Antipsychotic polypharmacy and clozapine prescribing patterns: evolution and correlates before and after a psychiatric hospitalisation

Lagreula Juliette[1], de Timary Philippe[2], Elens Laure[3], Dalleur Olivia[4]

1. juliette.lagreula@uclouvain.be
   Clinical Pharmacy research group (CLIP)- Louvain Drug Research Institute (LDRI), UCLouvain, Brussels, Belgium.
   Fonds de la Recherche Scientifique – FNRS, Brussels, Belgium.
2. philippe.detimary@saintluc.uclouvain.be
   Institute of Neuroscience, UCLouvain, Brussels, Belgium.
   Psychiatry department, Cliniques Universitaires Saint-Luc, Brussels, Belgium.
3. laure.elens@uclouvain.be
   Integrated PharmacoMetrics, PharmacoGenomics and PharmacoKinetics (PMGK)- Louvain Drug Research Institute (LDRI), UCLouvain, Brussels, Belgium.
   Louvain centre for Toxicology and Applied Pharmacology (LTAP)- Institut de Recherche Expérimentale et Clinique (IREC), UCLouvain, Brussels, Belgium.
4. olivia.dalleur@saintluc.uclouvain.be
   Clinical Pharmacy research group (CLIP)- Louvain Drug Research Institute (LDRI), UCLouvain, Brussels, Belgium .
   Pharmacy department, Cliniques universitaires Saint-Luc, Brussels, Belgium.

Correspondence:

Lagreula Juliette,

Clinical Pharmacy research group (CLIP)- Louvain Drug Research Institute (LDRI),

Université Catholique de Louvain,

Avenue Mounier 72, 1200 Brussels, Belgium

Phone: +3227647370

Email: juliette.lagreula@uclouvain.be

Abstract

Aim: To explore the evolution of antipsychotic polypharmacy (APP) and other psychotropic prescribing patterns during psychiatric hospitalisations, to detect characteristics associated with APP on admission and at discharge, and to examine clozapine prescribing patterns.

Methods: Data on adult inpatients diagnosed with schizophrenia spectrum disorders were collected retrospectively from 6 Belgian hospitals.

Results: Of the 516 patients included, APP prescribing increased significantly from 47.9% on hospital admission to 59.1% at discharge. On admission and at discharge, APP was associated with prior clozapine use ($OR_{admission}$=2.53, CI=1.1-5.84, $OR_{discharge}$=11.01, CI=4.45-27.28), treatment with a first-generation antipsychotic ($OR_{admission}$=26.79, CI=13.08-54.86, $OR_{discharge}$=25.2, CI=12.2-52.04), increased antipsychotic exposure ($OR_{admission}$=8.93, CI=5.13-15.56, $OR_{discharge}$=19.89, CI=10-39.54), and a greater number of hypno-sedatives ($OR_{admission}$=1.88, CI=1.23-2.88, $OR_{discharge}$=4.18, CI=2.53-6.91). APP was negatively associated with involuntary admission ($OR_{admission}$=0.31, CI=0.14-0.7, $OR_{discharge}$=0.3, CI=0.13-0.68). When using an alternative definition of monotherapy (i.e., including patients with an add-on low-dose antipsychotic for sleep disorders), alcohol use disorder ($OR_{admission}$=0.26, CI=0.13-0.54) and higher age ($OR_{discharge}$=0.53, CI=0.29-0.95) were negatively associated with APP, and living in a residential facility ($OR_{discharge}$=2.39 CI=1.21-4.71) and a higher daily dosage of benzodiazepines during the stay ($OR_{discharge}$=1.32 CI=1.03-1.69) increased the odds of being discharged on APP. On admission, 9.3% of patients were being treated with clozapine. Although 28.1% of patients were eligible for clozapine treatment, only 11% of patients were discharged with a clozapine prescription. For 7 of the 10 patients with a new clozapine prescription, it was directly prescribed in combination with another antipsychotic, without a prior trial of clozapine monotherapy.

Conclusion: Suboptimal prescriptions of antipsychotics in patients with schizophrenia persist after psychiatric hospitalisations and are associated with identifiable characteristics.

Main text

1. Introduction

Antipsychotic polypharmacy (APP), defined as prescription of at least two different antipsychotics, is frequent worldwide in the treatment of schizophrenia (1). Justifications given for APP use include attempting to reduce psychotic symptoms, targeting a comorbid condition (e.g., substance use disorder, anxiety), reducing adverse effects, and increasing adherence (2, 3). Despite these beliefs, high-quality evidence reveals that APP, excluding some combinations with clozapine, has no benefit over monotherapy on the reduction of positive or negative symptoms, or hospital readmissions (4-6). Moreover, it is associated with a higher prevalence of adverse effects, increased healthcare costs, poorer treatment adherence, and increased risk of drug-drug interactions (7-10). Some combinations are associated with an increased risk of hospital readmission (11). International prescribing guidelines for schizophrenia thus advise against the use of APP, even for patients with psychiatric comorbidities (12-14).

