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ORIGINAL ARTICLE

Prevalence of and factors associated with antipsychotic polypharmacy in patients with serious mental illness: Findings from a cross-sectional study in an upper-middle-income country

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Objective: The aim of our study was to examine the prevalence of and factors associated with antipsychotic polypharmacy (APP) among patients with serious mental illness in the current South African health care context.
Methods: We collected data on patient, illness, and treatment characteristics of patients discharged on one or more antipsychotic agents from January to June 2014. We analyzed the associations of APP with demographic and clinical variables using hierarchical multivariable logistic regression, and examined prescription patterns.
Results: The prevalence of APP in our study population of 577 patients was 28.4%. Demographic and clinical characteristics significantly associated with APP included age $>$ 29, male sex, diagnosis of schizophrenia, comorbid intellectual disability, comorbid substance use, greater number of hospital admissions, and high-dose prescribing. First-generation antipsychotics and long-acting injectable preparations were prominent in APP combinations. Co-prescription of anticholinergic agents and sodium valproate demonstrated a significant association with APP.
Conclusion: APP appears common in our population, despite lack of evidence for the practice and possible risk of harm. Our findings suggest a complex interplay among patient, illness, and treatment factors relevant to APP in our setting that could be targeted for intervention.

Keywords: Antipsychotic agents; polypharmacy; mental illness

Introduction

Antipsychotic agents form the mainstay of treatment for many patients with serious mental illness. These agents are used in a range of psychiatric disorders, including the schizophrenia spectrum, bipolar disorder, and substance-induced disorders. Local and international clinical practice guidelines for the treatment of schizophrenia[1,2] advocate antipsychotic monotherapy as the routine approach. Guidelines recommend avoiding antipsychotic polypharmacy (APP), which can be defined as co-prescription of more than one antipsychotic drug for a given patient.[3] Exceptions to this may be when APP is required for short periods when switching agents or in treatment-resistant cases, when augmentation of clozapine with another antipsychotic agent may be considered, although supporting evidence for this remains weak.[4,5] Treatment guidelines recommend use of antipsychotics as part of treatment options in bipolar disorder, but do not advocate an APP approach.[6,7] Use of antipsychotic agents in the treatment of psychosis with coexisting substance misuse is advised in accordance with individual guidelines on schizophrenia or bipolar disorder.[8]

The motivation behind these guideline recommendations is the lack of robust evidence to support the routine use of combined antipsychotics.[3-5,9,10] In addition, there is evidence for harm associated with APP. Research has shown an association of APP with increased adverse effects, including extrapyramidal effects,[11-13] hyperprolactinemia,[14-16] sexual dysfunction,[17] hypersalivation,[18] sedation,[14] cognitive impairment,[19] and diabetes.[20,21] Possible increased risk of sudden cardiac death[22] and mortality[23,24] has been suggested. Additional concerns include drug-drug interactions, problems in determining cause and effect of different treatments, complex drug regimens resulting in decreased compliance, and greater cost.[25]

Despite these adverse aspects, APP appears to be a common practice worldwide. A recent systematic review found a global median prevalence of APP of 19.6% over time, with factors such as clinical setting, geographical location, and time of study influencing prevalence rates.[26] In contrast to the fairly substantial international literature on APP, there is a paucity of research on APP from Africa, with only one previous study examining rates of APP in a South African setting, conducted in 2008.[27] There is clearly a need for investigation into this practice in the current South African health care context.

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Research into factors contributing to the practice of APP has shown that antipsychotic prescription patterns reflect complex interplay among patient, illness, treatment, and prescriber factors.[25] However, inconsistencies and gaps in the evidence remain. The patient characteristics age, sex, and marital status have received most attention, with a lack of information on other patient factors possibly associated with APP. APP is generally examined in the context of schizophrenia/schizoaffective disorders, with fewer studies investigating APP in other conditions. Few studies have explored the relationship of APP with comorbidities and co-prescription of other psychotropic medications. Moreover, there have been no previous studies examining patient, illness, and treatment characteristics associated with APP in South Africa.

Our study aimed to address some of these deficiencies in local and international research. We examined antipsychotic prescription patterns among patients with a variety of psychiatric disorders at discharge from an inpatient psychiatric unit in Cape Town, South Africa. We investigated a broad range of patient, illness, and treatment characteristics that may be associated with APP, including comorbidities and co-prescriptions. This allowed us to assess whether current local practice is comparable with standard treatment guidelines, and provided insight into the complexities of the practice of APP in our setting.

