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Clinical Characteristics of Patients with Schizophrenia Maintained without Antipsychotics: A Cross-sectional Survey of a Case Series

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Objective: While antipsychotics are necessary for relapse prevention in the treatment of schizophrenia in general, some minority of patients may be maintained without continuous antipsychotic treatment. However, the characteristics of such patients are not well known and previous reports have not evaluated key elements such as physical comorbidities and functioning.
Methods: Among 635 patients with schizophrenia who participated in a 12-year follow-up, those who were maintained without antipsychotic treatment for at least one year after the study were investigated. The patients underwent comprehensive assessments, including Positive and Negative Syndrome Scale (PANSS) for psychopathology, Cumulative Illness Rating Scale for Geriatrics (CIRS-G) for physical comorbidities, and Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz), Barthel Index, and EuroQoL five dimensions (EQ5D) for function.
Results: Six patients were included (mean ± standard deviation age, 66.8 ± 17.4 years; 4 inpatients). The four inpatients were old (77.8 ± 4.8 years) and chronically ill (duration of illness, 49.3 ± 12.5 years) with a high PANSS score (total score, 118.0 ± 9.8; negative syndrome subscale, 41.3 ± 6.9), low functioning (FACT-Sz, 9.8 ± 3.6; Barthel Index, 8.8 ± 9.6), and serious physical comorbidities (CIRS-G, 15.5 ± 1.1). By contrast, the two outpatients were relatively young (45.0 ± 12.0 years) and clinically in good condition (PANSS total score, 44.5 ± 0.5; Barthel Index, 100 for both; EQ5D, 0.85 ± 0.04).
Conclusion: Although the number is limited, two types of patients with schizophrenia were identified who were free from ongoing antipsychotic treatment; 1) older chronic inpatients with serious physical comorbidities, and 2) younger outpatients with milder impairments. Future explorations are needed to identify those who will be successfully withdrawn from continuous antipsychotic treatment.

KEY WORDS: Antipsychotics; Discontinuation; Maintenance; Schizophrenia.

INTRODUCTION

Maintenance treatment with antipsychotics is generally recommended for relapse prevention in patients with schizophrenia due to the chronic nature of the illness [1-3]. On the other hand, evidence suggests that some minority of patients may be maintained without antipsychotics [4-7]. This is of clinical relevance in consideration of side effects with antipsychotics such as extrapyramidal symptoms (EPS) [8-10], metabolic comorbidities [11-13], and cardiovascular events [14]. However, data are still scarce regarding the clinical characteristics of patients with schizophrenia who used to receive antipsychotic treatment but are currently no longer taking it [3,15,16]. A number of naturalistic long-term follow-up studies have reported better outcomes in subgroups of patients who discontinued antipsychotic treatment compared to those maintained on medications [4-6]. Despite

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the absence of antipsychotic treatment, somewhat counterintuitively, they were more likely in remission and had better clinical outcomes. Beyond the fact that these studies were non-randomized and strictly observational, they did not analyze other relevant conditions, including physical comorbidities and quality of life (QOL) as potential outcome predictors [17]. Moreover, subjective perspectives such as resilience and spirituality, which likely affect clinical outcomes [18-20] have not been evaluated. Therefore, we conducted a cross-sectional evaluation of a case series study to comprehensively characterize patients with schizophrenia who were maintained without antipsychotic treatment.

METHODS

A multi-site prescription survey was conducted for patients with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), who were receiving antipsychotic drugs in Japan in September 2002 [21]. A follow-up survey of the same patients was conducted in September 2014. Patients who received antipsychotic drugs in 2002 but were not taking them in 2014 were identified. Those who were continuously maintained without antipsychotics until September 2015 (i.e., at least one year) were included in the present study (Supplementary Fig. 1; available online).

