R E V I E W

Treatment of patients with comorbid depression and diabetes with metformin and milnacipran

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Abstract: Depression is twice as frequent in patients with diabetes as in the general population, and has a negative impact on self-care, adherence to treatment, and the general prognosis of diabetes. This underscores the importance of screening all diabetic patients for depression and, if necessary, treating it with an effective antidepressant drug in parallel with standard diabetes treatment. In a recent study, a simple two-question screening tool was used to screen diabetic patients for comorbid depression. The effects of the serotonin and norepinephrine reuptake inhibitor antidepressant, milnacipran, on metabolic parameters and depressive symptoms in 64 diabetic patients with comorbid depression detected by this screen were studied. Patients received milnacipran for 6 months, in addition to standard diabetes treatment with metformin. At the end of the study, 72% of patients had responded to antidepressant treatment ($\geq$50% reduction of baseline Beck Depression Score). The proportion of patients with <8% glycosylated hemoglobin HbA_{1c} (a common indication in diabetes of the need for intensive therapeutic intervention) had decreased significantly from 46.6% at baseline to 6.9%. HbA_{1c}, fasting blood glucose, body mass index, total and low-density lipoprotein cholesterol, and serum triglyceride levels were all significantly decreased in patients with an antidepressant response, but not in patients whose depressive symptoms had not responded to milnacipran.

Keywords: depression, diabetes, milnacipran, serotonin, norepinephrine, reuptake inhibitors

Introduction

Depression is common in patients with diabetes mellitus.[1] The prevalence of depression (major and minor) in patients with type 2 diabetes is reported to be almost twice that of the general population, ie, 17.6% versus 9.8%, respectively.[2] The relationship between comorbid depression and diabetes is complex (Figure 1) and the pathophysiology is still unclear. As with other severe chronic illnesses, psychologic factors associated with suffering and diminished quality of life related to diabetes may trigger or enhance depressive symptoms.[3] There is evidence, however, to suggest that depression may, in many cases, precede diabetes and act as a causal factor for weight gain and subsequent development of diabetes.[4] Approximately 80% of diabetic patients are overweight or obese, and a complex relationship exists between obesity and depression.[5–7] Depression can be a precursor or aggravating factor in the development of obesity, but there is also evidence that obesity may lead to depression.[8,9] The comorbidity of diabetes and depression is associated with a significantly increased risk of death from all causes, beyond risks inherent with diabetes or depression alone.[10–12] There appears to be a clear synergistic interaction between diabetes and depression, resulting in decreased metabolic control, a higher incidence of vascular complications, and decreased quality of life in

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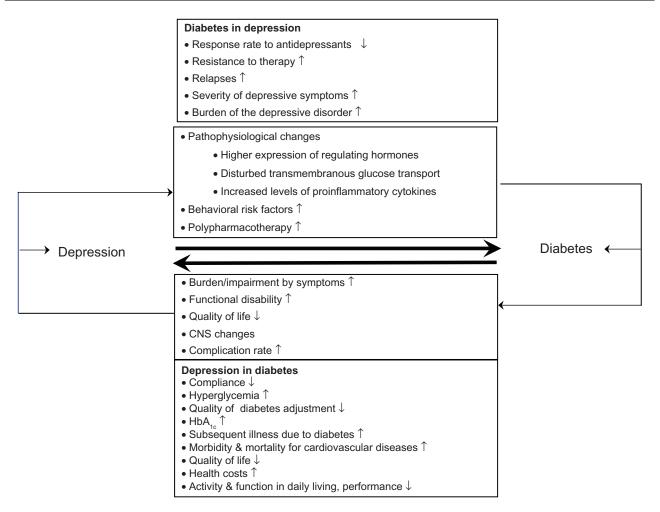Email p.hofmann@meduni-graz.at

Figure 1 Complex interactions between depression and diabetes.
Modified from Regen et al.[34]

comorbid sufferers.[1,10,13,14] Despite the importance of comorbid depression on the prognosis of diabetes, diabetic patients are rarely screened for depressive symptoms, and depression frequently goes undetected and therefore untreated.

