Annals of General Psychiatry

RESEARCH

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Predictors of continuation for asenapine from real-world data in patients with schizophrenia

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Abstract

Background The continuation rates of pharmacotherapy in schizophrenia exhibit variability, a phenomenon influenced by the specific antipsychotic agent prescribed and patient-related factors such as age and duration of illness. In this context, our study aims to elucidate the predictors of medication continuation for asenapine sublingual tablets, characterized by unique formulation properties.

Methods Our investigation leveraged real-world data collected through post-marketing surveillance in Japan, comprising 3236 cases. Utilizing multivariate logistic regression analysis, we identified patient-related factors associated with medication continuation as the primary outcome measure, subsequently employing survival analysis for further evaluation. Additionally, adverse event occurrence was assessed as a secondary outcome measure.

Results Multivariate logistic regression analysis unveiled significant predictors of asenapine continuation, notably including patient-related factors such as a chlorpromazine equivalent dose exceeding 600 mg/day and an illness duration of 25 years or more. While the overall continuation rate stood at 40.6%, patients exhibiting factors such as a chlorpromazine equivalent dose surpassing 600 mg/day or an illness duration exceeding 25 years demonstrated continuation rates of 46.3% and 47.9%, respectively. Remarkably, patients presenting both factors showcased the highest continuation rate at 52.5%.

Conclusions Our findings shed light on distinct patient-related predictors of asenapine continuation, deviating from those observed with other antipsychotic medications. This underscores the necessity of recognizing that predictive factors for antipsychotic medication continuation vary across different agents. Moving forward, elucidating these predictive factors for various antipsychotic medications holds paramount importance in schizophrenia treatment, facilitating the delivery of tailored therapeutic interventions for individual patients.

Keywords Schizophrenia, Predictor, Asenapine, Continuation rate, Real world data

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Background

The mainstay of schizophrenia treatment is pharmacotherapy using antipsychotics. However, it is reported that the interruption of antipsychotic treatment is associated with a five-fold increase in the risk of relapse after 5 years [1]. Therefore, treatment continuation is important for maintaining remission and preventing relapse. In addition, treatment

continuation is affected by the effectiveness (both efficacy and tolerability) of the drug [2].

It has been also reported that the continuation rate of pharmacotherapy for schizophrenia differs depending on the type of antipsychotics, and the patient's background factors such as age and disease duration [3]. Therefore, when starting treatment, it is important to select the most appropriate drug for each patient while considering the predictors of treatment continuation.

Asenapine is an antipsychotic approved by the Food and Drug Administration in August 2009 for the treatment of schizophrenia and bipolar I disorder [4]. Asenapine has been demonstrated to significantly improve the Positive and Negative Syndrome Scale (PANSS) total score compared to placebo in the treatment of schizophrenia [5, 6]. Large-scale network meta-analyses reported so far demonstrated the efficacy and tolerability of asenapine in both acute and maintenance phases, similar to several of the 32 antipsychotics [7, 8]. Asenapine was developed as a sublingual tablet because of the very high first-pass effect and the low bioavailability (less than 2%) when orally administered [9]. Asenapine is rapidly absorbed through the sublingual mucosa and enters into the systemic circulation, resulting in a rapid onset of action and significant improvement relative to placebo at 15 min post-dose [10], although specific adverse events following sublingual administration, such as bitter taste and oral hypoesthesia, have been reported [11]. Oral hypoesthesia is attributable to the local anesthetic effects of asenapine [12]. Although the symptom usually resolves within 1 h [13], it may affect the continuation of treatment.

A comparative study using real-world data showed that the treatment continuation rates at 6 months for asenapine and olanzapine were 27.3% and 50.8%, respectively, suggesting that the lower continuation rate of asenapine was owing to its specific characteristics such as bitter taste and the burden of the dosing method [14]. A clinical study reported that the incidence of oral hypoesthesia was approximately 10% in patients receiving asenapine [15, 16]; however, it is difficult to identify patients who will develop an adverse event.

As mentioned previously, asenapine has similar efficacy and tolerability to other antipsychotics; however, it has different pharmacodynamic and pharmacokinetic characteristics. Additionally, asenapine has specific formulation characteristics. Therefore, an understanding of patient background factors associated with the continuation of asenapine treatment is important not only to identify patients who will benefit from the drug, but also to prevent relapse by continuation of medication in terms of optimization of treatment strategies for patients with schizophrenia.

This study aimed to identify the predictors of continuation of asenapine by examining the patient's background factors at the start of the treatment in real-world settings using post-marketing surveillance data [17].