In the 2002 survey, 1668 patients participated; of these, 635 patients were included in the follow-up survey in 2014. Among them, 19 patients (3.0%) were antipsychotic-free. Of these, 13 patients were not included in this study due to the death (n = 6), resumption of antipsychotics (n = 5), and change of diagnosis (n = 2) since

Table 1. Characteristics of patients who were withdrawn from antipsychotics

Case	A	B	C	D	E	F	Inpatients	Outpatients
Age (yr)	79	70	83	79	33	57	77.8 ± 4.8	45.0 ± 12.0
Sex	M	F	F	M	M	M	NA	NA
Treatment setting	IN	IN	IN	IN	OUT	OUT	NA	NA
Onset of illness (yr)	23	36	17	38	19	24	28.5 ± 8.8	21.5 ± 2.5
Duration of illness (yr)	56	34	66	41	15	33	49.3 ± 12.5	24.0 ± 9.0
Number of psychiatric hospitalizations	4	6	4	4	1	0	4.5 ± 0.9	0.5 ± 0.5
Duration of current hospitalization (yr)	14	5	7	6	N.A.	N.A.	8.0 ± 3.5	NA
Duration of free from antipsychotics (yr)	1.6	1.8	2.4	7.1	8.0	4.3	3.2 ± 2.3	6.1 ± 1.9
Presence of physical comorbidity	Yes	Yes	Yes	Yes	No	Yes	NA	NA
BMI	18.3	15.2	12.8	15.2	32.5	20.4	15.4 ± 1.9	26.5 ± 6.0
PANSS								
Total	135	112	112	113	44	45	118.0 ± 9.8	44.5 ± 0.5
Positive symptoms	28	21	10	9	8	10	17.0 ± 7.9	9.0 ± 1.0
Negative symptoms	36	33	49	47	10	11	41.3 ± 6.9	10.5 ± 0.5
General symptomatology	71	58	53	57	26	24	59.8 ± 6.8	25.0 ± 1.0
SAS, total score	7	29	15	20	0	0	17.8 ± 8.0	0
BAS, global severity score	0	0	0	0	0	0	0	0
AIMS, total score of items 1–7	15	2	12	0	0	0	7.3 ± 6.4	0
FACT-Sz	15	10	5	9	65	60	9.8 ± 3.6	62.5 ± 2.5
Barthel Index	25	5	0	5	100	100	8.8 ± 9.6	100
CIRS-G, total score	16	17	14	15	2	12	15.5 ± 1.1	7.0 ± 5.0
EQ-5D	0.03	0.19	0.03	0.27	0.81	0.88	0.13 ± 0.11	0.85 ± 0.04
RS, total score	N/A	N/A	N/A	N/A	109	125	N/A	117.0 ± 8.0
FACIT-Sp, Spirituality score	N/A	N/A	N/A	N/A	20	17	N/A	18.5 ± 1.5
WHOQOL	N/A	N/A	N/A	N/A	2.7	3.4	N/A	3.1 ± 0.4

Values are presented as number only or mean ± standard deviation.
AIMS, Abnormal Involuntary Movement Scale; Barthel Index, Barthel Index of Activities of Daily Living; BAS, Barnes Akathisia Scale; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; EQ-5D, EuroQoL five dimensions; F, female; FACIT-Sp, The Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale; FACT-Sz, Functional Assessment for Comprehensive Treatment of Schizophrenia; IN, inpatient; M, male; MMSE, Mini Mental State Examination; NA, not applicable; N/A, not available; OUT, outpatient; PANSS, Positive and Negative Syndrome Scale; RS, Resilience Scale; SAS, Simpson-Angus Scale for Extrapyramidal Side Effects; WHOQOL, WHOQOL-BREF instrument Japanese version.

the year 2014. The remaining six patients were approached, and all of them agreed to participate in the present study and provided written informed consent after a full description of the study, which was performed in Tokyo Musashino Hospital, Asakadai Mental Clinic, Musashino-Chuo Hospital, Sakuragaoka Memorial Hospital, and Jiundo Hospital in Tokyo, Japan, and was approved by the Institutional Review Board at each participating site.

The scales used in this study to evaluate the respective domains and the detailed explanation of each scale is described in the Supplemental Document (available online) [22-35].

