



## **A Study on Drug Dose Analysis of Antipsychotics in Hospitalized Schizophrenia Patients**

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### **ABSTRACT**

The study was carried out to identify the high dose antipsychotic drug prescriptions in hospitalized schizophrenic patients. Antipsychotic drug dosing data of 200 patients were investigated during the study. The three methods applied were Chlorpromazine equivalents (CPZeq), percentages of the British National Formulary (BNF) maximum and Defined Daily Doses (DDD). Of the 200 patients who had been prescribed antipsychotics during the study period, 13.5% (n=27) were identified as receiving either more than 100% of the BNF maximum or more than 1000mg CPZeq/day. Eight of these patients taking high doses were identified by both methods; seventeen were identified by the percentage BNF maximum method only and another two by the CPZeq method only. Average dose of antipsychotics according to CPZeq were found to be 472.85 mg. Average doses of antipsychotics according to the BNF were found to be 61.39%. Depicting total antipsychotic dose by this way helps to ensure patients at the risk of antipsychotic toxicity. Regular monitoring of patients is essential especially those are prescribed with combination of antipsychotics and high dose of antipsychotics to avoid dangerous side effects.

**Keywords:** schizophrenia, antipsychotics, High dose.

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## INTRODUCTION

Antipsychotic drugs with high doses have been advocated in treating acute schizophrenia. On the other hand, there is a burden of increased adverse effects and concern has been rising that such dosage is associated with an increased risk of mortality<sup>1</sup>. As the evidence for better efficacy on high dosing is scanty, high doses should not be used until the patients who have failed to respond to conventional doses. Even then, careful dose escalation is required with ample time being given for equilibration after every increase in dose<sup>2</sup>. Calculation of the antipsychotics dose has been a matter for debate. The three methods that were applied to calculate the antipsychotic dose are chlorpromazine equivalents (CPZeq), percentage of British National Formulary (BNF) maximum and Defined Daily Dose (DDD)<sup>3</sup>. The high dose antipsychotics efficacy is also not supported by controlled studies<sup>4</sup>. But the high dose prescribing practice has continued despite the lack of credible evidence to support its effectiveness<sup>5</sup>. So far there is no compromise on what constitutes high dose prescribing. However, a chlorpromazine equivalent in excess of 1000mg/day is considered as high dose prescribing. Additionally, doses exceeding the maximum daily dose as stated in the BNF or a combination of percentages of maximum daily dose exceeding 100%, if a patient is prescribed more than one antipsychotic are considered as high dose<sup>6</sup>. At this background the aim of this study was to identify the prevalence of high dose antipsychotic prescribing among in-patients at a psychiatric unit of a teaching hospital.

## MATERIALS AND METHOD

The prospective observational study was conducted in a psychiatric unit of a 1200-bedded tertiary care teaching hospital located in Dakshina Kannada district. 200 in-patients aged between 18-60 years diagnosed with schizophrenia during August 2011 to March 2014 were enrolled after getting approval from Institutional Ethics Committee. The patient's case records were reviewed daily. Information's regarding, antipsychotic drug therapy, dosages and duration of therapy were documented in the suitably designed data collection form. The collected data were analyzed using SPSS software version 16.0.

### **Tested variables**

#### **Chlorpromazine dose equivalents (CPZeq)**

The CPZeq is a measure of the relative antipsychotic potencies of neuroleptics. They are commonly expressed in ratio, which corresponds to the antipsychotic effects of chlorpromazine. The dose of antipsychotic drug prescribed daily to each patient was converted into milligram equivalents of chlorpromazine as per the conversion factors derived from the literature<sup>7,8</sup>. Total

CPZeq was made by calculating a total daily dose of each antipsychotic listed in the case record. Then each converted antipsychotic-specific CPZeq amount is summed up to achieve the total dose. Early studies and audits of antipsychotic prescribing applied CPZeq to evaluate total antipsychotic dose<sup>9,10,11</sup> and high doses were defined as those in excess of 1000mg CPZeq/day.

### Percentage of BNF maximum

To find out the total daily prescribed antipsychotic dose as a percentage of the maximum BNF dose, we identified the percentage of BNF maximum dosage for each antipsychotic drug, and then we summed the percentages<sup>12</sup>. For single antipsychotic drug prescriptions, total daily dose exceeding the recommended BNF upper limit / the manufacturers Summary of Product Characteristic (SPC) was applied. When the percentage of the antipsychotic drugs respective BNF maximum dose exceeds 100%, the patient is considered to be receiving a “high-dose”.

### Defined Daily Dose (DDD)

The DDD is a unit of measurement defined as the assumed average maintenance daily dose for a drug, used for its chief indication in adults<sup>13</sup>. For DDDs, no description of high dose is available in the literature and therefore dealt as a continuous variable.

## RESULTS AND DISCUSSION

A total of 15 different antipsychotic drugs were prescribed during the study period. Olanzapine was the most commonly prescribed atypical antipsychotic drug followed by risperidone and clozapine. Haloperidol was the most commonly prescribed typical antipsychotic followed by zuclopenthixol, chlorpromazine and trifluoperazine. We also observed the change in trend of managing schizophrenia illness with more atypical antipsychotics than typical antipsychotic drugs. The detailed list of antipsychotics usage and the number of patients received the drug were depicted in the table 1.

