ORIGINAL ARTICLE

Analysis of polypharmacy in schizophrenia patients in Ponta Grossa

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Abstract

Introduction: Schizophrenia is a chronic disorder requiring significant healthcare resources, and its treatment is primarily based on antipsychotics, ideally prescribed as monotherapy. Polypharmacy is generally discouraged due to the increased risk of side effects without clear clinical benefits.

Objectives: This study aims to determine the prevalence of antipsychotic polypharmacy, occurrences of high doses and underdoses of antipsychotics, and the use of clozapine at CAPS II in Ponta Grossa, PR.

Methodology: A total of 483 medical records were analyzed, with 340 records excluded from the study. The prescriptions of 143 patients diagnosed with schizophrenia were reviewed for the period from 01/01/2021 to 26/09/2022 at CAPS II in Ponta Grossa, PR. Antipsychotic polypharmacy was defined as the prescription of two or more antipsychotic medications. High-dose was defined as any prescription with a dose exceeding the maximum recommended dose or a cumulative dose exceeding 100% of the maximum doses for each drug. Underdose was defined as any prescription below the recommended dose in the literature.

Results: Among the patients with schizophrenia, 59.44% were undergoing polypharmacy treatment, 21.67% were prescribed high doses of antipsychotics, and 29.37% were receiving underdoses.

Conclusion: The therapeutic profile of patients at CAPS II diverges from the existing literature. The rate of polypharmacy and high-dose prescriptions is higher compared to other studies, while the use of clozapine is considerably lower.

Keywords: Schizophrenia, Antipsychotics, Clozapine, Polypharmacy.

Introduction

Psychotic disorders, such as schizophrenia, are characterized by the presence of delusions, hallucinations, disorganized thought or speech, abnormal movements such as catatonia, and negative symptoms. These features may be present individually or in combination. Schizophrenia is a chronic disorder that causes severe dysfunctions, potentially affecting an individual's motivation, affective connections, and cognition. Symptoms typically emerge in late adolescence to early adulthood, with a gradual and progressive development that can vary in its course. A prodromal phase, often associated with negative symptoms, may precede the onset of psychotic symptoms, leading to significant impairment in social function and quality of life for both patients and their families.

Globally, it is estimated that approximately 0.32% of the population is affected by schizophrenia, with a prevalence of 0.45% in individuals over 20 years old. In Brazil, Carteri et al. (2020) reported the prevalence and impact of schizophrenia

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and other mental disorders, noting over 150,000 annual hospital admissions from 2009 to 2019, with hospital costs exceeding 67 million US dollars. Although the prevalence of schizophrenia is relatively low, the disorder contributes to 1.7% of the global years of life lost due to all disorders, with an estimated 13 million years of healthy life lost in 2016 alone. The impact of schizophrenia can reduce life expectancy, with meta-analyses indicating that patients with schizophrenia have, on average, lost at least 13 to 15 years of life expectancy. Additionally, patients with schizophrenia have a 51% higher mortality rate compared to the general population, although this rate can vary based on location and patient characteristics.

Treatment for schizophrenia is primarily based on antipsychotic medications, which should ideally be used in monotherapy at the lowest effective dose for treating psychotic episodes. The dose may be adjusted up to the maximum limit based on clinical needs. If the maximum recommended dose is reached with an unsatisfactory clinical response, a change in medication may be necessary. Higher doses are sometimes used for treatment-resistant cases, although this practice is generally discouraged.

Antipsychotic medications are categorized as either typical (first-generation) or atypical (second-generation). Typical antipsychotics are also antagonists of muscarinic cholinergic, alpha-1 adrenergic, and histamine receptors, leading to significant side effects, particularly extrapyramidal symptoms. Atypical antipsychotics, in contrast, antagonize both the D2 and serotonin 2A receptors, which improves the treatment of negative symptoms and reduces extrapyramidal effects.

The choice of antipsychotic medication is influenced by factors such as drug availability, socioeconomic conditions, the patient's support network, clinical history, and previous treatment attempts. In some cases, patients with schizophrenia may receive additional medications such as antidepressants or benzodiazepines for associated symptoms like anxiety. Antipsychotic polypharmacy, defined as the use of two or more antipsychotic medications, is sometimes employed to enhance therapeutic effects or reduce specific symptoms. However, this practice is generally discouraged due to the increased risk of side effects and potential for arrhythmias, without providing clear additional benefits.

