Eur Arch Psychiatry Clin Neurosci (2011) 261:173–177
DOI 10.1007/s00406-010-0164-4

ORIGINAL PAPER

# The effect of a 4-week treatment with reboxetine on metabolic parameters of depressed inpatients

**Georgios Paslakis · Maria Gilles · Florian Lederbogen · Claudia Schilling · Barbara Scharnholz · Michael Deuschle**

Received: 12 January 2010 / Accepted: 19 October 2010 / Published online: 30 October 2010


**Abstract** In the present study, we examined several metabolic parameters in a group of 19 acutely depressed inpatients with major depression (DSM-IV) at baseline and investigated their development after 4 weeks of antidepressant treatment with reboxetine (8–12 mg per day). We performed oral glucose tolerance tests and additionally assessed free saliva cortisol and post-dexamethasone cortisol levels, as well as whole cholesterol, HDL- and LDL-cholesterol, triglycerides, free fatty acids, waist and hip circumference, heart rate, systolic and diastolic blood pressure. Furthermore, we evaluated the incidence of a metabolic syndrome and investigated the metabolic changes in depressed patients with and without a metabolic syndrome. We found 42.1% of patients to fulfil the criteria for a metabolic syndrome. Overall, reboxetine was well tolerated with essentially no side effects during the observation period. A 4-week treatment with reboxetine showed a beneficial effect on several metabolic parameters that was independent from treatment outcome and could therefore theoretically be attributed to the pharmacological profile of the drug. Due to the preliminary character of the present investigation, no conclusions about the clinical efficacy of reboxetine can be drawn.

**Keywords** Depression · Metabolic syndrome · Antidepressant · Reboxetine · HPA axis · Cortisol

G. Paslakis (✉) · M. Gilles · F. Lederbogen · C. Schilling · B. Scharnholz · M. Deuschle
Central Institute of Mental Health, Department of Psychiatry and Psychotherapy, J5, 68159 Mannheim, Germany
e-mail: Georgios.Paslakis@zi-mannheim.de

## Introduction

Studies suggest that depression may be a risk factor for several metabolic disturbances. Thus, depression has been associated with visceral fat accumulation, a higher waist-to-hip ratio [17, 20], as well as blood pressure dysregulation [10]. Depressed patients frequently have insulin resistance, which may resolve after recovery from depression [4, 13, 18, 21, 22]. Also, the association between depression and diabetes [1, 3] has been recognised for many years and was confirmed in a meta-analysis [7]. It may be assumed that both behavioural as well as biological factors, e.g. hypercortisolemia [19], contribute to the relationship between affective and metabolic disorders. The concomitance of abdominal obesity, dyslipidemia (elevated triglycerides, reduced HDL-cholesterol), elevated blood pressure and elevated fasting glucose are a cluster of risk factors that constitute a syndrome, called the metabolic syndrome (MS). The prevalence of the MS in depression has been reported with up to 48.1% in inpatients [16].

In the present study, we assessed the metabolic parameters and cortisol levels at baseline in a group of acutely depressed inpatients and examined their development after 4 weeks of antidepressant treatment with reboxetine. Furthermore, we evaluated the incidence of a MS and investigated the metabolic changes in depressed patients with and without a MS.

## Methods

### Subjects

We included 19 inpatients with major depression according to DSM-IV (HAMD-21 $\geq$ 18). Exclusion criteria were other relevant axis-I disorders. Subjects gave written

informed consent, and the study was approved by the local ethics committee.

The diagnosis of a MS was verified according to the criteria of the American National Cholesterol Education Program (NCEP) Treatment Panel III (ATP III). The NCEP ATP III defines the MS as being the presence of three or more of the following criteria: waist circumference >102 cm (40 in.) in men, >88 cm (35 in.) in women, hypertriglyceridemia ≥150 mg/dl, HDL-cholesterol <40 mg/dl in men, <50 mg/dl in women, blood pressure ≥135/85 mmHg and fasting glucose ≥110 mg/dl. Patients taking cholesterol-lowering, blood-pressure-lowering or glucose-lowering medication were considered to have met the respective criterion.

### Treatment

After a 1-week washout period, patients were treated with reboxetine (8–12 mg per day) for 4 weeks. Throughout the study period, no other psychotropic medication except lorazepam and zolpidem was allowed. Treatment response was considered as a drop in HAMD score of at least 50% during the active treatment phase, and remission was assumed when the final score was below seven.

