Research Article

# Metabolic Adverse Effects with Drugs Used to Treat Common Psychiatric Disorders

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## Abstract

**Background:** Weight gain and metabolic disturbances are common side effects during psychopharmacological treatment with specific antipsychotics and antidepressants. The antipsychotics like clozapine, olanzapine and antidepressants like tricyclics antidepressants and mirtazapine are associated with high risk for inducing metabolic changes. The objective of this study was to analyze the metabolic changes caused by common psychopharmacological agents.

**Methods:** The study was observational and prospective. Hundred adult treatment naive patients (16-65 years of age) of both genders attending psychiatry outpatient department (OPD) of Chatrapati Shivaji Subharti Medical College, Meerut were observed. Patients who fulfilled inclusion and exclusion criteria and willing to give blood sample underwent random blood glucose and lipid profile analyses on their 1st visit (day 0), 2nd visit (day 7) and 3rd visit (day 21).

**Results:** Significant changes in random blood glucose and total cholesterol were seen in subjects receiving antidepressants, antipsychotics, anxiolytics and mood stabilizers. Among the metabolic adverse effect findings there was an increase in total cholesterol in 23% patients and increase in random blood sugar in 40% patients.

**Conclusion:** Various antipsychotics and antidepressants produce significant metabolic changes reflected in increased blood sugar and total cholesterol levels.

**Keywords:** Antidepressants, antipsychotics, glucose metabolism, obesity, weight gain.

## INTRODUCTION

Neuropsychiatric disorders are found in people of all countries and societies. About 450 million people are estimated to be suffering from neuropsychiatric conditions, which are one of the major causes of mortality and morbidity worldwide.[1]

The drugs commonly used to treat the neuropsychiatric illness include antidepressants, antipsychotics, mood

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stabilizers and anti-anxiety drugs. There are many common side effects of psychiatric medications, some of which are pretty similar across different classes of drugs.

Antipsychotic drugs are invariably associated with large number of side effects like sedation, psychomotor retardation, autonomic (dryness of mouth, blurring of vision, constipation, urinary hesitancy, postural hypotension and loss of postural reflexes), metabolic (weight gain, hyperlipidaemia, increased appetite, increase in blood glucose, etc.), cardiovascular, endocrinal effects and extra pyramidal side effects like acute muscular dystonia, parkinsonism, akathisia, neuroleptic malignant syndrome, tardive dyskinesia etc.

Pharmacologically induced weight gain and changes in metabolism profile are important side effects of antipsychotic and antidepressant agents. They are more associated with some antipsychotics like olanzapine and clozapine; antidepressants like mirtazapine and tricyclics. In patients where weight gain is one of the primary consideration during prescribing relevant drugs, clozapine, olanzapine, tricyclics and mirtazapine should be avoided and alternative medications with a low risk of weight gain should be prescribed. Antipsychotics with a lower risk for weight gain include second-generation antipsychotics like amisulpiride, aripiprazole, asenapine, lurasidone, ziprasidone and first generation antipsychotics like haloperidol and loxapine.[2,3,4] Among antidepressants, those which do not cause noticeable weight gain such as agomelatine, escitalopram or tranylcypromine could be considered.[2,5,6]

## MATERIALS AND METHODS

The study was conducted in Psychiatry OPD of Chatrapati Shivaji Subharti Hospital (CSSH), Meerut. Study was approved from Institutional Ethics Committee & executed in accordance with the GCP guidelines. Patients who full filled the inclusion criteria and were willing to undergo metabolic function testing were included in the study. The patient's demographic characteristics recorded, presumptive diagnosis was made and treatment was started by the psychiatrist. Randomly selected patients were explained the whole study process. Informed consent was taken from all patients who were included in study. They were tested for metabolic functions (random blood glucose and lipid profile). The baseline data and metabolic function tests were recorded on 1st visit (Day 0). On subsequent visits 2nd and 3rd visit (on Day 7 and Day 21 respectively) same patients were followed up and data were recorded.

Inclusion criteria: Age: 16-65yrs, major depressive disorder, generalized anxiety disorder, new onset schizophrenia

Exclusion criteria: Age <16yrs and >65yrs, pregnancy, resistant schizophrenia, severe depression, pre-existing metabolic disorders

Statistics: All data were tabulated as Mean ± S.E. Nominal and ordinal data were analyzed by non-parametric test and interval/ratio scale by parametric test. A p-value of $\leq 0.05$ was considered significant. Data were analyzed by using 'Excel' and SPSS software.