Methods

Study design and patients

The post-marketing drug use-results survey was approved by the safety review committee of the Meiji Seika Pharma Co., Ltd. and was conducted from January 2017 to December 2019. The study subjects were patients operationally diagnosed with schizophrenia by specialists and newly treated with asenapine. The following parameters were investigated during the 52-week follow-up period: patient demographic characteristics, duration of asenapine treatment, concomitant medications, adverse events, biochemical parameters, and the Clinical Global Impression-Improvement (CGI-I) scale. All adverse events were coded using MedDRA/J [17]. Patients who started asenapine were enrolled, and survey responses were entered into an Electronic Data Capture (EDC) system. Answers to the survey items were stored in the EDC system at the time of each observation.

The primary endpoint of this study was to identify patient's background factors predicting asenapine continuation. The secondary endpoint was to evaluate the occurrence of adverse events in patients according to the presence or absence of the predictors.

Statistical analysis

Univariate analysis was performed to identify factors associated with the continuation of treatment with asenapine in patients who were registered and followed up for 52 weeks using the background information at the start of the treatment. To investigate the effects of the dose of antipsychotics immediately before starting the treatment with asenapine, patients were divided into those receiving a chlorpromazine (CP) equivalent dose of <600 mg/day and those receiving a CP equivalent dose of ≥ 600 mg/day according to the report by Howes et al. [18], and the two groups were treated as categorical variables. Univariate analyses were performed using the Mann–Whitney *U* test for continuous variables and the chi-square test for categorical variables. Next, multivariate logistic analysis (variables were selected by stepwise selection) was performed with treatment continuation as the objective variable and each background factor as the explanatory variable. For background factors that were significant in the multivariate logistic analysis, survival time was analyzed using the multivariate Cox regression analysis with the discontinuation of treatment as the event of interest. For

continuous variables, the population was divided into two groups based on the cut-off value by the classification and regression tree (CART) analysis. Survival analyses were compared between the two groups.

With regard to safety assessment, the relationship between the continuation of asenapine treatment and the incidence of adverse drug reactions was evaluated. For adverse drug reactions with an incidence of ≥ 3%, the relationship between the predictors and the incidence of adverse drug reactions was evaluated using the chi-square test. Statistical significance was defined as $p < 0.05$. Each item was analyzed after excluding participants with missing data.

Results

A total of 3425 patients were registered at 543 institutions, and 3321 patients were eligible for safety analysis and whose data were fixed. A total of 3236 patients were analyzed after excluding 85 patients who could not be followed for 52 weeks. The percentage of male patients was 45.3%. The age and disease duration at the start of the treatment with asenapine were 46.7 ± 15.4 years [mean ± standard deviation (SD)] and 16.7 ± 14.2 years (mean ± SD), respectively. The proportion of patients with first-episode schizophrenia was 35.9%.

In addition, 2488 patients (76.9%) were taking other antipsychotics at the start of asenapine treatment, and 1190 patients (36.8%) were taking antipsychotics with a CP equivalent dose of ≥ 600 mg/day before the start of asenapine treatment (Table 1). During the 52-week surveillance period, 1315 patients (40.6%) continued to receive asenapine.

Predictors and continuation rate

Univariate analyses were performed to identify patients' background factors associated with asenapine continuation. Univariate analyses demonstrated that the following three factors were significantly associated with treatment continuation: age at the start of asenapine treatment ($p = 0.0004$, Mann–Whitney U test), disease duration from the first onset ($p < 0.0001$, Mann–Whitney U test), and taking antipsychotics with a CP equivalent dose of ≥ 600 mg/day before the start of asenapine treatment ($p < 0.0001$, chi-square test). Older age, longer disease duration from the first onset, and taking antipsychotics with a CP equivalent dose of ≥ 600 mg/day before the start of asenapine treatment were associated with the continuation of asenapine treatment.

Following univariate analysis, multivariate logistic regression analysis was performed using the stepwise selection method. Multivariate analysis revealed that two factors were significantly associated with treatment continuation: CP equivalent doses of ≥ 600 mg/day ($p < 0.001$, chi-square test) and disease duration ($p < 0.001$, chi-square test). Before the survival analysis using the discontinuation of treatment as the event of interest, the disease duration as a continuous variable was categorized into two groups (≥ 25 years and < 25 years) using the CART method.

Log-rank test for survival analysis demonstrated significant differences between the two groups divided by the CP equivalent dose (≥ 600 mg/day or < 600 mg/day) and the disease duration (≥ 25 years and < 25 years) ($p < 0.0001$, data not shown), indicating that the predictors of continuation of asenapine for 52 weeks are CP equivalent dose of ≥ 600 mg/day and disease duration of ≥ 25 years.