### Study procedures

At study begin, we evaluated oral glucose tolerance (OGT-test) using a standard oral 75-g glucose loading after a washout period of 6 days and again after 28 days of treatment. In brief, a 75-g glucose load was given at 10.00 a.m. after an overnight fast. Blood was sampled at baseline and 90 and 120 min after glucose ingestion using a catheter in an antecubital vein. Samples were immediately centrifuged and stored at −80°C for analysis of insulin and glucose. We used the Insulin Sensitivity Index (ISI) by Stumvoll et al. [15] as to characterize insulin sensitivity. Each day, saliva was collected for the measurement of free cortisol at 08.00 a.m. The mean saliva cortisol concentrations during week 1 (washout) and week 4 were used for further analysis. Both at baseline and after the 4-week treatment following parameters were additionally assessed: whole cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, free fatty acids, BMI, waist and hip circumference. We also assessed heart rate and systolic and diastolic blood pressure as the mean value of four measurements in sedentary position (in 2-minute intervals). At study baseline and after 4 weeks of treatment, a standard dexamethasone suppression test (DST) using 1.5 mg of oral dexamethasone was carried out.

### Statistical analysis

Statistical analyses (*t*-tests, analysis of variance) were carried out using the SPSS version 16.0 for Windows. All values were given as mean ± standard deviation. A $P$ value <0.05 was considered as the level of significance.

## Results

Ten female and nine male patients were included in the analysis (age 43 ± 11 years). The NCEP ATP III criteria for a MS at study begin were met in 8 of 19 patients included (42.1%); 15.8% of patients met no criteria, 15.8% met 1 criterion, 26.3% met 2 criteria, 36.8% met 3 criteria and 5.3% met 4 criteria.

Patients fulfilling the criteria for a metabolic syndrome (MS+) had significantly higher levels for glucose in the OGT-test after 90 and 120 min, as well as for systolic and diastolic blood pressure, waist and hip circumference, waist-to-hip ratio and the BMI, while HDL-cholesterol and the index of insulin sensitivity $ISI_{Stumvoll}$ were significantly lower compared to those patients without a metabolic syndrome (MS−) (Table 1). Regarding all other parameters (including free saliva cortisol and the post-dexamethasone cortisol concentrations), no significant differences were seen between the two groups.

In addition, the rm-ANOVA with patient affiliation to either MS+ or MS− being the between subject factor showed that the presence of a MS was associated with a statistically significant decrease in several metabolic parameters over the course of treatment ("metabolic change x metabolic syndrome" interaction) with regard to whole cholesterol, LDL-cholesterol, BMI and mean systolic blood pressure (Fig. 1). Such an interaction could not be observed in all other parameters (including free saliva cortisol and the post-dexamethasone cortisol levels). Neither gender nor age as a covariate changed our observations mentioned above. By using remission status as the between subject factor in the rm-ANOVA, we also did not observe significant "metabolic change x remission status" interactions.

Finally, the overall change in mean HAMD scores after 4 weeks of reboxetine treatment was highly significant (23.2 vs. 7.6; $P < 0.001$), again with no influence of gender or age. The change in HAMD scores was significantly greater in the group of MS− patients (Fig. 1), although patients of the MS− group had significantly higher HAMD scores at baseline compared to the MS+ group (Table 1).

## Discussion

In this study, we examined the incidence of a MS in our group of acutely depressed inpatients and investigated differences between patients with and without a MS during the course of antidepressant treatment with reboxetine. We found 42.1% of patients to fulfil the criteria for a MS.

**Table 1** The comparison of several metabolic parameters at study baseline in patients with (MS+) and without a metabolic syndrome (MS−) using unpaired *t*-tests revealed significant differences for glucose in the OGT-test after 90 and 120 min, as well as for systolic and diastolic blood pressure, waist and hip circumference, waist-to-hip ratio, BMI, HDL-cholesterol and the index of insulin sensitivity $ISI_{Stumvoll}$

