

Research Report

EFFECT OF MIRTAZAPINE ON WEIGHT AND METABOLIC PROFILE AMONG PSYCHIATRIC PATIENTS: A PROSPECTIVE, OBSERVATIONAL STUDY FROM SOUTH INDIA

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Abstract

Background: Treatment with mirtazapine is reported to cause weight gain and adverse metabolic profile in several populations. Limited information is available regarding the metabolic adverse effects of mirtazapine in the Indian population. This study aims to compare the weight and metabolic profile of patients on mirtazapine at baseline and after six months of treatment in a tertiary care Indian setting. **Methodology:** This hospital-based, observational study was conducted in a tertiary care teaching institute in South India. Forty patients prescribed mirtazapine for various psychiatric disorders were included. Weight, body mass index (BMI), lipid profile, blood sugar, and HbA1c values were compared at baseline and after six months of treatment. Descriptive statistics used were mean and standard deviation (SD). **Results:** Statistically significant increases in mean weight (0.97 kg, SD - 2.2; $p = 0.008$), mean BMI (0.39 kg/m², SD - 0.85; $p = 0.006$), mean HbA1C (0.1, SD - 0.21; $p = 0.007$), and mean total cholesterol (6.6 mg/dl, SD - 13.5; $p = 0.005$) were observed after six months of treatment with mirtazapine. **Conclusion:** The study demonstrates the importance of close monitoring of patients who are started on mirtazapine to identify and treat metabolic deregulation promptly. Long-term, controlled studies in larger samples are needed to arrive at meaningful conclusions.

Keywords: Mirtazapine, weight gain, metabolic, tertiary care, India

Introduction

Weight gain is a common side effect of psychotropic drugs. Drug-induced weight gain not only increases the risk of metabolic and endocrine diseases but also reduces treatment compliance.¹ The atypical antidepressant mirtazapine has a unique mechanism of action and pharmacodynamics and is considered an effective, well-tolerated drug.^{2,3} The sedative, antiemetic, and anxiolytic properties of

mirtazapine explains its off-label use for several conditions, such as insomnia, anxiety and stress disorders, obsessive-compulsive disorder, headaches, and migraines.⁴ It is safe in terms of sexual and gastrointestinal adverse effects, has fewer cardiac adverse effects, and has a low propensity to induce seizures.³ Several studies have reported weight gain and worsening of metabolic parameters on treatment with

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mirtazapine.^{5,6} The South Indian state of Kerala has a high prevalence of diabetes and metabolic disorders.^{7,8} The prevalence of depressive and anxiety disorders is also high in this region.⁹ There is a shortage of literature related to the use of mirtazapine and its weight-related adverse effects from India. Hence, this study was done to assess weight gain following treatment with mirtazapine in a subset of the South Indian population taken from our institution.

The primary objective was to compare the weight at baseline and at six months after initiation of mirtazapine. The secondary objective was to compare glycosylated hemoglobin (HbA1c) and lipid profile values before and after six months of starting mirtazapine.

Materials and Methods

This prospective observational study was conducted at the Department of Psychiatry, Government Medical College, Thiruvananthapuram, a tertiary care teaching institute in South India. Patients aged 18 years and above of either sex who were newly prescribed with mirtazapine from the Department of Psychiatry were included in the study. Those patients who were receiving tricyclic antidepressants, MAO inhibitors, antipsychotics such as olanzapine & clozapine, and steroids were excluded.^{10,11} Pregnant and lactating women were also excluded.

Taking α as 5%, β as 20%, the mean and standard deviation (SD) of the pretest (weight at baseline) as 56.88 (11.96) kg, and the mean and SD of the posttest (weight after treatment with mirtazapine) as 67.29 (9.51) kg, based on a study by Uguz et al.,¹² the sample size was calculated to be 19. To improve the power, the sample size was doubled and rounded off to 40. The Institutional Ethics Committee approval was obtained (HEC.No.12/11/2018/MCT). The study period was from January 2019 to March 2020.

