

Trends in the prescribing of antipsychotic medicines in Pakistan; implications for the future

Short title: Antipsychotics in Pakistan

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Abstract:

Introduction and objectives: There is a paucity of antipsychotic prescribing and utilization data in Pakistan. This needs addressing especially with issues of availability, affordability, gender differences, and domestic violence, to develop pertinent strategies. The objective of this study was to address these issues by describing current antipsychotic utilization patterns in Pakistan among adult patients attending tertiary care hospitals and private practitioners. **Methods:** A three staged approach was used including 1/ assessment of total antipsychotic utilization, expenditure and costs per unit between 2010 and 2015, 2/ an in-depth retrospective study of prescribing patterns including co-morbidities among representative hospital patients in Pakistan, and 3/ assessment of the quality of prescribing against WHO targets. **Results:** Total use of antipsychotics increased 4.3-fold and the cost/unit increased by 13.2% during the study period. Risperidone and olanzapine were the most prescribed antipsychotics with more limited use of other typical and atypical antipsychotics. The number of medicines per encounter was 4.56. Prescription using generic instead of brand names was 21.4%. Seven percent was prescribed more than one antipsychotic concurrently. **Conclusion:** There has been an appreciable increase in anti-psychotic utilization in recent years in Pakistan especially atypical antipsychotics, with little polypharmacy. Ongoing utilization of typical antipsychotics may be due to comorbidities such as diabetes and cardiovascular disease. Issues of international non-proprietary name prescribing need investigating along with the high number of medicines per encounter and gender inequality.

Keywords: Antipsychotic drugs, Bipolar disorder, Drug Utilization, Generics, Pakistan, schizophrenia.

1. Introduction

Medicines including vaccines are a fundamental part of health care as they do not only help to reduce morbidity and mortality, but also help to prevent epidemics and illnesses. Consequently, access to appropriate medicines should be an essential right of every person (1, 2). Mental disorders account for 10 to 13% of the global burden of disease, although others have documented higher rates (3-9).

However, currently only a minority of people affected by mental health receive basic treatment (6, 9-11). Whereas there is evidence from higher income countries that not all people with mental disorders receive adequate treatment, this is worse in low and middle income countries (LMICs) where mental health services are traditionally lacking, and large segments of the population do not have ready access to health care or receive inadequate care (9, 10, 12, 13). Where services exist in LMICs, these tend to be based in hospitals and oriented predominantly towards urban conditions, although community care is now increasing (6).

The introduction of antipsychotics was a major breakthrough in the field of psychiatry, leading to their inclusion in a number of guidelines as well as Essential Medicine Lists (EML) across countries to enhance rational prescribing (9, 14-19). However, despite the plethora of guidelines, in clinical practice prescribing can differ appreciably from the suggestions (20-23).

Extrapyramidal side-effects are a concern with all antipsychotics, with the difference between first and second generation antipsychotics in terms of their development now less clear cut, although more likely to occur with first generation antipsychotics (24-26). Consequently, the treatment of schizophrenia and bipolar disorders should be tailored to individual patients, which is typically the case in developed countries (27, 28). This has resulted in changes in prescribing patterns as different antipsychotic medicines become available (29), with the World Health Organisation (WHO) EML recommending chlorpromazine, fluphenazine, haloperidol, with potentially risperidone depending on costs (9). Anticholinergic medicines have also been used to alleviate neuroleptic-induced extrapyramidal side-effects ((30). However, there are concerns with their use including cognitive effects, altered absorption of other oral medications and abuse potential (31). Short-term use may help prevent this in most patients (30).

One important side effect of many antipsychotics is weight gain (23, 32-35), although there appears to be less of an issue with amisulpride and aripiprazole (36) as well as potentially with risperidone among patients in Pakistan (35). The mechanisms for this are not well understood; however, factors such as sedation, decreased satiety, lack of movement as well as endocrine changes resulting in increased appetite and food intake, may well play a role (34, 37). In addition, schizophrenia itself is associated with higher rates of obesity and diabetes (35, 38). This is a concern given the increasing prevalence of diabetes worldwide, necessitating regular review of antipsychotic treatment (39). This is especially important in developing countries such as Pakistan with growing rates of obesity and diabetes (40, 41).

There are also concerns with antipsychotic polypharmacy in a number of countries (9, 22, 42-44), which has been linked with increased adverse events including the metabolic syndrome (45-47), increasing costs (42, 48) and lowering medication compliance (49). Consequently, schizophrenia treatment guidelines typically emphasize antipsychotic monotherapy (16, 22, 50). Despite this, antipsychotic polypharmacy can be common with published studies showing a broad range of polypharmacy rates from 4.1% to 48.0% (9, 21, 22, 51-55) depending on the study method and patient characteristics. Sim et al reported rates of antipsychotic polypharmacy at 45.7% in East Asia with wide intercountry variations, with the rates likely to be influenced by the clinical settings as well as cultural and personal practice factors (54). The high rate of polypharmacy may indicate that available pharmacological treatments and treatment guidelines are still far from meeting all needs (55). Alternatively, issues such as compliance may be a problem with additional treatments added before exploring these factors further and potentially switching formulations or modes of administration (56, 57).