| Baseline | MS+/MS− | *N* | Mean | Standard deviation | *P* |
|---|---|---|---|---|---|
| Glucose OGT-test 90 min. (mg/dl) | MS− | 11 | 108.5 | 28.8 | 0.004 |
| | MS+ | 8 | 157.0 | 34.9 | |
| Glucose OGT-test 120 min. (mg/dl) | MS− | 11 | 91.2 | 19.0 | 0.001 |
| | MS+ | 8 | 137.3 | 33.5 | |
| HDL-cholesterol (mg/dl) | MS− | 11 | 48.7 | 11.3 | 0.007 |
| | MS+ | 8 | 37.1 | 2.5 | |
| Systolic blood pressure (mm Hg) | MS− | 11 | 110.8 | 12.2 | 0.001 |
| | MS+ | 8 | 135.9 | 16.3 | |
| Diastolic blood pressure (mm Hg) | MS− | 11 | 73.0 | 9.1 | 0.024 |
| | MS+ | 8 | 84.0 | 10.2 | |
| Waist circumference (cm) | MS− | 11 | 88.1 | 11.9 | 0.001 |
| | MS+ | 8 | 110.5 | 12.9 | |
| Hip circumference (cm) | MS− | 11 | 104.6 | 8.6 | 0.011 |
| | MS+ | 8 | 115.9 | 8.5 | |
| Waist-to-hip ratio | MS− | 11 | 0.8 | 0.8 | 0.004 |
| | MS+ | 8 | 1.0 | 0.6 | |
| BMI ($kg/m^2$) | MS− | 11 | 25.2 | 4.3 | 0.001 |
| | MS+ | 8 | 33.3 | 4.5 | |
| $ISI_{Stumvoll}$ ($\mu mol\ kg^{-1}\ min^{-1}\ pM^{-1}$) | MS− | 11 | −1.0 | 0.2 | <0.001 |
| | MS+ | 8 | −1.4 | 0.2 | |
| HAMD | MS− | 11 | 24.4 | 4.7 | 0.022 |
| | MS+ | 8 | 20.3 | 2.3 | |

A 4-week treatment of unipolar depressed patients with reboxetine led to a statistically significant decrease in whole cholesterol, LDL-cholesterol, BMI and mean systolic blood pressure in patients with a comorbid MS. Our results were independent from treatment outcome.

A similar follow-up study by Richter et al. [14] examining the prevalence of the MS in a sample of depressed inpatients found no differences between the state of acute depression and remission regarding several laboratory values—with the exception of triglycerides. However, patients included in that study were still being treated with a great number of different classes of psychotropic drugs at study entry, thus complicating the interpretation of the results. Several psychotropic drugs, especially antipsychotics, have also been consistently associated with metabolic disturbances [e.g. 11]. Antidepressant treatment in general has been shown to have a beneficial effect on lipid regulation [8], to improve glycemic control in depressed diabetic patients [12] and to increase insulin sensitivity in nondiabetic depressed patients with response or remission to treatment [21, 22].

Overall, reboxetine was well-tolerated with essentially no side effects during the observation period, and the patients felt comfortable with this treatment. However, no final conclusions about the long-term safety of the drug can be drawn. The beneficial effects of the 4-week treatment with reboxetine on the metabolic parameters tested were independent from treatment outcome and could therefore theoretically be attributed to the pharmacological profile of the drug in terms of a selective noradrenergic reuptake inhibition and lack of the additional undesirable binding properties of other antidepressants (e.g. tricyclic antidepressants and H1-receptor antagonism). Even so, our observations of a metabolic amelioration cannot be attributed exclusively to the study drug, but probably also to factors like participation in physical activities during inpatient treatment, change in diet habits etc. As far as the efficacy of the drug is concerned, a recent multiple treatments' meta-analysis has suggested inconsistent efficacy in major depression with a less effectiveness than the SSRIs [2]. In our study, which was conducted before the publication of the meta-analysis by Cipriani and co-workers (2009), we chose to investigate the effect of reboxetine on metabolic parameters due to its above-mentioned noradrenergic mode of action. Reboxetine remains an approved antidepressant in Europe, but has never been approved in