Methods

Sample and setting

We conducted our study at Valkenberg Hospital, a large, government-funded psychiatric hospital in the suburb of Observatory, Cape Town, South Africa. The hospital provides psychiatric services to the Cape Peninsula and is a major specialist referral centre of the Western Cape Province. It is the principal teaching hospital for the University of Cape Town's Department of Psychiatry. The hospital currently comprises 340 inpatient beds, of which 200 are dedicated to acute psychiatric services, 125 to forensic psychiatric services, and 15 to a smaller psychotherapeutic component catering for people with mood, somatization, anxiety, and personality disorders in a life skills-based ward program. Patients admitted to the acute psychiatric units are almost exclusively involuntary admissions under the Mental Health Care Act (2002) with severe mental illness, posing a risk to themselves or others, and unable to be managed on an outpatient basis.

We performed a cross-sectional study of discharge records retrieved from the Valkenberg Hospital electronic patient record database (Clinicom). The study was approved by the University of Cape Town's Human Research Ethics Committee, the Faculty of Health Sciences, and the Department of Health. Data were collected for patients with serious mental illness prescribed one or more antipsychotic agents at the time of discharge from Valkenberg Hospital's acute and psychotherapeutic units. Serious mental illness can be defined as any mental, behavioral, or emotional disorder, diagnosable currently or in the past year according to DSM criteria, that results in serious functional impairment, substantially interfering with or limiting one or more major life activities.[28] We extracted discharge information for patients with diagnoses including schizophrenia (F20), acute and transient psychotic disorder (F23), delusional disorder (F22), schizoaffective disorder (F25), substance-induced mood and psychotic disorders (F10-F19), bipolar disorder (F31), and major depressive disorder (F32). We excluded patients with primary diagnoses relating to a medical condition, dementia, anxiety disorder, intellectual disability, or personality disorder, as these diagnoses were unlikely to feature significantly in our study population or contribute meaningfully to rates of APP in our setting. We examined the time period of January to June 2014.

Data and variables extracted

We used an electronic data extraction form to retrieve data from Clinicom. Variables including age, gender, marital status, and occupation for patients discharged on one or more antipsychotic agent were collected. These variables were routinely documented in the database at time of admission.

The illness-related variables retrieved from the database were length of hospital stay (measured in days from admission to discharge date), number of Valkenberg Hospital admissions, and time from first hospitalization at Valkenberg to most recent discharge (as approximate indicator of illness duration or time in treatment).

Patient diagnoses recorded in the database using ICD-10 coding methods were collected. Data on comorbid psychiatric conditions were gathered both from ICD-10 coding and from information contained in discharge summaries completed electronically for each patient by their attending psychiatric registrar at time of discharge. Where the attending case manager commented on the presence of significant coexisting depressive symptoms, anxiety symptoms, evidence of personality disorder or traits, or mild intellectual disability, these were captured as psychiatric comorbidities. Diagnoses and associated clinical features are discussed routinely (typically over four to eight clinical case discussion ward rounds, on average, during the admission period) by the members of a multidisciplinary team under consultant psychiatrist supervision, and include multiple sources of information. All diagnoses are confirmed by a consultant psychiatrist in charge of each multidisciplinary team. Discharge records are routinely audited by consultant psychiatrists. Data on comorbid substance use was likewise gathered from ICD-10 coding and clinical descriptors within patient discharge summaries. These included comorbid alcohol (F10), cannabis (F12), methamphetamine (F15), methaqualone (F13), heroin (F11), and cocaine (F14) misuse.

Antipsychotic agents prescribed at discharge were recorded in patient discharge summaries and captured according to names, dosages, types of agents, and route of administration. Agents classified by type as first-generation antipsychotics (FGAs) included haloperidol, chlorpromazine, trifluoperazine, flupentixol, zuclopenthixol, and fluphenazine. Second-generation antipsychotics (SGAs) included amisulpride, clozapine, olanzapine, risperidone, quetiapine and aripiprazole. Route of administration

was captured as oral or long-acting injectable (LAI). APP was defined as the prescription of any two or more antipsychotics to the same patient on discharge from hospital. To compare doses of different antipsychotic drugs, the prescribed daily dose (PDD) in milligrams was divided by the defined daily dose (DDD) to give a PDD:DDD ratio. The DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.[29] For LAIs, the DDD is based on the average recommended dose divided by the dosing interval.[29] This is the standard international unit recommended by the World Health Organization for drug utilization studies.[29] In keeping with previous studies, the PDD:DDD ratio for APP was calculated as the sum of the individual PDD:DDD ratios of all antipsychotics prescribed to a patient; high-dose prescribing was defined as a PDD:DDD of greater than 1.5.[30-32] In addition to antipsychotic agents, data on co-prescription of anticholinergic agents, mood stabilizers, antidepressants, and benzodiazepines were captured.