The management of patients with mental health conditions continues to be a concern in Pakistan, which is not help by the continuing violence in some regions (58). Overall, mental illness affects between some 10 – 16% of the population or more (59, 60); with a large majority of those affected being women. It is estimated there is only one psychiatrist for every 10000 people and one psychiatrist for 4 million children in Pakistan suffering from psychiatric conditions (60), although others have estimated psychiatrist-to-person ratios up to 1 to half a million people (61). Due to the scarcity of psychiatrists, the management of mentally ill patients may be inadequate. However, this lack of health care professionals is also common in other LMIC countries (6).

Mental health has continued to remain a subject of considerable debate in Pakistan, with the incidence and prevalence of mental disorders increasing against a background of growing insecurity,

terrorism, political uncertainty, unemployment and disruption of the social fabric (58, 62). This is not helped by the fact that social acceptance is crucial to an individual's livelihood and vitality in Pakistan, which includes getting married, working, socializing, and daily functioning. Unfortunately, people in Pakistan are typically unwilling to socialize with someone who suffers from mental disorders, exacerbated by oversimplified ideas about individuals based on a particular category, ongoing prejudices, as well as discrimination. This leads to active discrimination towards individuals with mental disorders in Pakistan. Anxiety, depression, and schizophrenia can frequently be written off, with sufferers told to bolster their faith to reduce the disease. This is a concern as there are medicines and other strategies available to help address mental health disorders. However, inaccessibility to mental healthcare, as well as beliefs that psychiatric illness may be due to evil spirits and the neglect of ritual obligations, can result in patients approaching local religious healers, faith healers, hakims, or practitioners of homeopathic medicine, and potentially ultimately finding only limited relief (63, 64). Pakistani women face an even greater risk as they can be targets of domestic violence and there are continuing concerns with gender-inequality including management of diseases such as mental health disorders. In addition, 39% of the citizens currently live below the poverty line in Pakistan adding to stresses of daily life, although there has been an improvement in recent years (65). Encouragingly, more people are now presenting to mental health professionals as a result of the growing awareness of their abilities. However, there is a continued concern that a large number of Pakistani psychiatrists emigrate to other countries including Australia, Canada, New Zealand, Middle East, UK and USA (62).

To date, there have been relatively few studies reporting on mental health conditions in Pakistan. Those that have been published include studies on common psychiatric disorders in outpatient care, general and major depressive disorders, factors associated with psychotic relapses and non-adherence of anti-psychotic medicines, gender differences in response to antipsychotics, cognitive disorders, and prescribing preferences of mental health professionals (7, 13, 64, 66-71). However, we are not aware of any study that has comprehensively assessed utilization and expenditure patterns of antipsychotic medicines across Pakistan as a first step to improving treatment options if concerns. Consequently, the objective of this study was to describe current antipsychotic utilization patterns in Pakistan and, more specifically, in adult patients attending tertiary care hospitals and private practitioners. This includes a comprehensive documentation of drug utilization patterns in recent years in accordance with WHO suggestions for LMICs (9). Subsequently, the findings will be used to suggest future research and initiatives in Pakistan to help improve the management of these patients, especially in view of the growing toll of neglecting mental health disorders among patients in LMICs, building on recent WHO recommendations.

2. Materials and Methods

The research was divided into three parts. Part one involved documentation of the utilization and expenditure patterns for antipsychotic medicines across Pakistan. This was undertaken to provide a benchmark for assessing whether the more detailed analysis of prescribing patterns in two Pakistani hospitals were representative. The second part involved researching the database of hospitals in Rawalpindi and Islamabad to gain a greater insight into antipsychotic prescribing patterns. This included evaluating the extent of co-morbidities, international non-proprietary name (INN) prescribing, and polypharmacy. The utilization patterns were appraised in terms of their respective prescribing patterns of both typical and atypical antipsychotics to see if there were similarities between the two databases. In this way, the representativeness of the hospital data could be assessed against antipsychotic utilization patterns across Pakistan to enhance the robustness of any suggestions made regarding potential future initiatives and research. The third part involved assessment of current utilization patterns against recognized WHO criteria to again provide suggested initiatives in the future to improve prescribing if concerns (72).

2.1 Part One - Utilization and expenditure of antipsychotic medicines across Pakistan

Utilization and expenditure data for the antipsychotics (N05A group apart from Lithium – N05AN (73)) from 2010 to 2015 were extracted from Intercontinental Marketing Services (IMS – now QuintilesIMS™) data to provide insight into current utilization and expenditure patterns. IMS collects data of drug statistic sales from a representative sample of pharmacies in Pakistan to provide representational data for Pakistan, with IMS data internationally recognized for comparing drug utilization statistics across countries (29, 74). IMS data was sourced via the Drugs Regulatory

Authority in Pakistan (DRAP) for academic purposes. The utilization units are IMS units, which are typically based on packs dispensed including their strength and number of tablets.

The data was further broken down into utilization and expenditure of the most utilized typical antipsychotics, e.g. chlorpromazine (N05AA01), fluphenazine (N05AB02), and haloperidol (N05AD01) as well as atypical antipsychotics, e.g. aripiprazole (N05AX12), clozapine (N05AH02), olanzapine (N05AH03), and risperidone (N05AX08), in terms of percentage share by value and units for comparative purposes.

Different brands of risperidone and olanzapine were also documented to see if appreciable competition would help to lower prices as seen in countries such as the Netherlands (75). This included different branded generics, which are common in Pakistan, with competition to potentially reduce prices seen as important given current high co-payment levels for medicines in Pakistan (76). The value of medicines has been documented in Pakistan Rupees [85 - 105 Pakistan Rupees = 1 US\$ - average from 2010 to 2015] (77).

