Comparative evaluation of metabolic adverse effects of mirtazapine versus paroxetine in patients with depression

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INTRODUCTION

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BACKGROUND

Background: Depression is the common psychological disorder worldwide and is a leading cause of disability. Second-generation antidepressants (mirtazapine [MIRT] and paroxetine [PAR]) are now acknowledged to be the first-line treatment for depression. The aim of the study was to comparatively evaluate MIRT and PAR with regard to metabolic adverse effects (body weight [BW], body mass index [BMI], fasting blood sugar [FBS], and lipid profile) in cases of depression.

MATERIAL AND METHODS

Material and Methods: A prospective, randomized, open-label, and interventional clinical study of 1 year duration was conducted at Rohilkhand Medical College and Hospital, Bareilly. A total of 100 naïve patients of depression of age group of 18–65 years of both the sexes were randomly divided into two groups and were administered flexible-dose of MIRT 15–45 mg and PAR 12.5–37.5 mg daily. Patient’s BW, BMI, FBS, and lipid profile were estimated at baseline and reassessed at 1 month, 3 months, 6 months, 9 months, and 12 months.

RESULTS

MIRT group shows statistically significant increase in BW (P < 0.0001), BMI (P < 0.0001), and FBS (P < 0.0001) after 12 months of therapy. Total cholesterol (TC), triglycerides (TG), and low-density lipoproteins (LDL) were also significantly raised (P < 0.05, P < 0.0001, and P < 0.0001, respectively). High-density lipoproteins (HDL) were declined significantly (P < 0.0001). However, none of the patients crossed the normal range. Significant rise in BW (P < 0.0001) and BMI (P < 0.05) (although lesser than mirtazapine) and no statistically significant changes in FBS, TC, TG, HDL, and LDL values were observed in PAR group.

CONCLUSION

Conclusion: PAR was found to be associated with lesser increase in BW and BMI as compared to MIRT in the treatment of depression. Other metabolic parameters were not affected with PAR. However, mirtazapine had adverse impact on FBS, TC, TG, LDL, and HDL levels. The results of this comparative, prospective, randomized, open-label, interventional, and flexible-dose clinical study revealed that PAR was a safer and well-tolerated as compared to MIRT in the long-term treatment of drug naïve patients of depression.

KEY WORDS: Depression, metabolic parameters, mirtazapine, paroxetine

INTRODUCTION

Moreover, the depressive patient has feelings of guilt or low self-esteem. Pharmacologic therapy is the foundation stone in managing depressive ailment. Antidepressants, at times referred to as happy pills, are psychotropic (mind-altering) drugs employed to abate depression.¹ These drugs impinge on frame
of mind, insight, awareness, and cognition. Antidepressants have been classified based on differing modes of action of drugs, although the majority of drugs performed by acting on one or more neurotransmitters at brain synapses. The scientific rationale for their use is the serotonin (or monoamine or catecholamine) hypothesis of depression. Depression is due to a deficiency in one or other of three biogenic monoamines, namely, serotonin, norepinephrine, and/or dopamine.[3]

The pharmacologic treatment strategies currently available include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin–noradrenergic reuptake inhibitors, and other atypical antidepressant drugs, such as monoamine oxidase inhibitors. The choice of treatment for major depressive disorder and its subtypes involves weighing the relative efficacy, side effect profile, and safety of treatment against the severity of illness as well as patient acceptance.[3] Newer class of antidepressants (e.g., mirtazapine [MIRT], venlafaxine, and reboxetine) offers advantages over TCAs and SSRIs in terms of superior safety indices. Compared with the SSRIs, they provide similar efficacy but different side effect profiles. The data pertaining to metabolic adverse effects of either MIRT or paroxetine (PAR) in patients of depression are not corroborated in the Indian population subset.[4] Thus, this novel study was planned with the aim and objectives mentioned as:

- To compare and evaluate the metabolic adverse effects of MIRT and PAR with regard to body mass index (BMI), lipid profile, and blood sugar levels in cases of depression
- To observe whether there exists any gross advantage of one drug over others in respect to metabolic adverse effects profile
- To assess the long-term metabolic effects and safety outcomes of these antidepressants.

**MATERIALS AND METHODS**

This study was conducted as a prospective, randomized, interventional, open-label, and flexible-dose clinical study in patients of depression receiving treatment with either MIRT or PAR at Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, India.

Approval from the Institutional Ethical Committee was obtained, and the number is IEC/IRB No. IEC/66/2014. Each subject signed an informed consent form before participation and could withdraw without prejudice at any time. Registration from Clinical Trial Registry India was also applied, and the reference number is REF/2016/09/012246.