About one third of individuals with schizophrenia will not respond sufficiently to treatment, with no or minimal symptom improvement after two or more antipsychotic trials at an adequate dose and duration, referred to as treatment-resistant schizophrenia (TRS). Clozapine is the first choice for TRS because of its superior effectiveness, but is underused in eligible patients worldwide (15, 16). Clozapine underuse might expose patients to greater risk of APP prescription. Both clozapine underuse and APP prescribing are considered inappropriate prescribing (12).

The majority of patients receiving APP can be safely switched to monotherapy without symptom worsening, especially when the combination involves clozapine or a long-acting injectable antipsychotic (LAI). Switching to monotherapy is also associated with reduction of side effects and improvement in attention and executive functions (17-19). Psychiatric hospitalisations, during which patients are closely observed by healthcare professionals, may be suitable occasions to re-evaluate patient pharmacotherapy and possibly to switch to monotherapy.

Most of the existing studies on APP were conducted in ambulatory settings and/or are characterised by a cross-sectional design, thereby limiting the possibility to monitor any modification in drug regimens. Therefore, little information is available on the evolution of APP and clozapine prescribing patterns during psychiatric hospitalisations.

Determining the evolution of APP, clozapine, and other psychotropic prescribing patterns during psychiatric hospitalisations and identifying associated factors (e.g., demographics, disease severity, co-treatment) may help detect patients or situations at higher risk of APP prescriptions, enabling future interventions to optimise antipsychotic prescriptions at discharge.

The objectives of this study were therefore: (1) to explore the evolution of APP and other psychotropics prescribing patterns during a psychiatric hospitalisation; (2) to detect characteristics associated with APP on admission and at discharge; (3) to examine clozapine prescribing patterns.

2. Methods

2.1. Setting and data sources

Retrospective data from six Belgian hospitals were analysed in 2020-2021. Potential factors associated with APP were extracted from patients' medical records and prescribing patterns from local prescription software. Patients treated with antipsychotics were identified using the Anatomical Therapeutic Chemical (ATC)-group N05A, with the exclusion of lithium (ATC N05AN01).

2.2. Study population

Records of all patients aged 18 to 64 years old discharged from psychiatric units after an acute hospitalisation (less than 1 year) between 1st November 2018 and 1st November 2019, who were receiving at least one antipsychotic on admission and had a diagnosis of schizophrenia or schizoaffective disorder (ICD-11 code 6A20 and 6A21 or DSM-5 295.xx) were analysed retrospectively. If a patient had more than one admission during the study period, only the last complete hospitalization was included.

2.3. Evolution of the use of APP and co-treatment

The prevalence of APP and associated factors on hospital admission and at discharge was explored. APP is defined as the prescription of at least two different antipsychotics. However, many patients receive a low-dose antipsychotic for sleep disorders (e.g., prothipendyl ≤80 mg, clotiapine ≤40 mg, levomepromazine ≤ 100 mg, quetiapine ≤50 mg) combined with an antipsychotic for the treatment of their psychotic symptoms, and this combination may not always be considered as a real APP. A sensitivity analysis was thus performed to evaluate the influence of this category of patients on the results using an alternative definition of monotherapy. In this alternative definition, patients were considered to be on monotherapy when they received two antipsychotics if one was prescribed at low-dose for sleep disorders. The prevalence of use of other psychotropic drugs (e.g., antidepressants, mood stabilizers, benzodiazepines, trazodone or sedating antihistamines) and anticholinergics was also examined. Anticholinergics, i.e., procyclidine, trihexyphenidyl and biperiden, are used for the treatment of extrapyramidal symptoms.

2.4. Variables potentially associated with APP

Different factors were considered for their potential association with APP, based on the literature (1, 20, 21). These factors encompassed demographics, disease characteristics, comorbidities, hospitalisation characteristics, antipsychotic treatment and co-treatment. The list of factors tested is available in the online Supplementary material (eTable 1).

Exposure to antipsychotics was expressed as the ratio of the prescribed daily dose (PDD) to the World Health Organization (WHO) approved defined daily dose (DDD). When patients were receiving more than one antipsychotic, the PDD/DDD ratio was calculated using the sum of PDD/DDD ratios for each prescribed antipsychotic.

The daily dose of benzodiazepines was calculated using a lorazepam equivalent dose based on the Belgian official compendium (CBIP/BCFI).

Hypno-sedative drugs used for the treatment of sleep disorders comprised low-dose antipsychotics, trazodone ≤100 mg, benzodiazepines, and sedating antihistamines, if they were taken at night to induce sleep.

The Global Assessment Functioning (GAF) score was used to estimate the severity of the patients' psychopathology. In Belgium, a GAF score is systematically determined on admission and at discharge for every patient hospitalised in a psychiatric unit.

Certain continuous variables were dichotomised (e.g., ≥2 or < 2 admissions in the year prior to the current hospitalisation and ≥2 or < 2 previous trials of an antipsychotic) to enable easier interpretation, based on different regression models.

