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## A CROSS-SECTIONAL STUDY TO ANALYSE PRESCRIBING PATTERNS AND TECHNIQUES OF SWITCHING OVER OF ANTIPSYCHOTICS IN VARIOUS PSYCHOTIC DISORDERS

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### Keywords:

Antipsychotics, Prescribing pattern, Polypharmacy, Switching over, Monotherapy, Polytherapy

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**ABSTRACT:** Patients with psychotic disorders often require long-term and intensive treatment. Several drug utilization studies have been carried out using WHO (World Health Organization) prescribing indicators, but these studies are deficient for psychiatry patients in India. To analyze antipsychotic prescriptions according to WHO core prescribing indicators and identify various techniques used for switching over from one antipsychotic to another, a cross-sectional, observational study was conducted with one year and six months duration. 128 patients were enrolled who fulfilled the inclusion criteria and gave written informed consent. This study revealed male (53.91%) predominance over female patients (46.09%). The average number of drugs prescribed per encounter was 4.56. The percentage of drugs prescribed by generic name was 48.79%, and 52.06% of drugs were prescribed from the essential drug list. Atypical antipsychotics (53.28%) were prescribed more than typical antipsychotics (46.71%). 56.25% of patients were treated with monotherapy, and 43.75% patients were treated with polytherapy. Switching over of antipsychotics was seen in 33 (25.78%) patients. The most commonly used technique for switching was immediate/abrupt switching (44.73%), followed by overlap switching (31.57%). This study concluded that polypharmacy needs to be carefully addressed, and practices like prescribing from essential medicines list and by generic name need to be encouraged.

**INTRODUCTION:** Psychosis is a symptom of mental illness and is characterized by a distorted sense of reality. It is the essential feature of schizophrenia spectrum disorders. The worldwide prevalence of Schizophrenia is 1%<sup>1</sup>. Psychosis can lead to disability, and it is also a barrier to productivity. The contribution of mental disorders to the total disability-adjusted life years (DALYs) in India increased from 2.5% in 1990 to 4.7% in 2017<sup>2</sup>.

In addition to environmental exposures, over 150 genes appear to contribute to schizophrenia risk that regulates neuronal migration, synaptogenesis, cellular adhesion and neurite outgrowth like neuregulin 1<sup>1</sup>. Antipsychotics are the mainstay treatment of schizophrenia and other psychotic disorders. Antipsychotic agents may be classified as older drugs (conventional or “typical” antipsychotics) and newer atypicals.

Patients with psychotic disorders often require long-term treatment and are vulnerable to the side effects such as extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) with typical antipsychotics and metabolic syndrome characterized by weight gain, hypertension, dyslipidemia and impairments in glycaemic control with atypical



antipsychotics<sup>3</sup>. Irrational use and polypharmacy of antipsychotics can lead to treatment failure, resistance and economic burden on patients and society.

WHO developed prescribing indicators intending to ascertain the therapeutic actions taken in similar institutions and determine the most frequently used medications in a given place<sup>4</sup>. These indicators help to know polypharmacy, which is a major factor contributing to adverse drug reactions (ADRs) and drug-drug interactions (DDIs)<sup>5</sup>.

The need to switch from one antipsychotic to another is a frequent challenge in the long-term management of psychotic disorders. Switching antipsychotics is frequently applied in clinical practice, but there are many open questions - Is the switch effective at all, for which drugs, and for how much time<sup>6</sup>. So, the knowledge of strategies for selecting and switching the medications can help the patient attain optimal therapeutic outcomes.

Studies have shown that the majority of prescriptions in India are of drugs of "doubtful efficacy"<sup>7</sup>. Studies related to prescription patterns in patients with schizophrenia have indicated a high rate of antipsychotic polypharmacy, but data in Asia are scarce. Studies on switching among antipsychotics in India are also limited in number. To promote the rational use of drugs in developing countries, assessment of prescription patterns with the WHO prescribing indicators is necessary.