Table 1 Patient's characteristics before administration of asenapine

		Total (N = 3236)
Male	[n, (%)]	1466 (45.3)
Mean age	[years, mean (SD)]	46.7 (15.4)
Inpatient	[n, (%)]	1471 (45.5)
Body weight	[kg, mean (SD)]	62.6 (15.5)
BMI	[mean (SD)]	23.8 (5.1)
Duration of illness	[years, mean (SD)]	16.7 (14.2)
First-episode	[n, (%)]	1162 (35.9)
Anxiolytics/hypnotic sedatives	[n, (%)]	1438 (44.4)
Anticonvulsant	[n, (%)]	607 (18.8)
Antiparkinson agent	[n, (%)]	609 (18.8)
Antipsychotics	[n, (%)]	2488 (76.9)
CP equivalent ≥ 600 mg/day	[n, (%)]	1190 (36.8)
Number of antipsychotics	[number of drugs, mean (SD)]	1.1 (1.0)

BMI: Body mass index; CP: Chlorpromazine; SD: standard deviation

The continuation rates in patients with a CP equivalent dose of ≥ 600 mg/day and those with a disease duration of ≥ 25 years were 46.3% and 47.9%, respectively, which were similar between the two groups (Table 2). In addition, the continuation rate in patients with both predictors (CP equivalent dose of ≥ 600 mg/day and disease duration of ≥ 25 years) was the highest at 52.5%. The continuation rates in patients with a CP equivalent dose ≥ 600 mg/day and a disease duration of < 25 years and those with a CP equivalent dose < 600 mg/day and a disease duration of ≥ 25 years were 43.2% and 43.7%, respectively, which were similar between the two groups. In addition, the continuation rate in patients with none of the predictors (CP equivalent dose of < 600 mg/day and disease duration of < 25 years) was the lowest (34.1%, Table 2).

Survival analysis with a combination of the two predictors (Fig. 1) revealed that the proportion of patients continuing asenapine for 52 weeks was the highest in those with both predictors and the lowest in those with none of the predictors. This trend is consistent over the 52-week follow-up period after starting the treatment with asenapine. Log-rank test for survival analysis displayed a significant difference between patients with both predictors and those with none of the predictors ($p < 0.0001$, Fig. 1).

Tolerability

Of the 3236 patients analyzed, 1098 (33.9%) experienced adverse drug reactions. Of the 1098 patients experiencing adverse drug reactions, 253 (23.0%) continued treatment for 52 weeks. Of the 2138 patients without adverse drug reactions, 1062 (49.7%) continued treatment for 52 weeks (Table 2).

The adverse drug reactions occurring at an incidence rate of ≥ 3% in any of the patient groups stratified by the presence or absence of predictors were akathisia, somnolence, and oral hypoesthesia. With regard to the incidence of these three adverse drug reactions, significant differences among these four groups were observed in akathisia and somnolence (Table 3).

Discussion

This is the first study to identify predictors of continuation of treatment with asenapine by examining the patients' background factors before the treatment. This study demonstrated that CP equivalent dose of ≥ 600 mg/day and disease duration of ≥ 25 years were predictors of continuation of treatment with asenapine. In addition, in the evaluation of the 52-week continuation rate with a combination of the two predictors, the continuation rate was the highest (52.5%) in patients with both predictors (CP equivalent dose of ≥ 600 mg/day and disease duration of ≥ 25 years), and low (34.7%) in patients with

Table 2 Continuation status with asenapine administration

	Continuation [n (%)]	Discontinuation [n (%)]	Total
Predictors from multivariate logistic regression analysis			
CP equivalent (n = 3190)			
< 600 mg/day	751 (37.6%)	1249 (62.5%)	2000
≥ 600 mg/day	551 (46.3%)	639 (53.7%)	1190
Duration of illness (n = 2506)			
< 25 years	673 (37.1%)	1142 (62.9%)	1815
≥ 25 years	331 (47.9%)	360 (52.1%)	691
Combination of predictors (n = 2469)			
< 600 mg/day and < 25 years	409 (34.1%)	791 (65.9%)	1200
< 600 mg/day and ≥ 25 years	145 (43.7%)	187 (56.3%)	332
≥ 600 mg/day and < 25 years	256 (43.2%)	336 (56.8%)	592
≥ 600 mg/day and ≥ 25 years	181 (52.5%)	164 (47.5%)	345
Safety status			
Side effect(s) (n = 3236)			
With	253 (23.0%)	845 (77.0%)	1098
Without	1062 (49.7%)	1076 (50.3%)	2138
Severe side effect (n = 3236)			
With	21 (20.6%)	81 (79.4%)	102
Without	1294 (41.3%)	1840 (58.7%)	3134

