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ORIGINAL ARTICLE

Antipsychotic drug prescription sequence analysis in relation to death occurrence and cardiometabolic drug usage: A retrospective longitudinal study

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Abstract
Background and objectives: The potential role of antipsychotics in increasing cardiovascular risk of mortality is still debated. The aim of this study was to assess the death risk associated with sequences of first-generation antipsychotic (FGA) and second-generation antipsychotic (SGA) prescriptions, including clozapine and lithium, and drugs for cardiometabolic diseases.
Methods: We conducted a retrospective longitudinal analysis involving 84,881 patients who received antipsychotics between 2008 and 2012. Data on deaths were collected from the National Death Registry. The sequence creation was performed according to an algorithm that iterates prescriptions in chronological order and appends them to the end of the patient's prescription sequence. Fuzzy set qualitative comparative analysis (FsQCA) was also used to produce causal combinations of conditions that best lead to survival.
Results: There were 1,095,518 antipsychotic prescriptions and 16,010 deaths among antipsychotic users. Among the reimbursement data, 85,272 drug sequences were identified. The most prevalent sequence consisted of FGA (69.1%). Subsequent groups consisted of FGA, followed by SGA (13.1%) and SGA-only (12.3%) sequences. The highest occurrence of death and cardiometabolic drug use after introducing antipsychotic treatment was observed for clozapine. The FsQCA analysis revealed the highest coverage for combinations of young age with FGA (40.6%) or with no cardiometabolic risk factors drug therapy (39.5%).
Conclusion: The sequence analysis suggests that clozapine is associated with an increased death risk compared to FGA and SGA.

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Introduction

There is an ongoing debate about whether second-generation antipsychotics are better than first-generation antipsychotics.[1–3] Second-generation antipsychotics (SGAs) are also referred to as atypical antipsychotic or serotonin-dopamine antagonists and include risperidone, olanzapine, quetiapine, clozapine, ziprasidone, amisulpride, aripiprazole, and others. SGAs are believed to improve negative symptoms and depression and to offer patients better functioning in terms of quality of life. These drugs carry a smaller risk of extrapyramidal symptoms than first-generation antipsychotic drugs (FGAs), which act mainly as dopamine receptor antagonists. Typical antipsychotics are most widely used in psychiatry drugs, such as chlorpromazine, perazine, haloperidol, sulpiride, and others. Lithium is a major mood-stabilizing drug used for the treatment of bipolar mood disorder.[4,5] Further, lithium alone is considered an effective treatment for schizophrenia, schizophrenia-like psychoses, and schizoaffective psychoses, and lithium is used as an augmentation of antipsychotic medication in the treatment of the same illnesses.[6]

People with schizophrenia or other severe mental illnesses have reduced life expectancy.[7,8] A major cause of mortality is cardiovascular disease.[9,10] The well-established adverse effects of antipsychotics include weight gain, leading to metabolic syndrome, diabetes, and ischemic heart disease.[11] The risk of QT interval prolongation and subsequent arrhythmia-related events is another important cardiovascular safety aspect of SGA.[12] The extent to which this effect may contribute to increased cardiovascular morbidity and mortality among people treated with antipsychotics remains unclear.[13–15] Clozapine, a 5-HT2A and D4 receptor antagonist, was the first antipsychotic to demonstrate efficacy in treatment-resistant patients and the first to be associated with the lowest risk of death; however, a recent network meta-analysis concluded that clozapine was no better than other antipsychotics in the treatment of refractory schizophrenia.[14,16] Clozapine is also an antipsychotic with serious side effects of bone marrow suppression, agranulocytosis, and a high risk of cardiovascular complications. Given the necessity of monitoring these effects, the drug is the most difficult to prescribe. Therefore, the role of antipsychotics in influencing overall and cardiovascular mortality in schizophrenia and psychotic patients remains unexplained.[17]

A meta-analysis of 13 studies found that schizophrenia is associated with an increased incidence of cardiovascular disease, stroke, and heart failure.[18] There is still an unresolved controversy concerning the effects of antipsychotics on mortality and cardiovascular morbidity, as the significant part of this mortality risk excess is attributable to the adverse effects of antipsychotics.[13,19]

A database of refunded prescriptions created by the National Health Fund in 2008 Poland provided an opportunity to monitor and analyze the pattern of antipsychotic use. The goal of transforming large datasets into new knowledge is to capture the opportunities and challenges related to analyzing and integrating datasets of diverse data types (e.g., drug prescriptions and deaths) and to manage and analyze these data effectively.[20]

Thus, this study aimed was to investigate whether the sequences of SGAs and FGAs prescriptions are associated with increased cardiometabolic and death risk compared to clozapine using prescription drug reimbursement data.