Residential facilities referred to group homes, nursing homes, or supervised residential facilities for individuals with mental disorders.

2.5. Clozapine prescribing patterns

Clozapine prescribing patterns on admission and at discharge were also investigated. A patient was considered eligible for clozapine if they had an inadequate response to at least two different

antipsychotic trials at a minimal dose of 400 mg of chlorpromazine equivalent, for at least 6 weeks (22). Clozapine antipsychotic polypharmacy (CAP) was defined as the combination of clozapine with at least one other antipsychotic.

2.6. Statistical analysis

Changes in the prevalence of APP, psychotropic and anticholinergic prescribing between admission and discharge were measured using McNemar tests. Change in antipsychotic exposure was tested using a paired-sample Wilcoxon test.

A logistic regression model was used to detect factors associated with APP on admission and at discharge, with multiple imputation for missing data. A backward stepwise elimination based on the Akaike information criterion was used to select the final model, in which p-values <0.05 were considered statistically significant. Changes in the prevalence of clozapine use, CAP, and other clozapine prescribing patterns between admission and discharge were examined using McNemar tests. The statistical analyses were performed using R software.

2.7. Ethics

The study protocol was approved by the Comité d'éthique hospitalo-facultaire Saint-Luc-UCLouvain (Belgium), as well as by ethics committee of each involved hospital (N°2019/27NOV/530).

3. Results

3.1. Baseline characteristics

Of the 516 patients with schizophrenia or schizoaffective disorder hospitalised between 1st November 2018 and 1st November 2019, 55.4% were men and the mean age was 40 (±11.3) years. The majority of the patients admitted were unemployed (94.8%), 20.3% lived in a residential facility, and 42.3% had a legal guardian. The mean duration of hospitalisation was 27 days, and 20.2% of the patients were involuntary admissions (Table 1).

Table 1. Baseline characteristics

Characteristics	Total (N=516) n, (%)
Sociodemographic characteristics	
Male	286 (55.4)
Female	230 (44.6)
Age (y), mean (SD)	40 (11.6)
Single	420 (81.4)
Living situation	
Residential facility	105 (20.3)
Homeless	48 (9.3)
Living alone or with relatives	363 (70.4)
Legal guardian	217 (42.3)
Unemployed	489 (94.8)
Medical characteristics	
Tobacco smoking	348 (67.6)
Alcohol use disorder	118 (22.9)
Substance use disorder	183 (35.6)
History of violent or aggressive behaviour	224 (43.6)
Intellectual disability	49 (9.5)
Prior suicide attempt	135 (26.6)
Illness duration (y), median (IQR)	12 (6-20)
Age of onset (y), median (IQR)	24 (19-30)
Hospitalisation characteristics	
Involuntary admission	104 (20.2)
Length of hospital stay (d), median (IQR)	27 (13-52)
GAF score on admission, mean (SD)	37 (13)
GAF score at discharge, mean (SD)	51 (16)
Antipsychotic adverse effect(s)	238 (46.2)
Primary diagnosis	
Schizophrenia	398 (77.1)
Schizoaffective disorder	118 (22.9)

Abbreviations: SD, standard deviation; IDR, Interquartile range

3.2. Evolution of antipsychotics and psychotropic prescribing patterns between admission and discharge

The prevalence of APP prescribing increased significantly from 47.9% on hospital admission to 59.1% at discharge ($p<0.001$) (Figure 1-A). At discharge, the daily number of antipsychotics had increased in 117 patients (22.7%), decreased in 48 patients (9.3%), and was unchanged in 351 patients (68%), compared to the situation on hospital admission. Although the daily number of antipsychotics decreased in 48 patients between admission and discharge, only 34 of the 247 patients (13.8%) admitted on APP were discharged on monotherapy (Figure 2). Antipsychotic exposure per patient increased significantly from 1.5 (IQR 1-2.3) to 1.8 (IQR 1.1-2.5) ($p<0.001$) between hospital admission and discharge. Using the alternative definition of monotherapy, APP was present in 35.5% (n=183) of patients on admission versus 44% (n=227) at discharge ($p<0.001$) (Figure 1-A). Of the 247 patients admitted on APP, 99 (40.1%) had a combination involving at least one LAI, and this figure increased to 145 of the 305

patients on APP (47.5%) at discharge (p<0.001). Paliperidone was the LAI antipsychotic most frequently prescribed to patients on APP, both on admission and at discharge (eTable 2 in Supplementary material). The proportion of patients taking mood stabilizers (16.9% versus 19.6%, p=0.008), benzodiazepines (45.5% versus 54.3%, p<0.001), anticholinergics (9.3% versus 11.6%, p=0.025), or low-dose antipsychotics for sleep disorders (22.1% versus 29.3%, p<0.001) increased significantly from admission to discharge, but there was no significant change in the prevalence of patients taking antidepressants (30.6% versus 33.1%, p=0.074) and trazodone or sedating antihistamines (12.8% versus 13.6%, p=0.635) (Figure 1-B).

