



## Prescription Patterns of Psychotropic Drugs and Non-Adherence in Patients with Schizophrenia

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### ABSTRACT

**Context** - Polypharmacy, rational or irrational, in psychiatry is a common phenomenon. One needs to understand various clinical and pharmaco-socio-economic factors associated to deal with it. Non adherence to treatment in schizophrenia leads to relapse, hospitalizations, increased cost of treatment and therapeutic failure. Complexity of treatment decreases adherence. It is important to understand relation between polypharmacy and adherence.

**Aims and objectives** - To find out prevalence of polypharmacy, most common causes of polypharmacy, level of medication adherence and correlation between polypharmacy and medication adherence in patients with schizophrenia

**Settings and Methodology** - A total of 277 consecutive diagnosed patients with schizophrenia were included in the study. Their latest prescriptions were studied to find out rate of polypharmacy and most common reasons for doing so. Patients were asked to answer Morisky 8-item medication adherence scale, a valid and reliable measure of self reported adherence. Obtained data was analyzed statistically.

**Statistical analysis and Results** - About 74 % of the patients received polypharmacy vs. 26 % received monotherapy. Three most common reasons for polypharmacy were to prevent adverse effects, to treat comorbidity and for augmentation. Polypharmacy did not have any association with age, sex, but polypharmacy had significant association with duration of illness.

36.5 % had low adherence, 21.7 % had high adherence while 41.9 % had medium adherence to prescribed regimen. Adherence did not show statistically significant association with age and sex but had significant association with total number drugs prescribed and duration of illness but failed to show any particular pattern.

**Conclusions** - Polypharmacy is common practice in patients with schizophrenia at our centre and most common reason for it was to prevent adverse effects of primary drug, which is a justified indication.

Adherence is a complex phenomenon, not related to factors such as age, sex but had association with duration of illness and total number of drugs prescribed. Most of our patients had medium adherence on MMAS. Polypharmacy did not have any significant effect on adherence across all age groups. Multiple complex factors influence polypharmacy and adherence in patients with schizophrenia like psycho-education, illness related factors and patient related factors. Probably rational polypharmacy is need of time.

**Keywords**- schizophrenia, polypharmacy, non-adherence, prescription pattern, psychotropic drugs

**Key message**- Rational polypharmacy is necessary in Schizophrenia to minimise non adherence and adverse effects of treatment.

## INTRODUCTION

'Polypharmacy' is simply a use of multiple medications than clinically indicated for the treatment of a patient's medical condition although there is no fixed definition. The commonly used definition of psychiatric polypharmacy is the use of two or more psychiatric medications in the same patient, or using two or more medications (of the same chemical class or same pharmacologic actions) to treat the same condition.<sup>1,2</sup>

Polypharmacy remains a controversial and alarming practice among psychiatrists and probably based more upon experience than evidence. In literature, the prevalence of polypharmacy in psychiatry varies between 13%-90%.<sup>3</sup>

Due to the increasing prevalence and complexity in psychiatric polypharmacy, it is categorized as follows by the National Association of State Mental Health Programme Directors as Same-Class Polypharmacy, Multi-class, Adjunctive or Augmentation polypharmacy, Total polypharmacy.<sup>2</sup>

Freudenreich *et al*<sup>4</sup> broadly described four etiological factors that can lead to polypharmacy:

1. Disease factors or Biological factors
2. Patient factors (Psychological factor I)
3. Physician factors (Psychological factor II)
4. The Systems (Sociological factor)

Preskorn and Lacey<sup>5</sup> suggested there are many reasons for polypharmacy; to treat two pathophysiologically distinct but co-morbid illnesses in the same patient; to prevent an adverse effect produced by the primary drug; to provide treatment for acute emergencies while awaiting the delayed effect of another medication; to treat intervening phases of an illness; and to augment the efficacy of the primary treatment.

Few reviews on the use of polypharmacy concluded that despite strong recommendation by experts to advise monotherapy wherever possible, the prevalence of antipsychotic polypharmacy has greatly increased, particularly since the advent of the Second Generation Antipsychotics (SGAs).<sup>6</sup>

There were very few studies about the prescription pattern and the issue of polypharmacy in

psychiatric patients from India. Practically, within the Indian context, polypharmacy is common. In a one year evaluation of discharge prescriptions of all patients of schizophrenia from St. Johns Medical College, Bangalore, Padmini *et al* reported polypharmacy in 9% of cases.<sup>7</sup> While another 6-monthly prescription evaluation done in schizophrenia patients a year later by Sawhney *et al* at Jammu revealed a high percentage of cases (72.72%).<sup>8</sup>

A recent cross-sectional study on a cohort from a long-term outcome study by Shrivastava *et al*<sup>9</sup> found that a large percentage of schizophrenia patients (30.1%) were taking more than one second-generation antipsychotic. Another study revealed, although polypharmacy is strongly discouraged in treatment guidelines, but is typically found in 25% of out-patients.<sup>10</sup>

In a number of situations, particularly in presence of psychiatric and physical co-morbidities, use of polypharmacy and/ or co-prescribing, results in better perceived outcomes when monotherapy provides insufficient improvement. Preskorn and Lacey described the conditions under which psychiatrists may justifiably use polypharmacy which they termed as 'rational polypharmacy'.<sup>5</sup>