CP: Chlorpromazine

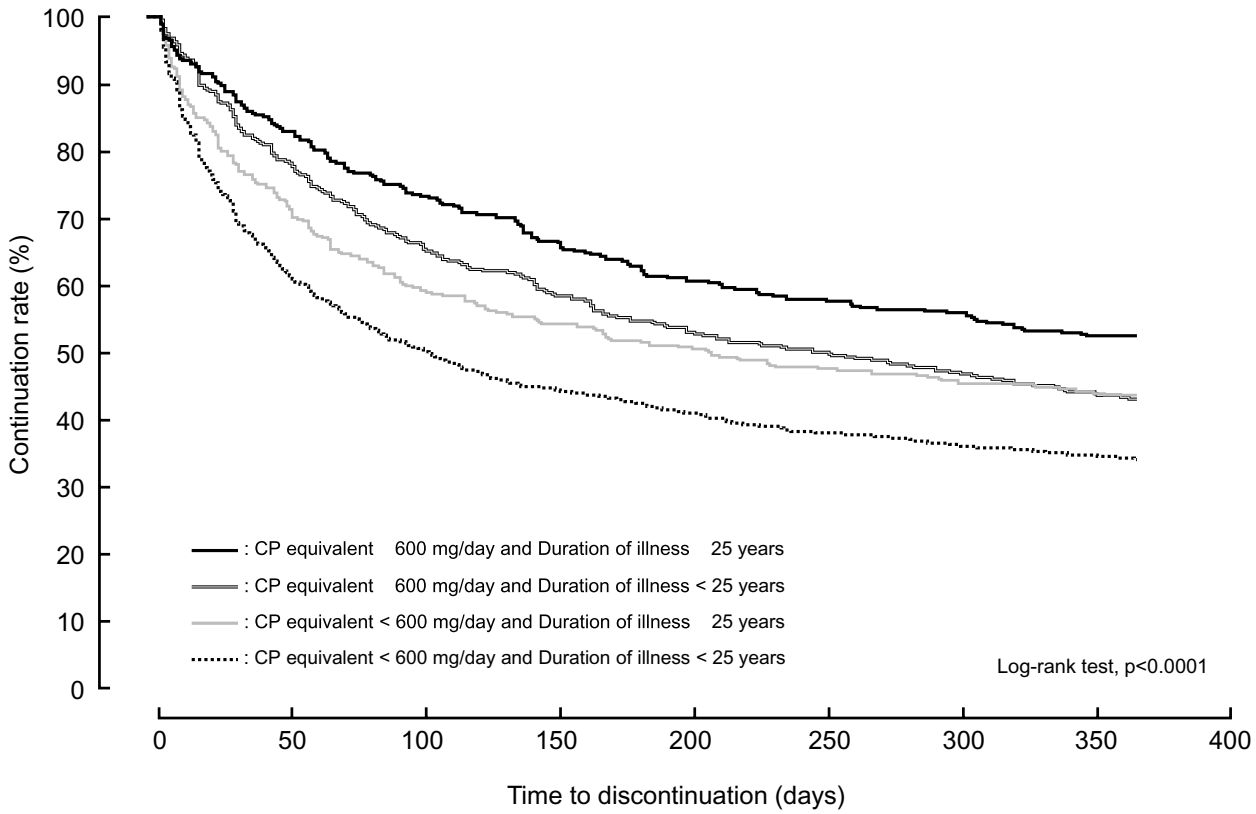

Fig. 1 Kaplan–Meier survival analysis of time to asenapine discontinuation for any reason. Analysis of patients treated with either more than 600 mg/day or less of antipsychotics (chlorpromazine-equivalent doses), and with a duration of more than 25 years or less at the initiation of treatment with asenapine. CP: Chlorpromazine

Table 3 Side effects status among each groups

	CP < 600 mg/day and < 25 years (n = 1200)	CP < 600 mg/day and ≥ 25 years (n = 332)	CP ≥ 600 mg/day and < 25 years (n = 592)	CP ≥ 600 mg/day and ≥ 25 years (n = 345)	Total (n = 3236*)	p value**
Patients with side effect(s) [n (%)]	456 (38.0)	101 (30.4)	201 (34.0)	108 (31.3)	1098 (33.9)	0.0117
Akathisia [n (%)]	94 (7.8)	11 (3.3)	27 (4.6)	9 (2.6)	163 (5.0)	< 0.0001
Somnolence [n (%)]	69 (5.8)	7 (2.1)	28 (3.0)	7 (2.0)	124 (3.8)	0.0003
Hypoaesthesia oral [n (%)]	66 (5.5)	9 (2.7)	36 (6.1)	9 (2.6)	155 (4.8)	0.1868

* Patients with missing data on CP-equivalent values at the initiation of asenapine administration or the duration of illness from onset (n = 767) are included

** Chi-square test with 1 degree of freedom

none of the predictors, indicating a significant difference between the two groups (Fig. 1).

