)
Number of psychiatric hospitalizations		
0	147,059 (73.1)	6661 (43.7)
1–4	46,689 (23.2)	6922 (45.4)
5–9	5228 (2.6)	1136 (7.5)
≥10	2069 (1.0)	519 (3.4)
Schizophrenia spectrum diagnosis (F20, F25, F29)		
Yes	20,405 (10.1)	15,238 (100.0)

Table 1 (continued). Baseline cohort characteristics at inclusion

Variable	Full cohort	Schizophrenia cohort
History of psychiatric conditions (by ICD-10 main category)		
F0 Organic, including symptomatic, mental disorders	12,713 (6.3)	577 (3.8)
F1 Mental and behavioral disorders due to psychoactive substance use	44,642 (22.2)	4308 (28.3)
F2 Schizophrenia, schizotypal and delusional disorders	28,788 (14.3)	15,238 (100.0)
F3 Mood [affective] disorders	95,960 (47.7)	5540 (36.4)
F4 Neurotic, stress-related and somatoform disorders	92,404 (46.0)	5444 (35.7)
F5 Behavioral syndromes associated with physiological disturbances and physical factors	14,844 (7.4)	927 (6.1)
F6 Disorders of adult personality and behavior	22,343 (11.1)	2408 (15.8)
F7 Mental retardation	5864 (2.9)	827 (5.4)
F8 Disorders of psychological development	10,758 (5.4)	1074 (7.0)
F9 Behavioral and emotional disorders with onset usually occurring in childhood and adolescence & Unspecified mental disorder	27,407 (13.6)	2158 (14.2)
History of somatic conditions or drugs associated with risk of studied cardiac adverse events ^a		
Risk history for myocarditis	24,530 (12.2)	1660 (10.9)
Risk history for cardiomyopathy	16,119 (8.0)	1326 (8.7)
Risk history for heart failure	37,397 (18.6)	1782 (11.7)

Table 1 (continued)

Variable	Full cohort N (%)	Schizophrenia cohort N (%)
History of medication increasing risk of studied cardiac adverse events ^a		
Yes	50,375 (25.1)	2721 (17.9)

^aSee Supplementary Tables 2.1–2.4.

relative risks were observed for perimyocarditis and heart failure but were attenuated. Exposure to either olanzapine or quetiapine was also analyzed separately, and the results remained statistically not significant.

4. Discussion

In this large, population-based cohort study, we observed a higher risk of developing perimyocarditis during the first two months of treatment with clozapine compared to no antipsychotic treatment, and we are the first to report that clozapine use was also associated with increased risk of heart failure within three years. However, no such associations were seen for the chemically related and widely used drugs olanzapine and quetiapine. The long-term outcome of heart failure involved more cases and subsequently narrower confidence intervals compared to the short-term outcome of perimyocarditis.

The only previous population-based study reported an incidence rate of perimyocarditis (myocarditis and/or pericarditis) of 0.03%, in Denmark, compared to 0.16% in our study (Rohde et al., 2018). A possible explanation for the large difference in incidence may be different strategies for managing possible cases of inpatient initiation of clozapine, where our study used time varying exposure that included a category for unknown inpatient medication (UIM) and did not exclude index prescriptions following recent inpatient care lasting less than 14 days. On the other hand, some clinical surveillance programs during treatment with clozapine and retrospective chart reviews have found much higher incidences than our population derived numbers, ranging between 3% in Australia and Canada (Higgins et al., 2019; Khan et al., 2017; Kilian et al., 1999; Ronaldson et al., 2015, 2011) to 3.8% in New Zealand (Bellissima et al., 2021). A recent study from the U.S. found that 5.3% initiating treatment with clozapine developed presumptive myocarditis within 4 weeks (Sandarsh et al., 2021). The term “presumptive myocarditis” was used to emphasize that the study relied on indirect methods—in this case a panel of lab measures of heart muscle damage—rather than the gold standard diagnostic tool of endomyocardial biopsy (Patel et al., 2019), where signs of inflammation, by definition, mean myocarditis. A possible contributing explanation for the high incidence of myocarditis in some clinical studies of patients initiating clozapine treatment may be that elevated cardiac markers reflect conditions other than clozapine-induced myocarditis.