RESULTS

A summary of the clinical characteristics of the six antipsychotic-free patients is shown in Table 1. The mean ± standard deviation duration of being free from antipsychotics was 4.2 ± 2.5 years. The age and the duration of illness of four inpatients (Patients A, B, C, and D) were 77.8 ± 4.8 years and 49.3 ± 12.5 years, respectively. These inpatients presented high Positive and Negative Syndrome Scale (PANSS) total scores (118.0 ± 9.8) with predominant negative symptoms (41.3 ± 6.9). They also demonstrated EPS burden (Simpson-Angus Scale for Extrapyramidal Side Effects total score, 17.8 ± 8.0), physical comorbidities (Cumulative Illness Rating Scale for Geriatrics total score, 15.5 ± 1.1), low activities of daily living (ADL) (Barthel Index, 8.8 ± 9.6), and low functioning (Functional Assessment for Comprehensive Treatment of Schizophrenia [FACT-Sz] score, 9.8 ± 3.6). In contrast, the two outpatients (E and F) were relatively young (45.0 ± 12.0 years) and in good condition with milder symptomatology (PANSS total score, 44.5 ± 0.5), high ADL (Barthel Index, 100 for both) and QOL (EuroQoL five dimensions, 0.85 ± 0.04).

Table 2. Reasons for antipsychotic cessation

Case	Reason
A	Gait instability, excessive sedation, parkinsonism,
B	Pneumonia
C	Gait instability, remission
D	Dysphagia, gait instability, ileus, parkinsonism,
E	Remission of psychosis
F	Cerebral infarction, pneumonia

The case description of the six patients is reported in the Supplemental Document (available online). The reasons for antipsychotic discontinuation are summarized in Table 2. Patient E discontinued antipsychotics because of having achieved remission, while the other five stopped them due to physical comorbidities such as gait instability, parkinsonism, ileus, and pneumonia.

DISCUSSION

Based on the comprehensive assessments of the patients who were maintained without antipsychotic drugs for at least one year, we identified two prototypes as follows. The first includes patients who have mild impairments. This is consistent with previous reports, such as a 10-year follow-up of a Finnish national database study that included 70 subjects and found that 24 non-medicated patients for the previous three months presented with lower symptom levels, fewer hospitalizations during the previous five years, and a low retirement rate than medicated patients [4]. A long-term prospective follow-up study including 70 subjects with schizophrenia in the US revealed that 38% of the patients were antipsychotic-free 20 years past the baseline assessment. These antipsychotic-free patients, compared to those on antipsychotics, showed a higher recovery rate at follow-up as well as more internal resources, better functioning, and a better self-image [6,36]. A seven-year follow-up of 103 remitted patients with first-episode psychosis after the open-label randomized controlled trial comparing the antipsychotic dose reduction/discontinuation (DR) and maintenance treatment (MT) reported that subjects originally assigned to DR demonstrated superior recovery rate compared to MT (40.4% vs. 17.6%), while only eight patients in the DR group and three patients in the MT group sustained medication discontinuation during the last two years of follow-up [5]. Although approximately 30−40% of the subjects in this longitudinal follow-up study were antipsychotic-free at the time of follow-up, interpretation of the findings needs to be cautious because of the observational study design, a limited number of antipsychotic-free patients, and lack of data regarding reasons for antipsychotic discontinuation and periods of being free from antipsychotics.

The other type represents the patients who suffer from physical comorbidities and therefore forced to quit anti-

psychotic treatment in fear of negative impact on their physical conditions. Indeed, the use of antipsychotics may result in a variety of negative consequences such as gait instability with a risk for falls, weight gain, metabolic and cardiovascular diseases, as well as dysphagia/dysarthria that is associated with aspiration pneumonia [37-42]. These side effects, when serious enough, discourage psychiatrists from continuing antipsychotic treatment at the cost of psychopathology. In the present study, the four patients in this subgroup predominantly presented with negative symptoms with low functioning and ADL, making them somewhat easier to manage by caregivers or nursing staff even without antipsychotics than those presenting with active positive symptoms [43]. Suzuki and Uchida [44] reported a similar case series of four elderly inpatients with schizophrenia who discontinued antipsychotic treatment. As ours, they were also old (77.0 ± 8.6 years) and chronic in their illness (46.0 ± 26.9 years) with moderate to severe psychopathology (Clinical Global Impression Illness Severity, 4−6) and low functioning (FACT-Sz, 30−40). Taken together, these findings represent a clinical challenge and dilemma regarding the use of antipsychotics in frail patients even though they still present with significant psychopathology.