2.2 Part Two - Hospitals in Rawalpindi and Islamabad

The database of adult (≥ 18 years) patients receiving any antipsychotic medicine in the outpatient departments of both public and private hospitals in Rawalpindi and Islamabad was retrieved from May 2016 to October 2016. These two cities were chosen as they are representative of other cities in Pakistan (76).

A standard data collection form was used to collect information on patient demographics including sex, age (as documented from the patient's medical journal), psychiatric diagnosis (based on DSM IV codes), comorbidities, current medicines for mental health conditions and the length of treatment as well as any concomitant drugs from the medical journal of the patients, which are paper based. Overall, the records of 5460 patients were retrieved and searched by hand by SM and TUR. This included the prescribing of antiepileptics (N03A), anti-parkinson medicines (N04A), antipsychotics (N05A), anxiolytics (N05B), and hypnotics and sedatives (N05C). The top 20 medicines by INN name were subsequently tabulated. This included the most common medicines for patients with mental health including antipsychotics, which enabled the utilization of antipsychotics in these two cities to be compared with the total population in Pakistan to give future guidance given the lack of electronic databases in Pakistan. This is important when reviewing the extent of co-prescribing of antipsychotics as well as the co-prescribing of other medicines based on the extent of co-morbidities. Such information is not available from the IMS database interrogated.

2.3 Part 3 – Assessing the quality of prescribing

The WHO indicators were used to initially assess the quality of prescribing for patients with mental health in the two cities including the antipsychotics. The quality of prescribing was assessed against pre-set goals (72, 78-80), which included the average number of medicines per prescriptions (<2), the rate of INN prescribing (100%), and the percentage of medicines prescribed from the national EML list (NEML) (100%) (80).

In addition, the quality of prescribing was further assessed by looking at the extent of any co-prescribing of antipsychotic medicines.

2.4 Statistical Analysis

Descriptive statistics were used to describe the utilization patterns. Univariate linear regression was used to evaluate the changes in the utilization (total consumption, total expenditure, percentage share by unit and value) over time, with time (the years 2010 to 2015) as the independent variable. A p-value of <0.05 was considered statistically significant. Data analysis was performed using SPSS 16.

2.5 Ethical Approval

Ethical approval was sought and obtained from the Medical Ethics Committee at Quaid e Azam University, Islamabad, Pakistan, before conducting the study.

3. Results

3.1 Utilization and cost data for Pakistan (IMS Data)

From 2010 to 2015 there was a progressive rise in the use and expenditure of antipsychotics in Pakistan (Table 1), with the population also growing.

Table 1 - Details of antipsychotic consumption and expenditure in Pakistan (2010-2015) based on IMS data

Year	Total Number of Units*	Total Sale in Pak Rupees (Rs) **	Population (in Millions)****	Cost per unit Rupees Rs (US \$)***
2010	3,216,920	552,081,540	173.5	171.61 (2.06)
2011	6,697,542	1,175,229,819	175.31	175.47 (1.99)
2012	7,469,569	1,358,045,338	178.91	181.81 (1.94)
2013	12,121,154	2,168,676,902	182.52	178.92 (1.75)
2014	12,549,712	2,429,619,514	189.87	193.60 (1.88)
2015	13,845,897	2,689,138,970	196.56	(1.89)
Extent of change (absolute)	4.30	4.87	1.13	1.13

NB: * P=0.001; ** p=0.003; *** p=0.006; **** Population figures taken from (81). Units = IMS Units. Source: IMS 2016.

Antipsychotic utilization in Pakistan has been dominated by risperidone and olanzapine in recent years (Table 2), with a significant decrease in the percentage share by value but not utilization of risperidone. There was a significant increase in the percentage share by value and units of fluphenazine, with a corresponding decrease in the value and utilization of haloperidol. The share by value of aripiprazole (% of total units) also decreased but from a low base, although utilization has marginally increased in recent years but also from a low base. There was a mixed pattern with the other antipsychotics in terms of their utilization and expenditure over the years.

Table 2: Percentage share and growth by value and units of the highest utilized antipsychotic medicines in Pakistan (negative or positive growth) from 2010 to 2015

