



# A study of adverse drug reactions and potential drug-drug interactions in the patients attending the Psychiatric Outpatient Department in a Tertiary Care Teaching Hospital: a cross-sectional study

 Adit Deshmukh, Sangeeta Dabhade\* 

Department of Pharmacology, B. J. Government Medical College and Sassoon General Hospital, Pune, India

## ABSTRACT

**Introduction:** The objective of this study was to record and analyze the adverse drug reactions (ADRs) due to psychotropic drugs and the potential drug-drug interactions (pDDIs) amongst different psychotropic drugs as well as pDDIs between psychotropic drugs and other co-prescribed drugs by using Medscape software (online).

**Methods:** A cross sectional study was carried out in patients visiting the Psychiatric Outpatient Department of a Tertiary Care Teaching Hospital. Total 500 prescriptions were analysed for the ADRs and pDDIs.

**Results:** Total 37 ADRs were observed in 32 (6.4%) patients. Antipsychotics was the most common group and olanzapine was the most common psychotropic drug suspected of causing ADRs. Tremors was the most common ADR observed. All of the ADRs were non-serious and were in a “Recovering” state when the data was collected. Total 1051 pDDIs were observed in all the 500 prescriptions surveyed, out of which 361 prescriptions were showing at least one pDDI.

**Conclusion:** The overall incidence of ADRs was not very high (6.4%), which reiterates the judicious use of the drugs in the study setting. Majority of prescriptions had only 1-2 pDDIs per prescription.

### Keywords:

Adverse drug reactions  
Drug interactions  
Psychotropic drugs  
Olanzapine  
Causality

## Introduction

Psychiatry is a branch of medicine that deals with mental, emotional or behavioural disorders (Perumal et al., 2018). Psychiatric or mental disorders constitute a significant problem worldwide. Four out of ten health conditions which contribute to the disability adjusted life years, are psychiatric disorders (Grover et al., 2012). Research findings indicate that 30 percent of the global

population each year has a mental disorder (Monteiro, 2015). Psychiatric illnesses result in the healthcare services being resorted to at frequent intervals and the costs associated with these services are mostly paid by the patients in developing countries (Grover et al., 2012).

Psychotropic drugs or psychopharmacological agents are those having primary effects on psyche (mental processes) and are used for treatment of psychiatric

\* Corresponding author: Sangeeta Sanjay Dabhade, sangeetadr99@gmail.com

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disorders (Tripathi, 2013). For the treatment of psychiatric disorders, diverse types of psychotropic drugs are available (Thakkar et al., 2013). In the last 20 years, the development of novel classes of drugs like selective serotonin reuptake inhibitors, atypical anti-psychotics and serotonin-noradrenaline reuptake inhibitors have drastically changed the drug therapy protocols (Perumal et al., 2018).

The literature defines psychotropic polypharmacy as the concurrent prescription of two or more psychiatric drugs to a patient. Psychotropic polypharmacy is a major problem in psychiatric practice, which can lead to development of adverse effects of those drugs in patients (Abeba et al., 2016).

Psychotropic drugs can cause a number of adverse drug reactions (ADRs) and some of them can be serious or even fatal (Sengupta et al., 2011). Polypharmacy is one of the leading causes of ADRs in patients with psychiatric disorders (Solanke et al., 2013). ADRs associated with psychotropic drugs can lead to lack of compliance, and at times discontinuation of the treatment (Sengupta et al., 2011). Under-reporting is a problem with ADRs due to psychotropic drugs, though their frequency is high. Therefore, pharmacovigilance in psychiatry plays a vital role to ensure therapeutic safety by detecting early alarming signals (Sharma et al., 2014).

A drug–drug interaction (DDI) is an event that occurs when the effects of a drug are modified by another drug that is administered simultaneously (Tesfaye and Nedi, 2017). Patients with psychiatric disorders are at risk for DDIs because most likely they receive chronic treatment with multiple medications (English et al., 2012). Growing evidence attributes DDIs as a major cause of hospital admissions, failure of treatment, avoidable medical complications and associated healthcare costs (Sandson et al., 2005). Keeping all these facts in consideration, the present study was undertaken with the objectives to observe and analyze the ADRs occurring due to psychotropic drugs and to study the potential drug-drug interactions (pDDIs) amongst different psychotropic drugs as well as pDDIs between psychotropic drugs and other co-prescribed drugs by using Medscape software (online) (<http://reference.medscape.com/drug-interactionchecker>).

