

Reversal of olanzapine-induced weight gain in a patient with schizophrenia by switching to asenapine: a case report

Kosuke Okazaki
Kazuhiko Yamamuro
Toshifumi Kishimoto

Department of Psychiatry, Nara
Medical University School of
Medicine, Kashihara, Japan

Aims: Antipsychotics are effective for treating schizophrenia, but atypical antipsychotics can cause several adverse side effects including weight gain, hyperprolactinemia, and extrapyramidal symptoms. Moreover, weight gain increases the risk of metabolic diseases.

Methods: We treated a case of olanzapine-induced weight gain in a 41-year-old man with schizophrenia by switching his medication from olanzapine to asenapine.

Results: The weight gain improved after switching the medication, from 80.3 to 75.0 kg, a weight loss of 6.6%, and there was no significant worsening of psychological symptoms or other adverse effects.

Conclusions: Asenapine might be effective for treating patients with schizophrenia who experience olanzapine-induced weight gain.

Keywords: olanzapine, weight gain, schizophrenia, asenapine

Introduction

Schizophrenia, which affects ~1% of the global population, is a psychotic disorder characterized by positive symptoms, negative symptoms, and progressive cognitive deficits.¹ It chronically impacts social relations, daily living, and vocational function,^{2,3} and can reduce life expectancy by up to 20 years.⁴

Schizophrenia is mainly treated with antipsychotics,⁵ which block dopaminergic, histaminergic, serotonergic, cholinergic, and alpha-adrenergic receptors. Their strong affinities for these receptors affect both positive and negative symptoms. Atypical antipsychotics (AAPs) are effective for treating schizophrenia and have fewer side effects than typical antipsychotics,⁶ but they can still cause extrapyramidal symptoms,⁷ hyperprolactinemia,⁸ sedation,⁹ and weight gain.^{7,8} These side effects can lead to patient nonadherence with treatment.⁷ Weight gain in particular is associated with metabolic complications such as lipid abnormalities, glucose intolerance, and hypertension.¹⁰ Recent guidelines, including those from the British Association for Psychopharmacology, recommend switching to a low-weight gain alternative antipsychotic if olanzapine-induced weight gain is excessive.¹¹ Olanzapine is an AAP that is classified as a multi-acting receptor-targeted antipsychotic agent (MARTA) and carries the second highest risk of weight gain among AAPs after clozapine.¹² Asenapine is another MARTA AAP and was approved for schizophrenia in 2009. Previous studies have shown that it carries a lower risk of weight gain than olanzapine.^{12,13}

Correspondence: Kazuhiko Yamamuro
Department of Psychiatry, Nara Medical
University School of Medicine, 840 Shijo-
cho Kashihara, Nara 634-8521, Japan
Tel +81 744 22 3051
Fax +81 744 22 3854
Email muro@naramed-u.ac.jp

Case presentation

A 41-year-old man with schizophrenia began experiencing auditory hallucinations when he was 19 years old, but had only been prescribed antipsychotics after being hospitalized for worsening psychosis when he was 29 years old. After the hospitalization, he was referred to our hospital, but he did not consistently adhere to treatment, so his psychosis exhibited cyclical remissions and relapses. When he was 41 years old, auditory hallucinations and delusions of persecution caused him to refuse food despite being prescribed quetiapine, so he was again referred to our hospital. He weighed 56 kg and had a body mass index (BMI) of 16.3 kg/m². He did not have a history of other comorbid medical illness.