Methods

The study was based on prescription drug reimbursement data from the Pomeranian Branch of the National Health Fund for the period between January 1, 2008, and December 31, 2012. The National Health Fund is a state institution that finances health care benefits from contributions paid by people insured by this organization. The National Health Fund is responsible for the provision of health care benefits for all insured persons and their family members. More than 93% of Polish citizens are entitled to prescription drug and health service reimbursement in Poland.

Reimbursement regulations

Antipsychotic agents are used in the treatment of schizophrenia, psychotic disorders, and bipolar disorder. According to the National Health Fund policy, SGAs were reimbursed only for patients with schizophrenia (during the whole period of analysis, 2008–2012), bipolar disorder (2010–2012), and dementia (since 2011). FGAs were reimbursed for individuals with an array of various psychiatric conditions (F00–F99). The restricted reimbursement policy for SGAs is associated with their higher cost and the limited resources of the Polish health care system.

Study population

We conducted a retrospective longitudinal analysis involving 84,881 patients who had drug insurance benefits in the Pomeranian region and who were receiving FGAs, SGAs, or lithium between 2008 and 2012. Therefore, the study population included all individuals who had been prescribed at least one reimbursed antipsychotic agent or lithium. All subjects were 18 years of age or older. The date of the first prescription was considered the date of the subject's entry into the study. Mortality data were obtained from the Death Registry as of December 31, 2012. The database does not contain information about earlier prescriptions; therefore, those who had been prescribed clozapine or any other antipsychotic prior to entering the observation period may have been included.

Sequence analysis

Five groups of prescriptions were considered:

1) Individuals to whom only SGAs (amisulpride, aripiprazole, quetiapine, olanzapine, risperidone, sertindole, tiapride, ziprasidone) were prescribed,
2) Persons to whom only FGAs (chlorpromazine, chlorprothixene, flupentixol, haloperidol, levomepromazine, perazine, perphenazine, prochlorperazine, promazine, sulpiride, zuclopenthixol, and clopenthixol) were prescribed,
3) Subjects to whom both FGAs and SGAs were prescribed,
4) Those to whom clozapine was prescribed,
5) Those to whom lithium was prescribed.

Clozapine and lithium were analyzed separately as specific agents used in drug-resistant schizophrenia and augmentation, respectively. Moreover, among those individuals with prescribed antipsychotics, data on any drug used in the treatment of cardiometabolic diseases or cardiovascular risk factors were collected. The cardiometabolic drug group contains any drug belonging to one of the following groups of drugs: 1) antihypertensive drugs, 2) antiarrhythmic agents, 3) lipid-lowering drugs, or 4) antidiabetic agents.

Sequence creation was performed according to an algorithm that iterates over antipsychotic prescriptions in chronological order and appends them to the end of the patient's prescription sequence. Patients were also assigned to cardiometabolic groups depending on the use of cardiometabolic drugs before, simultaneously, or after treatment with antipsychotics. To separate different patients' treatments, the gaps in prescription sequences longer than 90 days are considered the end of the sequence and the start of the new one. In uncut sequences, these gaps are not considered, and thus, each patient received exactly one sequence. In this step, patients were also assigned to "cardiometabolic groups" (CVD), depending on the use of cardiometabolic drugs before treatment with antipsychotics. We defined three of these CVD groups using 90 days as the threshold period for the difference between dates of prescriptions:

0 - Patients with at least one cardiometabolic drug prescription but with a time difference between the first antipsychotic prescription and first cardiometabolic drug prescription less than a threshold; this is the group with concomitant use of cardiovascular, lipid-lowering, or diabetes medication prescription,

1 - Patients not in group 0 but who had their first antipsychotic prescription before their first cardiometabolic drug prescription,

2 - Patients not in group 0 but who had first antipsychotic prescription after first cardiometabolic drug prescription.

Before analysis, the data were grouped to reduce the number of different sequences by grouping antipsychotics by generation—the name of the drug is substituted by its generation (FGA or SGA). Clozapine and lithium were considered different antipsychotic/drug groups. There are seven indexes, and each one indicates only sequences from patients that match the specified conditions. The mentioned indexes are:

Total − number of all occurrences of the sequences,
Deaths − number of occurrences for patients with confirmed death date in source data,
CVD − number of occurrences in patients with cardiometabolic drugs (CVD groups 0, 1, and 2)
CVD-deaths − number of occurrences in patients with death in source data and with cardiometabolic drugs (CVD groups 0, 1, or 2),
CVD0 − number of occurrences of patients from CVD group 0,
CVD1 − number of occurrences for patients from CVD group 1,
CVD2 − number of occurrences for patients from CVD group 2.