Statistical analysis

For categorical variables, we used chi-square tests to analyze data, with Fisher's exact test where appropriate. Confidence intervals for prevalence rates were calculated using the normal approximation of the binomial distribution. The main outcome of interest was the presence of APP, as previously defined. We coded a positive outcome (i.e., the presence of APP) as 1 and a negative outcome (no APP) as 0. To model the response variable of APP as a function of demographic and clinical variables, we conducted a hierarchical multivariable logistic regression analysis. We used penalized maximum likelihood estimation to handle sparse data with complete separation issues. Independent (predictor) variables were categorized into multilevel categorical variables using dummy coding to obtain reference-level categories. Cutoff points for continuous variables were decided on the basis of what constituted meaningful clinical categorizations. We followed a forward selection and backward elimination procedure and determined model fit using a combination of Likelihood-ratio chi-square tests and the Akaike information criterion (AIC). We entered each variable into the model one at a time, starting with demographic and then clinical variables. We removed variables one at a time if model fit was not improved by their addition, based on likelihood chi-square tests and AIC. The final model included all variables except reported symptoms of anxiety and depression. Model fit for the final model was determined using the Pearson chi-square goodness-of-fit test and Nagelkerke's pseudo R^2. The final model was checked for multicollinearity using variance inflation factors and tolerance measures. Statistical significance was set at $p < 0.05$. We used Stata version 13 for Windows to analyze the data.

Results

Antipsychotic polypharmacy: prevalence and clinical and demographic associations

A total of 579 patient records met criteria for inclusion. We excluded two records of patients diagnosed with acute and transient symptoms of psychosis (F23) and delusional disorder (F22), as these patients were low in number, resulting in a final sample of n=577. Overall, 59.6% of patients were male, and the median age was 32 years (interquartile range [IQR] = 25-42).

The prevalence of APP among our study population was 28.4% (95% confidence interval [95%CI] 24.7-32.2). The demographic and clinical characteristics of patients discharged on APP and antipsychotic monotherapy (APM) are shown in Table 1 and Table 2 respectively, with results

Table 1 Logistic regression model comparing demographic characteristics of patients discharged on antipsychotic polypharmacy (APP) and antipsychotic monotherapy (APM) (n=577)

Variable	Total sample	APP	APM	Adjusted OR	95%CI	p-value
Age						
18-29	242 (41.9)	52 (31.7)	190 (46.0)	1.0	1.0	1.0
30-44	223 (38.6)	81 (49.3)	142 (34.3)	2.81	1.61-4.89	< 0.001
45-60	112 (19.4)	31 (18.9)	81 (19.6)	2.20	1.04-4.62	0.037
Sex						
Female	233 (40.3)	38 (23.1)	195 (47.2)	1.0	1.0	1.0
Male	344 (59.6)	126 (76.8)	218 (52.7)	1.86	1.07-3.23	0.027
Marital status						
Single	505 (87.5)	151 (92.0)	354 (85.7)	1.0	1.0	1.0
Married	39 (6.7)	3 (1.8)	36 (8.7)	0.53	0.15-1.86	0.328
Divorced	26 (4.5)	9 (5.4)	17 (4.1)	2.05	0.68-6.18	0.200
Widowed	7 (1.2)	1 (0.6)	6 (1.4)	0.57	0.06-4.91	0.612
Employment						
Employed	26 (4.5)	1 (0.6)	25 (6.0)	1.0	1.0	1.0
Unemployed	551 (95.4)	163 (99.3)	388 (93.9)	5.69	0.59-54.81	0.132

Data presented as n (%).
95%CI = 95% confidence interval; AIC = Akaike information criterion; APM = antipsychotic monotherapy; APP = antipsychotic polypharmacy; OR = odds ratio.
Final model: Pearson χ^2 goodness-of-fit test = 541.99, degrees of freedom = 540, p = 0.322; likelihood ratio χ^2 = 62.9, $p < 0.001$, AIC = 457.6, Nagelkerke's pseudo R^2 = 0.47. Model with only age fitted: likelihood ratio χ^2 = 12.4, p = 0.002, AIC = 671.4, Nagelkerke's pseudo R^2 = 0.03.