Concerns with polypharmacy include possibilities of cumulative toxicity and increased incidence of adverse events<sup>10</sup>, adherence issues which emerge with increasing regimen complexity<sup>11</sup>, pharmacodynamic and pharmacokinetic interactions, lack of evidence-based strategies to guide this practice and drug costs for patients.<sup>10</sup> According to one study, polypharmacy is strongly associated with excessive dosing and risk of early death in patients. Antipsychotic polypharmacy, compared with monotherapy, is found to be independently associated with an increased risk of having premetabolic syndrome<sup>12</sup>, even after adjusting for patients' lifestyle characteristics. High-dose antipsychotic use is not supported by evidence of clinical efficacy and is linked to adverse effects, including a risk of sudden death.<sup>13</sup> Anticholinergic agents prevent neuroleptic-induced extra pyramidal side-effects (EPR), but have adverse cognitive effects, alter absorption of other oral

medications and have abuse potential.<sup>[14]</sup> Short-term use is required to prevent extra pyramidal side-effects in the vast majority of patients, but routine use is very common.

There are many guidelines recommending rational prescription for schizophrenia, including an Indian Psychiatric Society (IPS) guidelines and Maudsley prescribing guidelines; still prescribing in practical settings often differs from suggested guidelines.<sup>15</sup>

Polypharmacy often becomes a cycle of treating one condition, experiencing side effects, and treating the side effects, until the patient and the clinician cannot remember where the cycle began which ultimately may lead to consequences like the occurrence of adverse drug reactions (ADRs), increased drug costs and poor patient's quality of life. We felt it is necessary to evaluate current trend in prescribing psychotropic medications at our centre, which might help in future to predict polypharmacy practices around the country, which has very limited health resources to manage burdens caused by polypharmacy on health services and patient population and which also has an important effect on adherence of patients to prescribed medications.

Another important issue in the practice of psychiatry is non-adherence to prescribed treatment.

Non-adherence to treatment is the degree to which a patient does not carry out the clinical recommendations of a treating physician. In other words it is the failure of the patient to follow the prescribed treatment regimen.<sup>16</sup> Non-adherence is a significant problem in all patient populations, from children to the elderly. It applies to nearly all chronic disease states and settings, and tends to worsen the longer a patient continues on drug therapy. Non-adherence is now a day considered to be the major problem in the health services of both developed and developing countries. Most patients probably adhere to treatment only between 33% and 94%, with a median of approximately 50% for long-term therapy. Another set of patients will never start or will stop therapy completely within

the first year, and only a minority will continue taking drugs as prescribed.<sup>17</sup> Adherence is important because it is directly related to the prognosis of the illness and is significant in causing recurrent hospital admissions. Reasons for non-adherence are multiple in origin and to find out the different factors leading to non-adherence in our setup is the purpose of this study. There are very few studies which have evaluated the prescription pattern and the issue of polypharmacy in psychiatric patients from India and effect on adherence of patients to treatment. In view of this, an attempt has been made to study the pattern of drug combinations prescribed to patients with schizophrenia and analyze the same at a tertiary hospital setup like our hospital which caters to around 140-160 daily outpatients seeking advice about mental health.

## MATERIALS AND METHODS

### AIMS AND OBJECTIVES

1. To find out prevalence of polypharmacy in patients with schizophrenia
2. To find out most common causes of prescription of multiple medications to patients with schizophrenia
3. To find out level of medication adherence in patients with schizophrenia
4. To find out correlation between polypharmacy and medication adherence

### INCLUSION CRITERIA

- Subjects aged between 18-65.
- All subjects diagnosed of Schizophrenia by using the ICD-10 diagnostic criteria following up in the aforesaid OPD.
- Patients who were willing to participate and give consent.

### EXCLUSION CRITERIA

- Patients with psychiatric diagnosis other than schizophrenia.
- Patients with a diagnosed cognitive disorder.
- Patients not willing to give consent.

Approval for the protocol and the study was sought from the Institutional Ethics Committee prior to implementation. It was a cross-sectional study. All consecutive participants chosen as per the inclusion and exclusion criteria were interviewed by an interviewer and were asked to answer patient questionnaire in a single setting. Patients giving consent and willing to fill patient questionnaire were included in the study. The data was collected in the form of a semi-structured interview record from the most recent prescription of the patient and checklist regarding reason for starting a medication/s was filled in by consultant starting the medication and patients were asked to fill in the patient questionnaire about non adherence. Data was collected and subjected to statistical analysis and results were obtained. Total 277 patients with schizophrenia diagnosed as per the ICD-10 diagnostic criteria for schizophrenia were interviewed in about 3 months duration.

## INSTRUMENTS

- A semi-structured record form to record socio-demographic profile of the subjects and to assess and evaluate polypharmacy or combination of drugs which also has a checklist to be filled by a consultant regarding reasons for prescribing medications
- A special scale for measuring self reported adherence in patients – ‘Morisky 8-item medication adherence scale’<sup>[17]</sup> which is an eight-item medication adherence scale which is reliable ( $\alpha = 0.83$ ) and with a sensitivity of the measure for identifying low versus higher adherers estimated at 93%, with specificity of 53%. It takes around 5-10 minutes to answer 8 questions about adherence.<sup>18, 19, 20, 21</sup>

## STATISTICAL ANALYSIS

Data was collected and entered in MS Excel document and was subjected to Statistical analysis using the Statistical Package for the Social Science version 20 (SPSS Inc., Chicago, IL, USA). The descriptive analysis was done for

demographic variables. Pearson Correlation was used to find out correlation between different variables.