Antipsychotic (N05A)	Year						P value
	2010	2011	2012	2013	2014	2015	
Risperidone (N05AX08)							
% share by value	57.1	55.0	55.9	44.4	41.8	44.3	0.018
% share by units	41.9	40.2	40.9	34.8	35.2	39.6	0.23
% Growth against previous year by value	-	8.1	17.4	17.7	4.4	15.8	
% Growth against previous year by units	-	9.7	13.2	23.8	4.2	22.8	
Number of formulations available (recorded in IMS data): 20							
Olanzapine (N05AH03)							
% share by value	20.5	22.2	21.4	20.5	19.7	19.2	0.101
% share by units	27.9	30.1	29.5	29.9	28.6	27.2	0.49
% Growth against previous year by value	-	21.9	11.3	41.8	6.6	6.3	
% Growth against previous year by units	-	23.3	9.1	47.5	-1.7	3.8	
Number of formulations available (recorded in IMS data): 20							
Clozapine (N05AH02)							
% share by value	7.7	7.2	6.9	4.9	8.4	9.5	0.47
% share by units	0.5	0.5	0.5	0.3	0.7	0.8	0.23
% Growth against previous year by value	-	5.5	9.8	4.8	91.8	23.1	
% Growth against previous year by units	-	5.9	10.9	3.1	120.2	15.8	
Number of formulations available (recorded in IMS data): 4							
Fluphenazine (N05AB02)							
% share by value	5.2	6.0	7.4	16.9	17.3	14.6	0.029
% share by units	9.6	10.2	12.6	19.2	20.0	17.1	0.028
% Growth against previous year by value	-	26.9	42.1	241.6	13.5	-7.7	
% Growth against previous year by units	-	21.4	38.2	119.8	7.2	-6.4	
Number of formulations available (recorded in IMS data): 10							
Haloperidol (N05AD01)							
% share by value	4.3	4.2	3.3	2.6	2.1	2.0	0.001
% share by units	15.8	14.4	12.7	9.6	8.3	7.6	0.001
% Growth against previous year by value		10.8	-8.6	15.2	-11.2	3.2	
% Growth against previous year by units		4.2	-1.8	9.8	-11.3	0.6	
Number of formulations available (recorded in IMS data): 4							
Aripiprazole (N05AX12)							
% share by value	2.1	2.0	1.7	1.4	1.8	1.9	0.007
% share by units	1.6	1.5	1.3	1.2	1.8	1.8	0.91
% Growth against previous year by value		5.9	-3.4	26.3	41.5	11.6	
% Growth against previous year by units		7.9	-2.5	32.1	57.1	7.5	
Number of formulations available (recorded in IMS data): 4							
Trifluoperazine (N05AB06)							
% share by value	1.9	2.2	1.8	1.3	1.0	0.8	0.002
% share by units	1.8	2.2	1.6	1.3	1.5	2.2	0.006
% Growth against previous year by value		30.6	-4.6	4.8	-17.9	-6.4	
% Growth against previous year by units		35.6	-20.6	17.1	23.2	60.0	
Number of formulations available (recorded in IMS data): 2							
Flupentixol (N05AF01)							
% share by value	1.1	1.1	1.5	2.7	3.4	3.6	0.06
% share by units	0.6	0.7	0.8	1.9	2.2	2.2	0.17
% Growth against previous year by value	-	9.4	66.4	161.2	40.3	15.4	
% Growth against previous year by units	-	19.1	29.6	252.0	18.2	10.6	
Number of formulations available (recorded in IMS data): 7							
Chlorpromazine (N05AA01)							
% share by value	0.1	0.1	0.0	0.0	0.0	0.0	0.06
% share by units	0.2	0.1	0.1	0.0	0.0	0.1	0.17
% Growth against previous year by value	-	-27.1	-12.5	-43.7	-25.2	119.2	
% Growth against previous year by units	-	-32.2	-35.3	-44.5	12.6	144.5	
Number of formulations available (recorded in IMS data): 6							
Ziprasidone (N05AE04)							
% share by value	0.0	0.0	0.0	3.5	2.8	2.5	0.058
% share by units	0.0	0.0	0.0	1.2	0.9	0.7	0.093
% Growth against previous year by value	-	-	-	100.0	-13.1	-2.9	

% Growth against previous year by units	-	-	-	100.0	-21.6	-18.4	
Number of formulations available (recorded in IMS data): 5							
Zuclopenthixol (N05AF05)							
% share by value	0.0	0.0	0.0	1.7	1.7	1.7	0.02
% share by units	0.0	0.0	0.0	0.8	0.8	0.8	0.02
% Growth against previous year by value	-	-	-	100.0	9.6	10.7	
% Growth against previous year by units	-	-	-	100.0	6.5	9.5	
Number of formulations available (recorded in IMS data): 3							

NB. Units = IMS Units (usually a pack). Source: IMS 2016

Tables 3a and 3b document the utilization of different branded generics and originators of risperidone and olanzapine during the study period.

Table 3a – Utilisation of different brands of Risperidone in Pakistan (2010 to 2015) based on IMS data

Percentage Units of Risperidone from 2010-15						
Brand name	2010	2011	2012	2013	2014	2015
RISP	22	22	22	20	22	18
VEPRIDONE	13	11	14	16	18	13
RISPERDAL	8	8	8	7	6	5
ORIDONE	0	3	5	8	8	15
ESPIDONE	6	5	5	3	4	4
BUZON	8	8	7	6	5	4
NEORIS	6	8	8	11	8	6
RESPEROSE	0	0	0	0	0	8
RECEPT	6	6	4	3	3	4
PERSCH	4	5	4	4	5	4

NB. Units = IMS Units. Source: IMS 2016

Table 3b – Utilisation of different brands of olanzapine in Pakistan (2010 to 2015) based on IMS data

Percentage Units of Olanzapine from 2010-15						
Brand name	2010	2011	2012	2013	2014	2015
OLEPRA	35	33	37	29	28	22
OLANZIA	40	36	34	31	32	34
ZYPREXA	1	1	1	1	1	1
NIRVANOL	0	0	0	6	5	6
LEPINZA	0	0	0	5	6	6
OZAPINE	0	0	0	4	6	7
AMPREXA	5	9	8	7	6	6
ZANZIA	0	4	6	6	6	6
OZIP	0	0	0	0	0	2
OLAN	0	0	0	8	4	2
FURMIUM	0	0	0	7	1	2

NB. Units = IMS Units. Source: IMS 2016

3.2 Retrospective study (patient data) including analysis of quality indicators

Among the 5460 patients treated with antipsychotics in Rawalpindi and Islamabad there were 1462 (26.7%) women and 3978 (71.3%) men. Table 4 shows the distribution of the various age groups in the retrospective analysis. The maximum number of patients were in the age group 41-50 years (Table 4).