Table 2 Logistic regression model comparing clinical characteristics of patients discharged on antipsychotic polypharmacy (APP) and antipsychotic monotherapy (APM) (n=577)

Variable	Total sample	APP	APM	Adjusted OR	95%CI	p-value
Diagnosis						
Bipolar disorder	132 (22.8)	20 (12.2)	112 (27.1)	1.0	1.0	1.0
Schizophrenia	238 (41.2)	93 (56.7)	145 (35.1)	2.79	1.39-5.57	0.004
Schizoaffective disorder	79 (13.6)	36 (21.9)	43 (10.4)	1.59	0.69-3.66	0.274
Substance-induced disorder	116 (20.1)	15 (9.1)	101 (24.4)	1.30	0.53-3.19	0.561
Major depressive disorder	12 (2.0)	0 (0)	12 (2.9)	0.30	0.01-7.44	0.470
Psychiatric comorbidities						
Depression						
No	543 (94.1)	156 (95.1)	387 (93.7)	-	-	-
Yes	34 (5.8)	8 (4.8)	26 (6.3)	-	-	-
Anxiety						
No	570 (98.7)	161 (98.1)	409 (99.0)	-	-	-
Yes	7 (1.2)	3 (1.8)	4 (0.9)	-	-	-
Personality disorder						
No	547 (94.8)	152 (92.6)	395 (95.6)	1.0	1.0	1.0
Yes	30 (5.2)	12 (7.3)	18 (4.3)	2.48	0.92-6.67	0.071
Intellectual disability						
No	554 (94.8)	152 (92.6)	395 (95.6)	1.0	1.0	1.0
Yes	30 (5.2)	12 (7.3)	18 (4.3)	3.52	1.27-9.73	0.015
Substance use						
No	252 (43.6)	58 (35.3)	194 (46.9)	1.0	1.0	1.0
Yes	325 (56.3)	106 (64.6)	219 (53.0)	1.8	1.03-3.14	0.039
Illness duration (years)						
0-1 year	257 (44.5)	39 (23.7)	218 (52.7)	1.0	1.0	1.0
1-3 years	101 (17.5)	26 (15.8)	75 (18.1)	0.83	0.37-1.86	0.666
> 3 years	219 (37.9)	99 (60.3)	120 (29.0)	1.04	0.44-2.41	0.924
Length of hospitalization (months)						
< 1	164 (28.4)	30 (18.2)	134 (32.4)	1.0	1.0	1.0
1-4	376 (65.1)	110 (67.0)	266 (64.4)	1.36	0.77-2.41	0.284
> 4	37 (6.4)	24 (14.6)	13 (3.1)	1.8	0.67-5.08	0.230
Number of prior admissions						
< 3	325 (56.3)	53 (32.3)	272 (65.8)	1.0	1.0	1.0
3-6	142 (24.6)	50 (30.4)	92 (22.2)	2.06	0.96-4.40	0.062
> 6	110 (19.0)	61 (37.2)	49 (11.8)	2.64	1.07-6.51	0.034
High-dose prescribing						
No	470 (81.4)	81 (49.3)	389 (94.1)	1.0	1.0	1.0
Yes	107 (18.5)	83 (50.6)	24 (5.8)	8.99	4.97-16.29	< 0.001

Data presented as n (%).
95%CI = 95% confidence interval; AIC = Akaike information criterion; APM = antipsychotic monotherapy; APP = antipsychotic polypharmacy; OR = odds ratio.
Final model: Pearson χ^2 goodness-of-fit test = 541.99, degrees of freedom = 540, p = 0.322; likelihood ratio χ^2 = 62.9, p < 0.001, AIC = 457.6, Nagelkerke's pseudo R^2 = 0.47. Model with only age fitted: likelihood ratio χ^2 = 12.4, p = 0.002, AIC = 671.4, Nagelkerke's pseudo R^2 = 0.03.

of multivariable analysis examining associations between these characteristics and the likelihood of receiving APP reported as adjusted odds ratios (AOR). Patients in the age categories 30-44 and 45-60 were significantly more likely to receive APP compared to those in age category 18-29. The odds of receiving APP were significantly higher in males. There were no significant associations between marital status or occupational status and APP.

Patients with schizophrenia were significantly more likely to receive APP when compared to patients with bipolar disorder. Intellectual disability and substance use were both associated with significant increased odds of APP. Comorbid depressive and anxiety symptoms occurred in a small proportion of patients in the total sample, and were not significantly associated with APP on bivariate analyses (Table 2).

There was no significant association between illness duration and APP (measured as time from first admission to most recent discharge). Likewise, length of hospital stay was not significantly associated with APP. Compared to patients with fewer than three prior admissions to Valkenberg Hospital, there was a nonsignificant trend towards increased APP in those with three to six admissions, and significantly increased odds of APP for patients with more than six admissions.