For each sequence, the following ratios were calculated: cumulative mortality, CVD percentage (%), CVD in death percentage (%), CVD 0, CVD 1, and CVD 2.

The indexes used for calculating these ratios were as follows: cumulative mortality = deaths/total, CVD % = CVD/total, CVD in death % = CVD-deaths/deaths, CVD 0 = CVD0/CVD, CVD 1 = CVD1/CVD, and CVD 2 = CVD2/CVD.

Qualitative comparative analysis

In this study, we verified a working hypothesis (clozapine is associated with increased cardiometabolic and death risk compared to FGAs and SGAs) by utilizing the fuzzy set qualitative comparative analysis approach (FsQCA). The FsQCA is particularly important for investigating the intertwined relationships among multiple factors that affect a dependent variable (an outcome).[21] FsQCA may produce alternative multiple paths, that is, alternative causal combinations that can produce high consistency and coverage outcomes. In this method, the recommended number of cases is between 10 and 100; however, we could not find a study with a large number of cases. Unfortunately, good methodological texts on FsQCA with survey data are not yet available. Essentially, the number of cases is irrelevant for FsQCA. Of high relevance concerning survey data, however, is the number of factors (conditions, typically 5−8), as well as the number of levels within these factors.

In our study, the dependent variable (outcome) is mortality regarding the set of following conditions and assigned values (m = 7 in total):

- Use of antipsychotic drugs (4 conditions, FGA, SGA, lithium, and clozapine): These were discrete (binary) variables to which a value of 0 was assigned if the individual used the drugs or 1 otherwise;
- Use of medications for cardiometabolic disease (CVD): We assigned 0 for no use of CVD. medication, 0.33 if CVD medications were used after using antipsychotic drugs in the treatment process, 0.66 if CVD medications were used during the treatment process, and 1 if CVD medications were used before using antipsychotic drugs in the treatment process.
- Gender: We assigned a value of 0 for males and 1 for females.
- Age: The membership functions used for the assessment of this condition were as follows:

The data vector modeled every case of medical data from the described dataset and represented a single person who used antipsychotic drugs. The input vector was a $1 \times m$ vector, which considered the conditions mentioned above in the same order, that is, <FGA, SGA, lithium, clozapine, CVD, gender, age, death>. The neglected variable *death* was the outcome.

All vectors established a data matrix. Using the FsQCA software package, the truth table was built, and the best combination in terms of consistency and coverage was identified. Thus, this study considered a consistent rate above a threshold set at 0.8 and the highest possible coverage. We omitted configurations in which the number of cases was below 10 (less than 0.1%). The QCA theory assumes that the best casual combinations exhibit as high possible consistency and coverage. However, the higher the consistency, the lower the coverage

becomes. The software used generates various solutions (complex, parsimonious, and intermediate). Due to the low variance between them, we present a parsimonious one, which is the most concise.

Results

A total of 1,095,518 prescriptions were issued for 84,881 patients during the period analyzed. Among the reimbursement data, 85,272 drug sequences were identified. The most common antipsychotic sequences were sole prescriptions of first-generation antipsychotics (FGA only). This sequence accounted for 69.15% of the total antipsychotic sequences. Subsequent groups consisted of FGA followed by SGA (FGA→SGA; 13.13%) and the 'SGA only' sequence (12.30%). Among clozapine sequences, FGA followed by SGA and then clozapine (FGA→SGA→Clozapine) was reported as the most common sequence, which preceded the clozapine-only sequence (Table 1).

A total of 16,010 patient deaths were reported during the analyzed period. The highest mortality rate (29%) was calculated in the 'Clozapine only' (29%), followed by the 'FGA→Clozapine' (21%) and 'FGA only' (20%) sequences. The lowest mortality rate was reported among the various lithium sequences (Table 1). The highest ratio of patients using cardiometabolic drugs among those who died was in the 'Clozapine→Lithium' sequence (100%); however, the percentage of patients with CVD drugs (in general) was one of the lowest in this sequence (38%). Sequences with low CVD 1 group and high CVD 2 group percentages had the highest CVD death properties, which included mono-drug sequences with FGA, SGA, and clozapine. On the opposite side—lower CVD deaths—were multidrug sequences with relatively lower proportions of CVD 2 and higher CVD 1 groups.