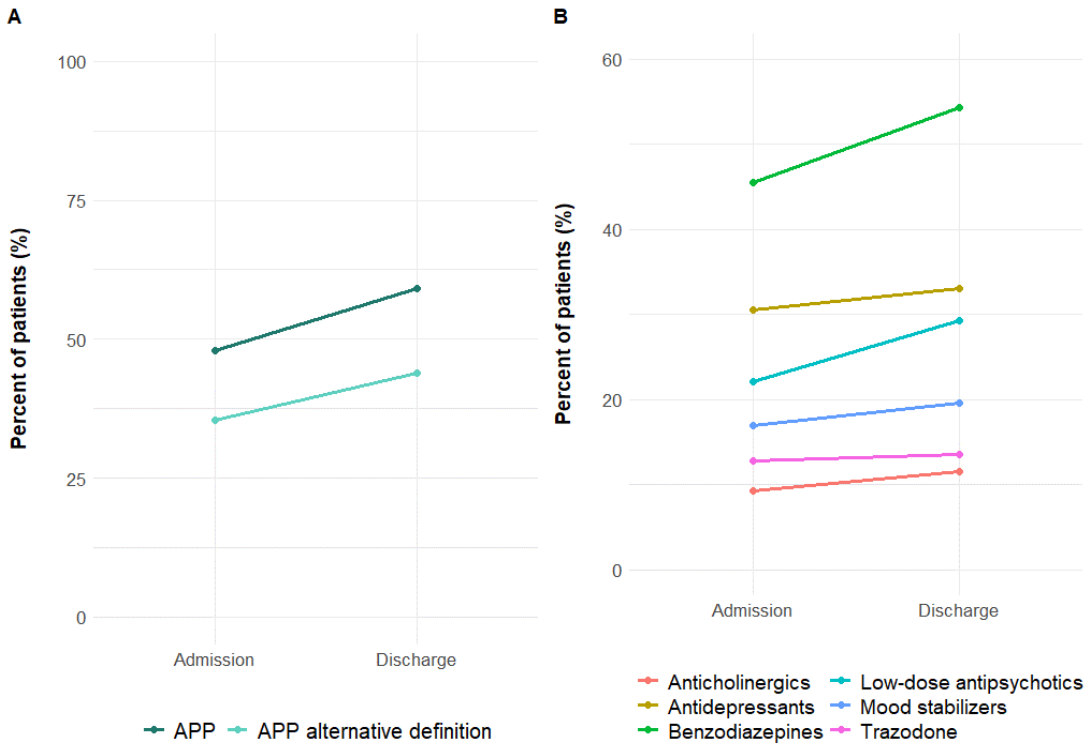

Figure 1

A. Evolution of the prevalence of antipsychotic polypharmacy prescribing between admission and discharge of psychiatric hospitalisations, with both definitions of monotherapy (N=516). There was a significant increase in the prevalence of APP after the psychiatric hospitalisations, independent of the definition used. APP, Antipsychotic polypharmacy; APP alternative definition, Antipsychotic polypharmacy with the alternative definition of monotherapy (i.e. including patients with one antipsychotic at a therapeutic dosage and one low-dose antipsychotic for the treatment of sleep disorders).

B. Evolution of the prevalence of psychotropics and anticholinergics between hospital admission and discharge (N=516). Prescriptions of benzodiazepines, mood stabilizers, anticholinergics and low-dose antipsychotics increased significantly after the hospital stay. There was no significant change in the prevalence of antidepressants or trazodone.