Frequency, dosing, and different combinations of antipsychotics

Of the 164 participants who were prescribed two or more antipsychotics, the majority (n=161, 98.1%) were prescribed two antipsychotics; only three patients (1.9%) were prescribed three different antipsychotics. Table 3

Table 3 Antipsychotics prescribed to patients discharged on antipsychotic polypharmacy (APP) and antipsychotic monotherapy (APM) (n=577)

Antipsychotic	Total sample	APP	APM	Test statistic	df	p-value
FGA						
Haloperidol	210 (36.4)	63 (38.4)	147 (35.5)	$\chi^2 = 0.40$	1	0.525
Chlorpromazine	50 (8.6)	22 (13.4)	28 (6.7)	$\chi^2 = 6.52$	1	0.011
Trifluoperazine	21 (3.6)	7 (4.27)	14 (3.3)	$\chi^2 = 0.25$	1	0.611
Flupentixol (LAI)	56 (9.7)	49 (29.8)	7 (1.6)	$\chi^2 = 106.39$	1	< 0.001
Zuclopenthixol (LAI)	97 (16.8)	82 (50.0)	15 (3.63)	$\chi^2 = 180.46$	1	< 0.001
Fluphenazine (LAI)	25 (4.3)	22 (13.4)	3 (0.7)	$\chi^2 = 45.59$	1	< 0.001
SGA						
Amisulpride	17 (2.9)	13 (7.9)	4 (0.9)	Fisher's exact test	-	< 0.001
Clozapine	55 (9.5)	27 (16.4)	28 (6.7)	$\chi^2 = 12.76$	1	< 0.001
Olanzapine	43 (7.4)	12 (7.3)	31 (7.5)	$\chi^2 = 0.00$	1	0.938
Risperidone (oral)	162 (28.0)	31 (18.9)	131 (31.7)	$\chi^2 = 9.54$	1	0.002
Risperidone (LAI)	4 (0.6)	1 (0.6)	3 (0.7)	Fisher's exact test	-	0.999
Quetiapine	3 (0.5)	2 (1.2)	1 (0.2)	Fisher's exact test	-	0.196
Aripiprazole	1 (0.1)	0	1 (0.2)	Fisher's exact test	-	0.999

Data presented as n (%).
APM = antipsychotic monotherapy; APP = antipsychotic polypharmacy; df = degrees of freedom; FGA = first-generation antipsychotic; LAI = long-acting injectable; SGA= second-generation antipsychotic.

contains a summary of the frequency of the different types of antipsychotic medications prescribed in the total sample. The most commonly prescribed agent among all patients discharged was haloperidol, followed by risperidone (oral preparation) and zuclopenthixol LAI. The most common agents among patients discharged on APM were haloperidol, risperidone (oral), and olanzapine. In those discharged on APP, zuclopenthixol LAI was most frequently prescribed, followed by haloperidol, flupentixol LAI, oral risperidone, and clozapine. When associations were examined, APP was found to be significantly associated with use of flupentixol LAI, zuclopenthixol LAI, fluphenazine LAI, amisulpride, clozapine, chlorpromazine, and oral risperidone. The odds of APP were significantly higher in patients with high-dose prescribing (Table 2).

The frequency of antipsychotic combinations prescribed at discharge is demonstrated in Table 4. The most common combination of antipsychotics was that of haloperidol and zuclopenthixol LAI, which was found in a large proportion of APP prescriptions. This was followed by the combinations of haloperidol and flupentixol LAI, chlorpromazine and zuclopenthixol LAI, risperidone oral and flupentixol LAI, and risperidone oral with zuclopenthixol LAI.

Regarding the nature of combinations according to antipsychotic agent class and route of administration, oral FGA + LAI FGA combinations predominated, being found in 55.49% of patients discharged on APP, followed by oral SGA + LAI FGA in 35.97% and a combination of two oral SGA agents in 5.49%.