There was a lower occurrence of death in atypical antipsychotic sequences compared to typical drug sequences but a similar prevalence of cardiometabolic drugs. The highest proportion of cardiometabolic drugs occurring after antipsychotic drugs (CVD 1 group) was observed in multidrug sequences that started with FGA (Table 1). The lowest proportion of cardiometabolic drugs prescribed after antipsychotics was observed in the case of SGA-only or FGA-only drug sequences (19% and 21%, respectively).

Table 2 shows the consistency and coverage of the selected casual combinations from FsQCA. The total solution coverage was 0.632, and the total solution consistency was 0.899. The highest coverage was observed for combinations of young age with FGAs (40.6%) and young age with no cardiometabolic drug therapy (39.5%). Combinations of the female gender with no cardiometabolic drug therapy and no clozapine or FGA use were also associated with relatively high coverage (28% and 24.5%, respectively).

The other two causal combinations consisted of SGA with no cardiovascular risk factor drug therapy or young age (coverage 19.8% and 15.5%, respectively).

Discussion

Using our sequencing model, we observed the highest proportion of deaths in clozapine sequences, 29% for clozapine-only prescriptions and 21% for sequences starting with FGA, followed by clozapine. The lowest death ratio was observed for sequences containing lithium, especially those ending with lithium. The lowest proportion of cardiometabolic drugs was observed for the SGA or FGA-only sequences. The highest proportions of cardiometabolic drugs were observed in multidrug sequences. This may reflect the severity of the disease and the cumulative unintended metabolic effects of these antipsychotics.

Younger age is an obvious prognostic factor for survival, but the FsQCA analysis confirmed that the use of only FGA or SGA in younger patients was associated with good survival outcomes. Unfortunately, after reversing variables for causal combinations and changing the outcome from being

Table 1 Characteristics of drug sequences.

Sequence	Total Number	Cum. Mortality	CVD %	CVD in death %	CVD 0	CVD 1	CVD 2
CLOZAPINE	916	29%	63%	79%	19%	23%	56%
FGA→CLOZAPINE	564	21%	61%	83%	24%	35%	40%
FGA	58574	20%	62%	82%	15%	21%	63%
FGA→SGA	11119	15%	54%	83%	20%	37%	41%
SGA	10416	15%	52%	84%	12%	19%	67%
FGA→CLOZAPINE→LITHIUM	35	14%	37%	60%	7%	69%	23%
SGA→CLOZAPINE	572	9%	41%	73%	20%	47%	31%
FGA→SGA→CLOZAPINE	1033	8%	48%	82%	22%	60%	16%
FGA→LITHIUM	397	6%	59%	76%	20%	41%	37%
LITHIUM	506	5%	58%	92%	16%	29%	54%
FGA→SGA→CLOZAPINE→LITHIUM	215	5%	45%	58%	23%	65%	10%
SGA→CLOZAPINE→LITHIUM	70	5%	32%	50%	30%	47%	21%
SGA→LITHIUM	245	3%	42%	66%	17%	41%	40%
FGA→SGA→LITHIUM	538	2%	50%	73%	20%	56%	23%
CLOZAPINE→LITHIUM	72	1%	38%	100%	10%	60%	28%

FGA — first generation antipsychotics, SGA — second generation antipsychotics, CVD — cardiometabolic drugs.

Table 2 Selected causal combinations' consistency and coverage.

Causal combinations	raw coverage	consistency
FGA*∼AGE	0.406079	0.920922
∼CVD*∼AGE	0.394863	0.938538
∼CLOZAPINE*∼CVD*GENDER	0.279652	0.886739
FGA*∼CVD*GENDER	0.245299	0.884913
SGA*∼CVD	0.198586	0.918955
SGA*∼AGE	0.155229	0.949771
LITHIUM	0.0285925	0.952839
FGA*CLOZAPINE*∼CVD	0.0172289	0.9289
FGA*SGA*CLOZAPINE*GENDER	0.0076391	0.912069

FGA — first generation antipsychotics, SGA — second generation antipsychotics, CVD — cardiometabolic drugs.

alive to death, we did not reach consistency in the FsQCA analysis at the level of at least 80% (we obtained approximately 40%). More research is needed to build causal combinations with additional variables/conditions to achieve higher solution consistency. Findings of FsQCA analysis regarding the better outcome for causal combinations without clozapine and cardiometabolic drugs corresponded to our sequencing model, but only the latter was following conclusions from the literature.

