Letter to the Editor
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Mild Decrease in Blood Glucose Levels May Predict Efficacy of Antipsychotic Lurasidone

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TO THE EDITOR

Atypical antipsychotics carry the risk of metabolic abnormalities such as weight gain and elevated blood glucose levels. Lurasidone is an atypical antipsychotic approved for the treatment of schizophrenia and bipolar depression. Meta-analysis found that it had little effect on metabolic parameters but caused mild weight gain compared to placebo [1]. I read with great interest the two articles on lurasidone published in this journal. Siwek and Gorostowicz [2] reported that lurasidone is effective in a patient with rapid cycling bipolar disorder who are obese or have metabolic abnormalities. Reynolds *et al.* [3] showed that lurasidone suppressed olanzapine-induced weight gain in rats. We also reported that lurasidone showed improvement in metabolic parameters, including mild decrease in blood glucose levels after one month of treatment [4]. These reports indicate that lurasidone, although an atypical antipsychotic, may be less likely to cause concomitant metabolic disturbances and be more effective. Patients whose psychiatric symptoms improve with lurasidone may show metabolic improvements, such as reduced weight gain and mild reductions in blood glucose levels.

Therefore, we examined the relationship between changes in psychiatric symptoms and changes in blood glucose levels using pooled data from patients with schizophrenia and bipolar depression whose psychiatric symptoms were controlled with lurasidone. Data from 47 patients were used in this analysis, 25 with schizophrenia and 22 with bipolar depression, 35 females (mean age 44.4 years) and 12 males (mean age 42.1 years) [4]. The data used in the analysis is described in detail in our previous report and appropriate ethical considerations have been taken into account. Psychiatric symptoms were assessed using the Global Assessment of Functioning (GAF) score. Changes in fasting blood glucose (FBG) and GAF scores after one month of lurasidone treatment were tested with the Wilcoxon signed-rank test. The association between change in FBG and change in GAF was examined using Spearman's correlation coefficient, with $p < 0.05$ considered a significant difference. The results are shown below. GAF before lurasidone administration was 30.7 ± 1.7 (mean ± standard error), and after one month was 52.8 ± 2.2, with significantly improved psychiatric symptoms ($p < 0.01$). FBG before lurasidone was 94.9 ± 3.0 mg/dl and after one month of treatment was 86.9 ± 2.1 mg/dl, a statistically significant decrease ($p = 0.001$).

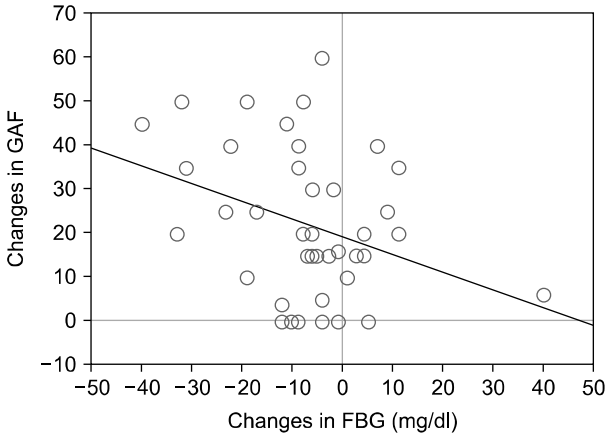

Fig. 1. Correlation between the changes in Global Assessment of Functioning (GAF) scores and the changes in fasting blood glucose (FBG) levels.

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The correlation coefficient (r) between the changes in FBG and the changes in GAF was −0.388 with a p value of 0.027, indicating a statistically significant correlation was observed (Fig. 1). A mild decrease in blood glucose with lurasidone is associated with an improvement in psychiatric symptoms. Lurasidone may have a common site of action centrally in the control of psychiatric symptoms and blood glucose levels.

Unless there is a metabolic disorder such as diabetes, blood glucose levels are tightly controlled by the autonomic nervous system, which uses catecholamines as neurotransmitters [5]. However, in patients with severe mental illness, blood glucose tends to increase with psychomotor excitement via catecholamine secretion, even in the absence of metabolic disorders [6]. Therefore, the first possible link between blood glucose and psychiatric symptoms is central dopamine D2 receptors that involve catecholamine regulation. Hong *et al.* [7] showed that intrathecal administration of dopamine D2 receptor agonists to mice increased blood glucose levels in a dose-dependent manner, and that this increase in blood glucose levels was significantly suppressed by dopamine D2 receptor antagonists. Second, lurasidone's unique receptor profile may link psychiatric symptom improvement and blood glucose via the 5HT1A receptor, as Reynolds *et al.* [3] showed in this Journal. Lurasidone not only has no affinity for the 5HT2c receptor, which is associated with increased appetite and metabolic disturbances, but also has a high affinity for 5HT1A, which antagonizes 5HT2c, making weight gain unlikely. Lurasidone's high 5HT1A receptor affinity has been associated with improvement in depression [8]. The 5HT1A receptor has been noted to be important not only for its antidepressant effects, but also for its role in non-cortisol-mediated control of blood glucose levels. Hypothalamic 5HT1A receptors play an important role in the regulation of satiety, blood glucose, and endocrine status, and antagonism of 5HT1A receptors is expected to lead to the discovery of novel antidiabetic agents [9]. Lurasidone is a 5HT1A partial agonist that acts as a net antagonist in the hypothalamus and may lower blood glucose. Lurasidone's affinity for 5HT1A affects both the relief of psychiatric symptoms and mild reductions in blood glucose levels.

Both psychiatric symptoms and blood glucose levels are controlled by the central nervous system. Because lurasidone has few adverse metabolic effects, as reported by Siwek and Gorostowicz [2] and Reynolds *et al.* [3] in this Journal, it is possible to examine the relationship between psychiatric symptoms and blood glucose levels in a naturalistic manner. Further studies are needed to determine whether small changes in blood glucose levels can be used as an indicator of improvement in psychiatric symptoms.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Takahiko Nagamine. Data acquisition: Masaru Nakamura. Formal analysis: Takahiko Nagamine, Masaru Nakamura. Writing−original draft: Takahiko Nagamine. Writing−review & editing: Takahiko Nagamine, Masaru Nakamura.

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