## RESULTS

**Table No.1** : Sex Distribution among the patients with Schizophrenia

Sex	No.	Percentage
Female	122	44.0%
Male	155	56.0%
Total	277	100.0%

**Table No.2** Age (years) Distribution among the patients with Schizophrenia

Age (years)	No.	Percentage
18 to 27	44	15.9%
28 to 37	63	22.7%
38 to 47	93	33.6%
48 to 57	53	19.1%
58 & >	24	8.7%
Total	277	100.0%

**Table No.3** : Distribution among the patients with schizophrenia – Duration of illness (in years)

Duration of illness (years)	No.	Percentage
< 1	12	4.3%
1 to 5	127	45.8%
6 to 10	53	19.1%
11 to 15	36	13.0%
16 to 20	13	4.7%
21 to 25	24	8.7%
>= 26	12	4.3%
Total	277	100.0%

Total of 277 patients with schizophrenia were included in the study. The study population included 155 males (56 %) and 122 females (44 %). The mean age of patients included in the study was 40.41 years with standard deviation of 11.63. The duration of illness in study sample was ranging from <1 year to >26 years, with maximum number (45.8 %) of patients having duration from 1-5 years.

The following parameters were assessed in the study

## 1. PRESCRIPTION PATTERNS IN PATIENTS WITH SCHIZOPHRENIA

**Table No.4 :** Distribution among the patients with schizophrenia – Prescription pattern of Anti-psychotics

Anti-psychotics	No.	Percentage
Yes	213	76.9%
No	64	23.1%
Total	277	100.0%

Out of 277 patients assessed, 213 patients (76.9 %) with Schizophrenia were on Anti-psychotic drugs, 64 (23.1 %) of them were not prescribed Anti-psychotics. Various Anti-psychotic drugs like First generation Anti-psychotics (Typical) e.g. Haloperidol, Trifluoperazine, Chlorpromazine, Fluphenazine depot etc. and Second generation Anti-psychotics (SGA) like Olanzapine, Risperidone, Clozapine etc. were prescribed.

**Table No.5 :** Distribution among the patients with schizophrenia- Number of Anti-psychotic agents

Anti-psychotics	No.	Percentage
1	155	72.8%
2	55	25.8%
3	3	1.4%
Total	213	100.0%

Out of 213 patients who were prescribed Anti-psychotics, 155 were on single anti-psychotic drug, 55 were receiving 2 anti-psychotics simultaneously, while 3 patients were prescribed 3 anti-psychotic agents simultaneously.

**Table No.6 :** Distribution among the patients with schizophrenia – Prescription pattern of Anti-depressants

Anti-depressants	No.	Percentage
Yes	30	10.8%
No	247	89.2%
Total	277	100.0%

**Table No.7 :** Distribution among the patients with schizophrenia – Prescription pattern of number of Anti-depressant agents

Anti-depressants	No.	Percentage
1	29	96.7%
2	1	3.3%
Total	30	100.0%

Total 30 patients were on Anti-depressant medications which formed 10.8 % of study population and among them, 29 patients were receiving single anti-depressant agent and one patient received 2 anti-depressant agents. Drugs like Imipramine, Amitryptiline, Escitalopram etc. were used.

**Table No.8 :** Distribution among the patients with schizophrenia – Prescription pattern of Mood stabilizers

Mood stabilizers	No.	Percentage
Yes	24	8.7%
No	253	91.3%
Total	277	100.0%

**Table No.9 :** Distribution among the patients with schizophrenia – Prescription pattern of number of Mood stabilizer agents

Mood stabilizers	No.	Percentage
1	22	91.7%
2	2	8.3%
Total	24	100.0%

In total, 24 patients with schizophrenia had Mood stabilizers on their prescriptions which constituted 8.7 % of total study population, 22 of them had one mood stabilizer and 2 patients had two mood stabilizers on their prescriptions. Carbamazepine, Valproate were most commonly used mood stabilizers.

**Table No.10 :** Distribution among the patients with schizophrenia – Prescription pattern of Tranquilizers/hypnotics

Tranquilizers/hypnotics	No.	Percentage
Yes	104	37.5%
No	173	62.5%
Total	277	100.0%

Tranquilizers/hypnotics like Benzodiazepines, hypnotics were prescribed to 104 patients out of 277 (37.5 %), only one among them had 2 Tranquilizers/hypnotics on his prescription but rest 103 were receiving only one agent.

**Table No. 11:** Distribution among the patients with schizophrenia – Prescription pattern of Anti-cholinergics

Anti-cholinergics	No.	Percentage
Yes	209	75.5%
No	68	24.5%
Total	277	100.0%

Anti-cholinergic drugs were second most commonly prescribed agents for patients with schizophrenia after Anti-psychotics. Total 209 patients (75.5 %) were prescribed anti-cholinergic agents, all of them had only one anti-cholinergic agent on their prescription. Trihexyphenidil was the commonest anti-cholinergic drug prescribed.

