Effect of Mirtazapine Treatment on Body Composition and Metabolism

Markus Laimer, M.D.; Karin Kramer-Reinstadler, M.D.; Markus Rauchenzauner, M.D.; Theresia Lechner-Schoner, M.D.; Robert Strauss, M.D.; Julia Engl, M.D.; Eberhard A. Deisenhammer, M.D.; Hartmann Hinterhuber, M.D.; Josef R. Patsch, M.D.; and Christoph F. Ebenbichler, M.D.

Objective: Weight gain is a common side effect of psychotropic medications. Mirtazapine, a widely used antidepressant, induces adverse metabolic effects such as an increase in body weight. The aim of this study was to investigate the influence of mirtazapine treatment on body weight, body fat mass, glucose metabolism, lipoprotein profile, and leptin and its soluble receptor in a prospective, controlled study design.

Method: Seven women who met the ICD-10 diagnostic criteria for a depressive episode (ICD-10: F31–F33) were assigned to monotherapy with mirtazapine and observed for a 6-week period. Seven mentally and physically healthy female volunteers matched for age and body weight served as a control group. Data were collected from November 2002 to December 2003.

Results: The mean ± SD body weight increased from 63.6 ± 13.1 kg to 66.6 ± 11.9 kg during mirtazapine treatment (p = .027). Fat mass increased in study subjects from 20.9 ± 9.6 kg to 22.1 ± 9.3 kg (p = .018). Insulin, glucose, and the homeostasis model assessment (HOMA) index for insulin resistance and lipid parameters remained stable. Leptin concentrations increased from 23.0 ± 17.1 ng/mL to 40.9 ± 27.2 ng/mL (p = .018), whereas the soluble leptin receptor concentrations remained stable during mirtazapine treatment. In the control subjects, the investigated parameters remained stable. Between-group analyses of change scores revealed significant differences for body weight (p = .010), body mass index (p = .013), fat mass (p = .035), and leptin (p = .013).

Conclusion: The antidepressant therapy with mirtazapine was associated with a significant increase in body weight, body fat mass, and leptin concentration. In contrast to other psychotropic medications inducing weight gain, such as some second-generation antipsychotics, mirtazapine treatment did not influence the glucose homeostasis.

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Received July 27, 2005; accepted Oct. 6, 2005. *From the Department of Internal Medicine, Division of General Internal Medicine (Drs. Laimer, Rauchenzauner, Engl, Patsch, and Ebenbichler), and Department of Psychiatry, Division of General Psychiatry (Drs. Kramer-Reinstadler, Lechner-Schoner, Strauss, Deisenhammer, and Hinterhuber), Innsbruck Medical University, Innsbruck, Austria.*

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Corresponding author and reprints: Christoph F. Ebenbichler, M.D., Universitätsklinik für Innere Medizin, Universität Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria (e-mail: Christoph.Ebenbichler@uibk.ac.at).

Weight gain is a common side effect of psychotropic medications.[1] Mirtazapine, a widely used tetracyclic antidepressant, induces adverse metabolic effects such as an increase in body weight.[2]

Mirtazapine enhances noradrenergic and 5-HT_{1A}–mediated serotonergic neurotransmission via antagonism of central α_2-adrenergic autoreceptors and heteroreceptors and postsynaptic blockade of 5-HT_2 and 5-HT_3 receptors.[3] It does not inhibit norepinephrine or serotonin reuptake. As a noradrenergic and specific serotonergic antidepressant (NaSSA), mirtazapine is an antidepressant with a low frequency of side effects, such as an influence on heart rate and blood pressure, a low potential to induce epilepsy, and a low degree of induction of the cytochrome P450 system.[4]

Several antidepressants are known to induce substantial weight gain, partly due to an increase in fat mass, which is the major source of serum leptin levels. One of them, amitriptyline, a tricyclic antidepressant, increased leptin levels.[5] Additionally, excessive weight gain was observed with discontinuation of therapy in 44% of amitriptyline patients.[6] Mirtazapine, when compared with amitriptyline, is associated with a lower rate of weight gain, which occurred mainly within the first weeks of treatment.[1,7]

Patients treated with mirtazapine often report ravenous appetite, so-called carbohydrate craving. Mirtazapine, when compared with placebo, increased appetite (17% vs.

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2%) and weight (12% vs. 2%).[8] A disturbance of neurobiological regulations controlling food intake is one possible pathomechanism for weight gain. Fernstrom[9] showed a reduction of the basal metabolic rate in patients treated with antidepressants, thus contributing to the reported weight gain.