Table 4 – Distribution of ages among the 5460 patients treated with antipsychotics

Age (years)	Number of patients (5460)	Percentage (%)
18 – 30	543	9.98
31 – 40	1478	27.17
41 – 50	1924	35.36
52 – 60	1357	24.94
> 60	642	11.80

The number of patients diagnosed with schizophrenia were 2144 (39.4%), followed by bipolar disorders 1390 (25.5%), depressive disorders 724 (2.07%) and anxiety disorders 113 (2.07%), insomnia 83 (1.52%) and other diagnoses 988 (18.16%).

The total number of medicines prescribed were 24806, representing 142 different molecules. The average number of medicines per prescription was 4.56 and the percentage of medicines prescribed by their generic name (INN) as opposed to a branded generic was 21.4% (Table 5). Less than 40% of medicines were prescribed from the NEDL.

Table 5 – Assessment of prescribing practices among the 5460 patients treated with antipsychotics against WHO indicators (WHO targets adapted from references 70,78)

Parameters	Number/percentage	WHO Target
Total number of drugs prescribed among the 5460 patients	24806	
Average number of medicines/prescriptions (encounter)	4.56	Less than 2, acceptable between 2 and 2.5
Percentage of the drugs prescribed by generic name (INN)	21.4%	100%, acceptable 80%
Percentage of the drugs prescribed from the National Essential Drugs List	Less than 40%	100%

NB: INN = International non-proprietary name

The most common psychotropic medicines prescribed were risperidone (31%), olanzapine (18.4%), procyclidine (8.4%), alprazolam (8.4%), and haloperidol (7.7%) (Table 6).

Table 6 – Most common mental health medicines prescribed among the 5460 patients treated with antipsychotics

Medicines Prescribed	% of total mental health medicines prescribed out of the 24806 medicines
Risperidone	31%
Olanzapine	18.4%
Procyclidine	8.4%
Alprazolam	8.4%
Haloperidol	7.7%
Carbamazepine	3%
Quetiapine	2.4%
Citalopram	2.4
Clonazepam	2.3
Escitalopram	2.2
Fluoxetine	2.1
Aripiprazole	1.2
Lamotrigine	1.2
Venlafaxine	1.2
Sertraline	1.2
Paroxetine	1.1
Lithium Carbonate	0.7
Flupentixol	0.7

Divalproex sodium	0.4
Fluphenazine	0.2
Topiramate	0.2
Others	3.6

NB: Unit = Prescription

Antipsychotics were the most prescribed medicines among the mental health medicines (55.6% of total prescriptions), followed by antidepressants 29.6%, anxiolytics 1.9%, medicines for mania and mood stabilizers 4% (Table 7). Other medicines prescribed for these patients reflects the fact that many had other co-morbidities including hypertension, diabetes and cardiac problems (Table 8 and Appendix Table 1A).

Table 7 – The breakdown of medicine classes prescribed (all medicines) among the 5460 patients treated with antipsychotics

Category of Drugs	No. of Patients	Percentage (%)
Anti-psychotics	3024	55.6
% of patients prescribed one antipsychotic concurrently	2813	93
% of patients prescribed 2 antipsychotics concurrently	154	5.1
% of patients prescribed more than 2 antipsychotics concurrently	58	1.9
Anti-depressants	1610	29.6
% of patients prescribed one anti-depressant concurrently	1345	83.02
% of patients prescribed 2 anti-depressants concurrently	177	10.99
% of patients prescribed more than 2 anti-depressants concurrently	88	5.46
Anti-manic/Mood stabilizers	220	4
Anxiolytics	55	1.0
Others	531	9.8

NB: Unit = Prescription

Table 8 – The extent of co-morbidities among the 5460 patients treated with antipsychotics

Psychiatric disorder	Comorbidities	No. of patients	Percentage (%)
Schizophrenia		2142	39.4
	Diabetes	334	15.6
	HTN	313	14.6
	Diabetes+ HTN	147	6.9
	CVD	190	8.8
	Diabetes+ HTN+ CV	42	2.0
	Hyperlipidemia	37	1.7
Bipolar Depression		1390	
	Diabetes	119	8.6
	HTN	122	8.8
	Diabetes+ HTN	103	7.4
	CVD	87	6.3
	Diabetes+ HTN+CVD	05	0.4
	Migraine	27	2.0
	Obesity	56	4.0
	Eating Disorders	44	3.2
Depression		724	
	Diabetes	51	7.0
	HTN	11	1.5
	Diabetes+ HTN	13	1.8
	CVD	46	6.3
	Diabetes+ HTN+ CVD	04	6.6
	Hypothyroidism	32	4.4
	Antisocial Personality Disorders	08	1.1
	Obesity	21	2.9
	Migraine	14	1.9
Anxiety		113	
	Diabetes	07	6.2
	HTN	11	9.8
	Diabetes+ HTN	03	2.6
	CVD	14	12.4
	Diabetes+ HTN+ CVDs	02	1.8
	Inflammatory bowel syndrome	02	1.8
	Hyperlipidemia	04	3.5
Insomnia		83	
	Diabetes	06	7.2
	HTN	10	12.0
	Diabetes+ HTN	04	4.8
	CVD	08	9.6
	Diabetes+ HTN+CVD	08	9.6
	Dementia	04	4.8
	Gastric Problems	12	14.4
	Migraine	04	4.8
Others		988	
	Obesity	07	0.7
	Smoking	32	3.2
	Eating Disorders	15	1.5
	Panic disorders	17	1.7
	Simple phobia	31	3.1

