ORIGINAL ARTICLE

NEUROPSYCHOPHARMACOLOGY REPORTS

WILEY

Association between functional recovery and medication adherence in schizophrenia

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Abstract

Aim: Medication adherence is important for achieving functional recovery from schizophrenia and is commonly assessed using the Drug Attitude Inventory-30 (DAI-30). Subscales of the DAI-30, including *"awareness of the need for medication," "awareness of the effects of psychiatric drugs,"* and *"impression of medication,"* have been used to assess medication adherence. To determine which of these subscales are associated with the prognosis of schizophrenia, this study followed patients with schizophrenia to identify the prognosis and examine the subscales related to "recovery."

Methods: In total, 89 patients were recruited, 78 of whom were registered in the study. After assessing adherence using the DAI-30, Positive and Negative Syndrome Scale and Global Assessment of Functioning scores were assessed at 0 and 24 week to define the functional prognosis.

Results: At the end of the 24-week follow-up period, 36% of patients showed recovery from schizophrenia. A comparison of subscales revealed that the score for *"impression of medication"* was significantly higher in the recovery than in the non-recovery group. Logistic regression analysis identified only the *"impression of medication"* score as being predictive of recovery.

Conclusion: The results indicated that among the three DAI-30 subscales, *"impression of medication"* was the most closely associated with recovery in patients with schizophrenia.

KEYWORDS
functional recovery, medication adherence, prognosis, schizophrenia, trait anxiety

1 | INTRODUCTION

The longitudinal course in patients with schizophrenia is defined by a combination of social functioning and psychotic symptom severity. A previous study suggested the concept of "recovery" from schizophrenia, which is defined as a high degree of social adaptation, in addition to remission of clinical symptoms.[1] "Recovery" has also been found to be achieved in approximately 30% of patients with schizophrenia.[2,3]

The discontinuation of antipsychotic drugs is known to increase the risk of schizophrenia relapse almost fivefold.[4] Although schizophrenia relapse is thought to lead to greater treatment resistance and poor outcomes, numerous factors influence the prognosis of schizophrenia, and the relationship between medication adherence and the functional prognosis remains unclear.

The Drug Attitude Inventory-30 (DAI-30) is commonly used to assess medication adherence. In previous studies, subscales of the DAI-30 have been used to assess medication adherence, including "*awareness of the need for medication*," "*awareness of the effects of psychiatric drugs*," and "*impression of medication*".[5] Previous studies have also reported that symptoms such as anxiety and depression affect medication adherence.[6,7] In addition, neuroticism has been reported to be associated with medication non-adherence.[8] Therefore, various factors have been reported to be associated with medication adherence, and whether these factors are related to the prognosis of schizophrenia remains unclear.

To investigate which of the three medication adherence-related subscales are associated with the functional prognosis of schizophrenia, this study followed patients with schizophrenia to determine the functional prognosis and examine the subscales related to "recovery."

2 | METHODS

2.1 | Study design and patients

The study was performed as a part of a multicenter observational study (the Predictors of Recovery in Patients with Schizophrenia [PREPS] study). From April 2015 to January 2019, 89 patients with schizophrenia based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) were recruited from the outpatient section of the Department of Psychiatry, Jikei University Hospital, Jikei University Katsushika Medical Center, Sobu Hospital, and Otaki Hospital. The details of the study have been described elsewhere.[9] Five expert psychiatrists (JI, FK, HM, HS, and WY) with at least 5 years of clinical psychiatric experience diagnosed all the enrolled patients.

The inclusion criteria for the study were as follows: (1) a diagnosis of schizophrenia according to the DSM-IV-TR; and (2) age between 20 and 59 years. The exclusion criteria were: (1) presence of severe physical illness, (2) comorbid substance use disorder, and (3) inability to understand fully the study protocol or provide informed consent.

