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# Satisfaction Survey on Antipsychotic Formulations by Schizophrenia Patients in Japan

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**Objective:** To identify factors affecting adherence to medication, a subjective questionnaire survey was administered to schizophrenia patients regarding the prescribed antipsychotic formulations.
**Methods:** We evaluated the patients' satisfaction and dissatisfaction with prescribed antipsychotic formulations, and patients answered the Drug Attitude Inventory-10 Questionnaire (DAI-10). Inclusion criteria for patients are as follows: age between 20 and 75 years and taking antipsychotic agents containing the same ingredients and formulations, for at least 1 month.
**Results:** In total, 301 patients answered the questionnaire survey. Tablets were found to be the most commonly used antipsychotic formulations among schizophrenia patients (n = 174, 57.8%), followed by long-acting injections (LAIs, n = 93, 30.9%). No significant differences in the formulation satisfaction level and DAI-10 scores were observed between all formulations. Formulations, except for LAI, were selected by physicians in more than half of the patients. Patients who answered "Decided by consultation with physicians" had significantly higher satisfaction levels and DAI-10 scores compared to those who answered "Decided by physicians" (4.11 ± 0.77 vs. 3.80 ± 1.00, $p = 0.0073$ and 6.20 ± 3.51 vs. 4.39 ± 4.56, $p < 0.001$, respectively). Satisfaction levels moderately correlated with DAI-10 scores (r = 0.48, $p < 0.001$).
**Conclusion:** No formulation had a high satisfaction level in all patients, and it is important to be reflect the patients' individual preferences in pharmacotherapy. Shared decision-making in the selection of the formulations is seen to be useful for improving medication adherence.

**KEY WORDS:** Antipsychotic agents; Schizophrenia; Surveys and questionnaires; Patient satisfaction; Medication adherence; Drug formulation.

## INTRODUCTION

The long-term treatment goal for schizophrenia is the prevention of relapse, for which the continuation of antipsychotic medication is essential. The maintenance and increased adherence to medication represent important clinical challenges associated with pharmacotherapy treatments for schizophrenia. Although non-adherence is often associated with an approximately fivefold increase in the risk of relapse [1,2], only half of all outpatients were determined to adhere to their antipsychotic regiment, as directed by their physicians, according to a study that used the Medication Event Monitoring System [3]. Non-adherence to medication may be associated with various factors in patients with schizophrenia. Medication-related risk factors include high antipsychotic doses, complex medication regimens, and the use of typical antipsychotics [4]. Conversely, one strategy to improve adherence is the use of an appropriate formulation for each patient (e.g., medications with long half-lives, depot medications, and

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transdermal medications) [5].

Recently, various formulations, such as orally disintegrating tablets (ODTs) and long-acting injections (LAIs), have been developed for the administration of antipsychotics, besides general tablets and powdered medicines. Risperidone has a large number of formulations, among which, five are currently available in Japan. Each formulation has been identified to have characteristic advantages and disadvantages. For example, powdered medicines are useful when fine dose adjustments are necessary or when patients have difficulty swallowing; however, it has a bitter taste. Approximately 40% of the general practice population report difficulties swallowing tablets, and powdered medicines may be suitable substitute for these patients [6]. Although LAIs may be associated with the risk of injection site reaction (e.g., pain, edema, and induration), they may improve adherence and do not require patients to remember to take their medications [7]. A previous questionnaire survey reported that over two-thirds of the patients have felt better having received LAI, and over half of the patients considered LAI to be more effective than prior therapy [8]. Therefore, the selection of antipsychotic formulation is important not only for their pharmacological profiles but can also improve medication adherence when considering patients' preferences.

We administered a subjective questionnaire survey regarding antipsychotic formulations. Questionnaire surveys are deemed useful for subjective assessment in study designs. This present study aimed to investigate the patients' satisfaction levels with antipsychotic formulations and to examine the relationship between the formulation selection process and medication adherence.