Swedish recommendations for cardiac monitoring during clozapine initiation follows European guidelines, which does not include routine cardiac blood markers. Such testing is likely to matter more for discovery of subclinical or transitory conditions and less for serious conditions that will typically lead to health care contact. Guidelines recommending gradual titration and rapid dose increase are therefore unlikely to play a major role in the development of cardiac adverse events in Sweden—at least during outpatient treatment. Our results should primarily be compared to other register-based studies. We find a clinically relevant risk increase for cardiac adverse events during clozapine treatment, but not at a level suggested by some clinical surveillance studies.

The widely used medications olanzapine and quetiapine, which are chemically related to clozapine, have been implicated as causing myocarditis in a recent pharmacovigilance study and several case

Table 2
Incidence rates and hazard ratios for perimyocarditis, censored at 60 days.

Exposure	Full cohort				Schizophrenia cohort								
	n persons	n events	% events	Person-years	n persons	n events	% events	Person-years	IR (95% CI)	HR (95% CI)	aHR (95% CI)		
Clozapine	5 493	9	0.16	4674	1.93 (0.88,3.65)	4.89 (2.33,10.27)	3.40 (1.59,7.25)	2516	6	0.24	2.33 (0.85,5.04)	5.85 (1.40,24.44)	5.38 (1.20,24.08)
Olanzapine/quetiapine	145 912	25	0.02	72,047	0.35 (0.22,0.51)	0.78 (0.46,1.32)	0.75 (0.42,1.34)	12,216	6	0.05	0.66 (0.24,1.44)	1.50 (0.37,6.10)	1.64 (0.35,7.57)
Other antipsychotic	104 831	23	0.02	49,052	0.47 (0.30,0.70)	1.05 (0.61,1.79)	1.05 (0.61,1.81)	11,167	5	0.04	0.60 (0.19,1.39)	1.40 (0.33,6.00)	1.61 (0.39,6.57)
UJM	55 912	4	0.01	8204	0.49 (0.13,1.23)	1.15 (0.42,3.20)	1.41 (0.30,6.68)	8140	3	0.04	1.52 (0.31,4.36)	3.80 (0.80,18.03)	17.12 (1.49,197.09)
Unexposed	180 013	32	0.02	72,049	0.44 (0.30,0.63)	REF	REF	13,544	3	0.02	0.43 (0.09,1.23)	REF	REF

Abbreviations: Clozapine, Any antipsychotic treatment including clozapine.
 Olanzapine/quetiapine, Any antipsychotic treatment including either or both olanzapine and quetiapine but not clozapine.
 Other antipsychotic, Any other antipsychotic treatment not including clozapine, olanzapine, or quetiapine.
 UJM, Unknown inpatient medication (exposure periods comprising psychiatric inpatient care).
 Unexposed, Individuals who are currently unexposed to antipsychotic medication but have previously been prescribed such medication.
 IR, Incidence rate (per thousand person-years).
 HR, Crude hazard ratio (adjusted for age and sex).
 aHR, Adjusted hazard ratio.

Table 3
Incidence rates and hazard ratios for heart failure, censored at 3 years.

Exposure	Full cohort				Schizophrenia cohort								
	n persons	n events	% events	Person-years	n persons	n events	% events	Person-years	IR (95% CI)	HR (95% CI)	aHR (95% CI)		
Clozapine	5486	87	1.59	17,229	5.05 (4.04,6.23)	1.36 (1.09,1.69)	1.33 (1.06,1.67)	2516	25	0.99	2.44 (1.58,3.59)	1.12 (0.68,1.83)	1.05 (0.61,1.81)
Olanzapine/quetiapine	145,842	720	0.49	220,786	3.26 (3.03,3.51)	0.93 (0.85,1.03)	0.95 (0.86,1.06)	12,207	57	0.47	1.80 (1.36,2.33)	0.83 (0.56,1.25)	0.80 (0.50,1.26)
Other antipsychotic	104,744	876	0.84	146,376	5.98 (5.59,6.39)	1.23 (1.12,1.35)	1.12 (1.01,1.23)	11,162	58	0.52	2.17 (1.65,2.81)	0.93 (0.62,1.39)	1.01 (0.66,1.54)
UJM	55,756	50	0.09	11,580	4.32 (3.20,5.69)	1.73 (1.30,2.30)	1.53 (1.08,2.16)	8124	10	0.12	2.86 (1.37,5.25)	1.62 (0.82,3.23)	1.80 (0.78,4.13)
Unexposed	179,780	1207	0.67	430,362	2.80 (2.65,2.97)	REF	REF	13,559	43	0.32	1.78 (1.29,2.40)	REF	REF