A two-wave (at 0 and 24 weeks) prospective survey was performed to examine the association between the functional prognosis of patients with schizophrenia. These patients were followed up for 24 weeks, and the functional prognosis was classified as "recovery" or "non-recovery" according to assessments made using the Positive and Negative Syndrome Scale (PANSS) and Global Assessment of Functioning (GAF) scale at 0 and 24 weeks. In the PREPS study, approximately 30% of patients were identified as having achieved recovery.[8] At 0 weeks, medication adherence was assessed using the DAI-30 questionnaire and trait anxiety was assessed using the State–Trait Anxiety Inventory (STAI-T).

This study was approved by the Ethical Committee of the Jikei University School of Medicine (approval No. 7493) in compliance with the principles laid down in the Helsinki Declaration of Human Rights.

2.2 | Clinical assessment

2.2.1 | Assessment of functional prognosis

To assess the functional prognosis, "recovery" and "non-recovery" were defined according to the definitions given in previous studies.[1,3,10] The participants were classified into two groups, namely the "recovery" group and the "non-recovery" group, according to scores on eight PANSS subscales (delusions [P1], disorganization [P2], hallucinatory behavior [P3], blunted affect [N1], social withdrawal [N4], lack of spontaneity [N6], mannerisms [G5], and unusual thought content [G9]) and the GAF score at 24 weeks. The GAF scale measures the degree of mental illness by rating psychological, social, and occupational functioning. Patients with "mild" or "low" scores (≤3 points) for all of P1, P2, P3, N1, N4, N6, G5, and G9, and a GAF score ≥ 81 at 0 and 24 weeks were classified into the "recovery" group, and otherwise, into the "non-recovery" group.[1,3,10]

2.2.2 | Assessment of medication adherence

The DAI-30, which is a self-administered questionnaire composed of 30 questions, each used to assess whether the patient responds favorably to psychotropic drugs, was used to assess medication adherence. A higher score indicates a more favorable attitude. The DAI-30 is divided into three subscales based on factors that influence adherence, each with a total score ranging from −10 to 10 points: "*awareness of the need for medication*" (eg, "I need medication"), "*awareness of the effects of psychiatric drugs*" (eg, "taking medication makes me feel relaxed"), and "*impression of medication*" (eg, "taking medication for a long time is poisonous to the body").[5]

2.3 | Statistical analysis

All data analyses were performed using SPSS version 21.0 (IBM, Chicago, IL). The statistical significance level was set at $P < 0.05$.

2.3.1 | Comparison of medication adherence between the recovery and non-recovery groups

To compare medication adherence between the recovery and non-recovery groups, the DAI-30 total score and the scores on the three subscales ("*awareness of the need for medication*," "*awareness of the effects of psychiatric drugs*," and "*impression of medication*") were compared using *t* tests. As there were three subtests, the Bonferroni correction was used with a significance level of $P < 0.0166$.

2.3.2 | Association between functional prognosis and medication adherence in schizophrenia

Logistic regression analysis was performed using three subscales of the DAI-30 to examine the relationships between the functional prognosis of patients with schizophrenia and the medication adherence subscales. The three subscales of the DAI-30 were adopted as independent variables, and the functional prognosis after 24 weeks (ie, recovery and non-recovery) was used as the dependent variable.

2.3.3 | Relationship between the subscales of the DAI-30 and anxiety characteristics in the recovery and non-recovery groups

To estimate the influence of anxiety characteristics on medication adherence, a post-hoc correlation analysis was conducted between the DAI-30 subscale and STAI-T scores that were found to be associated with recovery in logistic regression analysis. Pearson's product–moment correlation coefficients (*r*) were used to examine the correlation between "*impression of medication*" and the STAI-T.

3 | RESULTS

3.1 | Demographic characteristics

Of the 89 patients recruited for the study, 78 who provided informed consent for participation were enrolled in the study. Four patients dropped out because of being lost to follow-up and four patients were excluded because of missing values. The functional prognosis at 24 weeks for the remaining 70 patients was 26 in the recovery group and 44 in the non-recovery group. After removing missing values, 57 patients were finally included in the analysis: 24 in the recovery group and 33 in the non-recovery group (Figure 1).

