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- Title: Efficacy of asenapine in drug-resistant psychotic patients with dopamine supersensitivity psychosis: Two cases
- Running Title: Dopamine supersensitivity and asenapine
- Article Type: Case Report
- KeyWords: Asenapine, Clozapine, Dopamine D2 receptor, Dopamine supersensitivity, Treatment-resistant schizophrenia, Relapse

Abstract

Dopamine supersensitivity psychosis (DSP) is an unstable clinical condition observed in individuals with schizophrenia who have been treated with an antipsychotic medication at a high dosage and/or for a long period. An up-regulation of dopamine D2 receptors (DRD2) is thought to be involved in the essential pathology of DSP. An antipsychotic agent with both tight binding to DRD2 and a long half-life is generally effective for treating DSP, but a patient who meets the criteria of treatment-resistant schizophrenia sometimes needs treatment with clozapine. We report the case details of two patients whose DSP was not controlled with several antipsychotics but was successfully controlled with asenapine. Asenapine binds to a broad range of dopamine receptors and serotonin receptors, and it is thus distinct from other atypical antipsychotics. The unique profile of asenapine may contribute to the control of severe DSP symptoms in individuals with schizophrenia.

Keywords: Asenapine; Clozapine; Dopamine D2 receptor; Dopamine supersensitivity; Treatment-resistant schizophrenia; Relapse

Introduction

The majority of individuals with schizophrenia experience relapses of psychosis within 5 years from the onset of disease. Repeated relapses can lead to both an increase in the dosage of antipsychotic(s) necessary to control psychosis and the development of the dopamine supersensitivity (DS) state, which is due to the compensatory up-regulation of dopamine D2 receptors (DRD2) [1]. The DS state is clinically observed as dopamine supersensitivity psychosis (DSP), which is characterized by rebound psychosis and tolerance to an effect of antipsychotic(s). Tardive dyskinesia, another DS antipsychotic induced-disorder that usually develops after the long-term use of one or more antipsychotics, is also an important sign of DSP [2, 3]. Patients with DSP have generally responded well to the initial pharmacotherapy for their first episodes of psychosis, but they have tended to exhibit extrapyramidal symptoms (EPS) [1].

Once DSP has developed in a patient, he or she often shows severe psychopathology and exhibits an unstable clinical course which is difficult to control. The risk of rebound psychosis occurs when an on-going antipsychotic regimen is tapered or there is a switch to another antipsychotic with less potent binding affinity to DRD2 (except for clozapine) [4]. An abrupt switch to a dopamine partial agonist may pose a greater risk of worsening psychosis [5]. At present, the use of an agent with a long half-life and tight binding to DRD2—i.e., a long-acting antipsychotic injectable (LAI)—might

be the most reliable approach to counter DSP [4]. However, such a medication might further worsen DSP if it is continued for a long time.

The present two patients' profound DSP was well controlled with asenapine, although it was not managed by other antipsychotics. Their cases suggest that asenapine has the potential to control psychosis caused by DSP.

Patient 1

Patient 1 was a Japanese female in her late 30s. At 12 years old, she had been diagnosed with juvenile myoclonic epilepsy, which has been controlled with valproate 400 mg. At the age of 25 years she quit her job, since she felt that she was being bullied. At 27 years old, she complained of experiencing persecutory delusions and auditory hallucinations; she stated that a bugging device must have been placed in her home and that she heard someone's voice telling lies about her. At the age of 28 years, she came to our hospital and was diagnosed as having schizophrenia.

Treatment with risperidone 2 mg was initiated, and most of the patient's positive symptoms disappeared. The mild delusional mood remained, and risperidone was switched to aripiprazole 12 mg, which provided good effectiveness; the patient showed a complete disappearance of positive symptoms at home, but a slight delusional mood was observed when she was outside her home. Aripiprazole was eventually dosed-up to 30

mg.