**Table No. 12 :** Distribution among the patients with schizophrenia – Prescription pattern of Other drugs

Other drugs	No.	Percentage
Yes	50	18.1%
No	227	81.9%
Total	277	100.0%

**Table No.14:** Association among the patients with schizophrenia – Duration of illness (years) \* Total number of psychotropic drugs prescribed

Duration of illness (years)		Total number of psychotropic drugs prescribed						Total
		1	2	3	4	5	6	
< 1	No.	3	1	4	2	2	0	12
	%	25.0%	8.3%	33.3%	16.7%	16.7%	0.0%	100.0%
1 to 5	No.	55	38	20	14	0	0	127
	%	43.3%	29.9%	15.7%	11.0%	0.0%	0.0%	100.0%
6 to 10	No.	5	21	17	7	3	0	53
	%	9.4%	39.6%	32.1%	13.2%	5.7%	0.0%	100.0%
11 to 15	No.	3	10	12	3	8	0	36
	%	8.3%	27.8%	33.3%	8.3%	22.2%	0.0%	100.0%
16 to 20	No.	1	2	5	3	2	0	13
	%	7.7%	15.4%	38.5%	23.1%	15.4%	0.0%	100.0%
21 to 25	No.	4	3	8	4	3	2	24
	%	16.7%	12.5%	33.3%	16.7%	12.5%	8.3%	100.0%
≥ 26	No.	1	3	5	2	0	1	12
	%	8.3%	25.0%	41.7%	16.7%	0.0%	8.3%	100.0%
Total	No.	72	78	71	35	18	3	277
	%	26.0%	28.2%	25.6%	12.6%	6.5%	1.1%	100.0%

When duration of illness (years) was compared with total number of psychotropic drugs prescribed association between two was found to be statistically significant (Pearson Chi – Square, p value = < 0.05)

‘Other drugs’ category included medications like anti-histaminics, anti-epileptics other than those used as mood stabilizers and other miscellaneous agents. 50 patients (18.1 %) from study population were prescribed drugs from ‘Other drugs’ category.

**Table No.13:** Distribution among the patients with schizophrenia – Total number of psychotropic drugs prescribed

Total number of psychotropic drugs prescribed	No.	Percentage
1	72	26.0%
2	78	28.2%
3	71	25.6%
4	35	12.6%
5	18	6.5%
6	3	1.1%
Total	277	100.0%

Looking at the complete prescriptions of patients with schizophrenia, in a sample size of 277 patients, patients were receiving total number of drugs ranging from 1 to 6. Number of patients who were on monotherapy was 72 (26.0 %), whereas rest 205 patients (74 %) were receiving polypharmacy. Mean of total number of psychotropic drugs prescribed was 2.49 with standard deviation of 1.24.

## 2. REASONS FOR POLYPHARMACY

**Table No.15:** Distribution among the patients with schizophrenia – Most common reasons for polypharmacy

Most common reasons for polypharmacy	No.	Percentage
To prevent adverse effect of primary drug	121	43.7%
To treat co-morbidity	78	28.2%
Augmentation of primary drug	29	10.5%
To treat intervening phase of illness	15	5.4%
Cross titration of drugs	8	2.9%
To treat acute phase of illness	2	0.7%
No reason	24	8.7%
Total	277	100.0%

We studied prescriptions of patients with schizophrenia to find out commonest reasons for polypharmacy. Data was collected in the form of reasons to start a new medication as decided by a consultant. Data is represented as 3 most common reasons for polypharmacy.

The most common reason for starting multiple medications was to prevent adverse effect of primary drug, where 43.7 % patients were receiving drugs like Anti-cholinergics to prevent adverse effects of Anti-Psychotics. Second most common reason for polypharmacy was to treat co-morbid psychiatric illness. 28.2 % of total study population were prescribed additional medications like Anti-depressants, Mood stabilizers and Tranquilizers/hypnotics to manage co-morbid conditions like mood features, behavioural disturbances and sleep disturbances. Augmentation of primary drug with another drug from same category was reason for polypharmacy in 10.5 % of total study population. Few patients had first generation ‘typical’ antipsychotics as primary drugs with a second generation (SGA) antipsychotic agent for augmentation purpose. 5.4 % patients from study population were receiving polypharmacy to treat intervening phase of illness. Many of them had Injectable depot antipsychotic preparation like Fluphenazine to treat intervening phase and to prevent relapse. Cross titration of drugs to change primary agent for treatment was

reason for polypharmacy in 2.9 % of cases. Very few patients (0.7 %) who were being treated for acute phase of illness were prescribed polypharmacy. Almost 8.7 % patients were prescribed polypharmacy for which no reason could be determined.

## 3. LEVEL OF ADHERENCE IN PATIENTS WITH SCHIZOPHRENIA

**Table No.16:** Distribution among the patients with schizophrenia – Level of adherence

Adherence level	No.	Percentage
Low	101	36.5%
Medium	116	41.9%
High	60	21.7%
Total	277	100.0%

Determining level of adherence in patients with schizophrenia to prescribed treatment whether it is monotherapy or polypharmacy was an important objective of the study. We used Morisky 8-item medication adherence (MMAS) scale devised by Morisky *et al* to determine adherence to treatment as reported by patients. A first step in understanding adherence, or lack thereof, would be assessing or measuring adherence. In outpatient clinical settings, 8-item MMAS is a valid, reliable, cost-effective tool that is accepted by both health care providers and patients for measuring medication adherence. Its use could provide insight into modifiable factors regarding adherence in patient populations like patients with schizophrenia, would lead to better understanding of non-adherence and lay the groundwork for interventions aimed at increasing adherence to advised treatment.