Looking to the above needs and paucity of literature of research in the Indian population, the present study aimed to assess antipsychotic prescription patterns, techniques of switching over antipsychotics and recognize the most commonly used method of switching in patients with various psychotic disorders in the tertiary care hospital in Punjab, India.

## **MATERIALS AND METHODS:**

**Study Design:** The study was designed as a hospital-based observational study cross-sectional in nature.

**Study Population:** The study population included inpatients and outpatients visiting the psychiatry department of Rajindra Hospital, Patiala.

**Study Duration:** The study was conducted for a period of one and a half years.

**Ethical Clearance:** The study was conducted after taking approval from Institutional Ethics Committee (BFUHS/2K19p-TH/8021)

## **Inclusion Criteria:**

- All patients of age 18 years or above.
- Both male and female.
- Outpatients and Inpatients.
- Any patient who has been prescribed one or more antipsychotic drugs for any psychotic disorder within the period of 3 months.
- Patients who had a level of understanding sufficient to communicate with research staff and co-operate with all tests and examinations required as per protocol.
- Patients who gave the willingness to sign written informed consent.
- Patient accompanied by a family member who was a reliable informant and gave written informed consent

## **Exclusion Criteria:**

- Patients with substance abuse disorder and dependence (except nicotine and caffeine - occasional use was not exclusion criteria).
- Pregnant or nursing females.
- Patient who was judged clinically to be a suicide risk too serious about being included in the study

**Informed Consent:** Patients and their attendants were made to understand the purpose of the study and their rights with the help of written informed consent prepared in Hindi, Punjabi, and English. Thumb impression was taken in the presence of the appropriate witness for illiterate patients. In case if special consent procedure was needed, then the person next to kin or legal signatory was enrolled to sign the informed consent form.

**Data Collection:** Prescription of patients visiting Psychiatric Department OPD (Out-patient department) and IPD (In-patient department) fulfilling the inclusion criteria was collected and analyzed for prescribing patterns. The WHO (World Health Organisation) drug prescribing indicators were used for the analysis of prescribing patterns.

**Statistical Analysis:** Statistical analysis was done using IBM SPSS (Statistical Product and Service Solutions) version 22.0. Qualitative data were expressed in frequency and percentage. Quantitative data were analyzed using mean and standard deviation.

**RESULTS:** In this study, male (53.91%) predominance was seen over females (46.09%). The mean age was 32.88 (12.91), and the maximum patients (45.31%) were in the age group of 18 to 27 years. 32.81% of patients were having a positive family history of any psychiatric disorders. 39.84% of patients were unemployed,

**TABLE 1: BASELINE CHARACTERISTICS OF STUDY POPULATION**

	Value	N (%)
Age (years)	18-27	58 (45.31)
	28-37	33 (25.78)
	38-47	18 (14.06)
	48-57	10 (7.81)
	58-67	9 (7.03)
	Total	128 (100)
Gender	Mean±SD	32.88±12.91
	Range	18-67
	Female	59 (46.09)
Marital status	Male	69 (53.91)
	Unmarried	56 (43.75)
Occupatio	Married	63 (49.22)
	Divorced	7 (5.47)
	Separated	2 (1.56)
	Unemployed	51 (39.84)
	Housewife	30 (23.44)
Family history	Students	13 (10.16)
	Labour	11 (8.59)
	Private job	11 (8.59)
	Retired	5 (3.91)
	Skilled Worker	4 (3.13)
Diagnosis	Govt Job	3 (2.34)
	Present	42 (32.81)
	Absent	86 (67.19)
	Schizophrenia (F20)	54 (42.19)
Diagnosis	Bipolar disorder (F31)	42 (32.81)
	Other psychotic disorders (F23, F25)	32 (25%)

10.15% of patients had co-morbid diseases like hypertension and diabetes mellitus<sup>2</sup>.