Table 4 Antipsychotic combinations in patients with antipsychotic polypharmacy (APP) at discharge (n=164)

Antipsychotic combination	n (%)
Haloperidol + zuclopenthixol (LAI)	37 (22.5)
Haloperidol + flupentixol (LAI)	16 (9.7)
Chlorpromazine + zuclopenthixol (LAI)	14 (8.5)
Risperidone (oral) + flupentixol (LAI)	13 (7.9)
Risperidone (oral) + zuclopenthixol (LAI)	12 (7.3)
Amisulpride + clozapine	9 (5.4)
Haloperidol + fluphenazine (LAI)	9 (5.4)
Clozapine + zuclopenthixol (LAI)	7 (4.2)
Olanzapine + zuclopenthixol (LAI)	7 (4.2)
Chlorpromazine + flupentixol (LAI)	6 (3.6)
Olanzapine + flupentixol (LAI)	5 (3.0)
Clozapine + flupentixol (LAI)	4 (2.4)
Clozapine + fluphenazine (LAI)	4 (2.4)
Risperidone (oral) + fluphenazine (LAI)	4 (2.4)
Trifluoperazine + fluphenazine (LAI)	3 (1.8)
Trifluoperazine + zuclopenthixol (LAI)	2 (1.2)
Trifluoperazine + flupentixol (LAI)	2 (1.2)
Chlorpromazine + fluphenazine (LAI)	2 (1.2)
Haloperidol + risperidone (oral)	1 (0.6)
Amisulpride + zuclopenthixol (LAI)	1 (0.6)
Quetiapine + flupentixol (LAI)	1 (0.6)
Quetiapine + zuclopenthixol (LAI)	1 (0.6)
Risperidone (oral) + risperidone (LAI)	1 (0.6)
Amisulpride + clozapine + flupentixol (LAI)	2 (1.2)
Amisulpride + clozapine + zuclopenthixol (LAI)	1 (0.6)

LAI = long-acting injectable.

Co-prescriptions of other psychotropic medications with antipsychotic polypharmacy

Psychotropic co-prescriptions are displayed in Table 5. Anticholinergic agents were significantly associated with APP. Sodium valproate and lithium were also significantly more commonly co-prescribed among patients on APM compared to patients on APP. An additional subgroup exploratory analysis confined to patients with APP (n=164) demonstrated a significant association between diagnosis and valproate co-prescription ($p < 0.001$), with as many as 40.2% of sodium valproate co-prescriptions occurring in patients with diagnosis of schizophrenia, followed by 34.4% in schizoaffective disorder, only 17.2% in bipolar disorder, and 8.0% in substance-induced disorders. Exploratory analysis in this group revealed that valproate co-prescriptions were not significantly associated with intellectual disability or clozapine treatment. Lithium co-prescriptions in those receiving APP occurred only in patients with diagnoses of bipolar and schizoaffective disorder, each contributing 50% of the total. Fluoxetine was

Table 5 Psychotropics co-prescribed to patients discharged on antipsychotic polypharmacy (APP) and antipsychotic monotherapy (APM) (n=577)

Psychotropic co-prescription	Total sample	APP	APM	Test statistic	df	p-value
Anticholinergic	185 (32.0)	73 (44.5)	112 (27.1)	$\chi^2 = 16.30$	1	< 0.001
Mood stabilizer						
Sodium valproate	252 (43.6)	87 (3.0)	165 (39.9)	$\chi^2 = 8.18$	1	0.004
Lithium	84 (14.5)	16 (9.7)	68 (16.4)	$\chi^2 = 4.24$	1	0.039
Lamotrigine	3 (0.5)	1 (0.6)	2 (0.4)	Fisher's exact test	-	0.999
Carbamazepine	3 (0.5)	1 (0.6)	2 (0.4)	Fisher's exact test	-	0.999
Topiramate	1 (0.1)	0 (0)	1 (0.2)	Fisher's exact test	-	0.999
Antidepressant						
Amitriptyline	1 (0.1)	0 (0)	1 (0.2)	Fisher's exact test	-	0.999
Clomipramine	1 (0.1)	0 (0)	1 (0.2)	Fisher's exact test	-	0.999
Citalopram	11 (1.9)	2 (1.2)	9 (2.1)	Fisher's exact test	-	0.737
Fluoxetine	21 (3.6)	6 (3.6)	15 (3.6)	$\chi^2 = 0.00$	1	0.988
Venlafaxine	2 (0.3)	1 (0.6)	1 (0.2)	Fisher's exact test	-	0.488
Benzodiazepine	41 (7.1)	8 (4.8)	33 (7.9)	$\chi^2 = 1.72$	1	0.189

Data presented as n (%).
APM = antipsychotic monotherapy; APP = antipsychotic polypharmacy; df = degrees of freedom.

the most frequently co-prescribed antidepressant, but no significant associations between antidepressant co-prescriptions and APP were found. Benzodiazepine co-prescription was also associated, though not significantly, with APP.