The patient was diagnosed with schizophrenia according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition. His symptoms were assessed using the Japanese version of the Positive and Negative Syndrome Scale (PANSS), in which higher scores indicate greater severity according to the 7-point Likert scale. Sub-scale scores were calculated using small sets of variables from the three PANSS domains: positive, negative, and general psychopathological symptoms. Higher PANSS scores indicate more severe psychotic symptoms. He obtained a PANSS score of 159. He was continuously prescribed quetiapine at a dose starting at 400 mg/day and increasing to 600 mg/day, but this failed to ameliorate his hallucinations and delusions; while on quetiapine his PANSS score was 150. After 4 weeks, his prescription was, therefore, switched to aripiprazole at a dose that increased to 30 mg/day, but his PANSS score was still 139. His prescription was then switched to olanzapine at a dose that increased to 20 mg/day over 2 weeks, and he showed gradual improvement in his positive symptoms. After 3 months of olanzapine at 20 mg/day, his PANSS score was 68. Although he experienced markedly reduced psychosis, olanzapine-induced overeating increased his weight to 80.3 kg and his BMI to 23.5 kg/m². At this point, he did not appear to have any physical illness such as diabetes, dyslipidemia, or hypertension. We, therefore, tapered his olanzapine dose over 2 weeks until discontinuation while giving him asenapine at a dose that increased to 20 mg/day. His overeating reduced within a week after the tapering had ended without exacerbation of psychosis. After a month of asenapine at 20 mg/day, his weight decreased to 78.0 kg with BMI of 22.7 kg/m², and his PANSS score was 66, indicating no worsening of psychosis. Over the following 1 year, the dose was maintained, his weight gain did not recur (75.0 kg with BMI of 21.8 kg/m²), and he had few side effects. Importantly, he never received other interventions that could affect weight loss during the observation period, such as dietary

counseling or changes in diet and exercise. The patient was also taking benzodiazepines, but the quantity and types of benzodiazepines did not change during this period.

Discussion

To the best of our knowledge, this case represents the first evidence that asenapine is an effective and well-tolerated therapy for improving olanzapine-induced weight gain without exacerbating psychotic symptoms.

AAPs increase the risk of weight gain¹⁴ by blocking 5-HT_{2C} serotonin receptors and H₁ histamine receptors, with olanzapine carrying a particularly high risk.¹² This causes many metabolic abnormalities, including increased appetite¹⁵ and elevated blood levels of glucose,¹⁶ fasting triglycerides, and leptin,¹⁷ but these effects are smaller with asenapine treatment than with olanzapine treatment.^{13,18} The difference might result from asenapine's unique receptor-binding profile, which includes antagonism of dopamine receptors, serotonin receptors, and adrenergic receptors.^{19–21} Unlike olanzapine, asenapine has moderate histamine receptor affinity and no appreciable muscarinic receptor affinity.²² In rats, treatment with asenapine for 5 weeks decreases weight and triglyceride levels.²³ In short- and long-term clinical studies, asenapine was well tolerated and carried a lower risk of weight gain and metabolic abnormalities than olanzapine in adult patients with schizophrenia or bipolar I disorder.^{18,24} Further, Bak et al have shown that a significant proportion of patients may experience >7% weight loss after starting asenapine without showing a duration response pattern.²⁵ Asenapine may, therefore, be an effective option for treating weight gain induced by other AAPs in patients with schizophrenia.

In a meta-analysis comparing antipsychotics, asenapine was no less effective than olanzapine for acute schizophrenia.²⁶ Patients with schizophrenia can, therefore, transition from olanzapine to asenapine without significant exacerbation of positive or negative symptoms. However, it is important that the olanzapine dose be tapered because rapid withdrawal may trigger cholinergic withdrawal syndromes, such as agitation, headache, insomnia, anxiousness, diarrhea, abdominal pain, and queasiness.²⁷ A previous report has shown that in Asian populations, a BMI of 23 or higher indicates a greater health risk.²⁸ Although the patient's BMI was well within the normal range while on olanzapine, it is important to control his weight considering the potential for metabolic comorbidities that could arise in the future.

In this case report, only a 6.6% weight loss was achieved with asenapine, where weight gain or loss must be at least 7% to be clinically meaningful. However, maintaining the weight loss is more important than reducing weight temporarily, even if

the weight loss is $>7\%$. This case suggests that asenapine is an effective and well-tolerated treatment for antipsychotic-induced metabolic abnormalities in patients with schizophrenia.

Conclusion

This case suggests that asenapine might be an efficacious and well-tolerated treatment for olanzapine-induced weight gain in patients with schizophrenia. Further studies with larger sample sizes are needed to validate the apparent efficacy, safety, and tolerability of asenapine in this application.

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Author contributions

KO collected data and wrote the first draft of the manuscript. KY and TK supervised the project, were critically involved in its design, and assisted in editing the final manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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