As described in **Table 2**, the average number of drugs per encounter was 4.56, the percentage of drugs prescribed by generic name was 48.79%, Only 5.4% antibiotics were prescribed, 83.59% prescriptions were with an injectable prescribed. Percentage of drugs prescribed from the essential drug list were 52.06%; injection/ Tablet Lorazepam was prescribed by generic name in most of prescriptions. Most commonly prescribed injectables were Injection lorazepam and Injection Haloperidol in IPD and Injection F-tensil (Fluphenazine) in OPD patients. Other Injectable prescribed were Inj. Diazepam. The most commonly prescribed medicine from the essential drug list was Injection haloperidol. Antibiotics used were Amoxicillin + clavulanic acid (1.56 %), Azithromycin (1.56%) followed by Cefaclor, Albendazole, and Ofloxacin + ornidazole 0.78 % each.

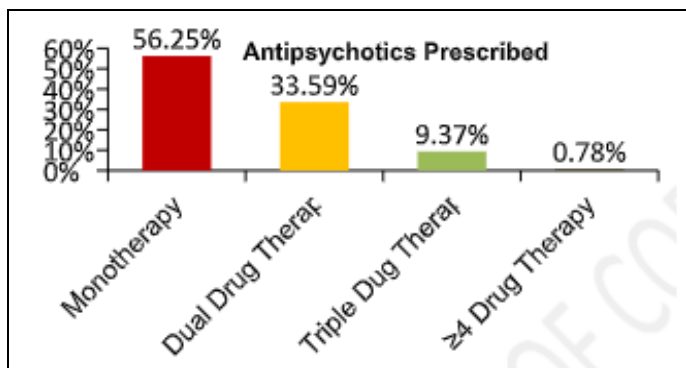
**TABLE 2: COMPARISON OF WHO PRESCRIBING INDICATORS OBSERVED WITH STANDARD REFERENCE RANGE**

S. no.	Name of Indicator	Result	Reference range
1	Average number of drugs per encounter	4.56	1.6 – 1.8
2	Percentage of drugs prescribed by generic name	48.79%	100%
3	Percentage of prescriptions with an antibiotic prescribed	5.4%	20.0% - 26.8%
4	Percentage of prescriptions with an injection prescribed	83.59%	13.4 – 24.1%
5	Percentage of drugs prescribed from essential drug list	52.06%	100%

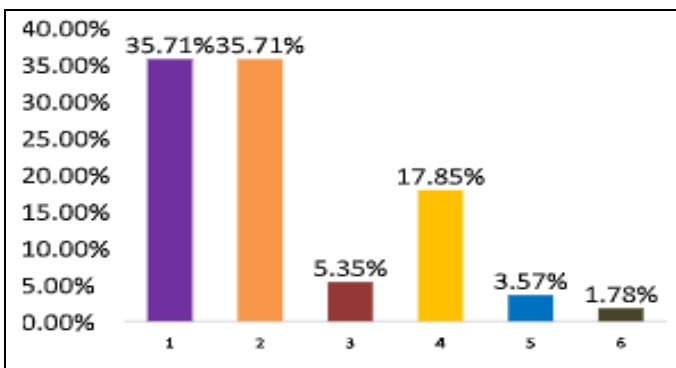
Antipsychotics were prescribed for a total of 304 times, out of which typical antipsychotics were prescribed 142 times (46.71%) and atypical 162 times (53.28%). Overall atypical antipsychotics were most commonly prescribed (risperidone (44.44%) > olanzapine (23.45%) > quetiapine (10.49%)) but individually haloperidol (76.76%) which is a typical antipsychotic was most commonly prescribed. As shown in **Fig. 1**, 56.25% of patients were treated with monotherapy, and 43.75% were treated with polytherapy.

As shown in **Fig. 2**, in dual drug therapy, where typical and atypical antipsychotics were used together, Haloperidol + Risperidone was most commonly used (12.50%) followed by Fluphenazine + Risperidone (5.35%), Chlorpromazine + Olanzapine (3.57%) and Haloperidol + Olanzapine (3.57%). When both atypical antipsychotics were used, Risperidone + Quetiapine was most commonly used (10.71%), followed by Risperidone +

Olanzapine and Risperidone + Clozapine (3.57% each). When both typical antipsychotics were used, Chlorpromazine + Trifluoperazine was used in 3.57% of patients and Chlorpromazine + Haloperidol was used in 1.78% patients. In triple drug therapy, most commonly used antipsychotics were Haloperidol+ Chlorpromazine + Risperidone together and Haloperidol + Risperidone + Quetiapine (3.57% each).