Abbreviations: Clozapine, Any antipsychotic treatment including clozapine.
 Olanzapine/quetiapine, Any antipsychotic treatment including either or both olanzapine and quetiapine but not clozapine.
 Other antipsychotic, Any other antipsychotic treatment not including clozapine, olanzapine, or quetiapine.
 UJM, Unknown inpatient medication.
 Unexposed, Individuals who are currently unexposed to antipsychotic medication but have previously been prescribed such medication.
 IR, Incidence rate (per thousand person-years).
 HR, Crude hazard ratio (adjusted for age and sex).
 aHR, Adjusted hazard ratio.

studies (Bhagal et al., 2018; Vang et al., 2016; Wassef et al., 2015). In our population-based study, we could however not observe any higher risk of developing perimyocarditis (pericarditis and/or myocarditis) during treatment with either or both olanzapine and quetiapine compared to no antipsychotic treatment.

Heart failure related to clozapine treatment has been reported in case studies, and left ventricular impairment has been documented in non-randomized clinical investigations (Chow et al., 2014; Murch et al., 2013). However, to our knowledge, our study is the first population-based study to report an increased risk of manifest heart failure and cardiomyopathy during treatment with clozapine. This differs from the absence of an association with cardiomyopathy in the aforementioned study from Denmark (Rohde et al., 2018). The increased risk of heart failure could be a complication of perimyocarditis, but could also have other causes. Early emerging subclinical cardiotoxic effects of clozapine has been documented but there are also case reports of cardiomyopathy during the first years of clozapine treatment (Curto et al., 2016). As the observed risk increase of heart failure in our study is already present already during the first years of treatment, it is probably not explained by the previously described unfavorable long-term cardiometabolic effects of clozapine; namely obesity and diabetes.

We also performed some subgroup analyses. An important conclusion is that the limited number of outcomes for comparatively rare cardiac adverse may make results statistically insignificant in subgroups. Even larger studies are likely to be required for detailed subgroup or stratified analyses, possibly using pooled observational data sets.

A limitation of our study is that we had no access to information about inpatient medication. Failure to take such exposure into account can potentially bias the results, which is why we constructed the UIM exposure group to assess the magnitude of this issue, in line with a previously described method (Palmaro et al., 2017). Generally, we observed no strong associations between UIM periods and the studied outcomes. The exception was an association with perimyocarditis in the schizophrenia cohort, but that was based on only three outcome events and thus had a very wide confidence interval. Nonetheless, possible explanations might include polypharmacy and a tendency for more rapid dose titration for inpatients with schizophrenia spectrum diagnoses. However, inpatient episodes constitute only a small part of overall exposure, as long-term hospitalization is rare. This may contribute to the finding that reassigning these episodes to the immediately preceding exposure did not materially change the results.

Another limitation is that while the Prescribed Drug Register provides information on filled prescriptions, it cannot be known whether an individual takes the medication as prescribed. One might speculate that patients on clozapine are probably more adherent, as they are under tighter surveillance and non-adherence to clozapine has more obvious clinical effects. The difference in follow-up is more prominent during the first 18 weeks when patients taking clozapine are seen for weekly blood tests. This could possibly promote earlier detection of subtler symptoms of cardiac adverse events, although the blood tests are not designed for this objective. However, the present study was based on national health registers that have nationwide coverage and are considered to be of good quality (Ludvigsson et al., 2016, 2011; Rosen, 2002). Severe cardiac adverse events are highly likely to lead to healthcare interventions that would be recorded in the health registers. Further, the effect of unexposed versus exposed could at least potentially partially reflect channeling bias. While we attempted to correct for relevant confounders using available register data, residual confounding is likely to exist. For instance, BMI and smoking status are not recorded in Swedish health registers.