## METHODS

### Study Design

This present study was a subjective questionnaire survey administered to Japanese schizophrenia patients. The questionnaire consisted of five questions regarding antipsychotic formulations (Table 1). We have evaluated the satisfaction levels for each antipsychotic formulation (tablets, ODTs, powdered medicines, liquid medicines, LAIs, and sublingual tablets), on a scale from 1 (extremely

**Table 1.** Questionnaire on antipsychotic formulations

1. Who decided on your formulations?
   - ☐ Decided by myself.
   - ☐ Decided by consultation with physicians.
   - ☐ Decided by physicians.

2. Did you recieve an explanation from your physicians or pharmacists about your formulations? (Check all that apply.)
   - ☐ Yes, I received an explanation from physicians.
   - ☐ Yes, I received an explanation from pharmacists.
   - ☐ No, I did not receive an explanation.

3. What are you most satisfied about your formulations?

   Please add any comments below.

   (  )

4. What are you most dissatisfied about your formulations?

   Please add any comments below.

   (  )

5. How satisfied are you with your formulations?

| Extremely dissatisfied | Moderately dissatisfied | Neither satisfied nor dissatisfied | Moderately satisfied | Extremely satisfied |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |

dissatisfied) to 5 (extremely satisfied). Patients using more than one antipsychotic formulation were asked to evaluate each formulation separately. Furthermore, we conducted a questionnaire with a clear distinction for antipsychotic agents at the beginning of the survey for them to avoid confusion with the evaluation of each antipsychotic formulation. We also performed the Drug Attitude Inventory-10 Questionnaire (DAI-10), to determine associations between the patients' satisfaction with their antipsychotic formulations and their medication adherence. The DAI-10 assesses patients' subjective experiences with treatment, which is certified the reliability and validity as a predictor of medication adherence [9,10]. The DAI-10 consists of 10 true/false questions, for which a positive answer is given a score of plus 1, whereas a negative answer is given a score of minus 1. The total score ranges from −10 to +10, and higher scores indicate improved attitudes toward antipsychotic medications. We assessed the relationship between satisfaction levels, for each formulation, and DAI-10 scores, in addition to the results of the questionnaire survey. The questionnaire was administered by pharmacists, in order to avoid inaccurate responses due to cognitive dysfunction. The questionnaire survey was administered to patients from December 2018 to May 2019. Data were collected at Fujita Health University Hospital, Okehazama Hospital, Kyowa Hospital, Holy Cross Hospital, and Kamibayashikinen Hospital. We adequately explained the study protocol to all participants, and we obtained oral consent. In addition, we recorded the consent date, the method of explanation, and the explainer, in the medical record. This study was approved by the Institutional Review Board of Fujita Health University and each individual hospital (HM18-238).

### Patients

Patients who were eligible for enrollment in this study included those aged between 20 and 75 years and diagnosed with schizophrenia or schizoaffective disorder, according to the definitions outlined in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition. Patients were also required to have used the same formulation of antipsychotic agents, containing the same ingredients, for at least 1 month.

### Statistical Analysis

The patients were divided into groups, according to their antipsychotic formulations and their answers to questions 1 and 2 in the questionnaire; further, their average satisfaction levels and DAI-10 scores between each group were compared. Between-group differences in satisfaction levels and DAI-10 scores were analyzed using Welch's $t$ test, followed by Games-Howell test for post hoc comparisons when significance was determined by Welch's $t$ test. The relationship between satisfaction levels with antipsychotic formulations and DAI-10 scores was assessed using Pearson's product-moment correlation coefficient. The sample size was set as the number of feasible cases during the term of this study, at each hospital. The $p$ values were two-sided, and those less than 0.05 were considered significant. All statistical analyses were performed using R, version 3.4.3 (the R Foundation for Statistical Computing).

## RESULTS

### Patient Characteristics

In total, 301 patients participated in this study, of which only one patient, who had incomplete questionnaire answers, was excluded from analysis. The patient characteristics are summarized in Table 2. Tablets were determined to be the most commonly used antipsychotic formulations among the schizophrenia patients in this study (n = 174, 57.8%), followed by LAIs (n = 92, 30.7%). Powdered medicines, liquid medicines, and sublingual tablets were used by less than 10 % of patients.