Continuation of medication is one of the most important issues to prevent relapse and maintain remission. However, the 52-week asenapine continuation rate varies widely among studies. In 2010, the 52-week asenapine continuation rate was reported as 38.0% [19]. In a 52-week long-term administration study (P06125 study) conducted as an extension study of a placebo-controlled study of asenapine, the continuation rate was reported as 42.8% [16]. In contrast, a retrospective study reported it to be 19.0% [20]. In a phase III study of asenapine (P06238 study) conducted in patients with residual schizophrenia, polypharmacy, overdose, treatment-resistance, or elderly schizophrenia, the 52-week continuation rate was 50.3%, which was the highest value so far reported [21]. Interestingly, in the study, 71.3% of patients had a disease duration of at least 20 years, and 68.0% of patients received antipsychotics at a CP equivalent dose of ≥ 600 mg/day [21]. However, in the aforementioned P06125 study [16],

the percentage of patients whose duration of disease was 20 years or longer was 25.9%. No medication was administered before the start of the treatment with asenapine because a washout period was conducted according to the study design. From these previous reports, it was considered that the continuation rate of asenapine varied among studies depending on the study design and characteristics of the patient population enrolled.

Several antipsychotics have been investigated on the predictors of treatment continuation in patients with schizophrenia. The CP equivalent dose, which is a predictor found in the present study, was reported as a predictor of the continuation of brexpiprazole and clozapine. However, contrary to asenapine, prior treatment with high-dose antipsychotics was associated with treatment discontinuation [22, 23]. Regarding the relationship between disease duration and continuation rate of antipsychotic drugs, studies of aripiprazole and brexpiprazole have reported that the risk of treatment discontinuation is higher in patients with a longer disease duration [22, 24], again showing conflicting results with the findings on asenapine.

Although it is difficult to explain biologically why these two factors contribute to the continuation of asenapine treatment, there could be two possible reasons: the uniqueness of the pharmacological action of asenapine and the impact of unique oral adverse drug reactions deriving from the route of administration. First, with regard to the unique pharmacological action, the binding affinity of asenapine for dopamine D2 receptors is similar to or greater than that of endogenous dopamine. However, unlike other drugs, asenapine has the unique pharmacological property of having a greater affinity for a variety of receptors involved in the pathology of schizophrenia [25]. Recently, accumulating evidence suggests that asenapine is highly efficacious for patients with treatment-resistant schizophrenia [26, 27] or dopamine supersensitivity psychosis [28]. The potential reason for this is the full antagonist activity against dopamine D2 and serotonin 2A receptors. In addition, pharmacological effects of asenapine such as calming effect associated with high affinity for α1A and histamine receptors, improvement effect on cognitive function and anxiety symptoms due to partial agonist effect on serotonin 1A receptors, and high safety derived from low affinity for muscarinic M1 receptors are listed. However, the effects of the combination of these pharmacological effects are unknown, and future studies are warranted. Second, aging is known to be associated with decreased oral sensory function and taste, especially bitter taste [29, 30]. For example, it is reported that the sensory threshold of the tongue is greatly affected by aging, and the sensory function declines with aging [31]. It is also reported that taste and smell are strongly affected by polypharmacy [32], suggesting that patients receiving multiple antipsychotics and other concomitant drugs for a long period could have a certain negative impact. In the future, it is necessary to accumulate evidence regarding the relationship between the pathological conditions and the changes in oral sensation and taste in patients with a long disease duration receiving high-dose antipsychotics.

In this study, asenapine-related adverse drug reactions were observed in 33.9% of patients, and the medication was generally well tolerated. In contrast, the proportion of patients who continued treatment for 52 weeks was 23.0% for those with adverse drug reactions and 49.7% for those without adverse drug reactions, reflecting the presence of patients who discontinued treatment due to tolerability issues (Table 2). The stratified analysis by the presence or absence of predictors demonstrated no marked difference in the type and incidence of adverse drug reactions between the groups. However, among adverse drug reactions with an incidence of 3% or higher, a significant between-group difference was noted in akathisia and somnolence using the chi-square test (Table 3).