As for the validity of adverse cardiac event diagnoses during treatment with an antipsychotic, previous research suggests that individuals with severe mental illness receive acute care comparable to other patients in cardiac wards in Sweden (Boden et al., 2015), and that heart failure diagnoses are largely accurate in specialized care (Ingelsson et al., 2005). Yet, discovery of cardiac events in patients undergoing

antipsychotic treatment is a different issue. Furthermore, it could be that health care workers and patients are aware of the risk of cardiac adverse events during treatment with clozapine, and this leads to greater vigilance in initiating care and diagnosis, compared to other antipsychotic medications, including olanzapine and quetiapine. If so, we would have a detection bias towards clozapine, compared to olanzapine and quetiapine.

In conclusion, we found an increased cumulative incidence of perimyocarditis during the first two months of treatment with clozapine, highlighting the importance of paying attention to signs of perimyocarditis during clozapine initiation. We also found a higher risk of heart failure during the first three years of treatment with clozapine. Thus, attentiveness to emerging signs of heart failure during the first years of clozapine use may be called for. We did not find that olanzapine or quetiapine were associated with an increased risk of perimyocarditis or heart failure.

Contributors

All authors took part in the design of the study and the interpretation of the results. LB and ML managed the data analyses in close collaboration with EC, who also managed the literature searches and wrote the first draft of the manuscript. All authors critically revised, contributed to, and have approved the final manuscript.

Declaration of Competing Interest

RB was supported by a Swedish Research Council Grant 2016–02,362. JS reports stock ownership in companies providing services to Itrim, Amgen, Janssen, Novo Nordisk, Pfizer, Takeda, AstraZeneca, and Vifor Pharma, outside the submitted work. JR, EC, LB, and ML are affiliated with/employed at the center for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities, contract research organizations) for the performance of drug safety and drug utilization studies.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115336.

References

- Bauer-Staeb, C., Jorgensen, L., Lewis, G., Dalman, C., Osborn, D.P.J., Hayes, J.F., 2017. Prevalence and risk factors for HIV, hepatitis B, and hepatitis C in people with severe mental illness: a total population study of Sweden. *Lancet Psychiatry* 4 (9), 685–693.
- Bellissima, B.L., Tingle, M.D., Cicovic, A., Alawami, M., Kenedi, C., 2018. A systematic review of clozapine-induced myocarditis. *Int. J. Cardiol.* 259, 122–129.
- Bellissima, B.L., Vara, A., Helsby, N., Garavan, F., Tingle, M.D., 2021. Incidence and investigation of potential risk-factors for clozapine-associated myocarditis and cardiomyopathy in a New Zealand cohort. *Psychiatry Res.* 299, 113873.
- Bhagal, S., Ladia, V., Paul, T.K., 2018. Quetiapine-associated myopericarditis. *Am. J. Ther.* 25 (5), e578–e579.
- Binder, D.A., 1992. Fitting cox's proportional hazards models from survey data. *Biometrika* 79, 139–147.
- Boden, R., Molin, E., Jernberg, T., Kieler, H., Lindahl, B., Sundstrom, J., 2015. Higher mortality after myocardial infarction in patients with severe mental illness: a nationwide cohort study. *J. Intern. Med.* 277 (6), 727–736.
- Bugge, E., Nissen, T., Wynn, R., 2016. Probable clozapine-induced parenchymal lung disease and perimyocarditis: a case report. *BMC Psychiatry* 16 (1), 438.
- Chow, V., Yeoh, T., Ng, A.C., Pasqualon, T., Scott, E., Plater, J., Whitwell, B., Hanzek, D., Chung, T., Thomas, L., Celermajer, D.S., Kritharides, L., 2014. Asymptomatic left ventricular dysfunction with long-term clozapine treatment for schizophrenia: a multicentre cross-sectional cohort study. *Open Heart* 1 (1), e000030.
- Cullen, A.E., Holmes, S., Pollak, T.A., Blackman, G., Joyce, D.W., Kempton, M.J., Murray, R.M., McGuire, P., Mondelli, V., 2019. Associations between non-neurological autoimmune disorders and psychosis: a meta-analysis. *Biol. Psychiatry* 85 (1), 35–48.
- Curto, M., Girardi, N., Lionetto, L., Ciavarella, G.M., Ferracuti, S., Baldessarini, R.J., 2016. Systematic review of clozapine cardiotoxicity. *Curr. Psychiatry Rep.* 18 (7), 68.