The procedure of the study

Forty consecutive patients from both outpatient clinics and inpatient wards who met the study criteria were recruited into the study after obtaining written informed consent. This included consent for participation in the study and obtaining blood samples. Each patient had a baseline assessment at the time of starting mirtazapine. The evaluation included body weight recorded in kilogram (kg) using a standardized digital weighing machine by the principal investigator, height recorded in centimeters (cm), body mass index (BMI), random blood sugar (RBS), HbA1c, and fasting lipid profile. Patient details were collected with a semi-structured proforma using patient interviews, physical examination, and clinical records. Psychiatric diagnosis, medical diagnosis, and medication details were obtained from the clinical records. Each subject was then sent to the institute's central biochemistry laboratory, where the lab tests were done. The results were collected and entered on the first scheduled visit a week later. The subjects were ensured follow-up by scheduling their visits and reminding their appointment date over the phone. All subjects reported compliance with treatment. A follow-up assessment was done six months later, similar to the initial evaluation. The study variables included weight in kg, BMI calculated as weight in kilograms/ height in metres² (Normal: 18.5-22.9kg/m², Overweight: 23-24.9kg/m², Obese: > 25kg/m²), lipid profile comprising of total cholesterol (TC) (normal value - <200mg/dL), triglycerides - <150mg/dL, low-density lipoprotein (LDL) cholesterol - <130mg/dL, high-density lipoprotein (HDL) cholesterol - Normal Range: males - 40-45mg/dL; females - 45-50mg/dL) and glycosylated hemoglobin (HbA1c) - 4%-5.6%.

Statistical Analysis

Data was entered in Microsoft Excel Software.

Table 1. Demographic and clinical profile of the study sample

Variables		Frequency (%) N=40
Age range (years)	21-30	4 (10.0)
	31-40	13 (32.5)
	41-50	8 (20.0)
	51-68	15 (37.5)
Gender	Male	15 (37.5)
	Female	25 (62.5)
Psychiatric diagnoses	<i>Mood disorder</i>	
	Depressive disorder	14 (35.0)
	Bipolar disorder	5 (12.5)
	<i>Anxiety disorders</i>	
	Generalized anxiety disorder	8 (20.0)
	Panic disorder	3 (7.5)
	Phobic anxiety disorder	2 (5.0)
	Insomnia	3 (7.5)
	Obsessive compulsive disorder	3 (7.5)
	Adjustment disorder	1 (2.5)
	Borderline personality disorder	1 (2.5)

Qualitative variables were expressed as proportions. Quantitative variables were described using mean and SD. Pre- and post-test comparison of quantitative variables was done using paired t-test. A p-value of <0.05 was considered statistically significant. Analysis was made using SPSS version 20 for Windows. Effect size (d) was calculated using Cohen's d for paired t-test. A d near 0.2 was taken as a small effect, near 0.5 as a medium effect, and near 0.8 as a large effect.¹³

Results

Of the 40 participants, 15 were male (37.5%) and 25 (62.5%) were female. The mean age of the patients was 46.3 (SD - 12) years. The demographic and clinical profile of the participants is summarized in Table 1. The most common psychiatric diagnosis was mood disorder (47.5%) followed by anxiety disorder (32.5%). Twenty-five out of the 40 participants

had a medical comorbidity. Diabetes mellitus was the most common medical condition, followed by dyslipidemia (See Table 2.)

Out of 40 patients initiated on mirtazapine, 38 had other psychiatric medications such as benzodiazepines, antipsychotics, other antidepressants, and anxiolytics. Nineteen patients had another antidepressant and a benzodiazepine (See Table 3.)

The mean weight increased from 64.55 kg (SD - 11.69) at baseline to 65.51 kg (SD - 10.76) at the end of six months. The rise in mean weight of 0.97 kg (SD - 2.2) was statistically significant ($p = 0.008$). The mean increase in BMI after six months by 0.39 kg/m² (SD - 0.85) was statistically significant ($p = 0.006$). The mean baseline HbA1c was 5.08% (SD - 0.80), which rose to 5.18% (SD - 0.90) at the end of six months. The mean rise of HbA1c by 0.1% (SD - 0.21) was statistically significant ($p = 0.007$). The mean increase in serum cholesterol at six months was statistically significant ($p = 0.005$). The changes in triglyceride, LDL, and HDL levels at six months were not significant (see Table 4). The effect size for change in weight, BMI, HbA1c, and lipid profile was small (less than or near 0.2).