The patient visited a facility for work transition support but gradually experienced a strong delusional mood and interpersonal tension and had difficulty continuing to attend that facility. When she was 34 years old, paliperidone palmitate (PP) 100 mg was introduced and provided clinical stability for the first 6 months, but the patient's delusional mood reemerged when she left her home. For this episode, oral paliperidone 3 mg was added. However, moderate akathisia, hyperprolactinemia (prolactin (PRL) 117 ng/mL), and hyperglycemia (HbA1c 6.5%) appeared. The PP was thus discontinued when the patient was 35 years old, and paliperidone 12 mg alone was administered. Despite this adjustment, she continued to experience opthalmophobia and sometimes suffered from strong emotional disturbance.

When aripiprazole was reintroduced at 12 mg (the patient was 36 years old), novel symptoms such as visual hallucinations of insects and a strong feeling of sight lines from outside her home appeared. The aripiprazole was dosed-up to 30 mg, but it did not control these symptoms. A switch from aripiprazole to blonanserin was thus conducted. Blonanserin at 16 mg provided clinical stability. The patient began to visit a day care facility, but she had repeated recurrences of strong interpersonal tension and delusional mood.

At the age of 37, the patient began receiving asenapine 5 mg. When the blonanserin

was tapered-off by slight dose increments over a period of several months, the patient's delusional mood worsened. A cross-titration between blonanserin and asenapine was thus performed over a >1-year period. At the time point at which the patient was taking blonanserin 4 mg and asenapine 15mg, her visual hallucinations disappeared, and she no longer presented with emotional disturbance.

Patient 2

Patient 2 was a Japanese male in his late 40s. At the age of 18, he entered a university but rarely attended classes. When he suffered appendicitis that required surgery at a hospital, he began to complain that his surgeon was telling lies about him and that the surgeon intentionally made surgical mistakes because the surgeon resented him. After the patient's discharge, he continued to repeatedly call and visit the hospital to express his complaints.

At the age of 20 years, the patient visited a psychiatric clinic and was diagnosed as having schizophrenia. Haloperidol 3 mg was initiated and was effective for his auditory hallucinations and persecutory delusions. He began to work for a company and stopped taking his daily medication. At 25 years old, he experienced a recurrence of the persecutory delusion about his surgeon and became angry at his family, showing occasional violent outbursts. He was involuntarily admitted to a psychiatric hospital and was treated with risperidone 3 mg; his psychopathology showed a good response. He was

then discharged from the psychiatric hospital, but he quit his job. He visited a day care facility and experienced four hospital admissions thereafter when he had stopped taking his medication.

When the patient was 41 years old, risperidone 9 mg was changed to aripiprazole, and an acute worsening of auditory hallucinations and persecutory delusions about his surgeon reemerged. He was readmitted to a psychiatric hospital with severe agitation. He was eventually discharged with treatment with paliperidone 12 mg, but he still had auditory hallucinations and persecutory delusions, saying that he heard his surgeon's voice or that his surgeon must have made surgical mistakes.

The patient was thus admitted to our hospital. He presented moderate EPS and hyperprolactinemia (PRL 168 ng/mL) as well. Asenapine was commenced (the patient was 47 years old) and was increased to 20 mg while the paliperidone was tapered-off over a 6-month period. The asenapine 20 mg provided an attenuation of his positive symptoms as well as his EPS and hyperprolactinemia (PRL 15 ng/mL). He continued to visit a day care facility.

Discussion

The two patients responded well to risperidone 2 mg and haloperidol 3 mg, respectively, for their first episodes of psychosis. A slight delusional mood remained for Patient 1, and

her medication was subsequently switched to aripiprazole with a final dose-up to 30 mg. However, the efficacy of this regimen declined and the patient experienced repeated moderate hallucinations. Patient 2 stopped taking the medication and experienced multiple relapses requiring involuntary admissions. His positive symptoms became persistent despite a switch in medication and an increasing dose of another antipsychotic. Both of these patients exhibited abrupt worsening of psychosis following the switch to aripiprazole. Their courses demonstrated that they had established typical DSP.