- De Berardis, D., Fornaro, M., Orsolini, L., Olivieri, L., Nappi, F., Rapini, G., Vellante, F., Napoletano, C., Serroni, N., Giannantonio, M.D., 2018. Clozapine-related sudden pericarditis in a patient taking long acting aripiprazole and valproate: a case report. *Clin. Psychopharmacol. Neurosci.* 16 (4), 505–507.
- De Las Cuevas, C., Sanz, E.J., Rohde, C., de Leon, J., 2022. Association between myocarditis and antipsychotics other than clozapine: a systematic literature review and a pharmacovigilance study using VigiBase. *Expert Rev. Clin. Pharmacol.* 15 (1), 65–78.
- Gammon, D., Cheng, C., Volkovskaia, A., Baker, G.B., Dursun, S.M., 2021. Clozapine: why is it so uniquely effective in the treatment of a range of neuropsychiatric disorders? *Biomolecules* 11 (7).
- Hagg, S., Spigset, O., Bate, A., Soderstrom, T.G., 2001. Myocarditis related to clozapine treatment. *J. Clin. Psychopharmacol.* 21 (4), 382–388.
- Hagiwara, H., Fukushima, A., Iwano, H., Anzai, T., 2018. Refractory cardiac myocarditis associated with drug rash with eosinophilia and systemic symptoms syndrome due to anti-bipolar disorder drugs: a case report. *Eur Heart J. Case Rep.* 2 (4), yty100.
- Halfdanarson, O., Zoega, H., Aagaard, L., Bernardo, M., Brandt, L., Fuste, A.C., Furu, K., Garuoliene, K., Hoffmann, F., Huybrechts, K.F., Kalverdijk, L.J., Kawakami, K., Kieler, H., Kinoshita, T., Litchfield, M., Lopez, S.C., Machado-Alba, J.E., Machado-Duque, M.E., Mahesri, M., Nishtala, P.S., Pearson, S.A., Reutfors, J., Saastamoinen, L. K., Sato, I., Schuiling-Veninga, C.C.M., Shyu, Y.C., Skurtveit, S., Verdoux, H., Wang, L.J., Yahni, C.Z., Bachmann, C.J., 2017. International trends in antipsychotic use: a study in 16 countries, 2005-2014. *Eur. Neuropsychopharmacol.* 27 (10), 1064–1076.
- Higgins, J.M., San, C., Lagnado, G., Chua, D., Mihic, T., 2019. Incidence and management of clozapine-induced myocarditis in a large tertiary hospital. *Can. J. Psychiatry* 64 (8), 561–567.
- Ingelsson, E., Arnlov, J., Sundstrom, J., Lind, L., 2005. The validity of a diagnosis of heart failure in a hospital discharge register. *Eur. J. Heart Fail.* 7 (5), 787–791.
- Kauermann, G., Carroll, R.J., 2001. A note on the efficiency of sandwich covariance matrix estimation. *J. Am. Stat. Assoc.* 96 (456), 1387–1396.
- Khan, A.A., Ashraf, A., Baker, D., Al-Omary, M.S., Savage, L., Ekmejian, A., Singh, R.S.H., Briennes, S., Majeed, T., Gordon, T., Drinkwater, V., Collins, N.J., 2017. Clozapine and incidence of myocarditis and sudden death - Long term Australian experience. *Int. J. Cardiol.* 238, 136–139.
- Khokhar, J.Y., Dwiell, L.L., Henricks, A.M., Doucette, W.T., Green, A.I., 2018. The link between schizophrenia and substance use disorder: a unifying hypothesis. *Schizophr. Res.* 194, 78–85.
- Kilian, J.G., Kerr, K., Lawrence, C., Celermajer, D.S., 1999. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 354 (9193), 1841–1845.
- Kodesh, A., Goldberg, Y., Rotstein, A., Weinstein, G., Reichenberg, A., Sandin, S., Levine, S.Z., 2020. Risk of dementia and death in very-late-onset schizophrenia-like psychosis: a national cohort study. *Schizophr. Res.* 223, 220–226.