### Questionnaire Survey

The results of the questionnaire survey are summarized in Figures 1 and 2. The formulations, except for LAI, were selected by physicians, for more than 50% of patients. More than 90% of patients received medication instructions for the use of sublingual tablets from physicians (88.9%), physicians and pharmacists (72.2%), and pharmacists (77.8%). Conversely, instructions for the use of liquid medicines were not explained by any physicians or pharmacists for 38.5% of patients.

The most common reason determined for high formulation satisfaction was "easy to take" (tablets, 31.2%; ODT, 30.9%; powder, 35.7%, and liquid, 15.4%). In contrast, some patients complained about "difficult to take," due to the size of the tablets (12.6%) and the taste of ODT medicines (5.9%), liquid medicines (23.1%), and sub-

**Table 2.** Patient characteristeics

| Variable | All (n = 300) | Formulations | | | | | |
|---|---|---|---|---|---|---|---|
| | | Tablet (n = 173) | ODT (n = 68) | Powdered medicine (n = 14) | Liquid medicine (n = 13) | LAI (n = 92) | Sublingual tablet (n = 18) |
| Age (yr) | 47.8 ± 12.9 | 46.6 ± 12.6 | 51.7 ± 12.8 | 55.1 ± 13.9 | 49.9 ± 8.6 | 47.6 ± 12.4 | 45.7 ± 10.1 |
| Male sex | 148 (49.3) | 88 (50.9) | 36 (52.9) | 8 (57.1) | 5 (38.5) | 43 (46.7) | 8 (44.4) |
| Polypharmacy | 108 (36.0) | 80 (46.2) | 29 (42.6) | 4 (28.6) | 7 (53.8) | 41 (44.6) | 13 (72.2) |
| Antianxiety agents use | 106 (35.3) | 68 (39.3) | 21 (30.9) | 9 (64.3) | 6 (46.2) | 31 (33.7) | 7 (38.9) |
| Hypnotic agents use | 138 (46.0) | 83 (48.0) | 29 (42.6) | 10 (71.4) | 8 (61.5) | 40 (43.5) | 11 (61.1) |
| Antiparkinsonian agents use | 66 (22.0) | 42 (24.3) | 20 (29.4) | 3 (21.4) | 3 (23.1) | 19 (20.7) | 5 (27.8) |
| Outpatients | 236 (78.7) | 134 (77.5) | 49 (72.1) | 13 (92.9) | 11 (84.6) | 74 (80.4) | 6 (33.3) |

Values are presented as mean ± standard deviation or number (%).
ODT, orally disintegrating tablet; LAI, long-acting injection.