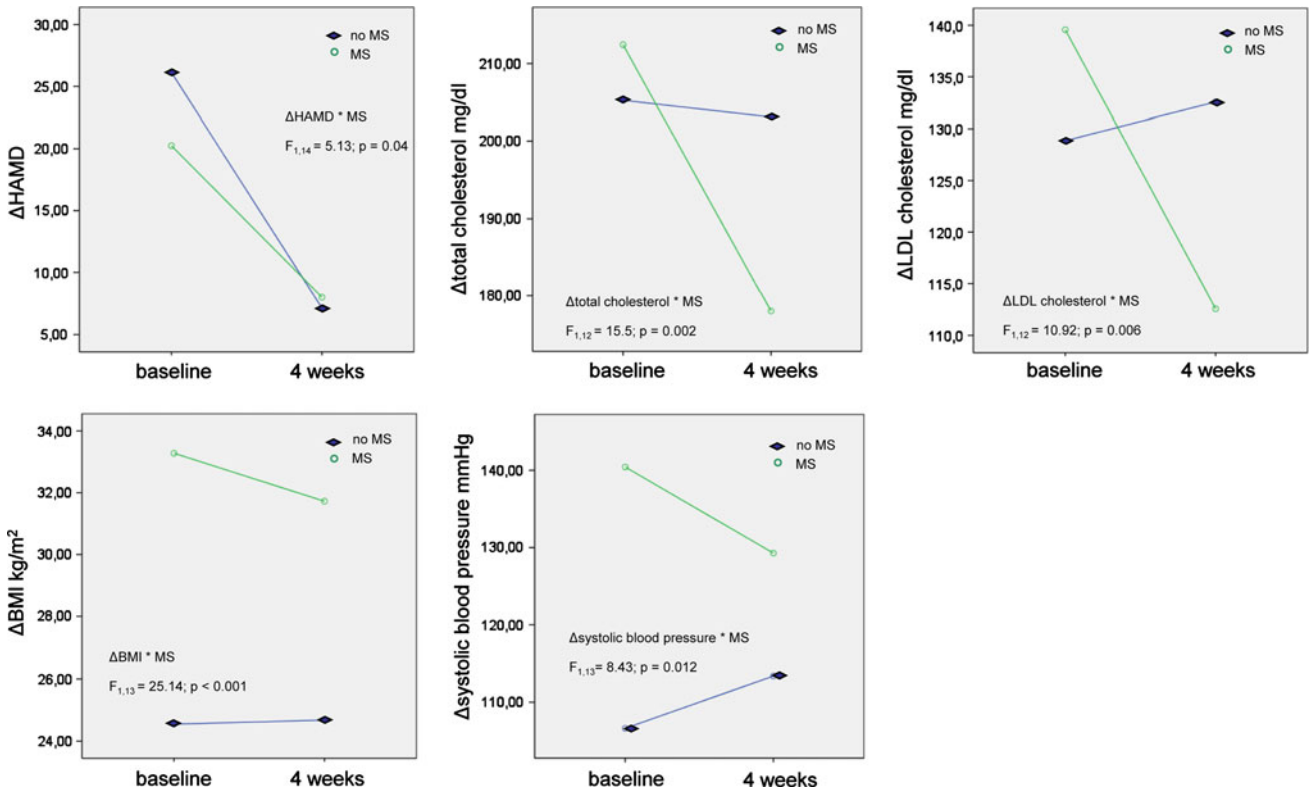


**Fig. 1** The univariate analysis of variance with repeated measures (rm-ANOVA) was used in order to evaluate the interaction of change (Δ) in *HAMD* scores and several metabolic parameters with the presence/absence of a metabolic syndrome (*MS*) (=between subject factor). The occurence of a *MS* was associated with a statistically significant decrease ("metabolic change x metabolic syndrome" interaction) with regard to *total cholesterol*, *LDL-cholesterol*, *BMI* and *systolic blood pressure*

the United States. The present investigation is not adequate to evaluate its efficacy; taking the lack of a control group into account, response and remission rates in our study cohort after the 4-week treatment were 18.75 and 68.75%, respectively.

The main methodological shortcoming of our study is the small sample size, the lack of a control group and the study period of only 4 weeks. Furthermore, the present patient sample proved to be eucortisolemic compared to other historical patient cohorts studied by our research group. As hypercortisolism is known to be associated with the metabolic syndrome, our results could have been different in hypercortisolemic patients. Patients of this study were not subtyped in, e.g. a melancholic subtype.

The association between depression and a MS has been studied extensively [e.g. 6, 9]. As the prevalence of MS and depression is increasing [5], the comorbidity of both presumably will increase as well. Therefore, the necessity of an integrated treatment for depressive patients with MS is rising as well. All depressive patients should undergo a screening for a MS. According to our results, a 4-week antidepressant treatment with reboxetine is associated with amelioration of metabolic parameters independent of treatment outcome. Further studies are warranted.