**Table 1: Prescribing Prevalence of Individual Anti-psychotic Drugs**

Drug Class	Drug	No of patients received the drug	Percentage
Antipsychotics (Atypicals)	T.Olanzapine	91	22.80
	T.Risperidone	70	17.54
	T. Clozapine	50	12.53
	T.Amisulpride	21	5.26
	T. Quetiapine	10	2.50
	T.Aripiprazole	8	2.00
	T.Asenapine	4	1.00
	T.Levosulpride	2	0.50
Antipsychotics (Typicals)	Inj. Haloperidol	81	20.30
	Inj.Zuclopenthixol	41	10.27

T.Chlorpromazine	11	2.75
T.Trifluoperazine	4	1.00
Inj.Fluphenazine	3	0.75
Inj.Flupenthixol	2	0.50
T.Haloperidol	1	0.25
	399	

T: Tablet, Inj: Injection

The list of antipsychotic medications encountered in the study and the corresponding CPZeq, %BNF max and DDD for each medication are detailed in Table 2.

**Table 2: Antipsychotic dosing equivalents**

Sl.No	Medication	Dose equivalent to 100mg of chlorpromazine	100% BNF max	DDD (mg)
1	Olanzapine	5mg	20	10
2	Risperidon	2mg	16	5
3	Clozapine	50mg	900	300
4	Amisulpride*	-	1200	400
5	Quetiapine	75 mg	800	400
6	Aripiprazole	7.5	30	15
7	Asenapine*	-	20	20
8	Levosulpride*	-	-	400
9	Haloperidol	2mg	30	8
10	Zuclopenthixol Depot	100mg per month	600 mg/week	15
11	Chlorpromazine	100mg	1000	300
12	Trifluoperazine	5mg	50	20
13	Fluphenazine	1mg per 21 days	50	10
14	Flupenthixol Depot	10mg per week	400 mg/week	4

\* Equivalent doses for atypical antipsychotics are not established and are not particularly useful and so manufacturers' guidelines should be followed.

We have noticed that 25 (12.5%) patients received more than 100% BNF maximum. The categorization of CPZeq dose showed that 57 (28.5%) patients were using sub-therapeutic dose (< 300mg CPZeq), 92 (46%) were using optimum dose (300-600 mg CPZeq) and 40 (20%) were using supra therapeutic doses (>600-1000 mg CPZeq). Only 11 (5.5%) patients were using supra-maximal dose (> 1000 mg CPZeq). A related study shows that 35.2% patients were using sub-therapeutic doses, 42.2% were using optimum dose, 22.8% were using supra therapeutic doses and 2.8% were using supra-maximal dose<sup>14</sup>. However, the CPZeq method has some negative aspects particularly the reason that the CPZeq values fluctuate across literature and might not be precise for SGA<sup>15</sup>. Moreover, the values for CPZeq do not go through regular rectification or modifications after marketing the antipsychotic drug<sup>16</sup>. Despite some

disadvantages, some researchers propose the use of the % BNF maximum instead of CPZeq method<sup>12</sup>.

**Table 3: Antipsychotic drug dose in the study population**

Sl.No	% BNF maximum			CPZeq		
	Range	Frequency	Percentage	Range	Frequency	Percentage
1	< 25%	16	8	< 300mg	57	28.5
2	25%-50%	85	42.5	300-600 mg	92	46
3	51%-75%	40	20	>600-1000 mg	40	20
4	76%-100%	34	17	> 1000 mg	11	5.5
5	>100%	25	12.5	-	-	-
Total		200	100	Total	200	100

Of the 200 patients who had been prescribed antipsychotics during the study period, 13.5% (n=27) were identified as receiving either more than 100% of the BNF maximum or more than 1000mg CPZeq/day. 29.62% of these patients taking high doses were identified by both methods; 62.96% were identified by the percentage BNF maximum method only and another 7.40% by the CPZeq method only. The average dose of antipsychotics according to the BNF was found to be 61.39% and the average dose of antipsychotics according to CPZeq was found to be 472.85 mg.

**Table 4: High Dose Antipsychotic Therapy (HDAT) in the study population**

Sl. No	Criteria	High dosing of antipsychotics	
		N=27	%
1	> 1000 mg CPZeq/day	02	7.40
2	> 100% BNF maximum	17	62.96
3	> 1000 mg CPZeq/day and > 100% BNF maximum	08	29.62

## CONCLUSION

We conclude that 13.5% of the study population was found to receive high dose of antipsychotics. When prescribing combination drugs it is suggested to record the respective percentages of the maximum permitted dose to prevent covert prescription of supramaximal doses. In those patients who are given combination of antipsychotics and high dose of antipsychotics adequate patient monitoring should be made mandatory to avoid dangerous side effects. The current study could serve as an outline upon which further studies in prescription assessment of psychotropic drugs can be conducted to examine the extent for improvement in prescribing patterns.

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