The MMAS scale helps in deciding level of adherence to treatment regimen as low, medium and high based on total scores as reported by patients. In our study, out of 277 patients with schizophrenia, 101 (36.5 %) had low adherence to treatment regimen. 21.7 % of them had high adherence while highest number 116 (41.9 %) had medium adherence to treatment.

**Table No.17 :** Association among the patients with schizophrenia between – Total number of psychotropic drugs prescribed \* Adherence level

Total number of psychotropic drugs prescribed		Adherence level			Total
		Low	Medium	High	
1	No.	26	35	11	72
	%	36.1%	48.6%	15.3%	100.0%
2	No.	28	25	25	78
	%	35.9%	32.1%	32.1%	100.0%
3	No.	28	34	9	71
	%	39.4%	47.9%	12.7%	100.0%
4	No.	10	18	7	35
	%	28.6%	51.4%	20.0%	100.0%
5 ^	No.	8	4	6	18
	%	44.4%	22.2%	33.3%	100.0%
6 ^	No.	1	0	2	3
	%	33.3%	0.0%	66.7%	100.0%
Total	No.	101	116	60	277
	%	36.5%	41.9%	21.7%	100.0%

Association between total number of drugs prescribed and level of adherence in different groups was found to be statistically significant (p value = 0.020) on application of chi square test for variables although no specific pattern was found. Among patients who were on monotherapy maximum (48.6 %) had medium adherence. Only

15.3 % of them had high adherence while 36.1 % had low level of adherence. Patients who were prescribed higher (5) number of drugs showed high adherence in 33.3% while 44.4 % of them showed low adherence. 22.2 % patients with 5 psychotropic drugs had medium adherence to treatment regime.

**Table No.18 :** Association among the patients with schizophrenia between – Age (years) \* Adherence level

Age (years)		Adherence level			Total
		Low	Medium	High	
18 to 27	No.	18	15	11	44
	%	40.9%	34.1%	25.0%	100.0%
28 to 37	No.	33	18	12	63
	%	52.4%	28.6%	19.0%	100.0%
38 to 47	No.	25	50	18	93
	%	26.9%	53.8%	19.4%	100.0%
48 to 57	No.	18	22	13	53
	%	34.0%	41.5%	24.5%	100.0%
58 & >	No.	7	11	6	24
	%	29.2%	45.8%	25.0%	100.0%
Total	No.	101	116	60	277
	%	36.5%	41.9%	21.7%	100.0%

Association between age (years) and adherence levels did not show any particular trend in chi-square analysis, statistically this association was found to be insignificant (p value = 0.061).

**Table No.19:** Association among the patients with schizophrenia between – Sex \* Adherence level

Sex		Adherence level			Total
		Low	Medium	High	
Female	No.	47	51	24	122
	%	38.5%	41.8%	19.7%	100.0%
Male	No.	54	65	36	155
	%	34.8%	41.9%	23.2%	100.0%
Total	No.	101	116	60	277
	%	36.5%	41.9%	21.7%	100.0%

Association between sex and adherence levels did not show any particular trend in chi-square analysis, statistically this association was found to be insignificant (p value = 0.772).

**Table No. 20:** Association among the patients with schizophrenia between – Duration of illness (years) \* Adherence level

Duration of illness (years)		Adherence level			Total
		Low	Medium	High	
<= 5	No.	53	51	35	139
	%	38.1%	36.7%	25.2%	100.0%
6 to 10	No.	20	27	6	53
	%	37.7%	50.9%	11.3%	100.0%
11 to 15	No.	6	19	11	36
	%	16.7%	52.8%	30.6%	100.0%
16 to 20	No.	4	8	1	13
	%	30.8%	61.5%	7.7%	100.0%
21 & >	No.	18	11	7	36
	%	50.0%	30.6%	19.4%	100.0%
Total	No.	101	116	60	277
	%	36.5%	41.9%	21.7%	100.0%

Duration of illness had significant association with adherence to drugs. Patients with lesser duration of illness have medium to high adherence to drugs whereas patients with very long duration of illness have low adherence to treatment regime. Statistical association between these two parameters was found to be significant (Pearson Chi – Square, p value = 0.029).