Treatment of comorbid depression in diabetic patients

If the presence of depression aggravates or precipitates diabetes, what are the effects on diabetic symptoms of treating the depression with antidepressant medication? The impact of antidepressant therapy on metabolic and anthropometric parameters in diabetic patients with comorbid depression is still poorly understood.[15–17]

Studies with antidepressants have shown variable effects on metabolic control. In a study with sertraline, glycosylated hemoglobin (HbA$_{1c}$) levels were reduced during treatment, but did not differ between the sertraline and placebo groups,[15,16] whereas no significant reduction in HbA$_{1c}$ levels was observed in patients treated with fluoxetine or paroxetine,

although their depressive symptoms were significantly improved.[17] Similarly, although escitalopram resulted in a significant reduction of depression score, there was only a small and nonsignificant reduction in fasting blood glucose (FBG) levels and HbA$_{1c}$ levels.[18] It would thus appear that selective serotonin reuptake inhibitors (SSRIs) do not have any major effect on metabolic control, even when they produce a significant effect on depressive symptoms.

The expression of norepinephrine transporter mRNA has been shown to be decreased in the locus coeruleus and other brain regions in experimentally diabetic rats,[19] suggesting a possible role for this neurotransmitter in the development of diabetes, especially in the case of comorbid depression where this monoamine is thought to be reduced.

A recent study[20] has evaluated the effect of long-term treatment with the antidepressant, milnacipran, on depressive symptoms and metabolic parameters in type 2 diabetic patients with comorbid depression. Milnacipran is a serotonin and norepinephrine reuptake inhibitor (SNRI)[21] which inhibits

the reuptake of the two monoamines with the most balanced potency ratio of all the SNRIs (1:1.6 for milnacipran; 1:10 for duloxetine, and 1:30 for venlafaxine).[22] Some studies have even shown that milnacipran inhibits norepinephrine uptake with greater potency than serotonin (2.22:1).[23] It is thus the most noradrenergic of the SNRI antidepressants. In addition to being effective and well tolerated,[21] milnacipran has a characteristic which makes it particularly attractive for treating diabetic patients with comorbid depression. It is one of the rare antidepressants that has no interaction with the cytochrome P450 enzyme system,[24] and thus possesses a very low risk of drug-drug interactions. Because diabetic patients, especially those with comorbid depression, are likely to be treated with multiple medications, the risk of drug–drug interactions should be of constant concern.

This open-label longitudinal study[20] was conducted in outpatients who fulfilled the criteria for type 2 diabetes mellitus as defined by the American Diabetes Association,[25] and who had been screened positively for comorbid depression. Because diabetologists are not psychiatrists, it was necessary to find a simple way of screening diabetic patients for depressive symptoms. A simple two-question screen, based on the questionnaire developed by Whooley et al[26] was used:

Question 1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?

Question 2. During the past month, have you often been bothered by little interest or pleasure in doing things?

A positive answer to both questions indicated the probable presence of depressive symptoms. A diagnosis of depression was subsequently confirmed according to ICD-10 criteria for a depressive episode using the 12-item Major Depression Inventory (MDI) questionnaire.[27]

FBG, HbA$_{1c}$, total cholesterol, LDL-cholesterol, high-density lipoprotein (HDL)-cholesterol, serum triglycerides, and weight were measured at baseline and after 6 months of treatment. Height was measured at baseline and was assumed to remain constant throughout the study. The severity of depression was measured at baseline and after 1, 3, and 6 months of treatment using the Beck Depression Inventory (BDI).[28]

All patients received standard diabetes treatment, ie, metformin (500–2000 mg/day) as recommended by the Guidelines of the Austrian Diabetes Association.[29] Milnacipran treatment was initiated at 25–50 mg/day, increasing to 100 mg/day (50 mg twice daily) after a few days. Clinicians chose the initial dose and subsequent dose adjustments on the basis of the patient's clinical response and tolerance of the drug.

Patients were generally obese, with a mean body mass index (BMI) of <30 and with moderate to poor glycemic control (see Table 1). Of the 58 patients who completed the trial, 47% had a baseline HbA$_{1c}$ < 8%, usually considered as an indicator of the need for intensive therapeutic intervention. The mean BDI score at baseline was 23.2, indicating a moderate to severe level of depression. Most of the patients (81%) had never taken antidiabetic drugs, their condition being managed by lifestyle adjustment only, and the majority (90%) had never taken antidepressant medication.