Thus, while there is a subgroup of patients who may not need antipsychotics in the maintenance treatment of schizophrenia, the evidence to reliably identify these patients is still scarce. Shimomura and colleagues reviewed the existing guidelines on the use of antipsychotics in the maintenance treatment of schizophrenia [16]. While antipsychotic discontinuation is not recommended for patients with multiple-episode schizophrenia in the majority of the guidelines and algorithms, recent guidelines do not completely dismiss this strategy in both first-episode schizophrenia and schizophrenia in general [45-51]. However, what is still unclear is who can be maintained without antipsychotics as well as when and how to stop medications. Previous reviews reported no replicated factors that predicted continuous remission after antipsychotic discontinuation in patients with first-episode psychosis [52,53]. Another recent review suggested that older age, later onset of illness, shorter duration of untreated psychosis, modest psychopathology, and being maintained on a lower dose of antipsychotics before drug discontinuation were associated with a lower risk of relapse after antipsychotic cessation in schizophrenia, while it should be acknowledged that the relapse rate was as high as 38.3% per year and the definitions of relapse differed widely across the studies [54]. Obviously, our small case series does not allow for generalizations but may serve as an example of clinical decision-making beyond existing guidelines.

There are some limitations to be noted in the present study. Since the present case series was not a prospective antipsychotic discontinuation study, the characteristics identified in this study need to be carefully considered in light of the existing literature. Moreover, the very limited number of subjects were included in this study and only a few outpatients were successfully withdrawn from antipsychotics. It precluded us to conduct meaningful analyses (e.g., pre-post mirror image comparison regarding relevant clinical outcomes such as hospitalization). Furthermore, it needs to be stressed that other subgroups of patients were not considered herein who voluntarily stop antipsychotics due to nonadherence [55]. In theory, prospective antipsychotic discontinuation trials would have been ideal for this purpose; however, ethical concerns with unequivocally high relapse rates need to be taken into account (even among first-episode patients [56]).

We found a tiny subgroup of patients with schizophrenia who may not need antipsychotics for the maintenance treatment in our longitudinal follow-up survey; those who are in relative remission and those who needed to stop antipsychotic treatment because of its negative impact on their physical comorbidities. Further studies are warranted to better identify patients with schizophrenia who will be successfully maintained without long-term antipsychotics.

■ Conflicts of Interest

Dr. Tani has received manuscript fees from Dainippon Sumitomo Pharma, Otsuka Pharmaceutical, Wiley Japan and Yoshitomi Yakuhin, fellowship grants from the Japanese Society of Clinical Neuropsychopharmacology and the Canadian Institutes of Health Research, and a research grant from Eli Lilly within the past three years. Dr. Tomita has received manuscript or speaker's fees from Dainippon Sumitomo Pharma, Janssen Pharmaceuticals, Meiji Seika Pharma, Otsuka Pharmaceutical, and Mochida Pharmaceutical. Dr. Suzuki has received manuscript or speaker's fees from Astellas, Dainippon Sumitomo

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■ Author Contributions

Conceptualization: Hideaki Tani, Hiroyuki Uchida. Data collection: Hideaki Tani, Masayuki Tomita. Formal analysis: Hideaki Tani. Supervision: Masayuki Tomita, Takefumi Suzuki, Masaru Mimura, Hiroyuki Uchida. Writing–original draft: Hideaki Tani. Writing–review & editing: Masayuki Tomita, Takefumi Suzuki, Masaru Mimura, Hiroyuki Uchida. All the authors contributed significantly to the manuscript and have approved the final manuscript.

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