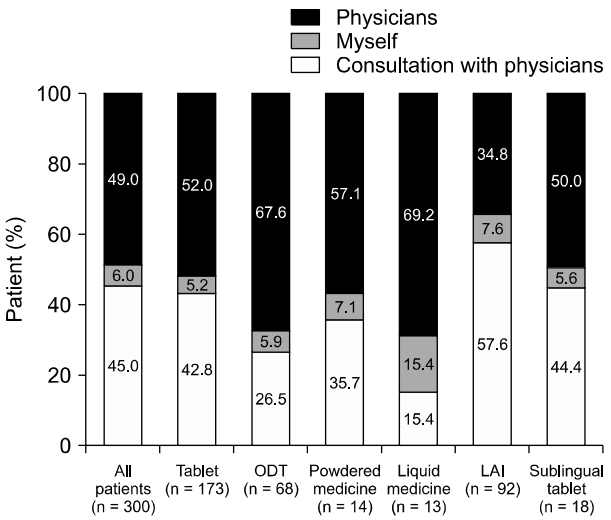


**Fig. 1.** Question 1, Who decided on your formulations?
ODT, orally disintegrating tablet; LAI, long-acting injection.

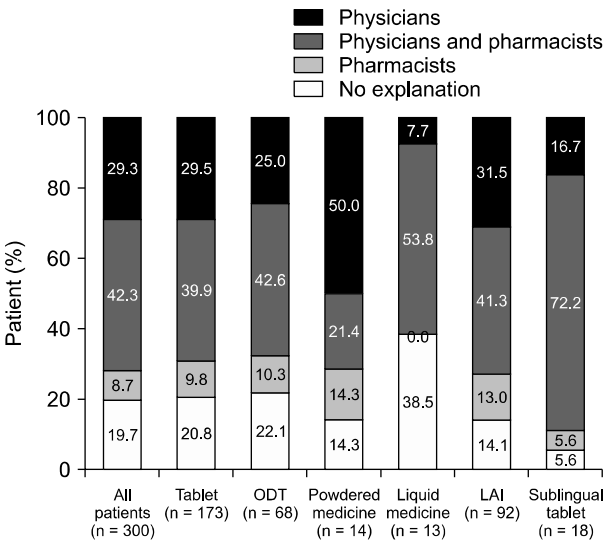


**Fig. 2.** Question 2, Did you receive an explanation from your physicians or pharmacists about your formulations?
ODT, orally disintegrating tablet; LAI, long-acting injection.

lingual tablets (16.7%). The reason given for high satisfaction among patients receiving LAI was "did not forget medication" (23.9%), whereas for sublingual tablets, the reason was "immediate effectiveness" (16.7%). In contrast, the reason given for high dissatisfaction among patients receiving LAIs was "injection site pain" (38.0%). The reasons given for satisfaction and dissatisfaction with each formulation are summarized in Table 3.

The mean satisfaction level was 3.96 ± 0.92, among all patients. Satisfaction levels were found to be not significantly different among formulations. The mean DAI-10 score was 5.24 ± 4.14, among all patients. DAI-10 scores were not significantly different among formulations. The satisfaction levels and DAI-10 scores for each formulation are shown in Table 4.

## Relationships between Questionnaire Results and Satisfaction Levels and DAI-10 Scores, according to the Formulation

Patients who answered "Decided by consultation with physicians" had a significantly higher satisfaction level for formulations and DAI-10 than those who answered "Decided by physicians" (4.11 ± 0.77 vs. 3.80 ± 1.00, $p$ = 0.0073; 6.20 ± 3.51 vs. 4.39 ± 4.56, $p < 0.001$, respectively; Table 5). Patients who received explanations regarding their formulations from "physicians," "physicians and pharmacists," and "pharmacists" were found to have significantly higher satisfaction levels and DAI-10 scores than those who did not (4.02 ± 0.94, 3.98 ± 0.82, and 4.26 ± 0.88 vs. 3.60 ± 1.11, $p$ = 0.0076; 5.22 ± 3.91,