Treatment-resistant schizophrenia is defined as the failure to achieve clinical improvement after trials with two different antipsychotics at maximum doses. Clozapine is the only medication recommended for this condition, and its use should be reserved for such cases. Approximately 34% of patients with schizophrenia may develop treatment-resistant schizophrenia.

This study aimed to evaluate the prevalence of antipsychotic polypharmacy, the occurrence of high doses and underdoses, and the rate of clozapine use among patients with schizophrenia receiving treatment at CAPS II in Ponta Grossa, PR.

Methodology

This is a descriptive, cross-sectional study with a quantitative approach, conducted through the analysis of medical records from the Psychosocial Care Center II (CAPS II) in Ponta Grossa, PR. The study aimed to assess the prevalence of

antipsychotic polypharmacy, as well as occurrences of underdoses and overdoses in patients with schizophrenia.

Inclusion Criteria: Medical records of patients at CAPS II in Ponta Grossa with a diagnosis of schizophrenia (ICD-10: F20) who were being monitored or had their last appointment after 01/01/2021.

Exclusion Criteria: Absence of a prescription record in the last registered appointment.

Data were collected from 26/09/2022 to 30/09/2022 following approval by the Ethics Committee of the State University of Ponta Grossa.

Data Analysis: From the included medical records, prescribed medications and their dosages were listed. Analysis focused on identifying instances of polypharmacy, defined as the simultaneous prescription of at least two antipsychotic medications. Patients using oral or depot haloperidol were considered as a single category.

Patients prescribed clozapine were identified and analyzed similarly to the general group if polypharmacy was present. Due to the absence of a longitudinal analysis of patients' medical histories, clozapine users were not classified as treatment-resistant, as clozapine could have been prescribed without two prior treatment trials. Therefore, these patients were categorized simply as "clozapine users."

The study analyzed the number of drugs prescribed at underdose and overdose levels. High-dose was defined as any antipsychotic prescribed at a dose exceeding the maximum recommended dose for that drug, or, in cases of polypharmacy, when the total percentage of maximum doses of all prescribed antipsychotics exceeded 100%. Underdose was defined as any prescription below the recommended dose in the literature.

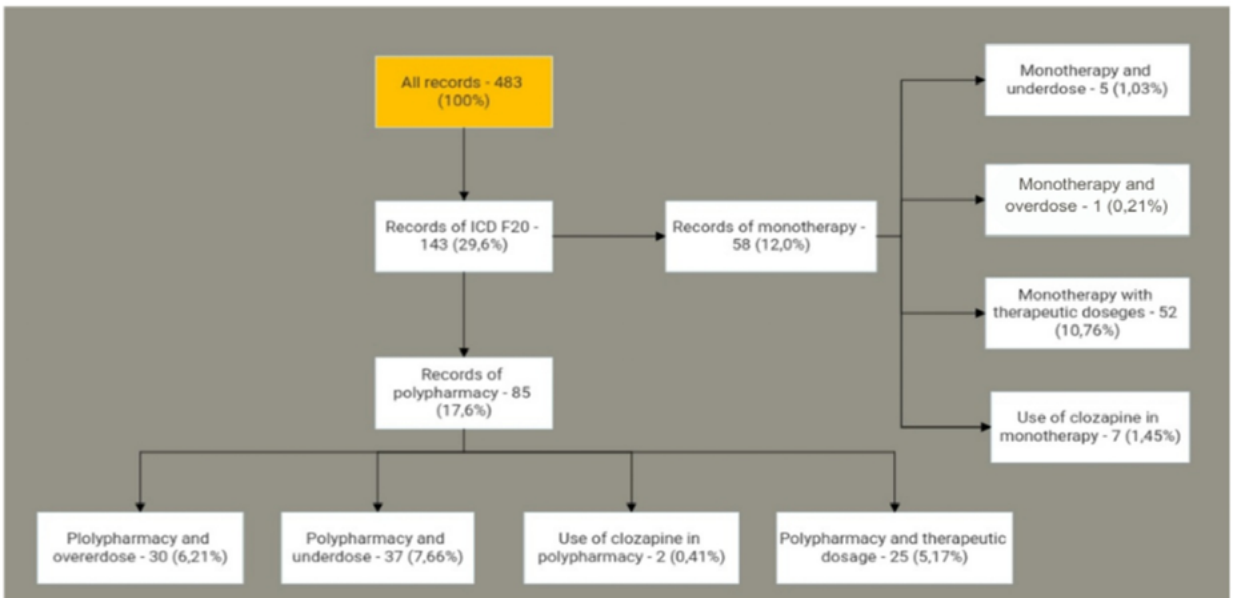
A total of 483 medical records were analyzed, with 143 meeting the inclusion criteria. Of the 340 excluded, 268 lacked a schizophrenia diagnosis, 70 did not have a recorded psychiatric consultation after 01/01/2021, and 2 had no record of the treatment used. The analysis of the included medical records is illustrated in a flowchart in Image 1.