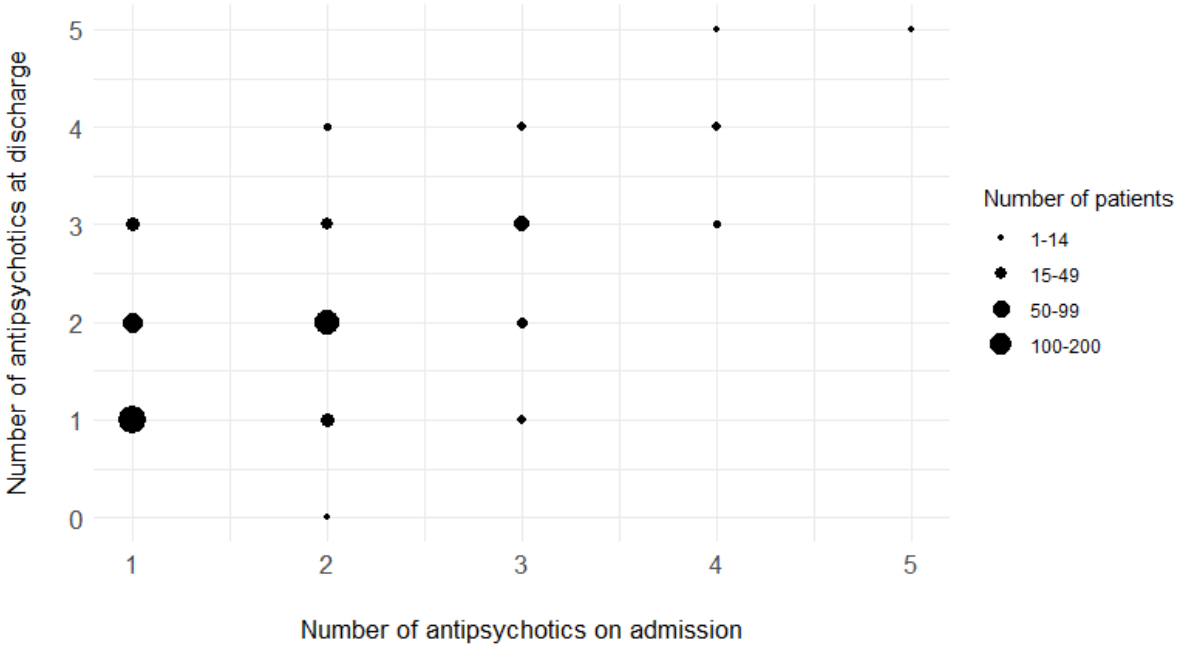

Figure 2. Number of antipsychotics per patient on hospital admission and at discharge.
Among patients admitted on antipsychotic monotherapy, 177 patients were discharged on monotherapy, 71 patients on two and 21 patients on three antipsychotics. Among patients admitted on two antipsychotics, 29 patients were discharged on monotherapy, 133 patients on two, 17 patients on three, and two patients on four antipsychotics. Among patients admitted on three antipsychotics, four patients were discharged on monotherapy, 12 patients on two, 36 patients on three, and five patients on four antipsychotics. Among patients admitted on four antipsychotics, two patients were discharged on three, four patients on four and one patient on five antipsychotics. One patient was admitted and discharged on 5 different antipsychotics.

3.3. Antipsychotic polypharmacy on hospital admission and associated factors

Among the 247 patients with APP on admission, 73.7% (n=182) were receiving two, 23.1% (n=57) three, and 3.2% (n=8) four or more different antipsychotics.

APP on hospital admission was significantly associated with a previous trial of two or more different antipsychotics (OR=5.1, 95% CI=1.95-13.33), prior clozapine use (OR=2.53, 95% CI=1.1-5.84), treatment with a first-generation antipsychotic (FGA) (OR=26.79, 95% CI=13.08-54.86), higher exposure to antipsychotics (OR=8.93, 95% CI=5.13-15.56), and a greater number of hypno-sedative drugs (OR=1.88, 95% CI=1.23-2.88). Involuntary admission (OR=0.31 95% CI=0.14-0.7) was negatively associated with APP on admission (Table 2).

Table 2. Factors associated with antipsychotic polypharmacy on psychiatric hospital admission in the multivariable analysis

Variables	OR [CI 95%]	P-value
Patients characteristics		
Alcohol use disorder	0.57 [0.28-1.15]	0.117
Antipsychotic treatment		
At least one FGA	26.79 [13.08-54.86]	**<0.001**
At least 2 antipsychotic's trials	5.1 [1.95-13.33]	**<0.001**
Prior clozapine use	2.53 [1.1-5.84]	**0.03**
Antipsychotic's adverse effect(s)	1.54 [0.86-2.74]	0.146
PDD/DDD ratio on admission	8.93 [5.13-15.56]	**<0.001**
Hospitalisation		
Involuntary admission	0.31 [0.14-0.7]	**0.005**
Psychiatric hospital	2.04 [0.98-4.25]	0.058
Cotreatment		
Number of hypno-sedatives	1.88 [1.23-2.88]	**0.004**

FGA : First Generation Antipsychotic(s); PDD : Prescribed Daily Dose; DDD= Defined Daily Dose. p-values <0.05 are considered significant.

Low-dose antipsychotics for the treatment of insomnia were prescribed to 22.1% of patients (n=114) on admission. Using the alternative definition of monotherapy, 35.5% (n=183) of patients had APP on admission. In the sensitivity analysis using the new definition for APP, the same characteristics were associated with APP, except for involuntary admission. Treatment with an antidepressant (OR=1.93 95% CI=1.07-3.46) or with trazodone or a sedating antihistamine (OR=4.29 95% CI=1.71-10.76) and not having an alcohol use disorder (AUD) (OR=0.26, CI=0.13-0.74) were also significantly associated with APP on admission (Table 3).