BDI scores improved progressively during the study (Figure 2). After 6 months, nearly 72% of patients had responded to treatment (defined as a ≥50% decrease in baseline BDI score). There was no difference between responders and nonresponders for age, severity of depression, metabolic control, or BMI at baseline.

Over the 6 months of the study, FBG levels, HbA$_{1c}$, body weight, BMI, total cholesterol, LDL-cholesterol, and serum triglycerides were all significantly improved (Figure 3) and the proportion of patients with HbA$_{1c}$ < 8% decreased significantly from 47% to 7%. Interestingly, this improvement in diabetic symptoms was principally due to reductions in patients with a response in their depressive symptoms. As shown in Figure 4, depression-responsive patients had significant improvements in all of the metabolic and anthropometric parameters studied, while nonresponders showed no significant improvements. Interestingly, there was a significant weight loss during treatment of these overweight or obese patients (Figure 5).

The contrast with the results of similar studies carried out with SSRIs is consistent with the importance of the role of noradrenergic neurotransmission which would

Table 1 Metabolic parameters at baseline and after 6 months of treatment with milnacipran for all patients completing the study

Parameter	Baseline	Six months	P
FBG (mg/dL)	155.0	113.0	<0.0001
HbA$_{1c}$ (% of total Hb)	7.9	6.9	<0.0001
Bodyweight (kg)	90.5	84	<0.001
BMI (kg/m^2)	30.4	28	<0.001
Total chol (mg/dL)	199.5	178	<0.0001
LDL-chol (mg/dL)	117	108	<0.001
HDL-chol (mg/dL)	47.0	48.0	NS
Triglyc (mg/dL)	190	157	<0.001

Note: All values are given as the median. P = significance of the difference between baseline and six-month values (paired t-test).
Abbreviations: HbA$_{1c}$, glycosylated hemoglobin; FBG, fasting blood glucose; BMI, body mass index; total chol, total cholesterol; LDL-chol, low-density lipoprotein cholesterol; HDL chol, high-density lipoprotein cholesterol; Triglyc, serum triglycerides; NS, not significant.
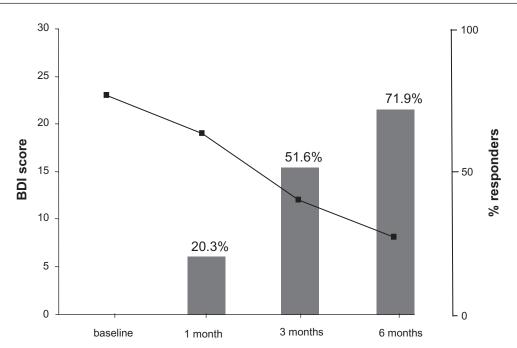
Figure 2 Evolution of depression rating throughout the study.
Note: The squares and single line refer to the depression rating as measured by the BDI (left hand axis). The gray columns refer to the percentage of patients responding to treatment (≥50% decrease in baseline Beck Depression Inventory score). Values are medians for all 64 patients who started the study.

be stimulated by the inhibition of the norepinephrine transporter by milnacipran. Indeed, another study of a compound with a marked noradrenergic component, bupropion, found that BMI and HbA_{1c} levels decreased significantly during the acute treatment phase with an association between reduction of depression severity and reduction of HbA_{1c} levels.[30] Clearly, further studies are required to investigate the possible importance of the noradrenergic component of antidepressant action on metabolic parameters in diabetes.

Discussion

Despite the negative impact of untreated depression on diabetes care and prognosis,[31,32] depression is still underrecognized in diabetic patients. Diabetes is one of the most psychologically and behaviorally demanding of the
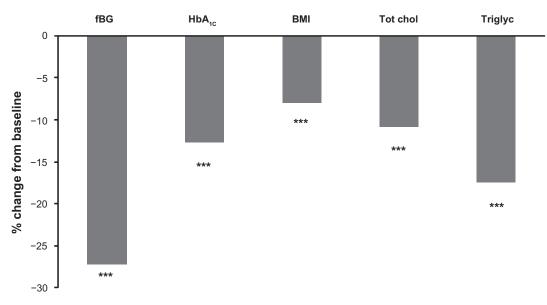

