# Study on the adverse reactions of antipsychotics and therapeutic drug monitoring of olanzapine in psychiatric patients

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**ABSTRACT:**
Antipsychotics used in the treatment of psychotic disorders such as schizophrenia are generally associated with potential adverse effects. They mainly act by blocking dopaminergic uptake by binding to its receptors in the post synaptic nerve terminals. However their potential peripheral and extra pyramidal adverse effects have led to patient non-compliance of medications. Hence a clear understanding of the adverse effects associated with anti-psychotic therapy could ultimately yield better therapeutic outcomes and increase patient adherence to medications. The study was designed to analyse the common adverse reactions caused by antipsychotic medications. Olanzapine was found to be associated with greater risk of adverse effects and hence the plasma concentration of olanzapine was monitored.

**KEYWORDS:** Psychotic disorders, Adverse drug reactions, Therapeutic drug monitoring, Olanzapine, Weight gain.

## INTRODUCTION:

Antipsychotics also called as neuroleptics are drugs used to treat patients with psychotic disorders such as schizophrenia. These drugs generally tend to decrease the symptoms of psychosis such as hallucinations, delusions and extreme personality disorganization[(1)]. Almost all antipsychotics generally act by specifically binding to dopamine D2 receptor thereby inhibiting neuronal dopamine release. Besides their actions in the CNS, antipsychotics also have effects in the peripheral sites which contribute to their adverse effects[(2).] However, extra pyramidal symptoms observed are due to dopaminergic blockade in the basal ganglia[(3)].The potential adverse effects of antipsychotics include weight gain, tremors, akathisia etc. These adverse effects have led to patient non-compliance and hence expected therapeutic outcome is not achieved[(4)].

Hence a clear understanding of the adverse effects associated with anti-psychotic therapy could ultimately yield better therapeutic outcomes and increase patient adherence to medications. The study was designed to analyse the common adverse reactions caused by antipsychotic medications. Weight gain and tremors were found to be the common adverse effects. Various studies have shown weight gain to be a potential adverse effect of olanzapine therapy[(5,6)]. Hence therapeutic drug monitoring of olanzapine was carried out in 10 patients to determine the concentration of olanzapine in plasma. The results showed the availability of olanzapine in plasma.



## MATERIALS AND METHODS:

The study was carried out for a period of 9 months in a hospital specialized in psychiatry. The inpatient department of the hospital which includes the general and intensive care units wa se reactions was high since the patients presented with a combination of d ategories of drugs. Institutional Ethical Committee clearance and the inform horities and patients, respectively to monitor the adverse drug reactions and monitoring of olanzapine. Adverse drug reactions were monitored in the selected departments in a regular ward round basis.

### Inclusion Criteria:

Psychiatric patients of both the genders diagnosed with mania, depression, bipolar disorder and schizophrenia.

### Exclusion Criteria:

Patients who are pregnant and breast feeding, patients with hepatic insufficiency and renal failure and patients taking antacids, cimetidine, biperiden, imipramine, desimipramine, rifampicin, theophylline, valproic acid, warfarin and carbamazepine.

Based on the inclusion and exclusion criteria, 50 patients were chosen for studying the adverse drug reactions whereas 10 patients were selected for therapeutic drug monitoring of olanzapine.

### Collection and Processing of Sample for Therapeutic Drug Monitoring:

Consent was obtained from patients who were on treatment with Olanzapine. A blood sample of about 5ml was withdrawn

Consent was obtained from patients who were on treatment with Olanzapine. A blood sample of about 5ml was withdrawn by venous puncture or finger print capillary after 21-50 hours of night dose intake of drug by individual patients. The blood sample was collected in tubes containing lithium heparin as anti-coagulant. Centrifugation of the collected blood sample was carried out at 3000g for 10 minutes. Following centrifugation, the plasma was immediately separated and was supplemented with 250g/L ascorbic acid (10µ/ml of plasma). The supernatant was stored at a temperature of -20°C until analysis was sent to determination of concentration of olanzapine after packing with ice pack and silica gel.