Table 3. Factors associated with antipsychotic polypharmacy on psychiatric hospital admission in the multivariable analysis using the alternative definition of monotherapy

Variables	OR [CI 95%]	P-value
Patients characteristics		
Alcohol use disorder	0.26 [0.13-0.54]	**<0.001**
Intellectual disability	2.4 [0.98-5.87]	0.056
At least 2 prior admissions in the year	1.6 [0.91-2.81]	0.102
Antipsychotic treatment		
At least one FGA	5.02 [2.68-9.38]	**<0.001**
At least 2 antipsychotic's trials	5.95 [2.01-17.59]	**0.001**
Prior clozapine use	2.27 [1.04-4.97]	**0.04**
PDD/DDD ratio on admission	10.76 [6.5-17.8]	**<0.001**
Hospitalisation		
Involuntary admission	0.51 [0.24-1.1]	0.085
Psychiatric hospital	1.84 [0.96-3.56]	0.067

Cotreatment		
Antidepressant	1.93 [1.07-3.46]	**0.029**
Trazodone or sedating antihistamine	4.29 [1.71-10.76]	**0.002**
Number of hypno-sedatives	0.44 [0.29-0.68]	**<0.001**

FGA : First Generation Antipsychotic(s); PDD : Prescribed Daily Dose; DDD= Defined Daily Dose. p-values <0.05 are considered significant.

3.4. APP at hospital discharge and associated factors

The same characteristics were associated with APP at hospital discharge as at hospital admission, except for the "previous trial of at least 2 different antipsychotics". In addition, APP at discharge was negatively associated with treatment with trazodone or a sedating antihistamine (OR=0.32 95% CI=0.13-0.80) (Table 4).

Table 4. Factors associated with antipsychotic polypharmacy at hospital discharge in the multivariable analysis

Variables	OR [CI 95%]	P-value
Antipsychotic treatment		
At least one FGA	25.2 [12.20-52.04]	**<0.001**
Prior clozapine use	11.01 [4.45-27.28]	**<0.001**
PDD/DDD ratio at discharge	19.89 [10-39.54]	**<0.001**
Hospitalisation		
Involuntary admission	0.3 [0.13-0.68]	**0.004**
Cotreatment		
Trazodone or sedating antihistamine	0.32 [0.13-0.80]	**0.015**
Number of hypno-sedatives	4.18 [2.53-6.91]	**<0.001**

FGA : First Generation Antipsychotic(s); PDD : Prescribed Daily Dose; DDD: Defined Daily Dose. p-values <0.05 are considered significant.

Using the alternative definition of monotherapy, 44% (n=227) of the patients were discharged on APP. In this sensitivity analysis, similar characteristics were associated with APP at discharge, with the addition of lower age (OR=0.53, CI=0.29-0.95), living in a residential facility (OR=2.39, 95% CI=1.21-4.71), and a higher intake of benzodiazepines per day during the hospitalisation (OR=1.32 95% CI=1.03-1.69) (Table 5).

Table 5. Factors associated with antipsychotic polypharmacy at hospital discharge in the multivariable analysis using the alternative definition of monotherapy

Variables	OR [CI 95%]	P-value
Patients characteristics		
Age	0.53 [0.29-0.95]	**0.032**
Residential facility	2.39 [1.21-4.71]	**0.012**
Legal guardian	1.66 [0.95-2.9]	0.075
Age of onset	1.4 [0.95-2.07]	0.088
Antipsychotic treatment		
At least one FGA	3.93 [2.25-6.89]	**<0.001**
Prior clozapine use	4.05 [1.82-9]	**<0.001**
Antipsychotic's adverse effects	1.64 [0.99-2.71]	0.056
PDD/DDD ratio at discharge	15.36 [8.97-26.31]	**<0.001**
Hospitalisation		
Involuntary admission	0.38 [0.19-0.75]	**0.005**
Cotreatment		
Trazodone or sedating antihistamine(s)	2.21 [1.02-4.79]	**0.046**
Number of hypno-sedatives	0.67 [0.47-0.97]	**0.032**
Daily dose of benzodiazepine(s)[a]	1.32 [1.03-1.69]	**0.03**

FGA : First Generation Antipsychotic(s); PDD : Prescribed Daily Dose; DDD: Defined Daily Dose. p-values <0.05 are considered significant.

[a]Referred to as daily dose of benzodiazepines administered during the hospital stay

3.5. Clozapine prescribing patterns

Of the 516 patients analysed, 48 (9.3%) were being treated with clozapine on admission, the majority (n=34, 70.8%) as part of CAP. The antipsychotics most frequently combined with clozapine on admission were paliperidone (n=12) and aripiprazole (n=8). Clozapine was combined with a LAI in 15 of the 34 patients on CAP on admission

Although 145 patients (28.1%) were identified as eligible for clozapine therapy, it was introduced in only 10 patients during the hospitalisation, one of whom was not eligible and two had missing information on clozapine eligibility (eTable 3 in Supplementary material). In one patient who was receiving clozapine on admission, it was deprescribed despite the patient being eligible for clozapine treatment; 57 (11%) patients were therefore discharged on clozapine, a significant increase compared to admission (p=0.016).