**Dose Schedule**

- Flexible doses of MIRT (15–45 mg/day) and PAR (12.5–37.5 mg/day) were administered as per the clinical response
- No other antidepressant drug therapy was given to patients.

**Inclusion Criteria**

The following criteria were included in the study:

- Patients of age group 18–65 years and of both genders
- Newly diagnosed patients (drug-naïve) of mild to moderate depression falling under the group (F32) as per the criteria of the 10th edition of the International Classification of Diseases.

**Exclusion Criteria**

The following criteria were excluded from the study:

- Patients with a history of taking antidepressants before the study
- Patients with a history of diabetes mellitus, cardiovascular, hepatic, renal, and thyroid diseases
- Dyslipidemic and obese patients
- Pregnant and lactating females. Patients taking antiepileptics, antipsychotics, birth control pills, steroids, propranolol, thiazide diuretics, and agents that induce weight loss.

**Sample Size**

- A total of 100 patients were included and each was allotted a reference number
- Simple randomization was done. Odd numbers were assigned to (MIRT = 50) and even numbers to group (PAR = 50)
- Of these six patients dropped out of MIRT group (n = 44) during the study period, due to dizziness and somnolence, and five patients dropped out of PAR group (n = 45) due to sexual dysfunction and insomnia.

**Data Collection Technique and Tools**

- A complete preliminary clinical examination was conducted on all the subjects included in the study to rule out any chronic ailments referred to in the exclusion criteria. After initial screening, the socio-demographic data regarding age, sex, socioeconomic status, family history, and other demographic parameters were recorded in the case report form. Patients were then evaluated by senior consultant psychiatrist
- For calculating BMI (kg/m²), patient’s height and weight were taken using measuring tape and weighing machine. Blood pressure was measured using standard protocol. Thereafter, relevant investigations were done. The patient’s fasting blood sugar (FBS) and lipid profile were estimated at baseline
- After baseline investigations, patients were randomly divided into two groups. One group was administered MIRT 15–45 mg daily, and the other group received PAR 12.5–37.5 mg daily as per the clinical response.

**Follow-up**

- Patients under study were subsequently monitored and reassessed at 1, 3, 6, 9, and 12 months
- During each follow-up visit, the weight of the patient was recorded to calculate BMI, fasting blood glucose level, and lipid profile which was also estimated
- Psychiatric evaluation of the patients was also done by the consultant psychiatrist during each visit. All adverse events or associated side effects during treatment were recorded in the case report form. The treatment compliance was
evaluated at each monthly visit using tablet counts and questioning the parents/relatives
• Tolerability assessment: All adverse events during treatment were recorded in the case report form. Evaluation of severity of adverse drug effect was assessed using adverse drug reaction (ADR) severity assessment scale (modified Hartwig and Siegel), which classifies ADR into mild, moderate, and severe.5

**Investigations Done During Follow-up**

• Blood sugar: FBS
• Lipid profile: Low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), and total cholesterol (TC).

**Statistical Analysis of Data**

Statistical analysis was performed using the software Statistical Package for the Social Sciences, windows version 21. Demographical data were compared by Chi-square test and continuous data such as change in body weight (BW), BMI, blood sugar level, and lipid profile (at baseline, 1, 3, 6, 9, and 12 months) were compared using unpaired t-test and paired t-test.

**RESULTS**

The two groups were found to be comparable with respect to age ($2 = 0.8557$, $P = 0.3943$) and sex ($2 = 0.042$, $P = 0.8376$).

Table 1 shows that there was a statistically significant increase in BW (up to 9.07 kg, $P < 0.0001$) in MIRT-treated group, and increase was evident as early as after 1 month. About 73% subjects experienced weight gain more than 7%. There was statistically significant rise in FBS (up to 8.32 mg/dL, $P < 0.0001$) from baseline to end point. Alterations in FBS were observed as early as 3rd month and became statistically significant 9 months onward. There was a statistically significant rise (up to 11.89 mg/dL, $P = 0.0037$) in TC levels in MIRT group. The TG levels also significantly amplified up to 6 mg/dL ($P < 0.0001$) at the end point. As shown in Table 1, LDL levels were significantly raised at the end point of study ($P < 0.0001$), whereas HDL levels showed statistically significant ($P < 0.0001$) decrease at 12 months in MIRT group.