**Table 3.** Most satisfied and dissatisfied about each formulation

| Formulations | Most satisfied | | Most dissatisfied | |
|---|---|---|---|---|
| Tablet (n = 173) | "Easy to take" | 54 (31.2) | "Difficult to take" | 22 (12.6) |
| | "Effective" | 23 (13.3) | "Not applicable" | 107 (61.5) |
| | "Not bitter" | 10 (5.8) | | |
| | "Not applicable" | 62 (35.8) | | |
| ODT (n = 68) | "Easy to take" | 21 (30.9) | "Taste bad (bitter or sweet)" | 4 (5.9) |
| | "Dissolve in the mouth" | 12 (17.6) | "Not applicable" | 48 (70.6) |
| | "Effective" | 11 (16.2) | | |
| | "Taste good" | 6 (8.8) | | |
| | "Dry-swallow" | 5 (7.4) | | |
| | "Not applicable" | 17 (25.0) | | |
| Powdered medicine (n = 14) | "Easy to take" | 5 (35.7) | "Not applicable" | 8 (57.1) |
| | "Not applicable" | 5 (35.7) | | |
| Liquid medicine (n = 13) | "Easy to take" | 2 (15.4) | "Bitter taste" | 3 (23.1) |
| | "Not applicable" | 5 (38.5) | "Not applicable" | 8 (61.5) |
| LAI (n = 92) | "Did not forget medication" | 22 (23.9) | "Pain" | 35 (38.0) |
| | "Stabilize symptoms" | 16 (17.4) | "Not applicable" | 34 (37.0) |
| | "No need to take a medicine" | 14 (15.2) | | |
| | "Only once a month" | 7 (7.6) | | |
| | "Not applicable" | 20 (21.7) | | |
| Sublingual tablet (n = 18) | "Immediate effectiveness" | 3 (16.7) | "Can not swallow for 10 minutes" | 4 (22.2) |
| | "Effective" | 2 (11.1) | "Bitter taste" | 3 (16.7) |
| | "Dissolve in the mouth" | 2 (11.1) | "Difficult to take" | 2 (11.1) |
| | "Not applicable" | 10 (55.6) | "Tongue numbness" | 2 (11.1) |
| | | | "Not applicable" | 7 (38.9) |

Values are presented as number (%).
ODT, orally disintegrating tablet; LAI, long-acting injection.

**Table 4.** Satisfaction level and DAI-10 of each formulation

| Scores | All (n = 300) | Formulations | | | | | | $p$ value |
|---|---|---|---|---|---|---|---|---|
| | | Tablet (n = 173) | ODT (n = 68) | Powdered medicine (n = 14) | Liquid medicine (n = 13) | LAI (n = 92) | Sublingual tablet (n = 18) | |
| Satisfaction level | 3.96 ± 0.92 | 3.92 ± 0.97 | 4.10 ± 0.83 | 4.14 ± 1.03 | 4.08 ± 0.76 | 3.80 ± 0.94 | 4.11 ± 0.96 | 0.35 |
| DAI-10 | 5.24 ± 4.14 | 5.01 ± 4.36 | 5.38 ± 4.05 | 6.71 ± 2.79 | 5.85 ± 3.11 | 5.37 ± 4.02 | 3.67 ± 4.91 | 0.28 |

Values are presented as mean ± standard deviation.
DAI-10, Drug Attitude Inventory-10 Questionnaire; ODT, orally disintegrating tablet; LAI, long-acting injection.
Formulation comparisons performed with the Welch's $t$ test.

**Table 5.** Association between question 1 and satisfaction level or DAI-10

| Scores | Who decided on your formulations? | | | $p$ value |
|---|---|---|---|---|
| | Physicians (n = 194) | Myself (n = 24) | Consultation with physicians (n = 160) | |
| Satisfaction level | 3.80 ± 1.00 | 4.08 ± 1.21 | 4.11 ± 0.77* | 0.0073 |
| DAI-10 | 4.39 ± 4.56 | 4.92 ± 3.63 | 6.20 ± 3.51* | < 0.001 |

Values are presented as mean ± standard deviation.
DAI-10, Drug Attitude Inventory-10 Questionnaire.
Group comparisons performed with the Welch's $t$ test. *Differed from Physicians at $p < 0.05$.

**Table 6.** Association between question 2 and satisfaction level or DAI-10

| Scores | Did you recieve an explanation from your physicians or pharmacists about your formulations? | | | | $p$ value |
|---|---|---|---|---|---|
| | Physicians (n = 108) | Physicians and pharmacists (n = 159) | Pharmacists (n = 39) | No explanation (n = 72) | |
| Satisfaction level | 4.02 ± 0.94* | 3.98 ± 0.82* | 4.26 ± 0.88* | 3.60 ± 1.11 | 0.0076 |
| DAI-10 | 5.22 ± 3.91* | 5.95 ± 3.80* | 6.21 ± 3.69* | 2.92 ± 4.78 | < 0.001 |

Values are presented as mean ± standard deviation.
DAI-10, Drug Attitude Inventory-10 Questionnaire.
Group comparisons performed with the Welch's $t$ test. *Differed from No explanation at $p < 0.05$.