Significantly more patients discharged on clozapine were prescribed CAP compared to at hospital admission (n=34 versus n=43 respectively, p=0.016), and the CAP more often involved a combination with a LAI (n=15 versus n=21 respectively, p=0.041). In the majority of patients on CAP, the regimen involved one antipsychotic combined with clozapine, but there was a significant increase in the number of patients with CAP that included at least three different antipsychotics, from 6 patients on admission to 12 at discharge (p=0.041). Of the 10 patients in whom clozapine was started during the hospitalisation, 7 were started directly on CAP without a prior trial of clozapine monotherapy (eTable 3 in Supplementary material).

4. Discussion

Almost half of our population on admission and about 60% of the patients at discharge were treated with APP, which is considerably higher than the average 23% prevalence of APP in Europe (1). APP was also more widely prescribed in the current study compared to the Belgian situation 20 years ago (42.2% of all patients), confirming recent observations of a trend to increased APP prescribing (23). This large difference from the European prevalence could in part be explained by the large use of low-dose antipsychotics for the treatment of sleep disorders in our population (n=151; 22.1%), which was considerably greater than the use of trazodone or sedating antihistamines (n=66; 12.8%). Indeed, sedating antihistamines are rarely used for insomnia in Belgium because they are not reimbursed by the national health insurance, whereas low-dose antipsychotics are. The use of low-dose antipsychotics for sleep disorders is controversial because of their risk of inducing daytime somnolence and worsening sleep-disordered breathing and sleepwalking (24). Nevertheless, this trend has also been reported in other European countries where antipsychotics are increasingly used at a low dosage for indications other than psychosis, and is therefore unlikely to fully explain the difference between our results and the European average (25). When the alternative definition of monotherapy was used to detect what is sometimes considered as real APP, 35.5% of patients were still classified as receiving APP on admission. In addition, APP prescribing increased between admission and discharge, independent of the definition of monotherapy used. Among patients admitted on APP, only 19.5% had a decrease in the number of prescribed antipsychotics per day and only 13.8% were discharged on monotherapy. This observation highlights that psychiatric hospital stays are not sufficiently used to deprescribe or re-evaluate the relevance of certain inappropriate prescribing patterns. In acute episodes (e.g., in patients recently admitted to hospital), a higher daily dosage of antipsychotics may be temporarily necessary, and it is recommended to choose an antipsychotic with sedating properties or to add a short-term benzodiazepine when symptoms are very disturbing. Nonetheless, combining several antipsychotics is not recommended (12). Thus, hospitalisations could be considered appropriate moments for deprescribing, because healthcare professionals can closely monitor the patients, and successful hospital-based deprescribing programs for antipsychotics have been described (26, 27).

Prior use of clozapine and having already tried at least two different antipsychotics increased the risk of being prescribed APP. These findings suggest that TRS or subjective TRS (i.e., no or poor response to two antipsychotic trials even when sufficient dosage or duration is not reached) increases the odds of having APP. In addition, when using the alternative definition of monotherapy, patients living in residential facilities are more at risk of being discharged on APP. These patients are not able to live on their own, because their symptoms are too severe. However, more severe GAF scores were not correlated with APP in our sample. This score is mandatory in Belgium for every psychiatric hospitalisation, and is often considered a burden for clinicians. It is likely that it does not completely represent the psychopathological state of patients. Moreover, this score was part of the DSM-IV but is no longer used in the fifth version of the DSM of the American Psychiatric Association because of poor reliability. Finally, involuntary admission was protective against APP. Patients admitted involuntarily are, by definition, patients who refuse any treatment; they are often anosognosic (i.e., not aware of their disease), and hence generally reluctant to take their medicines. Thus, it can be hypothesised from our data that severely ill patients still willing to be hospitalised are at increased risk of APP, whereas reluctance to be hospitalised may translate into reluctance to receive psychiatric care in general, making such patients less likely to receive APP.

Treatment with a FGA was highly correlated with the odds of APP at any point during the hospitalisation. It has been previously assumed that this effect was induced by the high utilisation of add-on low-dose antipsychotics for indications other than psychosis (e.g., sleep disorders, anxiety), because these antipsychotics are predominantly FGAs in Europe (1). However, FGA use was still strongly associated with APP when using the larger definition of monotherapy, excluding this theory. Our data shows that the odds of APP were higher in patients with more severe disease, leading to the

assumption that add-on FGAs are used for patients with poor treatment response as an attempt to further control symptoms. This finding is consistent with the previously reported justifications for APP (2, 3, 28). In fact, the different pharmacological profile between FGAs and second-generation antipsychotics (SGAs) might furnish the belief that combining a FGA with a SGA leads to greater efficacy, despite not being supported by the literature (29).

Similar to prior data, APP increased the risk of receiving a higher daily dose of antipsychotics (20, 21).