A recent study reported that the risk of akathisia varies depending on the type and dose of antipsychotics [33]. The risk of akathisia with asenapine is classified as moderate, and it changes gradually and monotonically within the dose range of 5 to 20 mg/day, without significant dose effects [33]. In a study comparing the risk of somnolence among antipsychotics, asenapine was classified as low somnolence [34]. However, in this study, 76.9% of patients received concomitant antipsychotics. Therefore, the risk factors could include not only the pharmacological action of asenapine but also certain patient background factors. A cluster analysis of the phase III clinical study suggests that the pharmacological effects of asenapine, such as akathisia and somnolence, are more likely to cause adverse drug reactions in mild patients [35]. In this study, there was a possibility that the proportion of patients with less severe schizophrenia was high in patients with none of the two predictors identified in this study (i.e., patients with lower doses of antipsychotics and shorter disease duration). Because the severity assessment was not performed in this study, future study is required on this issue.

Contrary to expectations, no significant difference was observed in oral hypoesthesia among groups (Table 3), which is an asenapine-related adverse drug reaction. The reason for this is unknown; however, it is suggested that background factors such as aging and high-dose antipsychotic therapy in the patients included in this study could have affected the results.

The results of this study showed that the patient background factors predicting the continuation of treatment may differ among drugs. Antipsychotics are usually selected on the basis of their efficacy and tolerability; however, treatment continuation is also an important consideration. Our results may support clinicians in their decision-making regarding the use of asenapine when treating patients with schizophrenia with complex backgrounds.

Limitation

Because this study used data from the post-marketing survey for safety evaluation, information on the assessment of the severity of schizophrenia is not included. Therefore, the relationship between the symptom characteristics of schizophrenia (positive and negative symptoms, cognitive impairment, and their outcomes) and predictors of continuation remains unknown. Given the heterogeneity of schizophrenia, the relationship between symptom characteristics and predictors of continuation requires further investigation.

In addition, adherence is unknown because it was not studied. Despite limitations in controlling confounding factors such as drugs used to treat complications, the findings of this study using real-world data led to the identification of predictors of continuation of treatment with asenapine in clinical practice.

Conclusions

This study demonstrated that the use of high doses of antipsychotics and long disease duration were predictors of continuation of asenapine treatment. Since the predictors found in this study were contradictory to those of other antipsychotics, our results may provide important suggestions to prevent relapse in patients with complex backgrounds in terms of optimizing treatment strategies for patients with schizophrenia.

The results of this study strongly suggest that background factors predicting the continuation of treatment with antipsychotics vary among drugs. The selection of drugs having a high probability of treatment continuation based on the patient's background is important for preventing treatment resistance or pseudo-resistance [36]. It is important to clarify the predictors of continuation of treatment with each antipsychotic using real-world data to provide optimal treatment for each patient in the future.

Abbreviations

PANSS	Positive and Negative Syndrome Scale
CGI-I	Clinical Global Impression-Improvement
CP	Chlorpromazine
CART	Classification and regression tree
BMI	Body mass index
SD	Standard deviation

Acknowledgements
We thank all study participants for their cooperation.

Author contributions
YT conceived and designed of the study. DM conducted data acquisition. YI developed the statistical analysis plan and conducted statistical analysis. NA, HO, TF, TS, YM, YS and YK contributed to the interpretation of the results. SH drafted the original manuscript. MK supervised the conduct of this study. All authors reviewed the manuscript draft and revised it critically on intellectual content. All authors approved the final version of the manuscript to be published.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board, and written informed consent was waived because of the retrospective design.

Consent for publication
Not applicable.