## RESULTS

### *Socio-demographic profile of the patients*

Out of 100 patients who participated in the study only 63 patients gave consent to undergo total cholesterol analyses as per schedule while 69 patients consented for random blood glucose testing according to the schedule given. Out of total patients, male patients were in much higher number than female patients (72% vs. 28%). Mean age of the patients was 34.44 years. Of the total, 64% of the patients were from rural areas surrounding Meerut city while 34% of them were from urban areas. (Table 1)

### *Morbidity profile and drug treatment*

Table 2 shows the morbidity profile of the patients along with their ICD-10 code of their diagnosis. Table 3 shows the details of the common diagnosis and the drugs commonly prescribed.

Table 1 Socio demographic profile

| Profile | Number (%) |
|---|---|
| Male | 72 |
| Female | 28 |
| Rural | 64 |
| Urban | 36 |
| Mean age | 34.44 years |
| Patient who got treatment for 4 week | 93 |
| Lost in follow up | 07 |

Table 2 Morbidity Profile (ICD – 10)

| S. No. | ICD – 10 Code | ICD 10 Code | Total | % |
|---|---|---|---|---|
| 1. | Mental disorder due to known psychological condition | F01 – F09 | 04 | 04 |
| 2. | Mental and behavioral disorder due to psychoactive substance use | F10 – F19 | 14 | 14 |
| 3. | Schizophrenia, schizotypical, delusional and non mood psychotic disorder | F20 – F29 | 08 | 08 |
| 4. | Mood (affective) disorder | F30 – F39 | 45 | 45 |
| 5. | Anxiety, dissociative, stress related somatoform & other non-psychotic mental disorders | F40 – F48 | 11 | 11 |
| 6. | Behavioral syndrome associated with psychological disturbances | F50 – F59 | 0 | 0 |
| 7. | Disorders of adult personality & behavior | F60 – F69 | 0 | 0 |
| 8. | Intellectual disabilities | F70 – F79 | 01 | 01 |
| 9. | Pervasive and specific developmental disorders | F80 – F89 | 0 | 0 |
| 10. | Behavioral and emotional disorder with onset in childhood and adolescence | F90 – F98 | 0 | 0 |
| 11. | Unspecified mental disorders | F99 | 0 | 0 |
| 12. | Episodic and paroxysmal disorders | G40 – G47 | 07 | 07 |
| 13. | Nerve, nerve root and plexus disorders | G50 – G59 | 06 | 06 |

Table 3 Drugs prescribed to treat neuropsychiatric conditions

| S. No. | Psychiatric diagnosis | No of cases | Predominant drug used |
|---|---|---|---|
| 1. | Depressive disorder | 39 | SSRIs (72%) and SNRIs (22%) |
| 2. | Schizophrenia | 08 | Olanzapine (62%) and Risperidone (36%) |
| 3. | Seizure | 07 | Carbamazepine (64%), Clobazam(42%) and Phenytoin (56%) |
| 4. | Substance abuse | 14 | Olanzapine (58%), Thiamine (52%) |
| 5. | Bipolar disorder | 06 | Olanzepine (68%), Divalproex (52%) |
| 6. | Social anxiety | 02 | Lorazepam (50%), Amisulpride (50%) |
| 7. | Trigeminal Neuralgia | 06 | Amitriptyline (84%), Clonazepam (84%) |
| 8. | Psychotic disorder (Acute & Transient) | 01 | Risperidone |
| 9. | Organic Amnesia | 03 | Clonazepam (66%), SSRIs(66%) |
| 10. | Unspecified Mental disorder with known physiological conditions | 01 | Risperidone, Clonazepam, Divalproex |
| 11. | OCD | 05 | SSRIs (100%), Clonazepam(74%) |
| 12. | Dissociative disorder | 01 | Escitalopram |
| 13. | Adjustment disorder | 03 | Clonazepam (100%) |

### *Changes in metabolic parameters*

Among the 69 subjects who were tested for random blood sugar (n=69), 40% (n=27) of those patients showed increase in random blood sugar from 108.59 mg/dl to 124.56 mg/dl over a period of 21 days which statistically significant ($p < 0.001$) (Figure 1). Total 63 subjects were tested