Discussion

The APP prevalence rate of 28.4% found in our study is fairly high in comparison to international rates, with a recent systematic review of studies reporting on APP across decades and regions finding a global median prevalence of APP of 19.6% across time.[26] In this systematic review, which examined studies of patients with a diagnosis of schizophrenia from inpatient, outpatient, urban and rural settings, the prevalence of APP varied across different regions, being higher in Europe (23%) and Asia (32%) compared to North America (16%) and Oceania (16.4%). The relatively high APP prevalence of 28.4% found in our sample is similar to that of regions such as Asia and is almost identical to that of an earlier South African study published in 2008. The latter study reviewed data on antipsychotic drug prescriptions for Xhosa patients with schizophrenia and schizoaffective disorder, particularly in terms of clozapine use, and found an overall low rate (10%) of clozapine use and a relatively high frequency of APP (28.6% of patients).[27] The study suggested that high rates of APP may have been partially explained by high rates of LAI use (49.4% of patients), with the most frequently used antipsychotic combination used being haloperidol and an LAI (54.2% of combinations). While this study investigated APP in a limited population, our study examined the practice among all patients discharged on antipsychotic agents, without restricting race or diagnosis. Although findings were similar, our analysis of antipsychotic drug prescriptions examined prescription patterns in greater detail and included several additional SGAs that were not widely available in the South African public sector at the time of the previous study. In addition, we examined APP in the context of a range of patient, illness, and treatment factors, increasing understanding of the complexity of the practice of APP in our setting.

Our study thus provides insight into various aspects that require consideration in relation to our relatively high rate of APP. The associations of APP with clinical and demographic characteristics was statistically significant for age > 29, male sex, diagnosis of schizophrenia compared to bipolar disorder, comorbid intellectual disability, comorbid substance use, and greater number of hospital admissions (more than six). The positive association of APP with increased age is of interest in that it contrasts with data from several international studies that have showed an association of APP with younger age.[25] It is possible that older patients hospitalized in our setting are those with greater illness severity, complexity, chronicity, and treatment resistance, factors which have been found to be associated with APP,[25,26] with additional antipsychotics possibly added as a result of poor response on monotherapy. Likewise, the associations of APP with male sex and greater number of hospital admissions could also be linked to greater illness severity, complexity, chronicity, and refractoriness in these patients,[25] as could the association with intellectual disability, given similar findings in previous studies and the suggestion that individuals suffering from intellectual disability may be poorly responsive to antipsychotic treatments.[33]

While higher rates of APP in patients with diagnoses of schizophrenia and schizoaffective disorder were anticipated, it was of interest that APP was also observed in a fair number of patients with bipolar disorder and several patients with substance-induced disorders. Co-prescription of sodium valproate showed a significant positive association with APP, occurring significantly more often in APP patients with diagnoses of schizophrenia and schizoaffective disorders. No association between mild intellectual disability or clozapine prescription and co-prescription of sodium valproate in patients

with APP was found. Patients with moderate or severe intellectual disability are managed at a separate institution in our setting and were not included in our sample. We were thus unable to investigate the association of valproate co-prescription with more severe forms of mental retardation or epilepsy. One reason for higher valproate co-prescription in APP may be that, in addition to its mood-stabilizing action, this agent may be used to treat residual psychotic symptoms and aggression in some cases of schizophrenia.[11] A previous systematic review demonstrated higher rates of mood stabilizer co-prescription in North America compared to Asia and Europe. This may reflect North American practice of treating symptoms of aggression in schizophrenia with mood stabilizers.[26]

There was a significant positive association between comorbid substance use and APP, on a background of high rates of substance use in our population. Research on this association is lacking, with only a few previous studies examining APP in patients with comorbid substance use.[11,33,34] These studies have produced mixed results, showing both higher and lower APP prevalence in such patients. Reasons for conflicting findings remain unclear, but could result from differences in disclosure or methods of assessing substance use. Previous studies have shown that lower remission rates of positive psychotic symptoms and poorer adherence are associated with co-occurring substance misuse in patients with psychotic disorders.[35] One could speculate that the positive association between comorbid substance use and APP found in our study could result from additional antipsychotics being added in an attempt to treat higher levels of positive symptoms or to provide better compliance (i.e., the addition of depot antipsychotics to oral medication). It is evident that APP is a practice that warrants further investigation across diagnoses, with careful attention to various contributing factors that could be targeted for intervention, including comorbid substance use.