**Analytical Method:**

Plasma concentration of Olanzapine was determined by high performance liquid chromatography (HPLC) using sample peak. HPLC was carried out in Shimadzu LC-20 HPLC system. Phosphate buffer (pH: 5.0) – Acetonitrile (65.35% v/v) was used as the mobile phase. The buffer solution was filtered by passing it through a 0.4 mill micron filter before preparing the mobile phase. The mobile phase was degassed prior to use in HPLC system. Phenomenex C18 HPLC column was used and the flow rate was set to 1.0ml/min. UV detectors were used at the wavelength range of 254nm.

## RESULTS AND DISCUSSION:

Based on the inclusion and exclusion criteria 50 patients were chosen for studying the adverse reaction pattern of antipsychotics. The patients were segregated on the basis of age, gender and social history and the data is given in Table 1.

Patients were also segregated on the basis of associated diseases or co-morbid conditions. A total of 45 patients (90%) had no associated disease whereas 3 patients (6%) had hypothyroidism, 1 patient (2%) had epilepsy and 1 patient (2%) had diabetes mellitus with hypertension and myocardial infection.

Out of the 50 patients 6 patients (12%) had an earlier family history of psychiatric illness whereas 44 patients (88%) had no family history. Segregation based on the type of patients showed that a total of 20 patients (40%) where newly diagnosed with psychiatric disorders whereas 30 patients (60%) had a relapse of previous illness. The patients were also segregated on the basis of diagnosis of disease and the distribution of data is shown in Table 2.

**Table 1: Segregation of Patients Based on Age, Gender and Social History**

| Age (in years) | (%) of patients | Gender | (%) of patients | Social History | (%) of patients |
|---|---|---|---|---|---|
| 11-20 | 8 | Male | 56 | Smokers | 16% |
| 21-30 | 40 | Female | 44 | Alcoholic | 8% |
| 31-40 | 26 | | | Drug addict | 6% |
| 41-50 | 16 | | | Alcoholic + drug addict | 4% |
| 51-60 | 10 | | | Smokers + drug addict | 4% |
| | | | | Smokers + alcoholic | 8% |
| | | | | Neither smokers nor alcoholic | 54% |

**Table 2: Segregation Based on the Diagnosis**

| . | Disease diagnosed | Total number of Patients (n=50) | Percentage |
|---|---|---|---|
| | Psychosis | 15 | 30% |
| | Mania with psychotic features | 8 | 16% |
| | Mania without psychotic features | 2 | 4% |
| | Depression with psychotic features | 1 | 2% |
| | Paranoid schizophrenia | 20 | 40% |
| | Mixed episode | 2 | 4% |
| | Hypomania | 1 | 2% |
| | Catatonia and affective schizophrenia | 1 | 2% |

The drugs that were used commonly included chlorpromazine, olanzapine, nitrazepam, risperidone, divalproate sodium, haloperidol, lorazepam, acamprosate, chlordiazepoxide, clozapine, trifluline and trihexyphenidyl. Adverse reaction of the anti-psychotic drugs used was studied. Weight gain was found to be the most common adverse drug reaction. Out of the 50 patients subjected to the study, weight gain was observed in 26 patients (52%). The second common adverse drug reaction was found to be tremor which was observed in 25 patients (50%). The adverse reactions to antipsychotics observed in the patients are shown in Table 3.



**Table 3: Adverse Drug Reactions**

| S.No. | Adverse Drugs Reaction | | |
|---|---|---|---|
| 1 | Dyspepsia | | |
| 2 | Dry mouth | 14 | 28% |
| 3 | Tremor | 25 | 50% |
| 4 | Weight gain | 26 | 52% |
| 5 | Increased Appetite | 19 | 38% |
| 6 | Sedation | 14 | 28% |
| 7 | Constipation | 12 | 24% |
| 8 | Drowsiness | 8 | 16% |
| 9 | Insomnia | 5 | 10% |
| 10 | Akathisia | 5 | 10% |
| 11 | Agitation | 4 | 8% |
| 12 | Head Ache | 12 | 24% |
| 13 | Dizziness | 7 | 14% |
| 14 | Abdominal pain | 8 | 16% |
| 15 | Asthenia | 1 | 2% |
| 16 | Blurred vision | 1 | 2% |
| 17 | Tardive dyskinesia | 1 | 2% |
| 18 | Depression | 2 | 4% |
| 19 | Anxiety | 8 | 16% |
| 20 | Nausea | 1 | 2% |