Table 2 shows increase in BW (up to 4.33 kg, $P < 0.0001$) and BMI (up to 1.78 kg/m²), which was also found to be significant in PAR subjects, but increase was evident after 6 months. Only 53% patients experienced more than 7% weight gain at the end point. There was no statistically significant rise in FBS in PAR-treated subjects ($P = 0.6455$, at end point) or TG ($P = 0.5551$, at end point) parameters were observed in PAR group. As also depicted from Table 1, both LDL and HDL parameters showed no statistically significantly alterations ($P = 0.1264$ and 0.165, respectively, at end point) in PAR treated subjects.
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Graphs 1 and 2 compare BW and BMI between the two groups.

Graph 3 compares the alterations in FBS between MIRT - and PAR-related groups from baseline to 1, 3, 6, 9, and 12 months. Graphs 4 and 5 also show a comparative analysis of TC and TG between both the groups. A comparison of LDL and HDL levels between two groups is also observed in Graphs 6 and 7, respectively. Table 3 shows the adverse effects seen in both groups. Almost all the adverse effects were mild according to Hartwig Severity Assessment Scale.

DISCUSSION

The drugs under investigation in this study, MIRT and PAR, in long-term comparative evaluation have confirmed nearly comparable efficacy\(^\text{[6,7]}\) but fewer long-term data are existing pertaining to their metabolic adverse effects particularly in Indian population.\(^\text{[8]}\)

The two groups in the present study were matched for proper comparative evaluation. All the patients who were enrolled for the purpose of the study were having first depressive episode.
and had never received antidepressant drugs for any purpose.

The groups were also in line with regard to mean age, gender, locality, educational, and socioeconomic status. Their baseline metabolic parameter values with respect to BW, BMI, FBS, and lipid profile were also noted to be statistically comparable between MIRT- and PAR-treated groups.

Flexible dose schedule of both drugs was used, PAR 12.5–37.5 mg/day and MIRT 15–45 mg/day depending on the evaluation of clinical condition and clinical response by the consultant psychiatrist, though initially lower doses were administered. Various studies have used similar dosage ranges with MIRT [7,8] and PAR [9,10].

Despite adequate control with the therapy, dropouts within the MIRT- and PAR-treated groups were six and five subjects, respectively. The primary reason for dropouts was adverse effects observed in two groups. Four subjects from MIRT discontinued due to weight gain and two subjects due to somnolence. From PAR group, three subjects due to sexual dysfunction and two subjects because of insomnia discontinued the treatment. Weight gain is a relatively common problem during both short-term and long-term treatment with antidepressants, and it is an important contributing factor to noncompliance. [11] Similar dropouts were also reported by various other studies. [12,13] Sexual dysfunction and gastrointestinal symptoms such as nausea and vomiting were
found to be reasons for discontinuation with PAR as observed with other studies also.\textsuperscript{[14,15]}

In this study, MIRT caused a significant rise in weight as early as after 1 month of the therapy and mean total weight gain of 9.07 kg was found at the end point (12\textsuperscript{th} month), whereas there is lesser increase in weight of approximately 4.33 kg in the PAR-treated group at the end point. There are plentiful researches which had confirmed that MIRT was responsible for rapid gain in weight.\textsuperscript{[16,17]} Surprisingly, in one placebo control, double-blind trial patients receiving MIRT gained only 1.4 kg weight over 1 year of continuation therapy, which did not support our findings.\textsuperscript{[18]}

With regard to PAR, there are diverse results concerning weight gain.\textsuperscript{[19]} A number of studies reported weight gain;\textsuperscript{[20-22]} nevertheless, many noted loss of weight.\textsuperscript{[23]}

One study also concluded that both PAR and MIRT may cause weight gain, but mean weight change among MIRT group was higher than among PAR group.\textsuperscript{[24]}

The probable reason for MIRT-induced weight gain is a disorder of the neurobiological controls that adjust food intake and also changes in leptin and the tumor necrosis factor-alpha cytokine system.\textsuperscript{[25,26]}