NB: Unit = Prescription; HTN = Hypertension, CVD = coronary vascular disease

4. Discussion

There has been a significant increase in the utilization of antipsychotics in Pakistan in recent years (Table 1), suggesting that more patients are being treated given the limited extent of antipsychotic polypharmacy (Table 7) and the comparably modest population growth (13.3%) during the study period (Table 1). The modest increase of cost/item (13.2%) during the period may also have promoted the wider use of antipsychotics (Table 1). The similarities with the high utilization of olanzapine and risperidone among the atypical antipsychotics and high utilization of haloperidol among the typicals in both data sets (Tables 2 and 6) gives credence to the suggestion that the 5460 patients in the retrospective analysis are representative of Pakistan as a whole.

The high ratio of atypical to typical antipsychotic utilization found in our study is similar to the ratios reported among Western countries, and higher than in other developing countries (82-88), which is encouraging. This may be helped by the competition among branded generic manufacturers to secure sales through reduced prices with high co-payments levels currently seen in Pakistan (76), with typically limited originator prescribing (Tables 3a and 3b). Potential reasons for any differences seen in the relative use of the different antipsychotics between countries may be due to the economic status of countries as well as the extent of any patient co-payments (82, 89). This is illustrated by relatively low use of atypical antipsychotics in countries with low income levels (83, 90); although this appears not to be the case in Pakistan (Tables 1 and 6), helped perhaps by the low costs per pack dispensed (Table 1). Hopefully, as more atypical antipsychotics become available as low cost generics, with generics in some countries priced as low as 2% of pre-patent loss prices, such issues will disappear (27, 57, 75) and treatment can be tailored to the individual and their needs in line with recommendations (24). This is also in line with the recent WHO guidance on improving access to care and treatment for patients with mental health conditions in LMICs (9). Lower cost for generics should also help with compliance (91), with no differences in effectiveness seen in practice between good quality generic antipsychotics and originators (92-97). However, the quality of generics can be an issue in Pakistan (9, 98), leading to high use of branded generics (Tables 3a, 3b and 5) unless concerns with the quality of generics are adequately addressed.

The continuing use of typical antipsychotics in Pakistan, especially for new cases, could also be due to the contraindications for atypical antipsychotics in patients with diabetes, or a high risk of diabetes, with the prevalence of diabetes up to 12% of adult males and growing in Pakistan (99), and glucose intolerance over 22% in some adult populations (100). Diabetes mellitus and hypertension were common comorbidities reported in our patients (Table 8 and Appendix A), potentially reducing the prescribing of atypical antipsychotics especially with currently low use of quetiapine and aripiprazole versus risperidone and olanzapine (Table 6), both of which have been associated with less weight gain (101, 102). Having said this, previous research among patients in Pakistan has suggested that the prescribing of risperidone does not increase the weight of Pakistani psychiatric patients (35). However, our data cannot further inform on this issue, because no clear time relation information was available in the patients' notes and we did not question the patients. In addition, data about weight was largely missing from the patient records. Furthermore, those patients who had been taking typical antipsychotics for a long time, and still showing improvements, will continue to be prescribed these antipsychotics unless they lead to adverse effects or decrease effectiveness. This is in line with prescribing practices in developed countries, emphasizing that patients should continue on their medicines even when generic versions of other atypical antipsychotics become available unless there are good reasons to change (27, 28).

Similar to other studies, more men were treated with antipsychotics in our study (44, 83) although others have shown different findings (84-86). We are not fully sure of the reasons for this. However, we will be exploring this further given general issues with mental illness among women in Pakistan due to for instance domestic violence as well as the appreciable gender inequality that currently exists in Pakistan. This includes researching further the identification and management of female patients with psychotic illnesses in Pakistan such as schizophrenia and bipolar disorders in view of local sociocultural issues, endorsing recent suggestions (103).

Risperidone was the most common prescribed atypical antipsychotic along with olanzapine, with little change in their overall utilization as a percentage of total units over the years in both the IMS data and the retrospective study (Tables 2 and 6), in line with WHO guidance (9). This is similar to other countries, although olanzapine may be more prescribed than risperidone (84, 85, 87). There is also

increased prescribing of quetiapine and aripiprazole in Europe with, as mentioned, concerns with weight gain with olanzapine and risperidone (27, 57, 104, 105), although not seen yet in Pakistan (Tables 2 and 6). If anything, there was a significant decrease in the prescribing of aripiprazole in some years, although marginally increased prescribing in recent years, albeit from a limited base (Table 2).

Overall, differences in prescribing habits within and between countries may be due to physician preferences, different patient responses to available treatments, availability of generic versus brand choices and costs (29, 35, 82). For typical antipsychotics, haloperidol was one of the commonest used medicines in both groups (Tables 2 and 6), which is similar to Canadian and Australian studies (84, 87), potentially enhanced by its inclusion in the WHO essential medicines list (9).