- Liang, C.S., Bai, Y.M., Hsu, J.W., Huang, K.L., Ko, N.Y., Chu, H.T., Yeh, T.C., Tsai, S.J., Chen, T.J., Chen, M.H., 2020. The risk of sexually transmitted infections following first-episode schizophrenia among adolescents and young adults: a cohort study of 220 545 subjects. *Schizophr. Bull.* 46 (4), 795–803.
- Ludvigsson, J.F., Otterblad-Olausson, P., Pettersson, B.U., Ekblom, A., 2009. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur. J. Epidemiol.* 24 (11), 659–667.
- Ludvigsson, J.F., Andersson, E., Ekblom, A., Feychting, M., Kim, J.L., Reuterwall, C., Heurgren, M., Olausson, P.O., 2011. External review and validation of the Swedish national inpatient register. *BMC Public Health* 11, 450.
- Ludvigsson, J.F., Almqvist, C., Bonamy, A.K., Ljung, R., Michaelsson, K., Neovius, M., Stephansson, O., Ye, W., 2016. Registers of the Swedish total population and their use in medical research. *Eur. J. Epidemiol.* 31 (2), 125–136.
- Manda, Y.R., Baradhi, K.M., 2022. Myopericarditis. In: *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.* <https://www.ncbi.nlm.nih.gov/books/NBK534776/> (accessed 18 April 2023).
- EMA, 2002. Committee for proprietary medicinal products (CPMP). Summary information on referral opinion following arbitration pursuant to article 30 of council directive 2001/83/ec for Leponex and associated names. <https://www.ema.europa.eu/en/documents/referral/summary-information-referral-opinion-following-arbitration-pursuant-article-30-council-directive/83/ec-leponex-associated-names-international-non-proprietary-name-inn-clozapine-background-inform-en.pdf> (accessed 12 April 2023).
- National Board of Health, 2010. Dödsorsaksstatistik: Historik, produktionsmetoder och tillförlitlighet [Cause of Death Statistics: History, Production Methods and Reliability]. Article number 2010-4-33. <https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2010-4-33.pdf> (accessed 21 April 2023).
- Murch, S., Tran, N., Liew, D., Petrakis, M., Prior, D., Castle, D., 2013. Echocardiographic monitoring for clozapine cardiac toxicity: lessons from real-world experience. *Australas. Psychiatry* 21 (3), 258–261.
- Nielsen, L.H., Lokkegaard, E., Andreassen, A.H., Keiding, N., 2008. Using prescription registries to define continuous drug use: how to fill gaps between prescriptions. *Pharmacoepidemiol. Drug Saf.* 17 (4), 384–388.
- Palmaro, A., Boucherie, Q., Dupouy, J., Micallef, J., Lapeyre-Mestre, M., 2017. Immeasurable time bias due to hospitalization in medico-administrative databases: which impact for pharmacoepidemiological studies? *Pharmacoepidemiol. Drug Saf.* 26 (5), 544–553.
- Patel, R.K., Moore, A.M., Piper, S., Sweeney, M., Whiskey, E., Cole, G., Shergill, S.S., Plymen, C.M., 2019. Clozapine and cardiotoxicity - a guide for psychiatrists written by cardiologists. *Psychiatry Res.* 282, 112491.
- Puttegowda, B., Theodore, J., Basappa, R., Nanjappa, M.C., 2016. Olanzapine Induced Dilated Cardiomyopathy. *Malays J. Med. Sci.* 23 (2), 82–84.
- Ringen, P.A., Engh, J.A., Birkenaes, A.B., Dieset, I., Andreassen, O.A., 2014. Increased mortality in schizophrenia due to cardiovascular disease - a non-systematic review of epidemiology, possible causes, and interventions. *Front. Psychiatry* 5, 137.