In individuals such as the present patients who develop DS, an antipsychotic agent with a profile of both high affinity to DRD2 and a long half-life can provide a sustainable blockade of DRD2 and narrow peak-trough fluctuation of the antipsychotic agent's blood concentration, which could lead to less rebound psychosis [1]. In this context, the use of an LAI other than aripiprazole once-monthly is a common strategy. Similarly, some oral antipsychotics with long half-lives such as blonanserin and paliperidone might be beneficial for patients with DSP [4] [**Table**]. However, both of the present patients showed persistent positive symptoms that were not controlled even by antipsychotic agents with long half-lives.

Asenapine was effective for both of our patients' unstable courses. Asenapine has profile that is beneficial for combatting DSP, as it has high affinity to DRD2 (inhibition constant [Ki] 1.26 nm) and a long half-life of 35.5 hr (in multiple dosing) [6]; these values

are similar to those of an LAI and other oral antipsychotics such as blonanserin and paliperidone. DRD3 and 5-HT2A receptors were reported to be related to the DS state [7, 8]. Asenapine has high affinity to DRD3 and 5-HT2A receptors, but blonanserin and paliperidone do as well [6, 9, 10]. Shahid et al. reported that the binding ratios of 5-THs receptor/DRD2 of asenapine are close to those of clozapine [11]. All of the aspects of asenapine's profile might have contributed to the amelioration of our present patients' DSP.

Several case reports have described asenapine's high efficacy for patients with severe psychopathology including DSP [12-14]. The reported patients were all treated with asenapine 20 mg; the chlorpromazine equivalent-dose is 800 mg. Our present two patients' symptoms were also successfully controlled with similar dose of asenapine. According to a recent sub-analysis of a clinical trial [15], a portion of patients with schizophrenia respond further to the higher dose (20 mg) of asenapine, which might also be the case for our patients. In addition, both of our patients showed EPS and hyperprolactinemia, which are common adverse effects of serotonin-dopamine antagonists (SDAs). Thus, treatment with 20-mg asenapine, which results in a lower rate of these adverse events, might also be beneficial for DSP patients who need high-dose medication.

In summary, the present two cases indicate that asenapine, with the above-described

pharmacodynamic (i.e., high affinity to DRD2/DRD3 and a broad 5-TH receptor) and pharmacokinetic (i.e., 35-hr half-life) profile, may contribute to the control of severe DSP.

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Conflicts of interest:

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Author contribution

Conceptualization: NK and YT,

Data acquisition: NK, HK and YT,

Writing draft: NK and YT,

Supervision: TK and MI.

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Table. Antipsychotic agents that were reported to be potentially effective for patients with dopamine supersensitivity psychosis (DSP)

Antipsychotic agent	Authors, Year, Ref	Comments
Asenapine	Rajkumar et al. 2014 [12]	Case report
	Takao et al. 2021 [14]	Case report
Clozapine	Chouinard et al. 1994 [16]	Case series showing that risperidone was also efficacious for DSP
	Nakata et al. 2017 [17]	Case series showing that tardive dyskinesia and repeated rebound psychosis disappeared in 15 patients with DSP
Risperidone long-acting injectable (RLAI)	Kimura et al. 2013 [18]	Case report
	Kimura et al. 2014 [19], 2016 [20]	RLAIs were more effective for patients with DSP (n=61) than those without DSP (n=33) in a 2-year observational study
Blonanserin	Tachibana et al. 2016 [21]	Case series
	Niitsu et al. 2020 [22]	This randomized controlled study showed that add-on treatment with both blonanserin (n=26) and olanzapine (n=29) similarly provided significant efficacy for DSP patients
Paliperidone	Kobayashi et al. 2020 [23]	Case report
Aripiprazole	Tadokoro et al. 2017 [24]	Case report
	Kanahara et al. 2018 [25]	Case series showing that the introduction of aripiprazole following ECT successfully stabilized two patients with severe DSP.
	Kanahara et al. 2020 [26]	Case series from a clinical trial: A very-slow switching strategy to aripiprazole from other agents provided DSP patients with potential clinical stability