Excess mortality in schizophrenia (as well as in other diseases requiring constant antipsychotic usage) remains the biggest challenge during long-term treatment.[22,23] Some studies have indicated an increasing number of CVD deaths related to the time of treatment—lower at the beginning of the drug course and constantly increasing with the treatment time.[24] The particular type of cardiovascular and/or metabolic risk burden in antipsychotic treatment varies from weight gain issue, metabolic syndrome, and diabetes to the possible cardiotoxic influence of these drugs.[9,11,25] A 2014 systematic review of antipsychotic adverse effects concluded that high metabolic syndrome risk varied from 23% to 50%, diabetes type II risk 2%—28%, obesity/weight gain risk about 30%, and dyslipidemia risk of about 32%.[26] The long-term metabolic effects may partially explain the increased cardiometabolic drug use for clozapine sequences observed in our study.

In the large German outpatient prescription database, cardiovascular agents were found to be most frequently co-prescribed with antipsychotics to 80% of all patients, regardless of treatment duration.[27] Analysis of 5712 antipsychotic prescriptions from 2,523 patients in France highlighted FGA as the preferred drug and accounted for 74% of patients who had been prescribed one of these agents at least once in one year.[28] The same indicator for SGA was about 68%, and co-prescription for several antipsychotics was frequent. There were a relatively small number of clozapine sequences in our study. Clozapine fulfills the criteria of a drug of last resort, and conclusions on mortality rates in clozapine users could be flawed due to selection bias.[17] In our study, we found the highest death ratios in clozapine sequences, unlike the mortality rate for clozapine in the study by Tiihonen et al.[14]. Clozapine has been found in large epidemiologic studies to have the lowest mortality rate, but in our previously published study, patients who ever used clozapine had higher mortality rates compared to patients treated with SGA.[29] According to findings from a randomized trial comparing clozapine and typical antipsychotic drugs in non-treatment-resistant schizophrenia, clozapine is more effective than typical antipsychotics for treatment retention and prevention of relapse, but it produces more severe metabolic side effects.[30] Combinations of female gender with no cardiometabolic drugs and no clozapine that were associated with good outcomes was an interesting finding in FsQCA analysis, as there were few reports on gender interactions with clozapine. A study that used U.S. national Medicaid data reported that female sex and clozapine treatment were associated with an increased risk of ileus and a fatal course.[31]

Study limitations

The main limitations of our study include the lack of psychiatric diagnosis as well as specific patients' clinical data on comorbid conditions in our database. The diagnoses of patients may contain the whole spectrum of mental diseases in the case of FGAs, which were refunded for the whole population of psychiatric patient's population in Poland. SGAs were refunded only for schizophrenia, and starting in 2010, they were also refunded for bipolar disease and dementia. Therefore, the population under study was significantly heterogeneous. We had no access to specific causes of death; therefore, we were unable to differentiate between cardiometabolic deaths, suicides, or external causes of death. The prescription data came from outpatient populations only. The gaps between different sequences may be the result of non-compliance as well as remissions or exacerbations resulting in hospitalization. The break in prescription sequence may also be associated with antipsychotic side effects, leading to stopping the use of the drug. Therefore, multidrug sequences or clozapine use may reflect the advanced stage of the disease requiring more intensive treatment. Our methodology did not take into account the cumulative effect of prescribed drugs on the entire course of the disease in an individual patient. We did not perform any longitudinal analysis aimed at calculating incidence rates. The longer-lasting sequences or antipsychotics that were chosen for treatment-resistant schizophrenia may be found in older patients, and the results of the FsQCA analysis reflected the effect of age (Table 2).

The observed higher death rates in clozapine sequences may be the result of selection bias, as only those patients with a history of lack of efficacy of other antipsychotics were referred for treatment with clozapine, and the effects of previous ineffective drugs may be carried over to the clozapine

period. There is sufficient published data to assume that cumulative antipsychotic exposure among those exposed is associated with the highest mortality rate among those with the highest doses of antipsychotics.[19] Co-prescription of atypical and typical antipsychotics usually occurs as a consequence of poor outcomes with single-drug treatment.[32] This selection phenomenon may be mixed with another mechanism: only those with severe forms of diseases were given higher doses of many different drugs for longer periods, and the disease severity may be associated with increases in cardiometabolic risk due to lifestyle factors or other unknown mechanisms.