**Acknowledgments** This study was supported by an unrestricted grant by Merz Pharmaceuticals, Frankfurt, Germany.

## References

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ (2001) The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 24:1069–1078
2. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, Watanabe N, Nakagawa A, Omori IM, McGuire H, Tansella M, Barbui C (2009) Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 373:746–758
3. Engum A (2007) The role of depression and anxiety in onset of diabetes in a large population-based study. J Psychosom Res 62:31–38
4. Everson-Rose SA, Meyer PM, Powell LH et al (2004) Depressive symptoms, insulin resistance, and risk of diabetes in women at midlife. Diabetes Care 27:2856–2862
5. Ford ES, Wayne HG, Mokdad AH (2004) Increasing prevalence of the metabolic syndrome among US adults. Diabetes Care 27:2444–2449
6. Heiskanen TH, Niskanen LK, Hintikka JJ et al (2006) Metabolic syndrome and depression: a cross-sectional analysis. J Clin Psychiatry 67:1422–1427
7. Knol MJ, Twisk JWR, Beekman ATF et al (2006) Depression as a risk factor for the onset of type 2 diabetes mellitus. A Meta-analysis Diabetol 49:837–845

8. Kopf D, Westphal S, Luley CW, Ritter S, Gilles M, Weber-Hamann B, Lederbogen F, Lehnert H, Henn FA, Heuser I, Deuschle M (2004) Lipid metabolism and insulin resistance in depressed patients: significance of weight, hypercortisolism and antidepressant treatment. J Clin Psychopharmacol 24(5):527–531
9. Koponen H, Jokelainen J, Keinänen-Kiukaanniemi S, Kumpusalo E, Vanhala M (2008) Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. J Clin Psychiatry 69:178–182
10. Lederbogen F, Gernoth C, Hamann B, Kniest A, Heuser I, Deuschle M (2003) Circadian blood pressure regulation in hospitalized depressed patients and non-depressed comparison subjects. Blood Press Monit 8:71–76
11. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209–1223
12. Lustman PJ, Freedland KE, Griffith LS, Clouse RE (2000) Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. Diabetes Care 23:618–623
13. Okamura F, Tashiro A, Utumi A et al (2000) Insulin resistance in patients with depression and its changes during the clinical course of depression: minimal model analysis. Metabolism 49:1255–1260
14. Richter N, Juckel G, Assion HJ (2010) Metabolic syndrome: a follow-up study of acute depressive inpatients. Eur Arch Psychiatry Clin Neurosci 260:41–49
15. Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Jarvinen H, Van HT, Renn W, Gerich J (2000) Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. Diabetes Care 23:295–301
16. Teixeira PJ, Rocha FL (2007) The prevalence of metabolic syndrome among psychiatric inpatients in Brazil. Rev Bras Psiquiatr 29:330–336
17. Thakore JH, Richards PJ, Reznek RH, Martin A, Dinan TG (1997) Increased intra-abdominal fat deposition in patients with major depressive illness as measured by computed tomography. Biol Psychiatry 41:1140–1142
18. Timonen M, Rajala U, Jokelainen J, Keinänen-Kiukaanniemi S, Meyer-Rochow VB, Räsänen P (2006) Depressive symptoms and insulin resistance in young adult males: results from the Northern Finland 1966 birth cohort. Mol Psychiatry 11:929–933
19. Vogelzangs N, Suthers K, Ferrucci L, Simonsick EM, Ble A, Schrager M, Bandinelli S, Lauretani F, Giannelli SV, Penninx BW (2007) Hypercortisolemic depression is associated with the metabolic syndrome in late-life. Psychoneuroendocrinology 32:151–159
20. Weber-Hamann B, Hentschel F, Kniest A, Deuschle M, Colla M, Lederbogen F, Heuser I (2002) Hypercortisolemic depression is associated with increased intra-abdominal fat. Psychosom Med 64(2):274–277
21. Weber-Hamann B, Gilles M, Lederbogen F et al (2006) Improved insulin sensitivity in 80 nondiabetic patients with MDD after clinical remission in a double-blind, randomized trial of amitriptyline and paroxetine. J Clin Psychiatry 67:1856–1861
22. Weber-Hamann B, Gilles M, Schilling C, Onken V, Frankhauser P, Kopf D, Lederbogen F, Deuschle M (2008) Improved insulin sensitivity in 51 nondiabetic depressed inpatients remitting during antidepressive treatment with mirtazapine and venlafaxine. J Clin Psychopharmacol 28:581–584