Competing interests
YT has received grant funding from the Japan Society for the Promotion of Science and speaker's honoraria from Meiji-Seika Pharma, Sumitomo Pharma, Janssen Pharmaceutical, Otsuka, Eisai, MSD K.K. Daiichi-Sankyo, Pfizer, UCB Japan, and Takeda Pharmaceutical. NA received speaker honoraria from Daiichi-Sankyo, Eli Lilly, Meiji-Seika Pharma, Janssen Pharmaceutical, Eisai, and Otsuka. TF has received grant funding from the Japan Society for the Promotion of Science and speaker's honoraria from Sumitomo Pharma, Otsuka, Meiji Seika Pharma, Janssen Pharmaceutical, Takeda Pharmaceutical, Lundbeck, Viatris Inc, Eisai, Mochida Pharmaceutical. TS has received speaker's honoraria from Meiji-Seika Pharma, Sumitomo Pharma, Janssen Pharmaceutical, and Mochida Pharmaceutical. YM received speaker honoraria from Sumitomo Pharma, Meiji-Seika Pharma, Takeda Pharmaceutical, Lundbeck, and Viatris Inc. YK has received speaker's honoraria, and consulting fees from Takeda Pharmaceutical Co., Ltd. MK has received grant funding from AMED, the Japanese Ministry of Health, Labour and Welfare, the Japan Society for the Promotion of Science, SENSHIN Medical Research Foundation, the Japan Research Foundation for Clinical Pharmacology, and the Japanese Society of Clinical Neuropsychopharmacology, and consulting fees from Sumitomo Pharma Co., Ltd., Shionogi & Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Lundbeck Japan K.K., Takeda Pharmaceutical Co., Ltd.; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Sumitomo Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Eli Lilly Japan K.K., MSD K.K., Janssen Pharmaceutical K.K., Shionogi & Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Lundbeck Japan K.K., Viatris Inc., Eisai Co., Ltd., Kyowa Pharmaceutical Industry Co., Ltd., Ono Pharmaceutical Co., Ltd. HO and YS declares no conflict of interest associated with this manuscript. SH, YI and DM are full-time employees of Meiji Seika Pharma Co. Ltd.

Received: 2 April 2024 Accepted: 29 July 2024
Published online: 02 August 2024

References

1. Tiihonen J, Tanskanen A, Taipale H. 20-year nationwide follow-up study on discontinuation of antipsychotic treatment in first-episode schizophrenia. Am J Psychiatry. 2018;175(8):765–73.

