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 (≥50% reduction of baseline Beck Depression Score). The proportion of patients with <8% glycosylated hemoglobin HbA1c (a common indication in diabetes of the need for intensive therapeutic intervention) had decreased significantly from 46.6% at baseline to 6.9%. HbA1c, 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...
comorbid sufferers.\textsuperscript{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.\textsuperscript{15–17}

Studies with antidepressants have shown variable effects on metabolic control. In a study with sertraline, glycosylated hemoglobin (HbA\textsubscript{1c}) levels were reduced during treatment, but did not differ between the sertraline and placebo groups,\textsuperscript{15,16} whereas no significant reduction in HbA\textsubscript{1c} levels was observed in patients treated with fluoxetine or paroxetine, although their depressive symptoms were significantly improved.\textsuperscript{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\textsubscript{1c} levels.\textsuperscript{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,\textsuperscript{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\textsuperscript{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)\textsuperscript{21} which inhibits

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**Figure 1** Complex interactions between depression and diabetes. Modified from Regen et al.\textsuperscript{34}
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).的一些研究已经表明，milnacipran抑制去甲肾上腺素的再摄取能力超越血清素（2.22:1）。它是目前最有效的SNRI抗抑郁药。在对待糖尿病患者和共病抑郁症方面，它是唯一的选择。因为它具有特别是吸引人的特性，而且容易处理与多种药物的相互作用，所以应该在BMI<30和中度至轻度的血糖控制的情况下考虑milnacipran。

患者主要是肥胖的，平均BMI为30.4，与中等至不良的血糖控制有关。结果表明，BMI<8%的患者比例从47%降低到7%。显著差异意味着在6个月的治疗期间，BMI<8%的患者比例从47%降低到7%。有趣的是，这种改善在糖尿病症状中主要是由于减少了BMI<8%的患者比例。

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Six months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose (mg/dL)</td>
<td>155.0</td>
<td>113.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (% of total Hb)</td>
<td>7.9</td>
<td>6.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>90.5</td>
<td>84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMi (kg/m²)</td>
<td>30.4</td>
<td>28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total Chol (mg/dL)</td>
<td>199.5</td>
<td>178</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-Chol (mg/dL)</td>
<td>117</td>
<td>108</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-Chol (mg/dL)</td>
<td>47.0</td>
<td>48.0</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>190</td>
<td>157</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Note: All values are given as the median. P = significance of the difference between baseline and six-month values (paired t-test). Abbreviations: HbA1c, glycosylated hemoglobin; FBC, fasting blood glucose; BMi, body mass index; total chol, total cholesterol; LDL-chol, low-density lipoprotein cholesterol; HDL-chol, high-density lipoprotein cholesterol; Triglycerides; NS, not significant.

治疗的共病糖尿病和抑郁

患者一般为肥胖，BMI<30，有中度至不良的血糖控制。在58名患者中，完成研究的47%的患者在基线HbA1c<8%，通常被视为需要进行更针对的治疗干预的指标。基线BDI分数为23.2，表明有中度至严重程度的抑郁症。大多数患者（81%）从未服用过抗抑郁药，他们的病情得到生活方式调整的管理，而90%的患者没有使用抗抑郁药。

BDI分数在6个月内逐渐提高（图2）。6个月后，72%的患者对治疗有反应（定义为在基线BDI分数基础上≥50%的改善）。没有治疗反应者（对年龄、抑郁程度、代谢控制或BMI有反应）。

在6个月的研究期间，FBG水平、HbA1c、体重、BMI、总胆固醇、LDL-胆固醇和血清甘油三酯均显著改善（图3）。与相似研究结果的对比显示，milnacipran与SSRIs相比，治疗抗抑郁效果显著。

The open-label longitudinal study conducted in outpatients who fulfilled the criteria for type 2 diabetes mellitus as defined by the American Diabetes Association, 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 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. FBG, HbA1c, 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). All patients received standard diabetes treatment, ie, metformin (500–2000 mg/day) as recommended by the Guidelines of the Austrian Diabetes Association. 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.
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 HbA1c levels decreased significantly during the acute treatment phase with an association between reduction of depression severity and reduction of HbA1c 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 2](https://www.dovepress.com/attachment.php?doi=10.2147/NPT.S124137&file=2.png)

**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.

![Figure 3](https://www.dovepress.com/attachment.php?doi=10.2147/NPT.S124137&file=3.png)

**Figure 3** Change in metabolic parameters during 6 months of milnacipran treatment.

**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.\(^3\) 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
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**
The author is a consultant for Germania Pharmaceutika, who sell milnacipran in Austria.

**References**