The observed better cardiometabolic risk profile in lithium users may be the result of baseline differences in clinical characteristics: lithium was prescribed to those patients with some features of bipolar disorder and not to those with disorganized schizophrenia, which is known to have a poor prognosis.

However, concerns about studies based on large datasets coming from EHRs include data validity, lack of detailed clinical information, and a limited ability to control confounding.[20] We did not use any classical statistical model to analyze our data, but instead, we applied the FsQCA approach, which adequately reflects the general processes of qualitative analysis and allows quantitative analysis for calibrated conditions.[21] Due to the large potential for bias, there is limited potential for the generalizability of our results.

Despite these limitations, our study has several strengths, including the attempt to capture the complexity and dynamics of the relationship between different antipsychotic drugs and lithium use in the treatment of mentally ill patients and the risk of death and cardiometabolic drug use. To our knowledge, this is the first investigation on antipsychotic drug effects in which prescription sequence analysis has been used. This study adds a new facet to our understanding of the potential harms associated with the use of clozapine. An additional strength is the size of the database used in our analysis; more than 1 million prescriptions were analyzed. Big data is an important new direction for most areas of medical science. Such a large sample size as ours allows for the study of infrequent events, and their representativeness of routine clinical care makes it possible to study real-world effectiveness and utilization patterns. In summary, the use of FsQCA as our methodology allows us to capture the advantages of both qualitative and quantitative analyses in the era of big data and electronic health records.

Conclusions

There is insufficient evidence regarding which antipsychotic is associated with the fewest cardiometabolic adverse effects and the lowest mortality rates. In this long-term longitudinal database study, clozapine prescription sequence was associated with higher rates of cardiometabolic drug subsequent use compared to first-generation antipsychotics and second-generation antipsychotics. Moreover, the clozapine prescription sequence was not superior to other antipsychotics in terms of mortality rates. These findings are in opposition to those from other cohort studies that have documented higher rates of relapse prevention and a lower risk of death for clozapine.

Fig. 1.

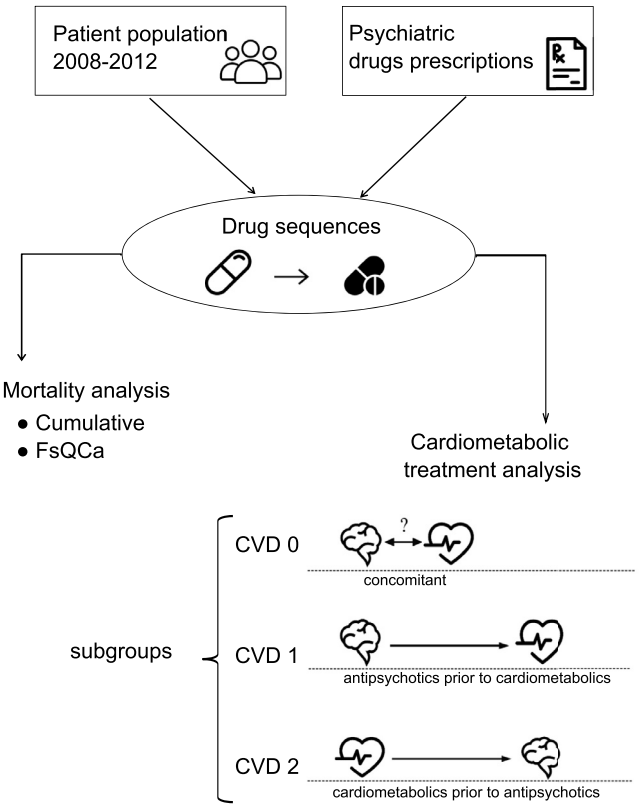

Fig. 1 Flowchart of the study design.

Ethical considerations

This research was based on a publicly available database of refunded drug use from the National Health Fund in Poland. This repository contains only anonymous data. This kind of database established for public health does not require review by an institutional board review and may then be used for research without institutional board review approval.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Authors from the Technology University of Gdansk, Piotr Dorozynski and Adam Harasimowicz, were responsible for preparing and performing the algorithm that iterates prescriptions from our database. Tomasz Dziubich performed the fuzzy set qualitative comparative analysis. Dr Przemyslaw Waszak was responsible for preparing figures, the bibliography, and the discussion. Pawel Zagozdzon conceived the

original idea and supervised the project. All authors discussed the results and contributed to the final manuscript.

Declaration of Competing Interest

All authors declared that there were no conflicts of interest in relation to the subject of this study.

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