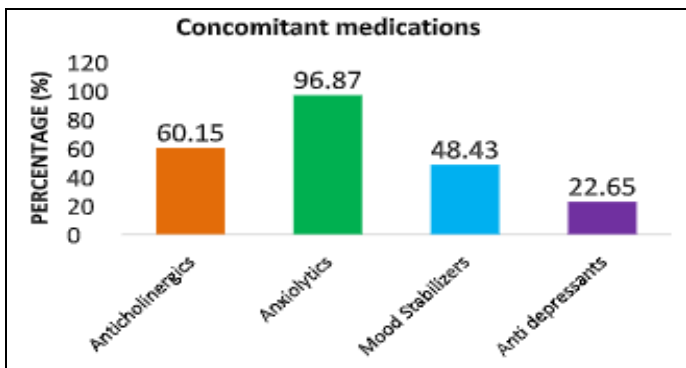
**FIG. 1: DISTRIBUTION OF STUDY POPULATION PRESCRIBED WITH POLYTHERAPY**



**FIG. 2: DISTRIBUTION OF ANTIPSYCHOTICS PRESCRIBED AS POLYTHERAPY**

As shown in **Fig. 3**, other concomitant medications used were anxiolytics, in 96.87% patients, anticholinergics (60.15%), mood stabilizers (48.43%) and anti-depressants were used in 22.65% patients along with antipsychotics. Trihexyphenidyl was most commonly prescribed anticholinergic agent which was used in 56.25% patients. Lorazepam was most commonly prescribed anxiolytic (87.50%) followed by Clonazepam (34.38%), followed by propranolol (31.25%) and diazepam (18.75%).

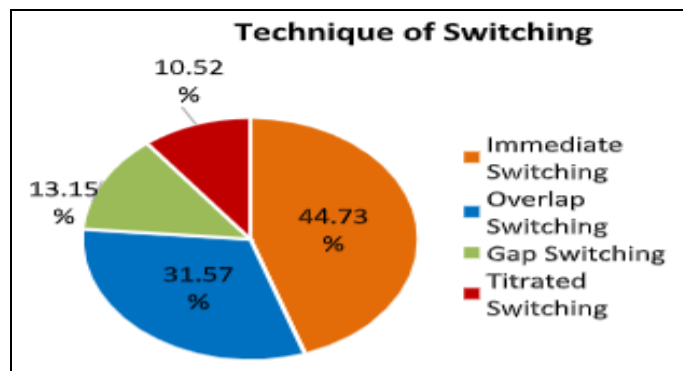
(4.69% each), followed by Venlafaxine (3.91%), Duloxetine, Paroxetine and Sertraline were prescribed in 1.56% patients. Switching over of antipsychotics was seen in 33 (25.78%) patients out of 128. In 28 patients switching was done for one time and in 5 patients switching was done twice so the total number of switches was 38.



**FIG. 3: OTHER CONCOMITANT MEDICATIONS PRESCRIBED ALONG WITH ANTIPSYCHOTICS IN STUDY POPULATION**

Most commonly prescribed mood stabilizer was divalproate sodium (32.81%), followed by lithium (15.63%), lamotrigine (6.25%) and carbamazepine (4.69%). Most commonly prescribed Antidepressants were Dotheipin, Escitalopram and Fluoxetine

For the maximum number of times, switching was done from risperidone to chlorpromazine (12.12%) and from olanzapine to risperidone (12.12%). As shown in **Fig. 4**, the most commonly used technique for switching was Immediate/Abrupt switching (44.73%), followed by Overlap switching (31.57%) and Gap switching (13.15%).