Table 1 - Antipsychotics with their respective minimum effective doses and maximum recommended doses

Antipsychotic	Minimum dosage	Maximum dosage
Haloperidol	2 mg/day	20 mg/day
Haloperidol depot	30 mg/week	300 mg/4 weeks
Chlorpromazine	200 mg/day	1000 mg/day
Clozapine	300 mg/day	900 mg/day
Olanzapine	5 mg/day	20 mg/day
Quetiapine	150 mg/day	750 mg/day
Risperidone	2 mg/day	16 mg/day
Ziprasidone	40 mg/day	160 mg/day
Levomepromazine	200 mg/day*	1200 mg/day
Zuclopenthixol depot	200 mg/week	600 mg/week
Aripiprazole	10 mg/day	30 mg/day

Source: Taylor D, E. BTR, Young A. The Maudsley prescribing guidelines in psychiatry. 14th ed. Hoboken, NJ, NJ: Wiley Blackwell; 2021. * Lal S, Nair NPV. Is levomepromazine a useful drug in treatment-resistant schizophrenia? Acta Psychiatrica Scandinavica [Internet]. 1992 Mar [cited 2022 Dec 18];85(3):243-5. Available from: https://pubmed.ncbi.nlm.nih.gov/1561898/

Image 1 - Flowchart of data collected from medical records.



Source: CAPS II data, prepared by the author

In order to minimize the risk of losing paper records and leaking patients' personal data, the data was collected by only one of the participating researchers on the premises of CAPS II. The information was entered into Microsoft Office Excel ® software for compilation.

Results

A total of 483 CAPS II's medical records of open cases were analyzed. A total of 340 were excluded because they did not show a diagnosis of schizophrenia or had no record of a psychiatric consultation after the stipulated date. Of these, 143 met the inclusion criteria, containing a previous diagnosis of schizophrenia with records of the treatment used.

Of the medical records included in the analysis, 85 (59.44%) of the patients with schizophrenia used more than one antipsychotic and 58 (40.56%) were being treated with monotherapy.

Of those treated with polypharmacy, 57 are using two drugs (39.86%), 24 (16.78%) are prescribed three different antipsychotic drugs and only 4 (2.80%) are treated with four antipsychotics. The number of antipsychotics used in patients with polypharmacy is shown in Graph 1.

Regarding the dosage administered to these patients, of those who were on therapeutic regimens with more than one antipsychotic, 25 (17.48%) had all the antipsychotics prescribed at therapeutic doses. On the other hand, 34 (23.77%) had drugs prescribed at doses below those recommended for the treatment of schizophrenia and 30 (20.98%) had drugs at doses above those recommended. Of the patients on monotherapy, 53 (37.06%) were on therapeutic doses of antipsychotics, 4 (2.8%) were on doses below those recommended and 1 (0.7%) has been treated on a high--dose of antipsychotics.

There were 42 patients with drugs below the therapeutic dose, and four different drugs were found in this condition. The drug that was most underdosed was chlorpromazine with 28 (19.58%). The others were quetiapine, with 5 (3.5%), risperidone with 8 (5.6%) and clozapine with 1 (0.7%). The data described is shown in figure 1.