## Materials and methods

### *Study design, study site and period of study*

A cross sectional study was carried out in the patients visiting the Psychiatry Out-Patient Department of a Tertiary Care Teaching Hospital, from December 2016 to May 2018.

### *Ethical considerations*

The Study was initiated after obtaining permission from the Institutional Ethics Committee (BJGMC/IEC/Pharmac/D-0916122-122). All data collected as a part of this study, was kept strictly confidential and used for the purpose of this study only. As it was a study in psychiatric patients, written informed assent was obtained from the sane guardian/relatives of the patients, instead of patients themselves, before the recruitment of the patients in the study.

### *Study population*

Total 500 patients were sequentially included in the study as they attended the Psychiatric Outpatient Department. Patients of either sex in the age group of 12 years to 60 years, who were diagnosed to be suffering from any psychiatric illness and prescribed at least one psychotropic drug, and were taking medications since less than or equal to 1 month and those willing to participate in the study were included in the study. whereas the patients having the age less than 12 years and more than 60 years, taking medications for more than 1 month, those with any medical comorbidity, patients having mental and behavioural disorders due to psychoactive substance use, pregnant women and patients/ their relatives not willing to give assent for the study were excluded. A case record form was prepared to collect all the relevant information from the patients.

### *Detailed research plan*

The collected data was analysed for age wise and gender wise distribution of study population. The patients exhibiting one or more ADRs were classified according to the psychiatric disorders they were suffering from, and the number of patients in each group of psychiatric disorders was calculated. This classification was done according to DSM–5 classification (American Psychiatric Association, 2013). Data of ADRs was recorded on Central Drugs Standard Control Organization suspected adverse drug reaction reporting form ([https://cdsco.gov.in/opencms/export/sites/CDSCO\\_WEB/Pdf\\_documents/Consumer\\_Section\\_PDFs/ADRRF\\_2.pdf](https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf_documents/Consumer_Section_PDFs/ADRRF_2.pdf)).

The ADRs were collected by the subjective reporting from the patients. Causality assessment was carried out as per Naranjo's algorithm (Naranjo et al., 1981). In Naranjo's algorithm the total score was calculated for every patient and based on that score, the causality of ADR was determined. The interpretation of the total score on Naranjo's algorithm is as follows: Total score 0 (Zero): doubtful; 01 to 04: possible; 05 to 08: probable;  $\geq 09$ : definite.

Data of ADRs was analysed as follows: Percentage of ADRs caused by different groups of psychotropic drugs; Most common psychotropic drug causing ADRs; Most common ADR observed due to psychotropic drugs; Causality assessment of all the ADRs due to psychotropic drugs using Naranjo's algorithm; Other parameters for assessment of ADRs including seriousness of ADRs, outcome of ADRs and management of ADRs.

An ADR is called "serious" if it results in any of the following outcomes (Indian Pharmacopoeia Commission, Ghaziabad, 2014): death, life-threatening, hospitalisation/ prolongation of the existing hospital stay, disability, congenital anomaly, required intervention to prevent permanent impairment/damage, or other (when the event does not fit the above conditions, but event may put the patient at risk and may require medical or surgical intervention to prevent one of the above conditions).

Potential drug-drug interactions amongst different psychotropic drugs as well as pDDIs between psycho-

tropic drugs and other co-prescribed drugs were studied using Medscape software (online). The pDDIs were then analysed as follows: total number of pDDIs observed in all the 500 prescriptions surveyed; number of prescriptions with no (Zero) pDDIs; number of prescriptions showing at least One pDDI; number of pDDIs observed per patient; range of pDDIs observed per patient.