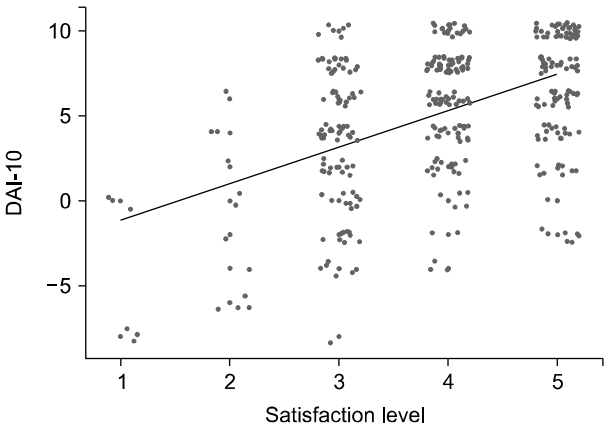


**Fig. 3.** Correlation between satisfaction level and Drug Attitude Inventory-10 Questionnaire (DAI-10).

5.95 ± 3.80, and 6.21 ± 3.69 vs. 2.92 ± 4.78, $p < 0.001$, respectively; Table 6). Figure 3 shows the correlation between satisfaction levels and DAI-10 scores. Satisfaction levels moderately correlated with DAI-10 scores (r = 0.48, $p < 0.001$).

## DISCUSSION

We examined the subjective assessments of antipsychotic formulations, using a questionnaire survey, in this study. When selecting antipsychotic formulation, although the efficacy and safety of those medicines must be balanced carefully, patients' individual preferences and comorbid medical issues should also be considered. A previous study reported that the adaption of drug regimens to individual preferences represents a promising strategy for improving adherence [11]. Our findings showed that patients who selected their formulations in consultation with their physicians were found to have significantly higher satisfaction levels and DAI-10 scores than those whose formulations were selected by their physicians alone, and satisfaction levels with the formulations correlated with DAI-10 scores. These results suggest that a shared decision-making model [12] for the selection of formulations may be useful in improving medication adherence. Conversely, even if a formulation is medically beneficial, a decision made by a physician alone (the paternalism model) will not necessarily result in sufficient patient satisfaction with treatment. For example, although LAI was shown to prevent hospitalizations, in a meta-analysis, using real-world data [13], it may not be acceptable to patients, due to several reasons. In this present study, approximately 40% of LAI users reported "pain" as the greatest source of dissatisfaction with this treatment. Moreover, LAI did not have higher satisfaction levels or DAI-10 scores than other formulations, indicating that evidence of treatment efficacy did not necessarily result in the positive assessment of pharmacotherapy by patients. Therefore, we must consider patient priorities regarding formulations.

Satisfaction and dissatisfaction may be contradictory among patients, even for the same formulations (e.g., "easy to take" and "difficult to take" were both reported for tablets, and "taste good" and "taste bad [bitter or sweet]" were both reported for ODT). Although tablets are the most common formulation and are easy to take for many patients, patients with dysphagia can have difficulties with this formulation. Taste is more strongly determined by patient preferences. The patients may not accept the flavors that are added to improve the original taste (e.g., bitterness) of the medicine. Furthermore, because ODT and powdered medicine stay longer in the oral cavity, taste is an important factor for these formulations [14]. Another issue that should be considered is the potential latency of subjective assessments [15]. The reported incidence of oral hypoesthesia after the administration of asenapine, a sublingual tablet, differed decidedly be-

tween a spontaneous report in a clinical trial [16] and an interview survey by patients [17] (approximately 10% vs. 70%). These factors can be difficult to predict before prescribing; therefore, continuous evaluations are deemed necessary.