Discussion

This observational study was conducted in a real-world clinical setting on 40 subjects. Each subject prescribed with mirtazapine had a baseline assessment and a follow-up assessment at six months. Follow-up was

Table 2. Distribution of medical comorbidity in the study sample

Medical comorbidity	Frequency (%) (N=40)
Diabetes mellitus	10 (25.0)
Dyslipidemia	14 (35.0)
Systemic hypertension	7 (17.5)
Thyroid disorders	2 (5.0)
Acid peptic disease	1 (2.5)
Bronchial asthma	1 (2.5)
Nil	15 (37.5)

Table 3: Prescription patterns of psychiatric drugs

Psychiatric medications	Frequency (%) (N=40)
Mirtazapine	2 (5.0)
Mirtazapine + antipsychotic*	2 (5.0)
Mirtazapine + benzodiazepine**	9 (22.5)
Mirtazapine + benzodiazepine + antipsychotic*	8 (20.0)
Mirtazapine + another antidepressant + antipsychotic***	19 (47.5)

* - Risperidone 1-4mg/Aripiprazole 2-15 mg/
 Quetiapine 25-200mg, ** - Lorazepam 1-2mg/
 Clonazepam 0.25-2mg, *** - Sertraline 25-200mg/
 Escitalopram 5-20mg/Venlafaxine 75-225 mg

ensured in all subjects by scheduling the appointment dates and sending reminders over the telephone. We compared weight, BMI, HbA1c, and lipid profiles at baseline and after six months of treatment with mirtazapine.

Our study observed a significant weight gain in patients taking mirtazapine after six months of treatment ($p = 0.008$). Weight gain associated with mirtazapine has been reported in several studies. Gafoor et al. (2018) conducted a population-based cohort study on subjects taking antidepressants.¹⁴ One of the outcome measures was an increase of 5% in body weight. Among the various antidepressants, mirtazapine was associated with the highest adjusted rate ratio of weight gain. A meta-analysis of studies comparing multiple antidepressants and their impact on weight was conducted by Serretti et al. (2010).¹⁵ They reported that compared to other antidepressants, mirtazapine was associated with a greater risk of weight gain. Other studies that reported weight gain with Mirtazapine include those by Uguz et al. (2015)¹² and Song et al. (2015).¹⁶ An open-label clinical trial of mirtazapine in healthy male volunteers by Hennings et al. (2019) reported no significant weight gain.¹⁷ Subjects of this study were provided a controlled environment with a standard diet, regular exercise, and regular sleep. The controlled setting and selection of healthy volunteers could be the reason for the

lack of weight gain in this study.¹⁷

Our study found a significant increase in mean BMI of 0.39 kg (SD - 0.85; $p < 0.0006$) after six months. A similar increase in BMI was reported by Song et al. (2015)¹⁶ and Kraus et al. (2002).¹⁹ Laimer et al. (2002) conducted an open 6-week trial of mirtazapine in seven depressed women. Compared to healthy age- and weight-matched controls, a significant increase in fat mass was observed in study subjects.⁵ Though not significant, a reduction in body weight and BMI following mirtazapine exposure was reported in the study by Hennings et al. (2019).¹⁷ In this study, healthy volunteers were observed in a controlled setting, hence the probable reduction in BMI.

Our study showed an increase in mean HbA1c by 0.1% (SD - 0.21), which was statistically significant ($p = 0.007$). Hennings et al. (2019) reported a slight increase in HbA1c.¹⁷ This is in contrast to the study by Song et al. (2014), which did not show any significant change in mean HbA1c ($p = 0.1$). This was a case-control study of cases with both diabetes and depression treated with mirtazapine and controls with diabetes and depression who were not on mirtazapine. Both groups showed a decrease in HbA1c levels at the end of six months.¹⁸ In this study, all the subjects had diabetes mellitus, whereas in our study, only 10% had diabetes. Several factors other than diabetes, such as exercise, diet, fatty liver, drugs, and hemoglobin levels, affect HbA1c values. Probable factors that could have affected HbA1c values in our study are diet and activity levels, which were not monitored.²⁰ It is not known whether other medications have contributed to the change.

A significant increase in mean total cholesterol was noted at the end of six months. The change in mean LDL, triacylglycerides (TAG), and HDL values after six months was not significant. In contrast, another study reported a favorable lipid profile after six months of treatment with mirtazapine, with a decrease in mean TC and mean LDL, an increase in mean HDL, and no

Table 4. Comparison of mean weight, lipid profile, body mass index, HbA1C, and lipid profile