## Results

### *Demographic details of study participants*

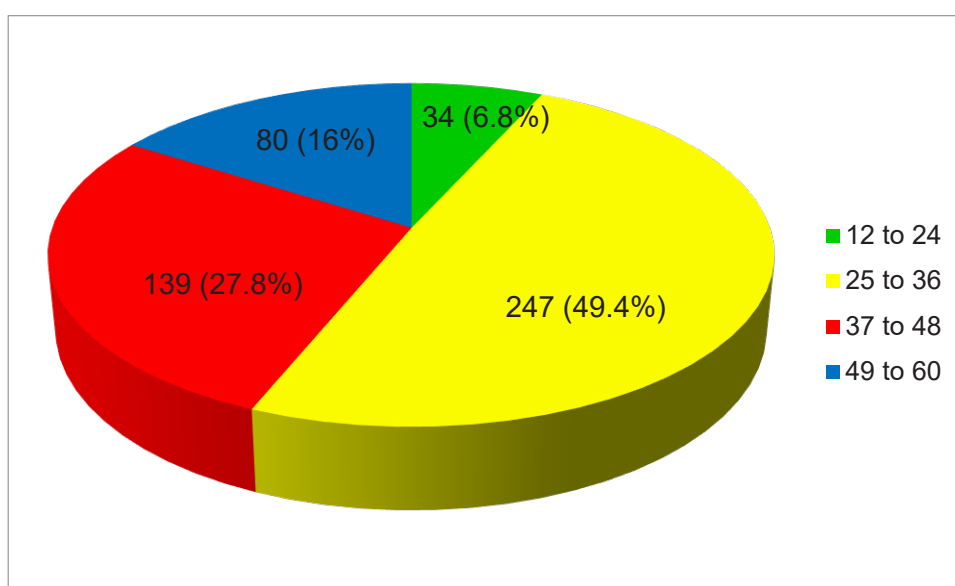
The age group of 25 to 36 years had maximum number of patients [247 (49.4%)] out of the total 500 patients enrolled (Fig. 1). The number of male participants [292/500 (58.4%)] was higher than that of female participants [208/500 (41.6%)].

### *Pattern of psychiatric disorders*

In this study, total 37 ADRs were observed in 32 patients (6.4% of the total participants). Table 1 demonstrates different psychiatric disorders observed in these 32 patients. Thus, Table 1 shows that the most common group of psychiatric disorders observed in the patients having ADRs was "schizophrenia spectrum and other psychotic disorders".

### *Adverse drug reactions due to psychotropic drugs*

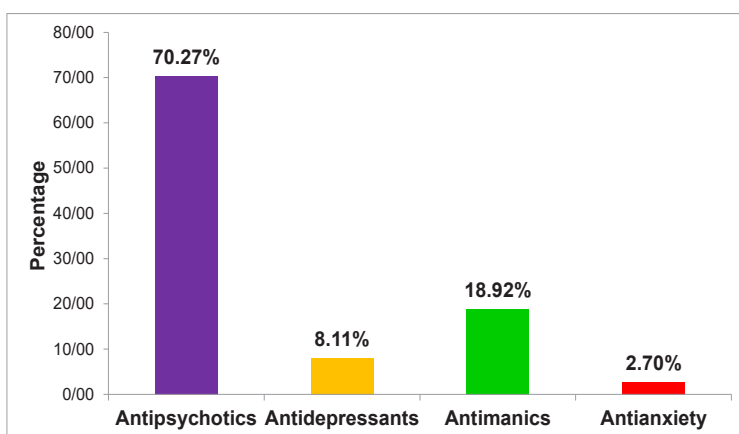
Figure 2 shows that antipsychotics were the most common drugs causing ADRs (70.27% of all the ADRs), when compared with all other groups. Figure 3 shows



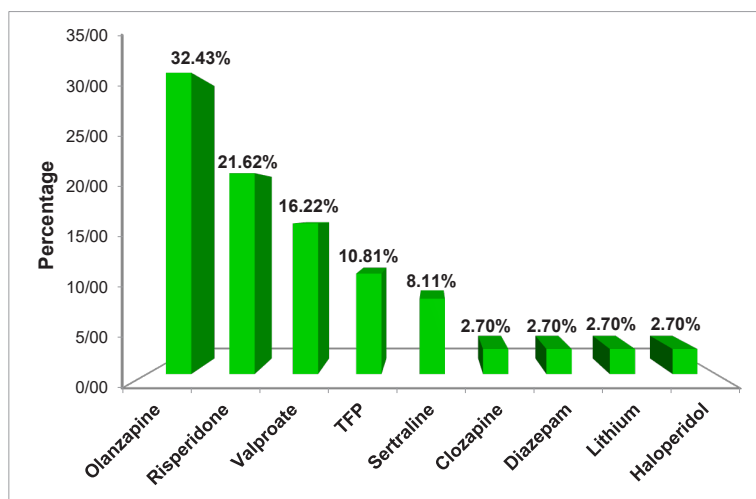
**FIGURE 1.** Age-wise distribution of study participants.