Having an AUD significantly reduced the probability of APP on admission when using the alternative definition of monotherapy, and remained in the model, although not reaching significance, with the stricter definition of monotherapy. The reasons underlying this finding remain unclear. The sedative and anxiolytic properties of alcohol might protect these patients from receiving an add-on low-dose antipsychotic for sedation or anxiety. However, as the effect of AUD was only significant when using the alternative definition of monotherapy, its effects were only protective against what is sometimes referred to as real APP. Thus, this protection against APP is perhaps induced by the fear of increased adverse effects in the AUD population. AUD increases the risk of obstructive sleep apnoea, which is already a frequent comorbidity in patients with schizophrenia and can be worsened by APP (13).

At discharge, increased age reduced the odds of APP prescribing when using the alternative definition of monotherapy. Similar to the situation with AUD, prescribers might be more cautious with older patients who are more susceptible to adverse effects and thus avoid APP.

A higher daily benzodiazepine dose during the hospital stay significantly increased the probability of being discharged on APP when the alternative definition of monotherapy was used. High benzodiazepine use might indicate anxiety, agitation, or insomnia during the stay. Yet, APP at any time was associated with an increased number of hypno-sedative drugs and/or with trazodone depending on the definition of monotherapy used, translating a greater likelihood of being treated with APP when having sleep disorders. APP on admission was also associated with antidepressant prescriptions, but not with a diagnosis of schizoaffective disorder. Together, this suggests that APP is often motivated by an attempt to treat comorbid mental health conditions, such as anxiety, depression, or sleep disorders. However, these comorbidities should be appropriately treated rather than having recourse to APP, especially as it is proven that APP does not reduce depressive symptoms compared to antipsychotic monotherapy (4).

Despite being associated with APP in previous trials, having an antipsychotic adverse effect was not significantly associated with APP in our population, although it remained in the final regression model (7, 9). This may be explained by an under-detection of adverse effects, as rating scales for adverse effects are not systematically used in routine clinical practice.

Although about one third of patients were identified as being eligible for clozapine, which is consistent with the literature, only 11% were discharged on clozapine. The majority of patients treated with clozapine on admission (70.8%) and at discharge (75.44%) were on CAP, although this regimen should be reserved for patients who are resistant to clozapine, estimated at around one third (22). It has been shown that most patients can be safely switched to monotherapy without symptom worsening, especially when the combination involves clozapine (17). Unfortunately, most patients who had clozapine introduced during the hospitalisation were directly prescribed CAP, without a prior trial of clozapine monotherapy. Moreover, less than one quarter of all patients on CAP received a combination of clozapine with aripiprazole on admission or at discharge, despite the fact that this is the only CAP with evidence of a greater efficacy than clozapine monotherapy (5). In almost half of the patients on CAP, the combination was with an LAI, perhaps to ensure some cover for patients in the event of poor adherence to clozapine. However, as clozapine is reserved for TRS patients, they will not be protected

against symptom worsening by the LAI in case of clozapine self-discontinuation. Another hypothesis could be that the psychiatrist was testing both lack of adherence and the presence of real TRS. However, poor adherence should be excluded in case of insufficient response by measuring the antipsychotic plasma concentration or by using a LAI to avoid using clozapine to patients who do not have real TRS (12). Finally, although a minority, six of the patients on CAP on admission were receiving at least three antipsychotics and this number increased significantly to 12 at discharge. These observations indicate that ultra-resistant patients are more exposed to poor quality prescribing because of the difficulty in rationalising prescriptions in the face of non-response.

It has been proven that adherence to schizophrenia prescribing guidelines is associated with decreased costs and increased quality-adjusted life-years, so strategies to improve prescribing patterns should be encouraged (30).

Our data should be interpreted within their limitations. Cofactors were extracted from patients' medical records. In routine clinical practice, patients are not systematically assessed for antipsychotic adverse effects using rating scales, reducing the robustness of detection. It has been shown that patients tend to underreport adverse effects, especially those considered embarrassing (e.g., sexual dysfunction, urinary incontinence) (31). The admission history and numbers of previous antipsychotic trials were also identified through chart review, and might have been underestimated. However, these variables were dichotomised to increase accuracy. Finally, our study focused on prescribing patterns during a psychiatric hospitalisation, and some prescriptions may have been rapidly modified after discharge.

Our trial concerns prescribing patterns in six Belgian hospitals, and enables us to accurately reflect the Belgian situation. By reviewing medical records, we had more precise information than that extractable from our national database, where no information on daily dosage or use of as-needed drugs is available. This design also enabled detection of real polypharmacy, by excluding situations of switch. In addition, it is the first study to examine the evolution of antipsychotic prescribing patterns during psychiatric hospitalisations outside specific programs aiming at deprescribing. Our results provide a better understanding of the evolution of prescribing in patients with schizophrenia during a hospital stay and may support the development of targeted hospital-based interventions in the future.

In conclusion, suboptimal prescription of antipsychotics for patients with schizophrenia persists and the risk of occurrence is associated with identifiable characteristics. Psychiatric hospitalisations do not lead to treatment optimisation and studies assessing interventions to optimise antipsychotic use are needed. Clinical pharmacy services may support psychiatrists in the management of psychotropic medications.

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