Positive and Negative Syndrome Scale scores at baseline, the chlorpromazine-equivalent dose (CED), and the duration of untreated psychosis (DUP) were significantly higher in the non-recovery than in the recovery group. The STAI-T score was significantly higher in the non-recovery than in the recovery group (54.0 ± 12.3 vs. 43.6 ± 8.4, respectively; $P = 0.02$) (Table 1), Appendix S1.

3.2 | Comparison of medication adherence between the recovery and non-recovery groups

No statistically significant differences in DAI-30 total scores were found between the recovery and non-recovery groups. Based on the comparison of subscales, the score for "*impression of medication*" was significantly higher in the recovery than in the non-recovery group at the 5% level, but the Bonferroni correction eliminated this significant difference ($P = 0.03$). DAI-30 scores were 13.3 ± 8.4 and 11.1 ± 13.9 in the recovery and non-recovery groups, respectively ($P = 0.47$), and the scores for "*impression of medication*" were 7.08 ± 2.4 and 4.97 ± 4.8, respectively.

No significant differences in the scores for "*awareness of the need for medication*" or "*awareness of the effects of psychiatric drugs*" were found between the recovery and non-recovery groups. The scores for "*awareness of the need for medication*" and "*awareness of the effects of psychiatric drugs*" in the recovery and non-recovery groups were 6.08 ± 3.8 and 5.33 ± 4.7 ($P = 0.50$), respectively, and 0.08 ± 6.4 and 0.79 ± 6.3, respectively ($P = 0.68$) (Table 2), Appendix S1

3.3 | Association between medication adherence and the functional prognosis of schizophrenia

Among the independent variables, the score for "*impression of medication*" was the only variable identified as being significantly predictive of recovery in logistic regression analysis ($\beta = -3.09$, $t = -2.02$, $P = 0.04$) (Table 3).

3.4 | Relationship between DAI-30 subscale scores and trait anxiety in patients with schizophrenia

A significant negative correlation was found between the scores for "*impression of medication*" and STAI-T ($r = -0.386$, $P = 0.003$) (Figure 2).

4 | DISCUSSION

The present study identified an association between "*impression of medication*" and the functional prognosis of schizophrenia.

A comparison of DAI-30 subscales showed that "*impression of medication*" was higher in the recovery than in the non-recovery group, but this difference disappeared after the Bonferroni correction. This finding suggests that having a positive impression of medication may be associated with schizophrenia recovery.