**TABLE 1:** Number of patients suffering from different psychiatric disorders.

Psychiatric disorders as per DSM-5 classification) (American Psychiatric Association, 2013)	Patients-Number (Percentage)
Schizophrenia Spectrum and Other Psychotic disorders	20
Bipolar and related disorders	8
Depressive disorders	1
Other psychiatric disorders	3
<b>TOTAL</b>	<b>32</b>



**FIGURE 2.** Percentage of adverse drug reactions caused by different groups of psychotropic drugs.



**FIGURE 3.** Percentage of adverse drug reactions caused by different psychotropic drugs.

that olanzapine (12 ADRs or 32.43% of total ADRs) was the most common psychotropic drug suspected of causing ADRs. Table 2 shows that “tremors” was the most common ADR observed due to psychotropic drugs.

*Causality assessment of all the ADRs due to psychotropic drugs using Naranjo’s algorithm*

Out of total 32 cases (patients) of ADR, 29 cases were

having causality assessment of ADRs as “possible” and remaining 3 cases had causality as “probable”. Among the cases with “possible” causality, risperidone was the most common suspected drug (8 cases), whereas among the cases with “probable” causality, olanzapine was the most common suspected drug (2 cases).

**TABLE 2:** Number and percentage of different adverse drug reactions (ADR) observed due to psychotropic drugs.

ADR	Number	Percentage
Tremors (EPS*)	18	48.65
Dry mouth	5	13.51
Constipation	3	8.11
Sedation	2	5.41
Anorexia	2	5.41
Blurred vision	2	5.41
Nausea	1	2.70
Weight gain	1	2.70
Insomnia	1	2.70
Dizziness	1	2.70
Polyuria	1	2.70
TOTAL	37	100

\*EPS: Extrapyramidal symptoms

**TABLE 3:** Adverse drug reactions in which dose was reduced.

Number	Adverse drug reaction	Suspected drug	Number of patients
1	Anorexia and Nausea	Sertraline	1
2	Dryness of mouth + Blurring of vision	Olanzapine	1
3	Insomnia	Sertraline	1
4	Blurring of vision	Olanzapine	1

**TABLE 4:** Analysis of potential drug-drug interactions (pDDIs).

Criteria	Result
Total number of pDDIs observed in all the 500 prescriptions surveyed	1051 pDDIs
Number of prescriptions with no (Zero) pDDIs	139 (27.8%) prescriptions
Number of prescriptions showing at least One pDDI	361 (72.2%) prescriptions

#### Other parameters for assessment of ADRs

Seriousness of ADRs: All of the ADRs reported due to psychotropic drugs were “non-serious”. Outcome of ADRs: In all the 32 cases of ADRs, the patients were “recovering” from the ADR when the data was collected. Management of ADRs: The suspected drug was not withdrawn in any of the patients who developed ADRs.

In all the 3 patients who developed constipation as an adverse reaction, suspected drug was olanzapine. All of them were treated for constipation. The dose of the suspected drugs was reduced in following cases as described in Table 3. In remaining 25 cases of ADRs, the

dose of the suspected drug was not changed.

#### Potential drug-drug interactions

The pDDIs observed using Medscape software were analysed as given in Table 4 and Table 5.

## Discussion

The results obtained from this study demonstrated that the majority of the patients were in their 3<sup>rd</sup> or 4<sup>th</sup> decade of life. Some other similar studies done in India also reported the same finding. The overall incidence of ADRs was not very high (6.4%), which reiterates the

**TABLE 5:** Number of potential drug-drug interactions (pDDIs) observed per patient

Number of pDDIs per patient	Number of Patients
2 – 1	220
5 – 3	92
6 ≤	49
TOTAL	361

judicious use of the drugs in the study setting. Almost 28% prescriptions were not having any pDDI. Among the remaining prescriptions, majority of the prescriptions had 1 to 2 pDDIs per prescription, which is not a very high number.

In the present study, maximum number of the patients (247 patients or 49.4% patients) were belonging to the age group of 25 to 36 years. This finding coincides with the study conducted by Thakkar et al. (2013). In the current study, males constituted higher percentage than females. This finding is similar to the study conducted by Mudhaliar et al. (2017). Our study revealed that, among all the psychiatric disorders observed in patients having one or more ADRs, the most common group of psychiatric disorders according to DSM-5 classification was schizophrenia spectrum and other psychotic disorders. The studies conducted by Thakkar et al. (2013) also depicted similar findings.