Single antipsychotics were prescribed in 93.0% of patients (Table 5). However, there are concerns at the extent of polypharmacy seen with patients prescribed on average 4.56 medicines concurrently (Table 5); appreciably above the WHO target of 2 medicines (80). This is no doubt exacerbated by the extent of co-morbidities among the studied patients and the associated medicines (Table 8 and Appendix). The most common concomitant medicines prescribed with the antipsychotics were those affecting the central nervous system (Table 7). This is perhaps not surprising since patients with psychiatric disorders may also suffer from other mental and brain related conditions, increasing concomitant prescribing with medicines targeted for the central nervous system and resultant polypharmacy (Table 7). The second most common concomitant medicines prescribed were the anti-muscarinic medicines. Whilst atypical antipsychotics are generally associated with less muscarinic side effects than typical ones, patients still experience these side-effects potentially explaining their joint prescribing. In addition, other comorbid conditions such as dizziness and dementia might require the use of anti-muscarinic medicines. As stated earlier, diabetes mellitus and hypertension were also common comorbidities in our patients, adding to the extent of polypharmacy (Table 8 and Appendix). Having said this, the rates of polypharmacy were high and this will be explored in future research with issues of compliance and adverse drug reactions being a concern with the increasing number of medicines prescribed (106-108).

The low rate of INN prescribing, as well as the low rate of prescribing as suggested by the NEDL, are also concerns (Table 5). This will again be explored in more detail to ascertain the rationale behind this. However, we are aware that pharmacists typically suggest the brands that will give them the maximum benefit financially, especially with incentives from pharmaceutical companies to preferentially dispense their brand. Suggested strategies will subsequently be proposed based on successful approaches in other countries. These include measures to improve the quality of generics in Pakistan, ensuring a regular supply chain given concerns with counterfeits, as well as education among all key stakeholder groups (9, 98, 109, 110). The provision of mental health services in Pakistan will also be explored in more detail following critical guidance from the WHO and others, as well as concerns that female patients in particular may be missing out (9).

Whilst we believe this is the first report exploring in depth the utilization of antipsychotics in Pakistan at a national and regional level in recent years, we are aware of a number of limitations with this study. Firstly, as with any retrospective study, some data were not available to make definitive conclusions especially with treatment outcomes, doses, tolerability, and side effects. Secondly, we could not follow up patient records to determine if the atypical antipsychotics being prescribed were first line or as a replacement for typical antipsychotics. Thirdly, we only undertook the study in two cities. Nevertheless, we believe our findings are robust with a good correlation between the retrospective study and IMS data, which will help formulate future strategies to better manage these patients in Pakistan and other similar countries.

5. Conclusion

The research showed an appreciable increase in the utilization of antipsychotics in Pakistan in recent years, which is encouraging. The atypical antipsychotics, olanzapine and risperidone, constituted more than two thirds of all antipsychotic prescriptions. In addition, almost all patients received one antipsychotic rather than multiple antipsychotics, in keeping with most standard therapeutic guidelines. However, further studies are required to examine the outcome of these prescriptions and their effects on metabolic and other physiologic profiles of patients. There is also a need to promote INN prescribing in Pakistan as well as enhance adherence to the NEDL. In addition, there is an urgent

need to reduce the extent of unnecessary polypharmacy where this exists. These are issues for the future, along with a greater understanding of the types of patients with appreciable mental health issues either seeking, or not seeking, care from healthcare professionals in Pakistan. This will enhance our understanding of mental health issues in Pakistan to improve future treatment including the use of medicines. This is particularly important among female patients in Pakistan given current concerns.

Author contributions

SM, SH, TuRH designed the study and were involved in the collection and analysis. SM, SH, CB, ABK and BG produced the initial draft manuscript. All authors critiqued successive drafts of the manuscript before submission, approved the final version and agreed to be accountable for all aspects of the work.

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The authors declare they have no other conflicts of interest.

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Appendix

Psychiatric disorders	Comorbidities	No. of patients	Drugs prescribed	Percentage
Schizophrenia		2142		
	Diabetes	334	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. 	15.6
	HTN(Hypertension)	313	<ul style="list-style-type: none"> • Thiazide diuretics • Beta blockers. • Angiotensin-converting enzyme (ACE) inhibitors. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. 	14.6
	Diabetes+ HTN	147	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. • Thiazide diuretics • Beta blockers. • Angiotensin-converting enzyme (ACE) inhibitors. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. 	6.7
	CVD (Cardiovascular Disease)	190	<ul style="list-style-type: none"> • ACE inhibitors • Aldosterone inhibitors • Angiotensin II receptor blockers (ARBs) • Beta-blockers • Calcium channel blockers • Cholesterol-lowering drugs 	8.9
	Diabetes+ HTN+ CVD	42	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. • Thiazide diuretics • Beta blockers. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. • ACE inhibitors • Aldosterone inhibitors • Beta-blockers 	1.9
	Hyperlipidemia	37	<ul style="list-style-type: none"> • Statins • Resins • Fibrates 	1.7
Bi-polar Depression		1390		
	Diabetes	119	<ul style="list-style-type: none"> • Metformin. 	8.6