Reliable information is a crucial factor for a working therapeutic alliance [18], which also applies to the dissemination of medication instructions for each formulation. We demonstrated that patients who received an explanation regarding the proper use of their formulations had significantly higher satisfaction levels and DAI-10 scores than those who did not. The Cochrane review reported that psychoeducation encouraged medication adherence and reduced relapse and readmission [19]. In this present study, no specific medication educations were provided, and only the patients' experiences of receiving medication instructions were examined. However, the results suggest that the routine intervention of providing medication instructions could potentially improve medication adherence. In addition, we also found that improved adherence associated with the receipt of medication instructions could be achieved by both physician-led and pharmacist-led interventions. Few studies have examined educational interventions performed by pharmacists on medication adherence in schizophrenia patients. One study that explored a pharmacist-led intervention reported an increase in insight among patients, but no effects on medication adherence were observed [20]. Our study was a cross-sectional study, with limited evidence, and should be validated using a further prospective study.

Our study had several limitations. First, because this study involved a self-reported questionnaire survey, the obtained answers may differ from actual medical examinations. For example, even if the formulations had been determined through a decision-making process with a physician, patients may feel that the physicians unilaterally decided the treatment if they have a poor relationship with their physician. Second, patients may have provided positive answers in this study because we only evaluated formulations that patients had been receiving for 1 month. This speculation is supported by the result that the average satisfaction level was "moderately satisfied." However, we did not evaluate formulations that were discontinued in the short-term and speculate that such formulations are generally associated with negative satisfaction. Patients may have been severely dissatisfied with these discontinued formulations; however, we were unable to evaluate this possibility, in this study. Third, our study has not assessed depression, anxiety, and psychotic symptoms of the patients, we should be aware that these symptoms may affect satisfaction levels with the formulations. Finally, powdered medicines, liquid medicines, and sublingual tablets are used more rarely than tablets; thus, we were unable to obtain sufficient opinions from patients regarding these formulations. The lack of sufficient sample size may have resulted in the lack of significant differences observed for satisfaction levels and DAI-10 scores among the various formulations.

In conclusion, patients have various preferences, and their priorities must be reflected in individual pharmacotherapy decisions. No superior formulation was identified for all patients. The shared decision-making process must be applied for the selection of formulations that are appropriate for the patients' preferences, and we believe that the utilization of proper formulations will improve medication adherence.

## ■ Conflicts of Interest

The authors have no direct conflicts of interest relevant to this study. No grant support or other sources of funding were used to conduct this study or prepare this manuscript. Dr. Hatano has received personal fees from Otsuka and Dainippon Sumitomo. Dr. Takeuchi has received personal fees from Otsuka, Meiji, Dainippon Sumitomo, and Janssen. Mr. Sakakibara has received personal fees from Otsuka. Dr. Yamada has received personal fees from AstraZeneca, Nippon Kayaku, Nipro, Dainippon Sumitomo, Towa Pharmaceutical, Eisai, Bayer, Japan Blood Products Organization, Aska Pharmaceutical, Mitsubishi Tanabe Pharma, Chugai Pharmaceutical, Merck Sharp, and Dohme, Daiichi Sankyo Company. Dr. Iwata has received research grants from Otsuka, GSK, Tanabe-Mitsubishi, Dainippon Sumitomo, Eisai, Daiichisankyo, Meiji, and has received personal fees from Eli Lilly, Janssen, Otsuka, Shionogi, GSK, Dainippon Sumitomo, Astellas, Yoshitomi, Meiji, Novartis, and Pfizer. Dr. Kamei has received personal fees from Otsuka, Meiji, and Dainippon Sumitomo.

## ■ Author Contributions

Conceptualization: Masakazu Hatano. Data acquisition: Masakazu Hatano, Ippei Takeuchi, Kanade Yamashita,

Aoi Morita, Kaori Tozawa, Takashi Sakakibara, Genta Hajitsu. Formal analysis: Masakazu Hatano. Supervision: Manako Hanya, Shigeki Yamada, Nakao Iwata, Hiroyuki Kamei. Writing original draft: Masakazu Hatano. Writing review & editing: Hiroyuki Kamei.

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