**FIG. 4: DIFFERENT TECHNIQUES USED FOR SWITCHING OVER OF ANTIPSYCHOTICS IN STUDY POPULATION**

The least common technique used for switching was titrated switching which accounts for only 10.52%. The techniques used for switching from Risperidone to Chlorpromazine were abrupt switching and overlap switching. Other commonly done switches were from Olanzapine to Risperidone and the technique used was abrupt and titrated switching.

**TABLE 3: FREQUENCY OF SWITCHING BETWEEN CLASS OF ANTIPSYCHOTICS AND INDIVIDUAL AGENT**

	Parameter	N (%)
Switching between Antipsychotic class	Atypical to Atypical	17 (44.7)
	Atypical to typical	16 (42.10)
	Typical to Atypical	03 (7.89)
	Typical to Typical	02 (5.26)
	Total	38
Drug undergoing switching	Risperidone	12 (31.57)
	Olanzapine	10 (26.31)
	Aripiprazole	06 (15.78)
	Quetiapine	04 (10.52)
	Haloperidol	02 (5.26)
	Chlorpromazine	02 (5.26)
	Fluphenazine	01 (2.63)
	Blonanserin	01 (2.63)
	Total	38

**TABLE 4: COMPARISON OF DEMOGRAPHIC VARIABLES (AGE AND GENDER) AND TYPE OF SWITCHING OVER OF ANTIPSYCHOTICS IN STUDY POPULATION**

AGE (years)	Type of Switching [N (%)]				X <sup>2</sup>	P VALUE
	Abrupt (%)	Overlap (%)	Gap (%)	Titrated (%)		
18-27	09 (23.68%)	06 (15.78%)	02 (5.26%)	02 (5.26%)	4.76	0.029
28-37	06 (15.78%)	03 (7.89%)	02 (5.26%)	00	2.22	0.136
38-47	00 (0%)	01 (2.63%)	01 (2.63%)	02 (5.26%)	3.20	0.074
48-57	01 (2.63%)	01 (2.63%)	00	00	0.75	0.387
58-67	01 (2.63%)	01 (2.63%)	00	00	0.75	0.387
Total	17 (44.73%)	12 (31.57%)	05 (13.15%)	04 (10.52%)		
Gender	Abrupt	Overlap	Gap	Titrated	X <sup>2</sup>	P Value
Male	11 (28.94)	06 (15.78%)	02 (5.26%)	02 (5.26%)	4.92	0.026
Female	06 (15.78%)	06 (15.78%)	03 (7.89%)	02 (5.26%)	2.04	0.153
Total	17 (44.73%)	12 (31.57%)	05 (13.15%)	04 (10.52%)		

(P value &lt; 0.05 = significant)

Taking into account the demographic profile of study population and techniques used for switching over the difference among various types of switching over of antipsychotics was found to be statistically significant in age group 18 – 27 years (p value = 0.029) and in male patients (p-value = 0.026). In rest of age groups and in female patients the difference was statistically insignificant as shown in **Table 4**.

**DISCUSSION:** The predominance of male patients over female patients was comparable to the studies done by Abolmagd *S et al.*, in which there were 53.8% male patients and 46.2% female patients and Nukala *S et al.*, in which 59.61% were males and 40.39% females<sup>8, 9</sup>. The mean age was 32.88 (12.91). This shows that psychotic disorders start early in life and hit the patients during the most productive years of their life. In the study population, taking into account the occupation of

patients, it was found that the maximum number of patients (39.84%) were unemployed. A study was done by Evenson *S et al.*, also showed that the employment rate for the schizophrenia population was consistently low<sup>10</sup>.

The average number of drugs prescribed per encounter was 4.56, which is higher than the studies done by Tejus A *et al.*, in Base Hospital Delhi Cantt, India, and Chawla *S et al.*, where an average of 2.35 and 2.69 drugs was prescribed per encounter, respectively<sup>11, 12</sup>. Prescribing large number of drugs increases the risk of drug interactions, patient noncompliance, and increased cost. In this study, 48.79% of drugs were prescribed by generic name. This was higher compared to a study done at Maulana Azad Medical College, New Delhi, India by Kumar *S et al.*, where only 6.22% of drugs were prescribed by generic name but is lower as compared to study

done at Burdwan by Ghosh S *et al.*, in which 92.66% drugs were prescribed by generic name<sup>13, 14</sup>. In a country like India where costly drugs pose a great burden to the economically weaker section, prescribing by generic names should be encouraged. However, it also indicates the availability of generic drugs in the hospital supply which is often very erratic.