A previous study reported that nonadherence is associated with functional outcomes, including decreased mental functioning, decreased life satisfaction, increased substance use, and increased alcohol-related problems.[11] This is consistent with the results of the present study. Another previous study found that negative attitudes
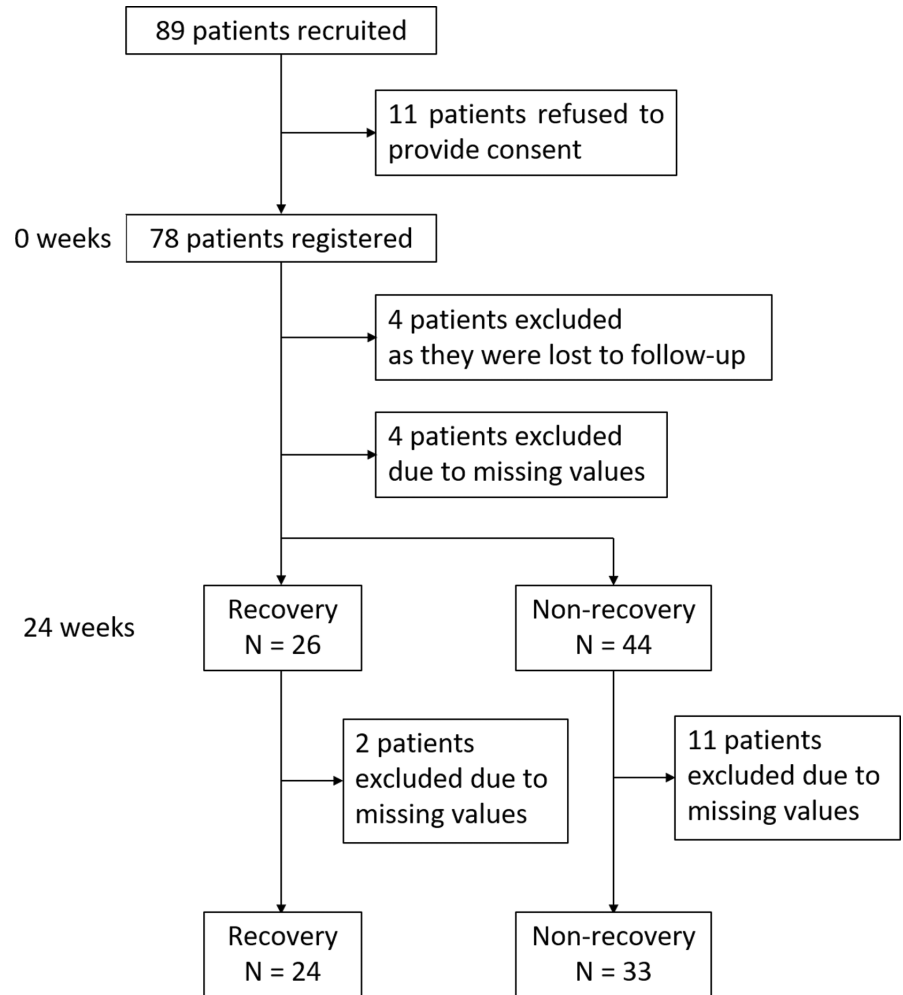
FIGURE 1 Consort diagram

TABLE 1 Comparison of demographic characteristics between the non-recovery and recovery groups

	Recovery group (N = 24) (mean ± SD)	Non-recovery group (N = 33) (mean ± SD)	P-value
Age (y)	39.3 ± 8.5	37.9 ± 9.3	0.55
Gender (% male)	12 (50.0)	16 (48.4)	0.91
PANSS total (wk 0)	35.0 ± 4.0	50.6 ± 13.6	<0.01[*]
PANSS 8 (wk 0)	9.7 ± 1.9	16.1 ± 5.7	<0.01[*]
PANSS 8 (wk 24)	9.3 ± 1.2	16.0 ± 5.8	<0.01[*]
GAF (wk 0)	82.5 ± 5.7	60.8 ± 10.9	<0.01[*]
GAF (wk 24)	84.5 ± 3.2	61.4 ± 11.1	<0.01[*]
CED (mg)	367.5 ± 300.2	814.1 ± 521.1	<0.01[*]
DUP (mo)	5.7 ± 7.5	17.8 ± 23.9	0.01[*]
Age at onset (y)	26.5 ± 7.9	24.0 ± 6.4	0.21
STAI-T	43.2 ± 8.4	54.6 ± 13.4	<0.01[*]

Abbreviations: CED, chlorpromazine-equivalent dose; DUP, duration of untreated psychosis; STAI-T, State–Trait Anxiety Inventory (Trait anxiety); GAF, Global Assessment of Functioning scale; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.
[*]P < 0.05.

toward treatment and negative subjective reactions toward medication are associated with nonadherence.[12] This suggests that the positive "*impression of medication*" shown in this study may have a positive influence on adherence and be associated with recovery.