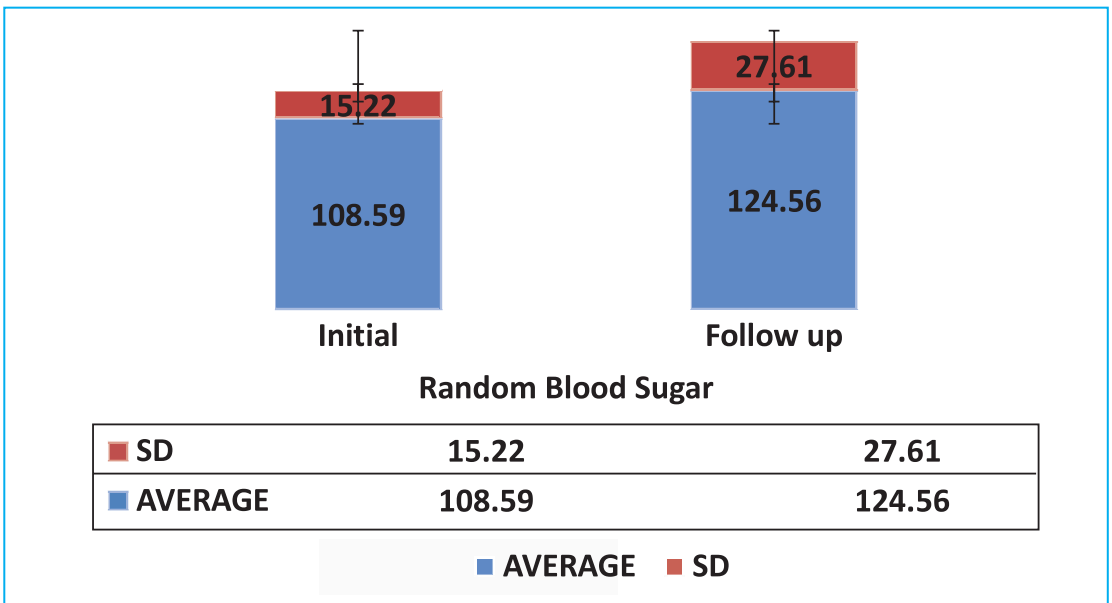


Figure 1 Overall change in random blood sugar

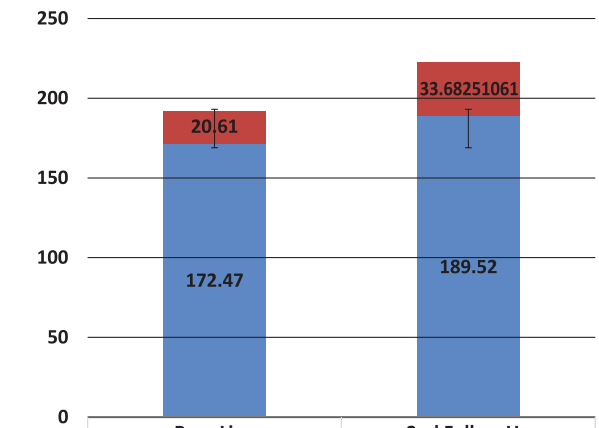


Figure 2 Overall change in total cholesterol

for total cholesterol (n=63). Out of which 23% (n=14) of the patients have shown statistically significant changes ($p < 0.001$). Average total cholesterol has increased from 172.47 mg/dl to 189.52 mg/dl over a period of 21 days (Figure 2).

## DISCUSSION

In the study, among the 100 patients screened, 45 (maximum) were categorized under F30-39 (Mood disorder) which includes bipolar disorder and various depressive disorders; and were prescribed antidepressants. Selective serotonin reuptake inhibitors (SSRIs; 72%) were the most commonly prescribed antidepressants followed by serotonin norepinephrine reuptake inhibitors (SNRIs; 22%), consistent with findings of earlier study by Dutta et al. and other previous studies.7,8 Tricyclic antidepressants like imipramine and atypical antidepressants like mirtazipine were less prescribed. Escitalopram and paroxetine were the most commonly prescribed SSRIs, similar to results found in study by Grover et al.9 and Piparva et al.[7] Venlafaxine and duloxetine among SNRIs were most commonly prescribed.[9,10]

SSRIs are generally free of sedative effects and safer at higher doses. Better tolerability, combined with their mild adverse effects, accounts for their popularity as the most widely prescribed antidepressants.[11,12]

Our study revealed that total cholesterol level was increased in 23% (n=14) of the patients. Average total cholesterol has increased from 172.47 mg/dl to 189.52 mg/dl. Random blood sugar increased from 108.59mg/dl to 124.56mg/dl on an average in 40% of the patients (n=27). All these increased values are statistically significant as compared to baseline values. In some patients this increase was minor which was not significant statistically.