Most of the antipsychotics were prescribed by oral route except haloperidol and lorazepam, which were given in injectable formulation to control the acute episodes. Overall, 83.59% prescriptions were with injectables, among which inj. Haloperidol and inj. Lorazepam was most commonly prescribed. Other than haloperidol and lorazepam, 8.5% injectables were prescribed, which was in accordance with a study conducted by Rode SB *et al.*, who reported use of 9% of injectable medicines but more than the study conducted by Shaifali I *et al.*, where 5.2% were administered via injectable route<sup>15, 16</sup>. In this study, 52.06% of drugs were prescribed from the WHO Essential drug list 2019, which is slightly more than the study conducted by Balaji R *et al.*, where 50% of medicines were prescribed from the essential drug list, and Patted UH *et al.*, who found only 47.33% of patients received antipsychotics which were in the essential drug list<sup>17, 18</sup>.

In this study, antipsychotics were prescribed 304 times, out of which 53.2% were atypical antipsychotics, and 46.71% were typical antipsychotics. This was in accordance with a study done by Varghese GA *et al.*, in Andhra Pradesh, India, and Malik M *et al.*, in Pakistan in which atypical antipsychotics were prescribed more than typical antipsychotics<sup>19, 20</sup>. This showed an increasing trend towards the use of atypical antipsychotics over the typical ones. Anticholinergics should be used only in selected patients who are on high potency antipsychotics like haloperidol, those who have a history of EPSEs or have developed EPSEs and showing no improvement even after switching the antipsychotic<sup>21</sup>. In this study, Trihexyphenidyl was used along with both typical and atypical antipsychotics. It was prescribed mostly in combination with risperidone containing risperidone + trihexyphenidyl. This was in accordance with the study conducted by Sushma HK *et al.*, in Karnataka, India, and Ushrani HP *et al.*, in Mysore, India, which also reported higher

usage of anticholinergic agents along with atypical antipsychotics<sup>22, 23</sup>.

Switching from one antipsychotic to another is frequently indicated due to inadequate treatment response or unacceptable adverse effects. It should be carried out cautiously and under close observation<sup>24</sup>. Risperidone was switched a maximum number of times (12 times) followed by Olanzapine (10 times) and Aripiprazole (06 times). These results are similar to the study done by Kumar S *et al.*, in which risperidone and olanzapine were maximally switched. This is probably due to the widespread use of these drugs<sup>13</sup>. Overall most commonly used technique for switching was Immediate or Abrupt switching, which was used 18 times, followed by Overlap switching (11 times). This is contrary to the study done by Kumar S *et al.*, in which Titrated switching was the most commonly used technique followed by Gap switching<sup>13</sup>. It is quite possible that the choice of switching strategy can also be affected by the cause and urgency for switching an antipsychotic<sup>25</sup>.

The major limitation of this study was the small sample size, and this was not a follow-up study, so efficacy and side effects of treatment were not properly assessed. Being this a follow-up study, there would be more scope of knowing the reason and duration of switching over antipsychotics.

**CONCLUSION:** From this study, an increasing trend of prescribing atypical antipsychotics was noted, risperidone being the most frequently prescribed drug followed by olanzapine. Many drugs were prescribed by brand name prescribed standards in prescription with generic names and prescriptions from the essential drug list have not been achieved in the study. During switching over of antipsychotics, the most commonly used technique was abrupt or immediate switching even when this technique is rarely recommended. Anticholinergic drugs were prescribed in high numbers even with atypical antipsychotics. Anticholinergics should be used judiciously and use of FDC risperidone and trihexyphenidyl should be reconsidered.

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