Analysis of prescription patterns in our sample demonstrated the prominent use of FGAs and LAI formulations in APP combinations, which is in keeping with previous local and international literature.[26,27] However, our finding that oral FGA and LAI FGA formulations were predominantly used together in combinations differed from international trends, which have demonstrated a move from FGA-FGA combinations to more FGA-SGA combinations over time, with FGA-SGA combination treatment being most common in recent studies.[26] FGAs remain common first-line prescriptions in our population, their lower cost making them particularly attractive in a resource-limited setting. SGA agents remain second-line choices in many cases, with restricted availability of certain agents including quetiapine and aripiprazole. LAIs are commonly used. They may frequently be added to existing regimens where concerns over compliance exist, contributing to their significant association with APP. In other cases, the positive association of APP with use of LAIs may result from the difficulty performing fine adjustments with LAIs alone, leading to oral medication being added for this purpose.[25] Often, oral medication is used as initial lead-in dosing for the first few weeks after LAI initiation while waiting for LAI plasma levels to reach steady state. As there is evidence that eventual discontinuation of the oral medication in such cases is often deferred and may even continue beyond its original purpose as lead-in medication,[36] an important implication for clinical practice and treatment planning would include instructions to community clinics to taper and stop such medications, as well as audits of whether such processes are in fact carried out. The majority of combinations found in our study remain unsupported by strong evidence, with the possible exception of clozapine augmentation strategies.[3,4]

The positive association of APP with clozapine, and the use of clozapine with amisulpride among the combinations recorded in our sample, demonstrates attempts by some prescribers to follow treatment guidelines in managing treatment-resistant patients. However, the rates of clozapine use in our study population (9.7%) remain relatively low in comparison to international rates.[37-40] Possible reasons for this include clinician concerns about treatment adherence, the side-effect profile of clozapine treatment, the need for regular follow-up for monitoring of leukocyte counts, and difficulties related to reintroduction of clozapine after discontinuation for longer than 48 hours.[27]

The results of our study also contribute to concern over the safety of APP. There was a significant positive association of APP with high-dose prescribing, as well as with co-prescription of anticholinergic medication. This may suggest risk for increased extrapyramidal side effects with APP, which in turn raises concerns about potential additional adverse effects possibly resulting from excess dopamine D2 blockade, including akathisia, tardive dyskinesia, and hyperprolactinemia.[11] In addition, anticholinergic agents themselves may produce adverse effects, such as sedation, cognitive impairment, and peripheral side effects. A previous systematic review demonstrated higher anticholinergic use in the context of APP in Asia compared to North America and Europe. As in our study, FGA + FGA polypharmacy predominated in Asia compared to North America and Europe, where SGA + SGA polypharmacy was more common.[26]

Our study does have several limitations that should be noted when interpreting results. Restriction to a single-center, hospital-based population may have produced results not readily generalizable to the community population, as inpatient status has been found to be associated with APP in previous studies.[25] In turn, as our sample was recruited from a referral hospital that screens out certain diagnostic categories, the exclusion of certain diagnoses such as dementia, disorders due a general medical condition, and principal anxiety disorders may further limit the generalizability of our findings. Some APP may have resulted from certain patients being discharged during a process of cross-titration while changing antipsychotic agents, or with oral medication being used as lead-in dosing for initiation of LAI, as discussed. However, none of the discharge summaries recommended continuing cross-titration or rationalizing medication in future. This suggests that discharge prescriptions reflected a plan for ongoing maintenance treatment in most patients. In addition, our study was cross-sectional in nature, with

the variables of interest being limited to administrative data and information contained in discharge summaries completed electronically for each patient by their attending psychiatric registrar at time of discharge. In some cases, the attending clinician may have failed to document comorbid psychiatric symptoms or substance use. We did not extract information from case files on sequential antipsychotic medications used or reasons for medication changes during hospital stay, making it uncertain whether prescribing of given combinations was preceded by failure of monotherapy trials in hospital. Certain relevant variables were not directly recorded; we attempted to overcome this problem by examining related variables. Length of time from first hospitalization to most recent discharge was used to provide some indication of duration of illness or time in treatment, although we acknowledge that the patient may have been diagnosed with mental illness prior to first hospital admission. Number of previous admissions and length of stay were recorded as indicators of illness severity and possibly treatment resistance, although we realize that these are not direct substitute measures.

Our study suggests that current local practice in South Africa deviates from standard local and international guidelines in that combination antipsychotic agents are prescribed for a number of patients with a wide range of psychiatric diagnoses, without evidence to support this practice and at the possible cost of increased adverse effects. Our findings indicate that antipsychotic prescription patterns reflect a complex interplay among patient, illness, and treatment characteristics in our population. Additional research is needed to examine the practice of APP across diagnoses, focusing on the multiple aspects affecting local practice and the various contributing factors that could be targeted for intervention. This would be a positive step towards improving the quality of our service, advancing mental health care practice, and providing optimal patient management in a resource-limited setting.

Disclosure

The authors report no conflicts of interest.

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