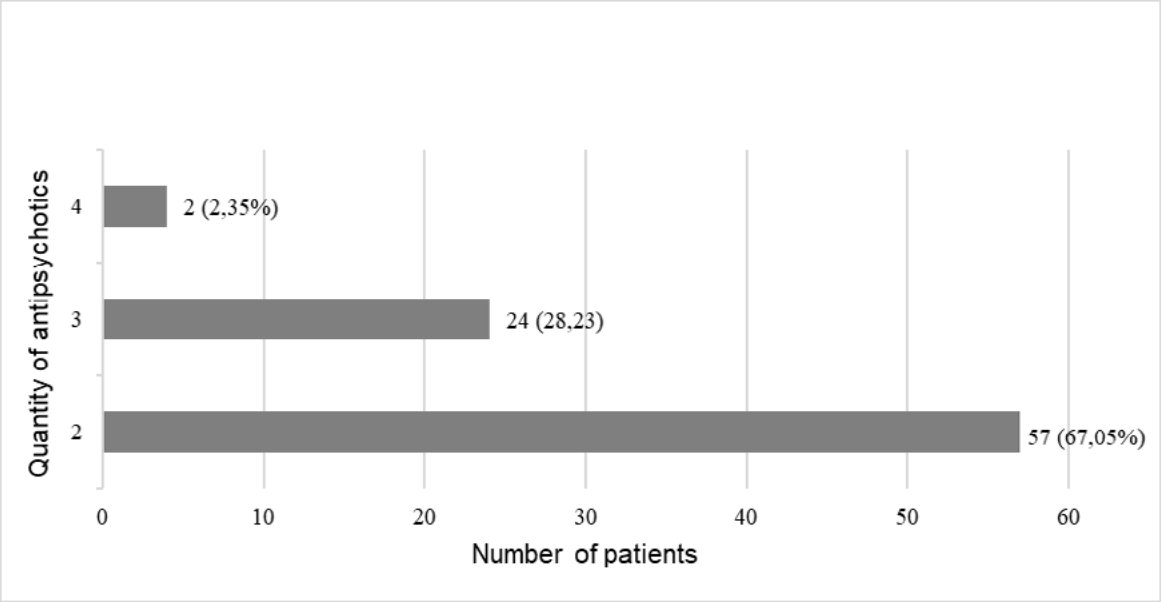
Considering high-dose, including patients on polypharmacy and monotherapy, there were 31 cases (21.67%) prescribed at higher dosages than recommended. Of these, 5 (3.5%) prescriptions were for olanzapine and 1 (0.7%) for haloperidol. The other cases were combinations of doses of more than one antipsychotic.

When analyzing the use of clozapine for patients with schizophrenia, 9 (6.3%) patients reported using the drug. Of these, 2 (1.4%) had a combination with another antipsychotic, one in high-dose and the other in underdose, while clozapine was at a therapeutic dose in both cases. The remaining 7 (4.9%) were treated with clozapine alone, with 1 (0.7%) being underdosed.

About the antipsychotics used, the most prescribed was haloperidol (49.65%), with 71 patients. The second was risperidone with 54 (37.76%), followed by olanzapine with 48 (33.56%) and chlorpromazine with 46 (32.16%). Other antipsychotics prescribed were quetiapine, with 10 prescriptions (7.0%), clozapine and levomepromazine with 9 (6.3%), zuclopenthixol with 6 (4.19%), aripiprazole with 5 (3.5%) and ziprasidone with 2 prescriptions (1.4%). The frequencies of antipsychotics are shown in Graph 2.