In our study regarding FBS, it was observed that MIRT altered blood sugar levels significantly from the 9\textsuperscript{th} month onward till the end point at 12\textsuperscript{th} month ($P < 0.0001$), with approximately 7.32 mg/dL rise in blood sugar level. However, PAR seemed to have no impact on FBS values. There is number of researches which confirmed our findings.\textsuperscript{[17,27]} Our findings are partially in contrast to that of study of Laimer et al.\textsuperscript{[26]} who found no effect on MIRT on FBS values despite gain in weight. Improved glucose tolerance during treatment with MIRT may, at least in part, be mediated by a reduction of cortisol secretion, because cortisol plasma levels are reported to be elevated in depressed patients and it was found that they can be lowered by antidepressant treatment with MIRT. In our study, PAR had no influence on FBS parameter. However, in literatures, PAR has diverse effect on FBS values. In one study, PAR was associated with an increased level in FBS.\textsuperscript{[10]} Conversely, FBS values improved in another study.\textsuperscript{[19]} A statistically significant increase in TC ($P < 0.05$) was observed in subjects of MIRT group. TG and LDL levels were also significantly raised ($P < 0.0001$ and $P < 0.0001$, respectively). MIRT also significantly lowered ($P = 0.0001$) serum HDL levels at the end point of the study. Various other studies also confirmed that MIRT is a drug that is known to cause dyslipidemia.\textsuperscript{[7,27]} PAR group, however, did not show any alterations in TC, TG, LDL, and HDL levels. Conversely, few studies revealed that treatment with PAR was associated with a significant increase in levels of TC, HDL, and LDL levels.\textsuperscript{[28,29]} Increased appetite, carbohydrate craving, reduced insulin sensitivity, and abnormalities in lipid metabolism, and hyperprolactinemia are believed to be the mechanisms behind the development of these metabolic effects.\textsuperscript{[7]} Hence, it is suggested that patients on MIRT or SSRIs should carefully be monitored for obesity and dyslipidemia as diverse results were obtained with respect to metabolic considerations. Our study findings nonetheless revealed that when these two drugs were compared for their effects on serum lipids MIRT disturbs lipid profile more unfavorably than PAR.

The adverse effect profile is an important consideration while prescribing the drug in the treatment of depression. Besides comparing metabolic parameters, the present study also compared various other adverse events over 12 months of

| Table 3: Main adverse effects associated with mirtazapine versus paroxetine |
|-----------------------------------------------|-----------------|-----------------|-----------------|
| **Adverse effects**                         | **Mirtazapine ($n=44$)** | **Percentage** | **Paroxetine ($n=45$)** | **Percentage** |
| Somnolence                                   | 25               | 57              | 2               | 4               |
| Dizziness                                    | 8                | 18              | 3               | 7               |
| Insomnia                                     | 0                | 0               | 20              | 44              |
| Anxiety                                      | 3                | 7               | 10              | 22              |
| Headache                                     | 8                | 18              | 2               | 4               |
| Nausea                                       | 7                | 16              | 22              | 49              |
| Dry mouth                                    | 4                | 9               | 3               | 7               |
| Constipation                                 | 8                | 18              | 4               | 9               |
| Tremors                                      | 1                | 2               | 8               | 18              |
| Sexual dysfunction                           | 0                | 0               | 10              | 22              |
| Fatigue                                      | 12               | 27              | 4               | 9               |
| Increased appetite                           | 33               | 75              | 25              | 56              |
| Weight gain                                  | 33               | 75              | 25              | 56              |
| Impaired fasting blood sugar                 | 15               | 34              | 0               | 0               |
| Increase body mass index                     | 33               | 75              | 25              | 56              |
| Dyslipidemia                                 | 12               | 27              | 0               | 0               |
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23. Chen JL, Spinowitz N, Karwa M. Hypertriglyceridemia, acute treatment with MIRT and PAR. The most common adverse experiences with MIRT were increased appetite (75%), followed by somnolence (57%), fatigue (27%), dizziness (18%), constipation (18%), headache (18%), nausea (16%), dry mouth (9%), anxiety (7%), and tremors (2%). With PAR treatment other common adverse events were increased appetite (56%), which were followed by nausea (49%), insomnia (44%), sexual dysfunction (22%), anxiety (22%), tremors (18%), constipation (9%), dry mouth (7%), dizziness (7%), and last experienced was somnolence (4%). In line with our findings, few studies noted that anticholinergic events and other events, including tremors and dyspepsia were less common and increased appetite, somnolence, headache, fatigue, constipation, and dizziness were more common with MIRT.[8,30,31]

This is probably as a consequence of the drug’s higher affinity for central histaminergic one receptor.[9] Consistent to our findings, few studies also reported that MIRT had no sexual side effects in contrast to SSRIs and less incidences of tremor and nausea.[6,31] As observed in the present study, sexual dysfunction and more gastrointestinal side effects such as nausea, vomiting, dry mouth, constipation, and headache with PAR treatment were also reported in few studies.[8-10,15,32]

However, in our study, almost all the adverse effects were mild, and no adverse effects which required hospitalization were found with either drug. Modified Hartwig and Siegel Assessment Scale was deployed to assess severity of adverse drug effect, which classifies ADR into mild, moderate, and severe.

CONCLUSION

This study reinforces the need to monitor depressed patients regularly for weight gain, glucose dysregulation, and lipid abnormalities. Baseline monitoring of weight, blood sugar, and lipid profile is necessary before initiating treatment with antidepressants.

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