In this study, out of total 500 patients enrolled, 32 patients (6.4%) developed at least one ADR due to psychotropic drugs. This finding is similar to the studies done by Hotha et al. (2016), Solanke et al. (2013) and Prajapati et al. (2013), where the incidence of ADRs due to psychotropic drugs was 4.68%, 5.01% and 8.68%, respectively. Antipsychotics was the commonest group and olanzapine was the most common psychotropic drug suspected of causing ADRs in current study. This finding matched with the study conducted by Gurung et al. (2018). Tremors (extrapyramidal symptoms) was the most common ADR observed due to psychotropic drugs in present study, which is in line with the findings reported by Prajapati et al. (2013) and Gurung et al. (2018). In present study, among the patients who had ADRs due to psychotropic drugs, the number of patients with causality assessment of ADRs as “possible” was more compared to the number of patients who had causality as “probable”. Some other studies like Hotha et al. (2016) and Sridhar et al. (2016) also reported similar findings. None of the ADRs reported due to psychotro-

pic drugs in our study was fulfilling any of the criteria of “seriousness” (Indian Pharmacopoeia Commission, 2014), that’s why all the reported ADRs were “non-serious”. In contrast to our findings, the study done by Hotha et al. (2016) reported that 73.26% ADRs were non-serious, whereas 26.73% ADRs were considered to be serious. In the present study, for management of ADRs, the suspected drug was not withdrawn in any of the patients who developed ADRs, because the adverse reactions did not significantly disrupt the normal activities of the patients. In contrast to our findings, a study done by Solanke et al. (2013) reported that the suspected drugs had to be withdrawn in cases of some of the ADRs due to psychotropic drugs, while other ADRs subsided on reduction of the dose of the suspected drug.

The literature search did not yield any study regarding pDDIs conducted on OPD basis in psychiatric patients. Therefore, the findings of pDDIs in this study had to be compared with the study done by Ismail et al. (2012) in the indoor psychiatric patients. Total 1051 pDDIs were observed in all the 500 prescriptions surveyed in this study. The study by Ismail et al. (2012) revealed that total 825 pDDIs were identified in 415 patients admitted in the psychiatry ward of a tertiary care hospital. In our study, 72.2% prescriptions showed at least one pDDI and amongst them majority of the prescriptions had 1 to 2 pDDIs per prescription. Both these findings coincided with those of Ismail et al. (2012). Range of pDDIs observed per patient was 1 to 21 pDDIs per patient. In the study by Ismail et al. (2012) the range was 1 to 10 pDDIs per patient. In patients suffering from psychiatric illnesses, sometimes the principal psychiatric disorder is accompanied by the symptoms of another psychiatric disorder in the same patient. For example, in our study, there were some patients having depressive disorder with anxiety features as the diagnosis. Now such patients have to be treated for depression as well as anxiety, which increases the number of psychotropic drugs prescribed to those patients, which in turn, leads to the

rise in the number of pDDIs. Same is the case with the patients with some other diagnoses in our study, like mania with psychotic features, paranoid schizophrenia with depressive features, etc. Therefore, the upper limit of the range of pDDIs observed per patient in our study went upto 21 pDDIs per patient.

### Limitations

As this was a cross-sectional study, the follow up of the patients under study was not done. In many patients, depending on their response to the treatment, the medications might be, in future, increased or tapered off. Hence, in later stages, the number of drugs may change, due to which the pattern of ADRs observed and the pDDIs might also change, which was not possible to be documented in this study. This study was conducted in a Tertiary Care Teaching Hospital, due to which the results may differ from the studies conducted in non-teaching and secondary care hospitals as many times they don't have a separate psychiatry OPD. In this study, some of the aspects of pDDIs were not covered, for example, mechanisms of interactions, severity of interactions, etc.

### Conclusion

The ADRs due to psychotropic medications can pose problems to the health of the patients as well as to the compliance of the patients taking those drugs. Psychotropic drugs can interact, either among themselves or with the other co-prescribed medications, which can lead to complications or failure of treatment. Therefore it is essential to identify and analyse the ADRs and pDDIs due to psychotropic drugs.

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### Conflict of interest

None

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