- Rohde, C., Polcwiartek, C., Kragholm, K., Ebdrup, B.H., Siskind, D., Nielsen, J., 2018. Adverse cardiac events in out-patients initiating clozapine treatment: a nationwide register-based study. *Acta Psychiatr. Scand.* 137 (1), 47–53.
- Ronaldson, K.J., Fitzgerald, P.B., Taylor, A.J., Topliss, D.J., McNeil, J.J., 2011. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust. N. Z. J. Psychiatry* 45 (6), 458–465.
- Ronaldson, K.J., 2017. Cardiovascular disease in clozapine-treated patients: evidence, mechanisms and management. *CNS Drugs* 31 (9), 777–795.
- Ronaldson, K.J., Fitzgerald, P.B., McNeil, J.J., 2015. Clozapine-induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatr. Scand.* 132 (4), 231–240.
- Rosen, M., 2002. National Health Data Registers: a Nordic heritage to public health. *Scand. J. Public Health* 30 (2), 81–85.
- Rubio, J.M., Kane, J.M., 2020. How and when to use clozapine. *Acta Psychiatr. Scand.* 141 (3), 178–189.
- Sahyouni, C., Hefazi, E., 2021. Clozapine induced pericarditis: a case report. *Psychiatry Res.* 305, 114250.
- Sandarsh, S., Bishnoi, R.J., Shashank, R.B., Miller, B.J., Freudenreich, O., McEvoy, J.P., 2021. Monitoring for myocarditis during treatment initiation with clozapine. *Acta Psychiatr. Scand.* 144 (2), 194–200.
- Scorza, F.A., Cavalheiro, E.A., de Albuquerque, M., de Albuquerque, J., Cysneiros, R.M., Terra, V.C., Arida, R.M., 2011. Thyroid gland and cerebellar lesions: new risk factors for sudden cardiac death in schizophrenia? *Med. Hypotheses* 76 (2), 251–253.
- Sharif, N., Dehghani, P., 2013. Emergency files: acute pericarditis, myocarditis, and worse! *Can. Fam. Physician* 59 (1), 39–41.
- Siskind, D., Sidhu, A., Cross, J., Chua, Y.T., Myles, N., Cohen, D., Kisely, S., 2020. Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy. *Aust. N. Z. J. Psychiatry*, 4867419898760.
- Siskind, D., Siskind, V., Kisely, S., 2017. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. *Can. J. Psychiatry* 62 (11), 772–777.
- Smolders, D.M.E., Smolders, W.A.P., 2017. Case report and review of the literature: cardiomyopathy in a young woman on high-dose quetiapine. *Cardiovasc. Toxicol.* 17 (4), 478–481.
- Vang, T., Rosenzweig, M., Bruhn, C.H., Polcwiartek, C., Kanters, J.K., Nielsen, J., 2016. Eosinophilic myocarditis during treatment with olanzapine - report of two possible cases. *BMC Psychiatry* 16, 70.
- Wassef, N., Khan, N., Munir, S., 2015. Quetiapine-induced myocarditis presenting as acute STEMI. *BMJ Case Rep.* 2015.
- Wettermark, B., Hammar, N., Fored, C.M., Leimanis, A., Otterblad Olausson, P., Bergman, U., Persson, I., Sundstrom, A., Westerholm, B., Rosen, M., 2007. The new Swedish prescribed drug register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol. Drug Saf.* 16 (7), 726–735.
- Whiskey, E., Yuen, S., Khosla, E., Piper, S., O'Flynn, D., Taylor, D., 2020. Resolution without discontinuation: heart failure during clozapine treatment. *Ther. Adv. Psychopharmacol.* 10, 2045125320924786.
- Zhang, Z., Reinikainen, J., Adeleke, K.A., Pieterse, M.E., Groothuis-Oudshoorn, C.G.M., 2018. Time-varying covariates and coefficients in Cox regression models. *Ann. Transl. Med.* 6 (7), 121.