The results of logistic regression analysis showed that scores for "*impression of medication*" were most closely associated with the functional prognosis of schizophrenia ($\beta = -3.09$, $t = -2.02$, $P = 0.04$). A previous study examining the risk of relapse in patients with first-episode

	Recovery group (N = 24) (mean ± SD)	Non-recovery group (N = 33) (mean ± SD)	P-value
DAI-30	13.3 ± 8.4	11.1 ± 13.9	0.47
DAI-medication	6.08 ± 3.8	5.33 ± 4.7	0.50
DAI-effects	0.08 ± 6.4	0.79 ± 6.3	0.68
DAI-impression	7.08 ± 2.4	4.97 ± 4.8	0.03*

Abbreviations: DAI-30, Drug Attitude Inventory-30, DAI-effects, score for the DAI-30 subscale *"awareness of the effects of psychiatric drugs"*; DAI-medication, score for the DAI-30 subscale *"awareness of the need for mediation"*; SD, standard deviation.
*P < 0.05.

TABLE 3 Association between medication adherence and the functional prognosis of schizophrenia

	β	t-value	P-value
DAI-medication	−0.23	−0.14	0.89
DAI-effects	1.77	1.14	0.26
DAI-impression	−3.09	−2.02	0.04*

Abbreviations: DAI-effects, score for the DAI-30 subscale *"awareness of the effects of psychiatric drugs"*; DAI-impression, score for the DAI-30 subscale *"impression of mediation."*; DAI-medication, score for the DAI-30 subscale *"awareness of the need for mediation"*.
*P < 0.05.

psychosis has identified adherence to medication as a significant predictor of relapse, but not insight into treatment or duration of untreated illness.[13] The results of the present study suggest that among the factors related to medication adherence, *"impression of medication"* has the greatest impact on the prognosis of schizophrenia.

Post hoc correlation analysis revealed a negative correlation between the *"impression of medication"* subscale of the DAI-30 and STAI-T scores, which indicates that patients with lower trait anxiety have a better impression of medication.

Harrow et al.[6] reported that personality tendencies with a high vulnerability to anxiety influence the long-term course of schizophrenia, and Na et al.[7] found lower medication adherence in depressive patients. The results of the present study suggest that trait anxiety may influence medication adherence and be associated with a poor long-term prognosis, which is consistent with a previous study by Harrow et al.[6]

5 | CLINICAL IMPLICATIONS

The potential clinical implication of this research is that assessing trait anxiety may help detect the risk of medication non-adherence at an early stage and increase the number of patients who achieve recovery through the provision of medication guidance and psycho-educational interventions.

6 | LIMITATIONS

Regarding the concept of recovery from schizophrenia, we applied the definition adopted in previous studies,[3,10] in which recovery was
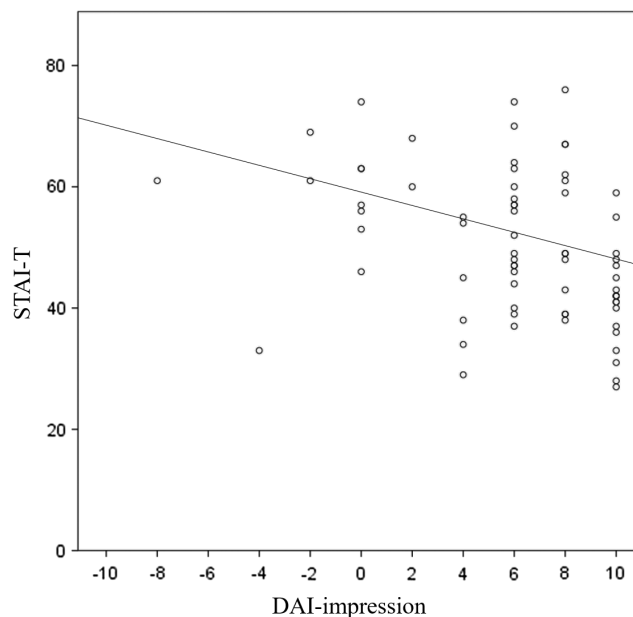

FIGURE 2 Relationship between Drug Attitude Inventory-30 (DAI-30) subscale scores and trait anxiety in patients with schizophrenia. STAI-T, scores for the State–Trait Anxiety Inventory (Trait anxiety); DAI-impression, scores for the DAI-30 subscale *"impression of mediation"*

defined in terms of feasibility based on a combination of PANSS and GAF scores at a 6-month follow-up at our institute.