## DISCUSSION

### 1. PRESCRIPTION PATTERNS IN PATIENTS WITH SCHIZOPHRENIA

Our aim was to find out prevalence of polypharmacy in patients with schizophrenia at our centre, to find out most common reasons for polypharmacy, level of adherence to medications

and to find out correlation of polypharmacy to adherence. We interviewed 277 patients in about 3 months, studied their latest prescriptions and asked them to fill up Morisky 8-item medication adherence scale, a self reported adherence scale. Data was collected and was analyzed statistically. In our study, 26.0 % patients were receiving monotherapy, whereas 74 % were receiving polypharmacy. Mean of total number of psychotropic drugs prescribed was 2.49 with standard deviation of 1.24. Similar observation has been found by other centres in India.<sup>8, 22</sup>

A French study on prescription patterns across France found, polypharmacy was more prevalent among patients with schizophrenia (39%).<sup>23</sup>

76.9 % with Schizophrenia were on Anti-psychotic drugs. Various Anti-psychotic drugs like First generation Anti-psychotics (Typical) e.g. Haloperidol and Second generation Anti-psychotics (SGA) like Olanzapine etc. were prescribed. Only particular drugs like Haloperidol, Olanzapine and Risperidone were prescribed to majority of patients as they are available as free from hospital pharmacy.

Anti-cholinergic drugs were second most commonly prescribed agents (75.5 %) for patients with schizophrenia after Anti-psychotics. Tranquilizers/hypnotics like Benzodiazepines, hypnotics were prescribed to 37.5 % patients. Anti-depressant medications were given to 10.8 % of study population. Drugs like Imipramine, Amitryptiline, Escitalopram which are available in hospital were used mostly. While 8.7 % of total study population received Mood stabilizers; Carbamazepine, Valproate were most commonly used mood stabilizers.

'Other drugs' were found in 18.1 % patients, included medications like anti-histaminics, anti-epileptics other than those used as mood stabilizers and other miscellaneous agents.

In analysis made by P. Sarcar *et al*; anticholinergics and tranquilizers/hypnotics were more commonly used in combination with other psychotropics, similar to our observation.<sup>22</sup>

In our study, no clear association was seen between gender, age and polypharmacy, as reported in other studies.<sup>24</sup>

The findings reflect a statistically significant association between duration of illness and total number of drugs prescribed ( $p = < 0.05$ ). Probably this suggests as the duration of illness of increases, total number of drugs prescribed also increases; as patients with chronic schizophrenia might have frequent relapses, resistance to treatment, other co-morbid psychiatric illnesses like mood disorders, anxiety disorders and substance use over the course of illness. Cognitive impairment, personality changes which could lead to adding newer drugs for other purposes and increase in polypharmacy practices. Similar to this, polypharmacy was associated with duration

of treatment which could correspond to an increase in the number of drugs on prescription over time.<sup>22</sup>

Regardless of the diagnoses associated with antipsychotic prescription, combination with other psychotropic drugs was more frequent for people over 45 years of age. This is consistent with the increased use of psychotropics observed in older subjects.<sup>23</sup>

Preskorn and Lacey described the conditions where rational polypharmacy can be used, while Pandurangi and Dalkilic emphasized, all polypharmacy and changes of antipsychotics need not always irrational.<sup>5,6</sup>

## 2. REASONS FOR POLYPHARMACY

We found, the most common reason for polypharmacy was to prevent adverse effect of primary drug in 43.7 % patients. Anti-cholinergic drugs were the second most commonly prescribed drugs to prevent adverse effects of primary drugs. As polypharmacy exposes patients to more side effects and more drugs are prescribed to counter adverse effects resulting in polypharmacy. Similar observation was made by Karadag H. *et al*, where the rate of using additional drugs for side effects was 44.7% in the polypharmacy group while it was 34.6% in the monotherapy group.<sup>25</sup>

Second most common reason for polypharmacy was to treat co-morbid psychiatric illness. 28.2 % of total study population were prescribed additional medications like Anti-depressants, Mood stabilizers and Tranquilizers/hypnotics to manage co-morbid conditions like mood features, behavioural disturbances and sleep disturbances. Augmentation of primary drug with another drug from same category was reason for polypharmacy in 10.5 % of total study population. Few patients had first generation 'typical' antipsychotics as primary drugs with a second generation (SGA) antipsychotic agent for augmentation purpose, which again is against standard treatment guidelines. Other reasons for polypharmacy were to treat intervening phase of illness (5.4 %), cross titration of drugs to change primary agent (2.9 %) and very few patients (0.7 %) were being treated

for acute phase of illness. Almost 8.7 % patients were prescribed polypharmacy for which no reason could be determined. Thus three most common reasons for polypharmacy in our study were to prevent adverse effects of primary drug, to treat co-morbidity and for augmentation.

In a study done in East India, though the reasons remained the same, the frequency was as follows; augmentation (43.8%) of primary drug followed by its use to prevent adverse effects of primary drug (39.6%) and to treat co-morbidity (34.9%).<sup>22</sup>

### 3. LEVEL OF ADHERENCE IN PATIENTS WITH SCHIZOPHRENIA

Determining level of adherence in patients with schizophrenia and its association to polypharmacy was an important objective of the study. We used Morisky 8-item medication adherence (MMAS) scale devised by Morisky *et al* to determine adherence to treatment as reported by patients. A first step in understanding adherence, or lack thereof, would be assessing or measuring adherence. In outpatient clinical settings, 8-item MMAS is a valid, reliable, cost-effective tool that is accepted by both clinicians and patients for measuring medication adherence.