Similar to mirtazapine, the second-generation antipsychotic agents (SGAs) clozapine and olanzapine induce weight gain and, consequently, increase serum leptin levels.[10,11] Disturbances in glucose homeostasis during treatment with these SGAs have recently been linked to induction of insulin resistance.[12–14] Olanzapine impairs glycogen synthesis via inhibition of the classical insulin-signaling cascade, and this inhibitory effect may lead to the induction of insulin resistance in olanzapine-treated patients.[15]

The aim of this study was to investigate the influence of mirtazapine treatment on body composition, on glucose and lipid metabolism, and, finally, on the adipocytokine leptin and its soluble receptor isoform (sOB-R) in a prospective, controlled study.

METHOD

Subjects

Seven consecutively admitted women who met the ICD-10 diagnostic criteria for a depressive episode (ICD-10: F31–F33) and who were assigned to monotherapy with mirtazapine (30–45 mg/day) were included in the study. The observation period was 6 weeks. Their mean (± SD) age was 42.7 (± 4.6) years. The comparison subjects were recruited from the hospital staff and were matched for age and body weight. Patients and control subjects were on a stable diet before study entry. All patients gave written informed consent to participate in this study. The study was approved by the Ethical Committee of the Innsbruck Medical University. Data were collected from November 2002 to December 2003.

Study Protocol and Outcome Measures

Body composition was determined at baseline and 6 weeks after mirtazapine treatment by impedance analysis with a multifrequency bioelectric impedance 2000-M analyzer (Data Input, Hofheim, Germany). Fat-free mass and fat mass were determined by using Nutri 4 software (Data Input).

Blood was obtained from a peripheral vein after an overnight fasting at baseline and 6 weeks after the initiation of the mirtazapine treatment. Blood was centrifuged, and sera were stored at –80°C.

Plasma glucose concentrations were measured using a standard enzymatic method (Roche Diagnostic Systems, Basel, Switzerland). Plasma insulin concentrations were measured using a microparticle enzyme immunoassay (Abbott, Vienna, Austria).

The homeostasis model assessment (HOMA) index for β-cell function and for insulin resistance were calculated as described in detail elsewhere.[16]

Lipid parameters were determined using standard methods on a Cobas Mira Analyser (Roche, Vienna, Austria).

Leptin was measured using an enzyme-linked immunosorbent assay kit (ELISA) (R&D Systems, Wiesbaden, Germany).

Soluble leptin receptor concentration was measured using a sOB-R ELISA (Chemicon International, Temecula, Calif.). The bound fraction of leptin was calculated as described elsewhere.[17,18]

Data Analyses

A Wilcoxon test was used for within-group comparisons (week 6 vs. baseline). A Mann-Whitney test was performed for the between-group comparisons with respect to changes in all investigated measures between baseline and week 6.

RESULTS

In the mirtazapine group, the study subjects gained a mean of 3.0 kg during the observation period of 6 weeks, a weight gain that was highly significant (Table 1). Maximum weight gain was 4.5 kg; 1 patient lost 1.0 kg of body weight. Mean fat mass as determined by body impedance analysis increased in the mirtazapine group by 1.2 kg (Table 1). Maximum fat mass gain was 2.9 kg in 1 patient. Paradoxically, the patient with the weight loss of 1.0 kg also gained 0.4 kg of fat mass, suggesting a substantial change in body composition. In the control group, weight and fat mass remained stable.

Glucose, insulin, and the HOMA index for insulin resistance increased in the mirtazapine group, though not statistically significantly (Table 1).

Similar to the glucose homeostasis parameters, the lipid parameters were not significantly changed during mirtazapine treatment (Table 1). The adipocytokine leptin increased significantly from 23.0 ± 17.1 ng/mL to 40.9 ± 27.2 ng/mL in mirtazapine-treated patients (Table 1). Soluble leptin receptor concentrations remained stable during mirtazapine treatment. The calculated bound fraction of leptin decreased significantly from 59% ± 37% before the initiation of mirtazapine treatment to 31% ± 19% after the 6-week observation period (Table 1).

DISCUSSION

Mirtazapine is a widely used, new-generation antidepressive agent. Weight gain is a frequent and unwanted side effect of psychopharmacotherapy and the most reported side effect of mirtazapine therapy.[2]

After a 6-week treatment period with mirtazapine, our patients gained a mean 3.0 kg of total body weight. The

Table 1. Weight, Body Fat, Glucose Homeostasis, Lipid, and Adipocytokine Parameters of Study and Control Subjects