Recovery from schizophrenia as proposed by Liberman[1] was defined based on a multidimensional concept of a low score on the Brief Psychiatric Rating Scale, employed at least 50% of the time, able to carry out activities of daily living independently, and participation in social or recreational activities at least once in a week for 2 years. This multidimensional concept of recovery is expected to be used in future studies.

In the present study, 26 of the 28 patients with baseline GAF scores ≥81 remained in the recovery group with high GAF score after 24 weeks. In other words, a higher baseline GAF score may have a greater influence on recovery than medication adherence. In addition, because adherence at 24 weeks was not assessed in this study, it was not possible to establish a causal relationship between adherence and recovery.

In the present study, we showed an association between *"impression of medication"* and the functional prognosis of schizophrenia. Of

the three DAI-30 subscales, "*impression of medication*" was the most closely associated with recovery. In addition, the results of a correlation analysis showed that lower trait anxiety was associated with a better "*impression of medication*."

AUTHOR CONTRIBUTIONS

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Appendix S1 of this article.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

This study was approved by the Ethical Committee of Jikei University School of Medicine (approval No. 7493).

INFORMED CONSENT

All participants provided written informed consent to participate in this study.

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REFERENCES

1. Liberman RP, Kopelowicz A. Recovery from schizophrenia: a concept in search of research. Psychiatr Serv. 2005;56:735–42.
2. Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry. 2004;161:473–9.
3. Bobes J, Ciudad A, Alvarez E, San L, Polavieja P, Gilaberte I. Recovery from schizophrenia: results from a 1-year follow-up observational study of patients in symptomatic remission. Schizophr Res. 2009;115:58–66.
4. Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry. 1999;56(3):241–7.
5. Murasugi K, Tsukahara T, Washizuka S. The development and trial of a medication discontinuation program in the department of forensic psychiatry. Ann Gen Psychiatry. 2015;14:11.
6. Harrow M, Jobe TH. Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications: a 15-year multifollow-up study. J Nerv Ment Dis. 2007;195(5):406–14.
7. Na E, Yim SJ, Lee J-N, Kim JM, Hong K, Hong MH, et al. Relationships among medication adherence, insight, and neurocognition in chronic schizophrenia. Psychiatry Clin Neurosci. 2015;69(5):298–304.
8. Jerant A, Chanpman B, Duberstein P, Robbins J, Franks P. Personality and medication non-adherence among older adults enrolled in a six-year trial. Br J Health Psychol. 2011;16(Pt 1):151–69.
9. Ishii J, Kodaka F, Miyata H, Yamadera W, Seto H, Inamura K, et al. Associations between parental bonding during childhood and functional recovery in patients with schizophrenia. PLoS One. 2020;15(10):e0240504.
10. Prinkryl R, Kholova M, Kucerova HP, Ceskova E. Prevalence of remission and recovery in schizophrenia in The Czech Republic. Compr Psychiatry. 2013;54:1111–6.
11. Svanum HA, Faries DE, Zhu B, Ernst FR, Swartz MS, et al. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry. 2006;67(3):453–60.
12. Acosta FJ, Hernández JL, Pereira J, Herrera J, Rodríguez CJ. Medication adherence in schizophrenia. World J Psychiatry. 2012;2(5):74–82.
13. Caseiro O, Iglesias RP, Mata I, Garcia OM, Terán JMP, et al. Predicting relapse after a first episode of non-affective psychosis: a three-year follow-up study. J Psychiatr Res. 2012;46(8):1099–105.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.