In our study, out of 277 patients with schizophrenia, 101 (36.5 %) had low adherence to treatment regimen. 21.7 % of them had high adherence while highest number 116 (41.9 %) had medium adherence to treatment. Similar observation was made by Razali SM *et al*; where the rate of non-compliance with medication was as low as 25.8%.<sup>26</sup>

Contrary to our finding, a study done at Chennai hospital suggests 21.50 % patients are adherent and rest were non adherent with use of DAI as self reported measure.<sup>27</sup>

With respect to factors affecting adherence, we found that association age and sex have no significant impact on adherence levels, but duration of illness had significant association ( $p = 0.029$ ) with adherence level. Patients with lesser duration of illness have medium to high adherence to drugs whereas patients with very long duration of illness have low adherence to treatment regime.

Association between total number of drugs prescribed and level of adherence in different groups was found to be statistically significant ( $p = 0.020$ ). Probably that suggests, total number of drugs prescribed has predictive value on adherence. It is said that, number of medications taken can negatively affect compliance and the more medications taken, the worse is the compliance.<sup>28, 29</sup>

We observed that even among patients who were on monotherapy, only 15.3 % of them had high adherence while 36.1 % had low level of adherence. Patients who were prescribed higher number of drugs showed high adherence in 33.3%, but at the same time, 44.4% patients had low adherence.

On applying one way ANOVA for specific drug categories vs. adherence levels, we found 'Other drugs' had significant association to adherence level and adherence to these drugs decreases in polypharmacy but not major classes like antipsychotics. Probably for patients 'Other drugs' have minimum impact on their primary illness. Similar observation made in another chronic medical illness like Diabetes also found polypharmacy alone does not lead to reduced medication adherence. Rather, patients with suboptimal adherence tend to have problems with one specific medicine either because of unreported side effects or because the patient feels that medicine is not of value to current or future health.<sup>30</sup>

Other probable reasons for high adherence to polypharmacy could be involving family members and patients alike to ensure adherence to medications.<sup>32</sup> Psycho-educational group counselling sessions like Schizophrenia group, which are conducted to educate family members about nature of illness and treatment. Most of the drugs are provided for free from hospital pharmacy which also probably contributes to maintenance of adherence to treatment, a factor which we did not study.<sup>32</sup>

## CONCLUSIONS

1. Polypharmacy is a common practice in patients with schizophrenia at our centre despite the research based standard treatment guidelines like Maudsley, IPS guidelines suggest otherwise.
2. The goal should not be to simply avoid polypharmacy, but to practice rational instead of indiscriminate, irrational polypharmacy e.g. Amisulpiride augmentation of clozapine is beneficial clinically.<sup>33</sup>
3. The most important reason for polypharmacy was to prevent adverse effects of primary drug and to treat comorbidity and augmentation of primary treatment for non response were another significant reasons for polypharmacy
4. Adherence is a complex phenomenon, which did not show any particular relationship to factors such as age, sex but has significant association to duration of illness and total number of drugs prescribed. Still, most of our patients were found to have medium adherence on MMAS.
5. At our centre, polypharmacy did not have any significant impact on adherence, probably due to efforts taken to minimize non-adherence in patients like involvement of family members, psycho-educational groups and providing free medicines. Although multiple complex factors influence polypharmacy and adherence in patients with schizophrenia.

## CLINICAL IMPLICATIONS

- 1) Recent increase in polypharmacy practices exposes patients to multiple adverse effects, drug-drug interactions and increase in cost of the treatment
- 2) Polypharmacy may be necessary and rational, particularly when there is nonresponse, to prevent adverse effects, or to treat comorbidities requiring more than one class of medication, when monotherapy provides insufficient

improvement and while making a gradual change from one drug to another.

- 3) Polypharmacy increases complexity of treatment regimen and it may reduce adherence but with appropriate psychoeducation and other psychosocial interventions, antipsychotic long acting injections, financial incentives like providing generic drugs for free, shared decision-making, regular assessment of adherence, simplification of the medication regimen, ensuring that treatment is effective and that side effects are managed and better communication will help in reducing non adherence to treatment.

## LIMITATIONS

- 1) Data used in study is only from tertiary care centre in Mumbai, results may not be applicable in all settings.
- 2) It is a cross-sectional study with a small sample size and the sample consisted of a heterogeneous group of patients with regard to chronicity and duration of illness.
- 3) As polypharmacy and adherence are complex phenomenon, several other confounding factors like illness factors such as history, severity, cognition, insight, other psychiatric co-morbidities; patient factors like education, financial support, family support, co-morbid medical illness were not taken into consideration.