Figure 3 Change in metabolic parameters during 6 months of milnacipran treatment.
***$P < 0.001$ compared with baseline values. Values are medians for all 58 patients who completed the study.
Abbreviations: FBG, fasting blood glucose; HbA_{1c}, glycosylated hemoglobin; total chol, total cholesterol; triglyc, serum triglycerides.
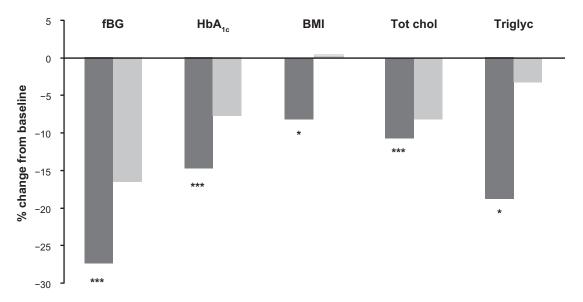
Figure 4 Change in metabolic parameters in antidepressant responders and nonresponders during 6 months of milnacipran treatment.
Note: Dark gray columns = antidepressant responders (≥50% decrease in baseline BDI score, n = 46); light gray columns = antidepressant nonresponders, n = 12). Values are medians.
*P < 0.05; ***P < 0.001 compared with baseline values.
Abbreviations: FBG, fasting blood glucose; HbA₁c, glycosylated hemoglobin; total chol, total cholesterol; triglyc, serum triglycerides.

chronic medical illnesses. At least 90% of diabetes management is conducted by the patient himself or herself. The effect of comorbid depression on the patient's motivation for self-care can result in unfavorable or even potentially fatal development of the disease.[33] Although many physicians are

aware of the importance of detecting comorbid depression in diabetic patients, many of them find it difficult to deal with in practice. Most diagnostic tools for screening depression are complicated, time-consuming, or require at least some psychiatric training. The simple two-question screen used
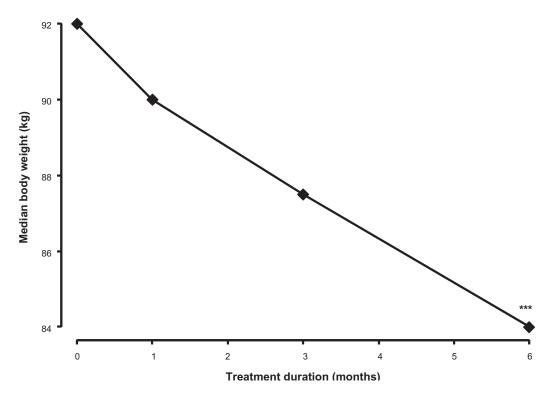

Figure 5 Change of body weight in antidepressant responders during 6 months of milnacipran treatment.
Values are medians for all 46 patients who responded to the antidepressant and completed the study (≥50% decrease in baseline Beck Depression Inventory score).
***P < 0.001 compared with baseline values.

in the above study was based on the two principal criteria of a depressive episode, ie, a period of at least 2 weeks during which there is either depressed mood and/or the loss of interest or pleasure in nearly all activities. A "no" response to both of the two questions means that depression is highly unlikely. For the rare patients who answer "yes" to only one of the questions, other symptoms should be elicited to confirm or refute a diagnosis of depression. Patients who reply positively to both questions are invariably depressed, and in the above study there were no "false positives", ie, patients identified as possibly depressive who were subsequently found not to have a diagnosis of depression.

Once comorbid depression has been diagnosed in a diabetic patient it needs to be aggressively treated with an effective antidepressant. Although the demonstration is not yet definitive, the available evidence suggests that an antidepressant with a noradrenergic component is more likely to have a favorable impact on both diabetic and depressive symptoms.[15–18] While SSRIs appear to be effective in treating depressive symptoms they seem to have little influence on diabetic symptoms in contrast with the SNRI, milnacipran,[20] and the catecholaminergic antidepressant, bupropion.[29]

As with all polymedicated patients, the physician needs to be particularly vigilant and wary of potential drug-drug interactions. The use of an antidepressant such as milnacipran, which has no interaction with any cytochrome P450 enzyme,[24] reduces the risk of interactions.

Increasingly in modern medicine patient health is being seen as an integrated whole rather than as a collection of more or less independent complaints. The interaction between depression and diabetes, while still poorly understood, is extremely clear. Studies like the one illustrated here show that successful therapy of depression can have far reaching consequences for prognosis of diabetes and thus provide important global benefit for the patient.

Disclosure

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