Weight gain and tremors were found to be the most commonly observed adverse effects. Weight gain was found to be the most common adverse effect induced by anti-psychotic therapy. The second generation antipsychotics clozapine and olanzapine are known to cause weight gain. A direct link between cytokines and increase in body mass index (BMI) following Olanzapine therapy was observed in a study[7]. Olanzapine also impairs glucose regulation and causes dyslipidaemia which leads to increase in body fat[8]. Increase in serum leptin level was also attributed as a cause of weight gain in patients treated with second generation antipsychotics[9,10]. Second generation antipsychotics olanzapine and clozapine have low propensity of extra pyramidal side effects compared to conventional anti-psychotics. However they induce tremors, akathisia and tardive dyskinesia[11]. 10% of the patients experienced akathisia during anti-psychotic therapy. Though the mechanism of development of akathisia is not well understood, it has been postulated that it is due to dopamine receptor blockade in areas other than the nigrostriatal such as the mesocortical areas[12]. In our current study, olanzapine was prescribed for 50% of the patients. Pathophysiological mechanisms of the other observed adverse effects are described in various other studies.

In order to avoid interference by endogenous substances in plasma, olanzapine was eluted from the column with retention time of 8 minutes. Determination of the concentration of olanzapine by HPLC showed the availability of drug in plasma. From the reverse phase HPLC, the plasma concentrations of olanzapine were found to between 0.30µg/ml to2.4µg/ml. The plasma concentrations of olanzapine observed in 10 patients are shown in Table 4 and Figure 1.

**Table 4: Observed plasma concentrations of olanzapine in the patient population**

| Patient ID | Plasma concentration of olanzapine(µg/ml) | log c |
|---|---|---|
| A1 | 0.7850912 | -0.10508 |
| A2 | 1.6105544 | 0.20697 |
| A3 | 1.7936702 | 0.25374 |
| A4 | 0.7057891 | -0.15132 |
| A5 | 0.4145339 | -0.38244 |
| A6 | 0.3179295 | -0.49767 |
| A7 | ND | ND |
| A8 | 0.9494629 | -0.02252 |
| A9 | ND | ND |
| A10 | 2.3415759 | 0.3695 |

***ND- Not Detectable**

**Figure 1: Comparison of standard and sample plasma drug concentration of olanzapine999**
*No significant difference between sample and standard plasma drug concentration of olanzapine was observed (p value>0.05).

## CONCLUSION:

The common adverse reactions caused by antipsychotic medications were studied. Weight gain and tremors were found to be the most common adverse effects. Since olanzapine was associated with a higher incidence of causing weight gain, therapeutic drug monitoring of olanzapine was carried out to determine the plasma concentrations of olanzapine. The results showed the availability of olanzapine in plasma after 21-50 hours of drug administration. Hence therapeutic drug monitoring of antipsychotics with potential adverse effects should be carried out to minimise the extent of adverse reactions and thereby increase patient compliance to medications and increase therapeutic outcomes.

## REFERENCES:


1. Rang and Dale. Text book of pharmacology.6th Ed; 2011: pp. 548-556.
2. Stahl SM. Describing an Atypical Antipsychotic: Receptor Binding and Its Role in Pathophysiology. The Journal of Clinical Psychiatry.5(3); 2003:9-13.
3. Blair DT, Dauner A. Extrapyramidal symptoms are serious side-effects of a 1992:62-67.
4. Perkins DO. Predictors of noncompliance in patients with schizophrenia. Tl
5. Poyurovsky M et al. Olanzapine induced weight gain in patients with first-e y of fluoxetine addition. The American Journal of Psychiatry.159(6); 2002:1058-1060.
6. Eder U et al. Association of olanzapine-induced weight gain with an increase in body fat. The American Journal of Psychiatry.158(10); 2001: 1719-1722.
7. Kluge M et al. Effects of clozapine and olanzapine on cytokine systems are closely linked to weight gain and drug-induced fever. Psychoneuroendocrinology.34; 2009: 118-128.
8. Wirshing DA et al. The effects of novel antipsychotics on glucose and lipid levels. The Journal of Clinical Psychiatry.63(10); 2002: 856-865.
9. Atmaca M et al. Serum leptins and triglyceride levels in patients on treatment with atypical antipyschotics. The Journal of Clinical Psychiatry.64(5); 2003: 598-604.