2. Swartz MS, Perkins DO, Stroup TS, McEvoy JP, Nieri JM, Haak DC. Assessing clinical and functional outcomes in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial. Schizophr Bull. 2003;29(1):33–43.
3. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353(12):1209–23.
4. Tarazi FI, Shahid M. Asenapine maleate: a new drug for the treatment of schizophrenia and bipolar mania. Drugs Today. 2009;45(12):865–76.
5. Hay A, Byers A, Sereno M, Basra MK, Dutta S. Asenapine versus placebo for schizophrenia. Cochrane Database Syst Rev. 2015;11: CD011458.
6. Kinoshita T, Bai YM, Kim JH, Miyake M, Oshima N. Efficacy and safety of asenapine in Asian patients with an acute exacerbation of schizophrenia: a multicenter, randomized, double-blind, 6-week, placebo-controlled study. Psychopharmacology. 2016;233:2663–74.
7. Schneider-Thoma J, Chalkou K, Dörries C, Bighelli I, Ceraso A, Huhn M, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. Lancet. 2022;399(10327):824–36.
8. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019;394(10202):939–51.
9. Citrome L. Role of sublingual asenapine in treatment of schizophrenia. Neuropsychiatr Dis Treat. 2011;7:325–39.
10. Pratts M, Citrome L, Grant W, Leso L, Opler LA. A single-dose, randomized, double-blind, placebo-controlled trial of sublingual asenapine for acute agitation. Acta Psychiatr Scand. 2014;130(1):61–8.
11. Plosker GL, Deeks ED. Asenapine: a review in schizophrenia. CNS Drugs. 2016;30(7):655–66.
12. Citrome L. Asenapine review, part II: clinical efficacy, safety and tolerability. Expert Opin Drug Saf. 2014;13(6):803–30.
13. Vieta E, Montes JM. A review of asenapine in the treatment of bipolar disorder. Clin Drug Investig. 2018;38(2):87–99.
14. Matsuzaki H, Hatano M, Iwata M, Yamada S. Treatment continuation of asenapine or olanzapine in Japanese schizophrenia patients: a propensity score matched study. Neuropsychiatr Dis Treat. 2021;17:3655–61.
15. Kinoshita T, Won K, Tamura F, Sasagawa Y. Long-term study of asenapine in subjects with residual subtype, receiving multiple or/and high dose drugs, or treatment refractory schizophrenia (Protocol P06238). Jpn J Clin Psychopharmacol. 2016;19(6):771–87.
16. Kinoshita T, Takekita Y, Hiraoka S, Tamura F, Iwama Y. Long-term safety and efficacy of sublingual asenapine for the treatment of schizophrenia: a phase III extension study with follow-up for 52 weeks (P06125)-Secondary publication. Neuropsychopharmacol Rep. 2023;43(3):328–37.
17. Kitamura Y, Kosuge N, Hiraoka S, Iwama Y, Tominaga Y, Matsui D. Evaluation of the safety and efficacy with asenapine sublingual tablets in acute clinical settings in patients with schizophrenia—final report on post-marketing surveillance study. Jpn J Clin Psychopharmacol. 2021;24(7):751–64.
18. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, et al. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am J Psychiatry. 2017;174(3):216–29.
19. Schoemaker J, Naber D, Vrijland P, Panagides J, Emsley R. Long-term assessment of asenapine vs. olanzapine in patients with schizophrenia or schizoaffective disorder. Pharmacopsychiatry. 2010;43(4):138–46.
20. Inoue Y, Suzuki H, Hibino H, Takaya A, Mikami K, Yamamoto K, et al. Continuation rate for asenapine and brexpiprazole treatment in patients with schizophrenia. Brain Behav. 2021;11(5): e02109.
21. Kinoshita T, Won K, Tamura F, Sasagawa Y. Long-term study of asenapine in subjects with residual subtype, receiving multiple or/and high dose drugs, or treatment refractory schizophrenia (Protocol P06238) (in Japanese). Jpn J Clin Psychopharmacol. 2016;19(6):771–87.
22. Yoshimura Y, Shimizu H, Yamashita R, Washida K, Takeda T, Aoki S. Association between previous high-dose antipsychotic therapy and brexpiprazole discontinuation after the initiation of brexpiprazole in patients with schizophrenia or schizoaffective disorder. Int Clin Psychopharmacol. 2020;35(2):98–104.
23. Iruretagoyena B, Castañeda CP, Mena C, Diaz C, Nachar R, Ramirez-Mahaluf JP, et al. Predictors of clozapine discontinuation at 2 years in treatment-resistant schizophrenia. Schizophr Res. 2021;235:102–8.
24. Takaesu Y, Kishimoto T, Murakoshi A, Takahashi N, Inoue Y. Factors associated with discontinuation of aripiprazole treatment after switching from other antipsychotics in patients with chronic schizophrenia: a prospective observational study. Psychiatry Res. 2016;236:71–4.
25. Shahid M, Walker GB, Zorn SH, Wong EH. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. J Psychopharmacol. 2009;23(1):65–73.
26. Kanahara N, Kimura H, Kinoshita T, Iyo M, Takekita Y. Efficacy of asenapine in drug-resistant psychotic patients with dopamine supersensitivity psychosis: two cases. Clin Psychopharmacol Neurosci. 2023;21(1):197–201.
27. Takao N, Murai T, Fujiwara H. Treatment-resistant schizophrenia characterised by dopamine supersensitivity psychosis and efficacy of asenapine. BMJ Case Rep. 2021;14(4): e242495.
28. Nakata Y, Kanahara N, Iyo M. Dopamine supersensitivity psychosis in schizophrenia: concepts and implications in clinical practice. J Psychopharmacol. 2017;31(12):1511–8.
29. Liu J, Cattaneo C, Papavasileiou M, Methven L, Bredie WLP. A review on oral tactile sensitivity: measurement techniques, influencing factors and its relation to food perception and preference. Food Qual Prefer. 2022;100:104624.
30. Frank ME, Hettinger TP, Mott AE. The sense of taste: neurobiology, aging, and medication effects. Crit Rev Oral Biol Med. 1992;3(4):371–93.
31. Bangcuyo RG, Simons CT. Lingual tactile sensitivity: effect of age group, sex, and fungiform papillae density. Exp Brain Res. 2017;235(9):2679–88.
32. Schiffman SS. Influence of medications on taste and smell. World J Otorhinolaryngol Head Neck Surg. 2018;4(1):84–91.
33. Wu H, Siafis S, Wang D, Burschinski A, Schneider-Thoma J, Priller J, et al. Antipsychotic-induced akathisia in adults with acute schizophrenia: a systematic review and dose-response meta-analysis. Eur Neuropsychopharmacol. 2023;72:40–9.
34. Fang F, Sun H, Wang Z, Ren M, Calabrese JR, Gao K. Antipsychotic drug-induced somnolence: incidence, mechanisms, and management. CNS Drugs. 2016;30(9):845–67.
35. Takekita Y, Hiraoka S, Iwama Y, Sunada N, Aoki N, Ogata H, et al. Divergence of dose-response with asenapine: a cluster analysis of randomized, double-blind, and placebo control study. CNS Spectr. 2022;27(3):369–77.
36. Potkin SG, Kane JM, Correll CU, Lindenmayer JP, Agid O, Marder SR, et al. The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic resistance and a roadmap for future research. NPJ Schizophr. 2020;6(1):1.

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