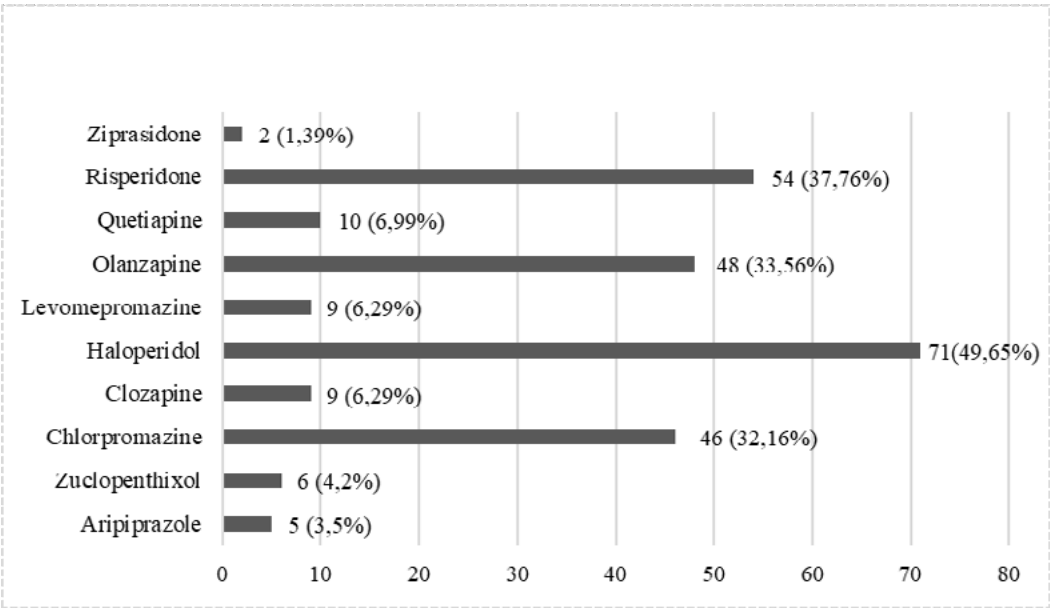
In patients prescribed two antipsychotics, the most common combinations were the ones with haloperidol, and the combinations with chlorpromazine having the highest incidence with 23 prescriptions (16.08%), followed by the combination with olanzapine, with 16 (11.18%), and risperidone with 13 (9.09%). Of the three-drug combinations, two had an occurrence greater than or equal to five: haloperidol, chlorpromazine and risperidone with 7 (4.89%) occurrences; haloperidol, olanzapine and chlorpromazine with 5 (3.5%) prescriptions. Combinations of four drugs were not repeated. The drug combinations can be analyzed in Table 2.

GRAPH 1 - Number of antipsychotics in patients with polypharmacy



Source: CAPS II data, prepared by the author
Legend: Percentages in relation to the number of polypharmacy patients

GRAPH 2 - List of antipsychotics recorded in CAPS II medical records and their quantities



Source: CAPS II data, prepared by the author
Legend: Percentages in relation to the number of patients diagnosed with schizophrenia

Table 2: Combinations of antipsychotics and their frequencies (n=85)(continued)

Antipsychotics	N (%)
Zuclopenthixol	1 (1,17%)
*Aripiprazole	1 (1,17%)
Chlorpromazine	3 (3,52%)
*Aripiprazole	1 (1,17%)
* Zuclopenthixol	1 (1,17%)
*Quetiapine	1 (1,17%)
Haloperidol	55 (64,70%)
*Aripiprazole	1 (1,17%)
*Chlorpromazine	23 (27,05%)
**Clozapine	1 (1,17%)
**Levomepromazine	1 (1,17%)
**Risperidone	7 (8,23%)
**Ziprasidone	2 (2,35%)
*Levomepromazine	2 (2,35%)
*Olanzapine	16 (18,82%)

**Chlorpromazine	5 (5,88%)
***Levomepromazine	1 (1,17%)
**Levomepromazine	2 (2,35%)
**Risperidone	2 (2,35%)
***Levomepromazine	1 (1,17%)
*Risperidone	13 (15,29%)
**Olanzapine	1 (1,17%)
***Chlorpromazine	1 (1,17%)
Olanzapine	13 (15,29%)
*Aripiprazole	1 (1,17%)
* Zuclopenthixol	2 (2,35%)
*Chlorpromazine	7 (8,23%)
**Risperidone	3 (3,52%)
*Clozapine	1 (1,17%)
**Levomepromazine	1 (1,17%)
*Levomepromazine	1 (1,17%)
*Quetiapine	1 (1,17%)
Quetiapine	2 (2,35%)
* Zuclopenthixol	2 (2,35%)
Risperidone	11 (12,94%)
*Chlorpromazine	6 (7,05%)
**Quetiapine	1 (1,17%)
*Olanzapine	4 (4,70%)
**Chlorpromazine	1 (1,17%)
***Quetiapine	1 (1,17%)
*Quetiapine	1 (1,17%)

Source: CAPS II data, prepared by the author

Key: Medication without an asterisk corresponds to the first drug in the combination; an asterisk corresponds to the second drug in the combination; two asterisks, the third; three asterisks, the fourth drug.