Variable	Baseline Mean (SD)	6 months Mean (SD)	Change in Mean (SD)	p-value	Effect size (d)
Weight (kg)	64.55 (11.69)	65.51 (10.76)	0.97 (2.2)	0.008*	0.085
Body Mass Index (kg/m ²)	24.36 (3.28)	24.76 (3.04)	0.39 (0.85)	0.006*	0.126
Glycosylated hemoglobin	5.08 (0.8)	5.18 (0.9)	0.1 (0.21)	0.007*	0.11
S. Cholesterol	201.7 (26.3)	208.2 (31.3)	6.6 (13.5)	0.005*	0.22
Triacylglycerides	151.9 (25.6)	153.8 (24.3)	1.9 (11.9)	0.374	0.075
Serum High-Density Lipoprotein	44.7 (7.7)	43.6 (9.5)	1.1 (4.2)	0.168	0.13
Serum Low-Density Lipoprotein	92.8 (8.8)	94.7 (7.9)	1.9 (12.5)	0.928	0.227

* – p value < 0.05

change in TAG.¹⁸ Nicholas et al. (2003) reported a significantly increased TC in the fourth week and a transient rise in triglycerides that normalized by week 4.²¹ Hennings et al. (2019) reported no change in lipid profile values in association with mirtazapine.¹⁷

Our study has several limitations. The study population was heterogeneous in terms of clinical diagnosis, comorbid medical conditions, and medications. The primary psychiatric diagnosis, its severity, and treatment response are also factors that can affect weight and metabolism^{24,25} Most patients were already receiving other psychotropic agents to which mirtazapine was an add-on drug²⁶. Twenty-nine out of 40 subjects were receiving an antipsychotic-risperidone 1-4mg, quetiapine 25-200mg, or aripiprazole 2-15mg. None of the patients were on olanzapine or clozapine. Risperidone and quetiapine are associated with a moderate risk of weight gain and metabolic changes, especially in higher doses. These drugs could have acted as confounders. Being an observational study in a naturalistic clinical setting, it was not feasible to exclude patients with all other psychotropic drugs.^{24, 25, 26} Rigid exclusion criteria would have resulted in an inadequate sample size. Hence, the exclusion criteria were set to exclude only drugs with a propensity to cause severe weight gain.^{10, 11}

Approximately two-thirds of the participants had one or more medical comorbidities.

Twenty-five percent of the study subjects had diabetes mellitus, 35% had dyslipidemia, and 17.5% had systemic hypertension. The South Indian state of Kerala is known to have high prevalence rates of non-communicable diseases – 23.6% for diabetes, 31.0% for hypertriglyceridemia, and 44.5% for systemic hypertension, respectively.²⁷ The participants in our study received one or more medications, such as metformin, glimepiride, atorvastatin, thyroxine, losartan, amlodipine, and cilnidipine. All of them had normal thyroid status. None of the patients received insulin, diuretics, steroids, or beta-blockers, which are drugs capable of causing marked weight changes.¹¹ Some other confounding factors that could have affected weight and metabolic parameters are diet, activity level, and sleep.^{28,29} This being an observational study, these confounders could not be adjusted for.

The effect size for change in weight, BMI, HbA1c value, and lipid profile was small (less than or near 0.2). Despite the small effect size, these parameters have clinical significance. Over the long term, even small amounts of weight gain and change in BMI can accumulate to a clinically significant one. Even small increases in BMI can be clinically significant, especially in patients already at risk for conditions such as hypertension, type 2 diabetes, and cardiovascular disease. HbA1c is a marker of long-term blood glucose levels. A slight worsening of glucose control, i.e., an increase in

HbA1c values, can be critical in patients with or at risk for diabetes.¹⁵

Our study was done on a limited sample of 40 patients. We did not select a healthy control group. Larger samples are required to make meaningful conclusions. We observed the subjects for a short duration of six months. Longer duration, controlled studies are needed to identify causative factors and to assess whether there would be a change in effect size. Only if subjects are followed up for a longer time can it be concluded whether the changes observed in our study are transient or whether there is a genuine long-term risk of a metabolic disorder. Further studies, taking into account other important variables such as psychiatric diagnosis, severity of depressive disorder, loss of appetite, atypical features, premorbid weight, activity level, and physical illnesses, are needed to understand the impact of mirtazapine on weight gain.

Conclusion

To conclude, mirtazapine use for six months in a clinical setting is associated with a statistically significant increase in mean weight. Even though the effect size is very small, increases in BMI, HbA1C, and total cholesterol are other findings associated with mirtazapine use. The study demonstrates the importance of monitoring patients started on mirtazapine closely, to detect changes in weight and metabolic parameters. A combination of mirtazapine with other psychotropic drugs could increase the risk of metabolic derangements. Long-duration, controlled studies in larger samples are required to conclude whether mirtazapine is a risk factor for weight gain and metabolic syndrome in the Indian setting.

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Conflicts of Interest: None

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