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## REFERENCES

1. Kingsbury SJ, Yi D, Simpson GM. Psychopharmacology: rational and irrational polypharmacy. *Psychiatry Serv.* 2001; 52:1033–6.
2. Medical Directors Council and State Medicaid Directors. Alexandria, Virginia: 2001. National Association of State Mental Health Program Directors: Technical Report on Psychiatric Polypharmacy.
3. Kukreja S, Kalra G, Shah N, Shrivastava A. Polypharmacy In Psychiatry: A Review. *Mens Sana Monogr* 2013; 11: 82-99.
4. Freudenreich O, Kontos N, Querques J. Psychiatric polypharmacy: A clinical approach based on etiology and differential diagnosis. *Harv Rev Psychiatry.* 2012; 20:79–85.
5. Preskorn SH, Lacey RL. Polypharmacy: When is it rational? *J Psychiatr Pract.* 2007; 13:97–105.
6. Pandurangi AK, Dalkilic A. Polypharmacy with second-generation antipsychotics: A review of evidence. *J Psychiatr Pract.* 2008;14 :345–67.
7. Padmini DD, Amarjeeth R, Sushma M, Guido S. Prescription patterns of psychotropic drugs in hospitalized schizophrenic patients in a tertiary care hospital. *Calicut Med J.* 2007; 5:e3.
8. Sawhney V, Chopra V, Kapoor B, Thappa JR, Tandon VR. Prescription trends in schizophrenia and manic depressive psychosis. *J K Sci.* 2005; 7:156–8.
9. Shrivastava A, Johnston M, Terpstra K, Stitt L, Shah N. Atypical antipsychotics usage in long-term follow-up of first episode schizophrenia. *Indian J Psychiatry.* 2012; 54: 248–52.
10. Stahl S. *Essential Psychopharmacology. Neuroscientific Basis and Practical Applications.* 2nd Ed. New York: Cambridge University Press; 2000.
11. Murray MD, Kroenke K. Polypharmacy and medication adherence: small steps on a long road. *J Gen Intern Med.* 2001; 16: 137–9.
12. Misawa F, Shimizu K, Fujii Y, Miyata R, Koshiishi F, Kobayashi M, et al. Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects: A cross-sectional study *BMC Psychiatry.* 2011; 11:118.
13. Mackay AV. High-dose antipsychotic medication. *Adv Psychiatr Treat* 1994; 1:16-23.
14. Marken PA, Stoner SC, Bunker MT. Anticholinergic drug abuse and misuse. *CNS Drugs* 1996; 5:190-9.
15. Indian Psychiatric Society. Clinical practice guidelines for Psychiatrists in India, 2004.
16. Kaplan HI, Sadock BJ. *Synopsis of psychiatry.* 8th ed. New Delhi: BI Waverly 1998.
17. Morris LS, Schulz RM. Patient compliance - an overview. *J Clin Pharm Ther* 1992;17:283-95.
18. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self reported measure of medication adherence. *Med Care.* 1986; 24:67–74.
19. Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive Validity of a Medication Adherence Measure for Hypertension Control. *Journal of Clinical Hypertension* 2008; 10(5):348-354
20. Krousel-Wood MA, Islam T, Webber LS, Re RS, Morisky DE, Muntner P. New Medication Adherence Scale Versus Pharmacy Fill Rates in Seniors With Hypertension. *Am J Manag Care* 2009; 15 (1):59-66.
21. Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. *J Clin Epidemio* 2011; 64:258-263. PMID:21144706
22. Sarkar P, Chakraborty K, Misra A, Shukla R, Swain SP. Pattern of psychotropic

- prescription in a tertiary care center: A critical analysis. *Indian J Pharmacol* 2013;45:270-3
23. Fourrier, A., Gasquet, I., Allicar, M. P., Bouhassira, M., Lépine, J. P. and Bégaud, B. (2000), Patterns of neuroleptic drug prescription: a national cross-sectional survey of a random sample of French psychiatrists. *British Journal of Clinical Pharmacology*, 49: 80–86.
24. Nolan L, O'Malley K. Prescribing for the elderly: Part II. Prescribing patterns: Differences due to age. *J Am Geriatr Soc*. 1988;36:245–54.
25. Karadag H, Orsel S, Akkoyunlu S, Kahilogullari AK, Guriz O, Turcpar H, et al. Comparison of polypharmacy in schizophrenia and other psychotic disorders in outpatient and inpatient treatment periods: a naturalistic one year follow-up study. *Klinik Psikofarmakoloji Bulteni - Bulletin of Clinical Psychopharmacology* 2012; 22(2):130-8.
26. Razali SM, Yusoff MZ. Medication adherence in schizophrenia: a comparison between outpatients and relapse cases. *East Asian Arch Psychiatry*. 2014 Jun;24(2):68-74.
27. Kousalya K, Vasantha J, Ponnudurai R, Sumitkumar G, Ramalakshmi S, Saranya P, et al. Study on non-adherence and the effect of counseling in the pharmacological management of psychiatric patients. *Int J Pharm Bio Sci* 2012;3:102-9
28. Buchanan A: A two-year prospective study of treatment compliance in patients with schizophrenia. *Psychological Medicine* 22:787-797, 1992
29. Meichenbaum D and Turk D C (1987): *Facilitating treatment adherence: A practitioner's guidebook*. New York: Plenum Press
30. Hulka BS, Cassel JC, Kupper LL, Burdette JA. Communication, compliance, and concordance between physicians and patients with prescribed medications. *Am J Public Health*. Sep; 1976, 66(9):847–853.
31. Xia J, Merinder LB, Belgamwar MR. Psychoeducation for schizophrenia. *Cochrane Database Syst Rev*. 2011;6:CD002831.
32. Eaddy MT, Cook CL, O'Day K, Burch SP, Cantrell CR. How patient cost-sharing trends affect adherence and outcomes: A literature review. *P T*. 2012;37(1):45–55.
33. Shiloh R, Zemishlany Z, Aizenberg D, Radwan M, Schwartz B, Dorfman-Etrog P, et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double-blind, placebo-controlled study. *Br J Psychiatry*. 1997;171:569–73.