			<ul style="list-style-type: none"> • Sulfonylureas. • Meglitinides. • Insulin therapy. 	
	HTN	122	<ul style="list-style-type: none"> • Thiazide diuretics • Beta blockers. • Angiotensin-converting enzyme (ACE) inhibitors. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. 	8.8
	Diabetes+ HTN	103	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. • Thiazide diuretics • Beta blockers. • Angiotensin-converting enzyme (ACE) inhibitors. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. 	7.4
	CVD	87	<ul style="list-style-type: none"> • ACE inhibitors • Aldosterone inhibitors • Angiotensin II receptor blockers (ARBs) • Beta-blockers • Calcium channel blockers 	6.2
	Diabetes+ HTN+ CVD	05	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. • Thiazide diuretics • Beta blockers. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. • ACE inhibitors • Aldosterone inhibitors • Beta-blockers 	0.4
	Migraine	27	<ul style="list-style-type: none"> • Pain relievers. • Triptans. • Ergots • Anti-nausea • Opioid medications • Glucocorticoids 	1.9
	Obesity	56	<ul style="list-style-type: none"> • Beta-methyl-phenylethylamine • Lipase Inhibitor • Phentermine • Sibutramine 	4
	Eating Disorders	44	<ul style="list-style-type: none"> • Anticonvulsant topiramate • Selective serotonin reuptake inhibitors (SSRIs) 	3.2

Depression		724		
	Diabetes	51	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. 	3.7
	HTN	11	<ul style="list-style-type: none"> • Thiazide diuretics • Beta blockers. • Angiotensin-converting enzyme (ACE) inhibitors. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. 	0.8
	Diabetes+ HTN	13	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. • Thiazide diuretics • Beta blockers. • Angiotensin-converting enzyme (ACE) inhibitors. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. 	0.1
	CVD	46	<ul style="list-style-type: none"> • ACE inhibitors • Aldosterone inhibitors • Angiotensin II receptor blockers (ARBs) • Beta-blockers • Calcium channel blockers 	3,3
	Diabetes+ HTN+ CVDs	04	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. • Thiazide diuretics • Beta blockers. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. • ACE inhibitors • Aldosterone inhibitors • Beta-blockers 	0.3
	Hypothyroidism	32	<ul style="list-style-type: none"> • Thioamides • Anion inhibitors • Iodides 	2.3
	Obesity	21	<ul style="list-style-type: none"> • Psychotropic appetite suppressant • Non- Psychotropic appetite suppressant • Impulse and craving suppressant • Lipase inhibitor 	1.5
	Migraine	14	<ul style="list-style-type: none"> • Pain relievers. • Triptans. • Ergots • Anti-nausea 	1

			<ul style="list-style-type: none"> • Opioid medications • Glucocorticoids 	
Anxiety		113		
	Diabetes	07	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. 	0.5
	HTN	11	<ul style="list-style-type: none"> • Thiazide diuretics • Beta blockers. • Angiotensin-converting enzyme (ACE) inhibitors. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. 	0.8
	Diabetes+ HTN	03	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. • Thiazide diuretics • Beta blockers. • Angiotensin-converting enzyme (ACE) inhibitors. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. 	0.2
	CVD	14	<ul style="list-style-type: none"> • ACE inhibitors • Aldosterone inhibitors • Angiotensin II receptor blockers (ARBs) • Beta-blockers • Calcium channel blockers • Cholesterol-lowering drugs 	1
	Diabetes+ HTN+ CVD	02	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. • Thiazide diuretics • Beta blockers. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. • ACE inhibitors • Aldosterone inhibitors • Beta-blockers • Cholesterol-lowering drugs 	0.1
	IBS	02		0.1
	Hyperlipidemia	04	<ul style="list-style-type: none"> • Statins • Resins • Fibrates 	0.3
Insomnia		83		
	Diabetes	06	<ul style="list-style-type: none"> • Metformin. 	7.2

			<ul style="list-style-type: none"> • Sulfonylureas. • Meglitinides. • Insulin therapy. 	
	HTN	10	<ul style="list-style-type: none"> • Thiazide diuretics • Beta blockers. • Angiotensin-converting enzyme (ACE) inhibitors. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. 	12
	Diabetes+HTN	04	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. • Thiazide diuretics • Beta blockers. • Angiotensin-converting enzyme (ACE) inhibitors. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. 	4.8
	CVD	08	<ul style="list-style-type: none"> • ACE inhibitors • Aldosterone inhibitors • Angiotensin II receptor blockers (ARBs) • Beta-blockers • Calcium channel blockers • Cholesterol-lowering drugs 	9.6
	Diabetes+ HTN+ CVD	08	<ul style="list-style-type: none"> • Metformin. • Sulfonylureas. • Meglitinides. • Insulin therapy. • Thiazide diuretics • Beta blockers. • Angiotensin II receptor blockers (ARBs). • Calcium channel blockers. • Renin inhibitors. • ACE inhibitors • Aldosterone inhibitors • Beta-blockers 	9.6
	Gastric Problems	12	<ul style="list-style-type: none"> • Proton pump Inhibitors 	14.4
	Migraine	04	<ul style="list-style-type: none"> • Pain relievers. • Triptans. • Anti-nausea • Opioid medications • Glucocorticoids 	4.8
Others		988		
	Obesity	07	<ul style="list-style-type: none"> • Psychotropic appetite suppressant • Non- Psychotropic appetite suppressant • Lipase inhibitor 	0.7
	Smoking	32		3.3
	Eating Disorders	15	<ul style="list-style-type: none"> • Anticonvulsant topiramate 	1.5

			<ul style="list-style-type: none">• Selective serotonin reuptake inhibitors (SSRIs)	
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