	Subjects Taking Mirtazapine (N = 7)					Control Subjects (N = 7)					Between-Group Analysis of Change Scores
	Baseline		Week 6		Analysis	Baseline		Week 6		Analysis	
Measure	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p	p
Weight (kg)	63.6	13.1	66.6	11.9	.027	64.9	7.8	64.2	7.9	.075	.010
Body mass index (kg/m^2)	23.3	4.5	24.4	4.2	.028	23.6	3.4	23.3	3.5	.075	.013
Fat mass (kg)	20.9	9.6	22.1	9.3	.018	16.5	6.4	16.1	6.4	.396	.035
Glucose (mg/dL)	93	10	94	9	1.000	96	8	93	5	.499	.701
Insulin (μU/mL)	5.3	2.1	7.4	4.7	.398	6.7	3.0	4.8	2.9	.063	.064
HOMA IR (mmol × mU^{-1} × 1^{-2})	1.3	0.5	1.7	1.2	.290	1.6	0.8	1.1	0.7	.063	.085
Cholesterol (mg/dL)	212	25	219	24	.128	185	39	180	48	.611	.141
Triglycerides (mg/dL)	109	53	115	66	.398	83	40	79	33	1.000	.522
LDL cholesterol (mg/dL)	134	25	135	23	.866	105	35	104	42	.735	.609
HDL cholesterol (mg/dL)	56	15	62	14	.128	63	14	60	13	.735	.225
Leptin (ng/mL)	23.0	17.1	40.9	27.2	.018	25.9	17.2	26.0	18.9	1.000	.013
Soluble leptin receptor (U/mL)	37.8	8.3	36.5	8.0	.612	38.5	11.9	43.4	10.7	.063	.085
Leptin bound/free ratio (%)	59	37	31	19	.018	54	39	56	37	.866	.013

Abbreviations: HDL = high-density lipoprotein, HOMA IR = homeostasis model assessment index for insulin resistance, LDL = low-density lipoprotein.

mean increase in fat mass—as determined by body impedance measurement—was 1.2 kg. Comparable studies in patients treated with the SGAs clozapine and olanzapine revealed a significant weight gain of 3 to 4 kg in a similar observation period.[10,19–22]

The disturbance in glucose metabolism is a well-known side effect of some SGAs. For instance, olanzapine induces disturbances in glucose metabolism, presumably by inducing insulin resistance.[14,15] Although mirtazapine leads to a comparable weight gain, glucose metabolism remained unaffected in our study. Fasting glucose levels remained stable after an average medication period with mirtazapine of 6 weeks. None of the patients developed overt diabetes or impaired fasting glucose according to American Diabetes Association (ADA) criteria. Fasting insulin concentrations increased from 5.3 ± 2.1 μU/mL at baseline to 7.4 ± 4.7 μU/mL after the study period, though the increase was not statistically significant.

As a model of the glucose-insulin feedback system in the overnight-fasted state, we calculated the HOMA index for insulin resistance. The model consists of a number of nonlinear empirical equations describing the function of tissues involved in glucose regulation. It allows the deduction of insulin sensitivity (or resistance) from pairs of fasting glucose and insulin measurements. Also, the HOMA index for insulin resistance remained unaltered in the mirtazapine-treated patients, arguing against the induction of insulin resistance in these patients.

As another metabolic side effect, an increase in the cholesterol levels of mirtazapine-treated patients was reported. However, low-density lipoprotein cholesterol levels and the ratio of total cholesterol to high-density lipoprotein cholesterol were not significantly affected by mirtazapine treatment.[23] In this study, mirtazapine treatment did not alter the lipid profile.

During the 6-week observation period, serum leptin levels increased significantly over baseline levels for mirtazapine-treated patients. Since the fat mass of our patients increased and fat mass is the major determinant of circulating leptin concentration, these results were not unexpected. Baseline and week-6 fat mass and leptin levels showed significant relationships ($r = 0.857$, $p = .014$ and $r = 0.893$, $p = .007$, respectively). In contrast, δ values of these parameters did not correlate to each other ($r = –0.536$, $p = .215$). However, leptin concentrations nearly doubled, despite the only modest increase in fat mass.[24] Also, the calculated bound fraction of leptin decreased from 59% before the initiation of mirtazapine treatment to 31% after the 6-week observation period, suggesting a substantial dysregulation of the leptin-sOB-R system during mirtazapine treatment.

Despite the limited number of study subjects, we could confirm our hypothesis that mirtazapine monotherapy is associated with significant weight gain and an increase in body fat. Both weight gain and increase in body fat were associated with a significant increase in serum leptin levels. One of the physiologic roles of leptin is as an appetite-reducing feedback signal in the event of fat increase. In this study, sOB-R concentrations remained stable during mirtazapine treatment. In a recent study,[18] insulin resistance and abdominal obesity were associated with low sOB-R and a low bound/free ratio of leptin independent of fat mass. Interestingly, in this study, the bound fraction of leptin decreased significantly after the treatment with mirtazapine. However, the absence of disturbances in glucose homeostasis may contribute to unchanged sOB-R levels during the treatment period.

In conclusion, the antidepressant therapy with mirtazapine is associated with a significant increase in body weight, body fat mass, and leptin concentration. In contrast to other psychotropic medications inducing

weight gain, mirtazapine treatment did not alter the glucose homeostasis.

Drug names: clozapine (Clozaril, FazaClo, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa).

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