In our study an average increase in weight of around 2%, random blood sugar around 19% and total cholesterol levels of around 10% were found. These findings are in accordance with the previous studies.[11,12,13] Adverse effects due to antidepressant treatment have heterogeneous mechanisms.. For example TCAs block histaminic, cholinergic and alpha1-adrenergic receptor sites, resulting in occurrence of adverse effects, including weight gain, dry mouth, constipation, drowsiness, and dizziness.[14] The newer generation of antidepressants, SSRIs are relatively selective drugs which target specific brain receptor site without agonizing or antagonizing unwanted receptor sites or transmitters, such as histamine and acetylcholine. Importantly, in the majority of cases those adverse effects usually appear with initiation of treatment while therapeutic benefits may be delayed. More recently designed antidepressants such as SNRIs and SNDRIs were suggested to cause fewer adverse effects than TCAs while yielding similar efficacy in the treatment of depression.[15]

SSRIs are reported to improve glucose regulation in the short term; and moreover, they may have few untoward effects in the long term. In DM-2 patients, SSRIs are the only class of antidepressants with confirmed favorable effects on glycemic control.[16] Therefore, SSRIs seem to be advantageous if the patient has to avoid adverse effects regarding body weight and glucose metabolism especially in high risk patients. Paroxetine, however, may be one exception as it is the SSRI most frequently associated with weight gain.[13,17]

As the risk for hyperlipidemia has repeatedly been found to be increased in patients suffering from depression; lipid metabolism should also be considered during treatment with antidepressants.[18] The available data suggests that the problem of hyperlipidemia during treatment with antidepressants is much lower compared to treatment with second-generation antipsychotics.[19]

In the present study most patients with schizophrenia were prescribed olanzapine (62%) and risperidone (36%). Most of the patients received atypical antipsychotics. This similar trend of atypical antipsychotic use was also seen in many previous studies.[9,20] Atypical antipsychotics are commonly prescribed, owing to their better tolerability, low relapse rate, efficacy against refractory cases, better control over negative symptoms and safer adverse effect profile.[21]

In the present study most common adverse effects with antipsychotics use were weight gain, tremors, constipation and drowsiness. On an average 4% weight gain was seen in almost 70% of the patients. Random blood sugar increased by 4% on an average while total cholesterol increased by around 2% on an average in more than 50% of the patients. Similar findings were seen in other studies also.[10,22] Weight gain is a common adverse effect of antipsychotic medications and can be rapid and difficult to control.[23] Weight gain does not seems to be dose dependent within the normal therapeutic range. The effect is worse with clozapine and olanzapine; minimal with aripiprazole and ziprasidone; and intermediate with other antipsychotics, including low-potency first generation antipsychotics (FGAs).[24] The mechanism of clozapine induced

weight gain is not clearly understood. Possible mechanisms include antagonism of the D2 receptor which is involved in feeding regulation, antihistaminic activity, anticholinergic effects on M4 receptors and antagonism of 5-HT2 receptor.[25,26] Other factors associated with increased body weight such as increased leptin secretion, cessation of smoking, decreased ghrelin and adiponectin serum levels may also be involved.[25,27]

Antipsychotic medications can contribute to a wide range of glycemic abnormalities, from mild insulin resistance to diabetic ketoacidosis as well as worsening of glycemic control in patients with preexisting diabetes.[28] The greatest risk is with clozapine and olanzapine. The magnitude of risk is difficult to quantify because so many other diabetes risk factors are present in this population. Although the weight gain associated with antipsychotics clearly attribute the same but there may be other independent effects as well.[29]

Dyslipidemia is also associated with several antipsychotic medications, with increases noted primarily in triglyceride levels. Low-potency FGAs and clozapine, olanzapine, and quetiapine are associated with a higher risk of hyperlipidemia.[30,31] Overall, metabolic disturbances appear to be greatest with clozapine and olanzapine, intermediate with quetiapine and low potency FGAs and lowest with aripiprazole, risperidone, ziprasidone, and high-potency FGAs.

The metabolic disturbances following weight gain during therapy with clozapine and olanzapine due to their affinity to the muscarinic M3 receptor (M3R) has been discussed as an additional cause for the dysregulation of glucose metabolism, because olanzapine and clozapine are both potent M3R antagonists.[32,33]

### *Limitations of the study*

- Limitations of observational study were part of the design chosen due to regulatory considerations
- Short duration of observation only shows a trend.
- Random blood sugar is a metabolic parameter having wide variation among individuals as compared to fasting blood sugar.
- Small sample size in subgroups restricted application of analytic tools.
- These findings can be considered only as trends that need to be confirmed by bigger and long term studies.

## CONCLUSION

There was a trend showing metabolic adverse effects (cholesterol profile impairment in 23%, and random blood sugar impairment in 40% of patients) on usage of psychopharmacological agents and these adverse effects should be an important consideration while prescribing psychopharmacological agents. Plasma blood glucose levels, lipid profile and other biochemical profiles can detect early warning signs so as to guide correct prescription, counseling and advice to the patient and his attendants about diet and the physical activities.

This can help to avoid harmful metabolic complications and related co-morbidities.

### *Conflicts of interest*

The Author(s) declare(s) that they have no conflicts of interest to disclose.

### *Funding*

This review received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

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