Note: N refers to the total number of polypharmacy patients.

Discussion

The study revealed that the proportion of patients diagnosed with schizophrenia at CAPS II is just under one-third (29.6%) of those receiving treatment. This rate varies significantly across other regions of Brazil. For example, Montes Claros, Minas Gerais, reported that 50.5% of service users were diagnosed with schizophrenia. Similarly, a study in Paulo Afonso, Bahia, found a prevalence of 41.3% for schizophrenia and other psychotic disorders. Other studies reported prevalence rates of 30.0% in Ilhéus and 53.9% in the public network in Maceió.

At CAPS II, 59.44% of patients diagnosed with schizophrenia were using antipsychotic polypharmacy, while 40.56% were on monotherapy. This suggests a higher tendency for polypharmacy compared to other studies. For instance, Qiu et al. (2018) reported that 87.3% of patients in Chinese mental health institutions and 80.1% in a Japanese database were on monotherapy. Similarly, a study of psychiatric hospital discharges in the USA found that 77% of patients with schizophrenia were on monotherapy.

Among the prescribed antipsychotics, haloperidol was the most common, used by 49.65% of patients with schizophrenia. It was also the most frequently used antipsychotic in combinations, particularly with chlorpromazine. Kantorski et al. (2021) found similar results in Pelotas, where haloperidol was also the most prescribed. However, a study by Roh et al. (2013) in Seoul found that while haloperidol was the most common antipsychotic in combinations in 2005, by 2010, quetiapine and risperidone had become more prevalent, which is inconsistent with the findings at CAPS II.

The study observed that 21.7% of schizophrenia patients were on high doses of antipsychotics, with only one case on monotherapy. Roh et al. (2013) reported that 18.4% of patients on monotherapy in a psychiatric hospital in Seoul had overdoses, a figure close to our findings. High doses of antipsychotics are associated with adverse effects such as QT interval prolongation, extrapyramidal symptoms, postural hypotension, and sedation. The higher incidence of high-dose prescriptions and polypharmacy at CAPS II may contribute to an increased risk of these complications.

Conversely, underdosing of antipsychotics can lead to exacerbations and relapses of psychotic episodes. At CAPS II, 29.37% of patients were prescribed antipsychotics below recommended dosages, compared to 17.6% reported by Kantorski et al. (2021).

Only 1.86% of all CAPS patients and 6.29% of patients with schizophrenia were prescribed clozapine. This is notably lower than rates observed in tertiary hospitals, where clozapine use ranged from 52.6% to 64.87% for resistant schizophrenia. In a study from England, 2.4% of patients with treatment-resistant psychosis were prescribed clozapine. Roh et al. (2013) found 10.7% clozapine use, with 5 patients on polypharmacy. Despite lower clozapine rates in other studies, the rate at CAPS II is even lower, suggesting possible underutilization of clozapine for resistant cases.

The study's limitations include the lack of longitudinal analysis of patients' clinical histories. Patients were classified based on current diagnoses rather than detailed treatment histories. Additionally, clozapine use was not directly linked to treatment resistance. There was no in-depth analysis of polypharmacy prescriptions and their justifications.

Conclusion

The data from CAPS II in Ponta Grossa reveal discrepancies with the literature regarding antipsychotic prescriptions for schizophrenia. The rates of antipsychotic polypharmacy and high-dose prescriptions are higher than reported elsewhere, which may increase the risk of adverse effects without clear patient benefits. Additionally, the low rate of clozapine use compared to other studies suggests possible underutilization for treatment-resistant cases. Further research is needed to explore these discrepancies and understand treatment practices better.

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Authors' contributions:

FPW – Data gathering and interpolation and writing
TFD –Study design, revision and final approval
FPM – Responsible for the integrady of the study and approval by the ethics committee
JHH – Revision and writing

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