A prospective comparative study of risperidone long-acting injectable for treatment-resistant schizophrenia with dopamine supersensitivity psychosis

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Abstract

Objective: Dopamine supersensitivity psychosis (DSP) is considered to be one cause of treatment-resistant schizophrenia (TRS). The authors investigated the efficacy of risperidone long-acting injections (RLAI) in patients with TRS and DSP.

Method: This is a multicenter, prospective, 12-month follow-up, observational study that included unstable and severe TRS patients with and without DSP. 115 patients with TRS were recruited and divided into two groups according to the presence or absence of DSP which was judged on the basis of the clinical courses and neurological examinations. RLAI was administered adjunctively once every 2 weeks along with oral antipsychotics. We observed changes in scores for the Brief Psychiatric Rating Scales (BPRS), Clinical Global Impression—Severity of Illness (CGI-S), Global Assessment of Functioning Scale (GAF), and Extrapyramidal Symptom Rating Scale (ESRS) during the study. Of the assessed 94 patients, 61 and 33 were categorized into the DSP and NonDSP groups, respectively.

Results: While baseline BPRS total scores, CGI-S scores and GAF scores did not differ, the ESRS score was significantly higher in the DSP group compared with the NonDSP group. Treatment significantly reduced BPRS total scores and CGI-S scores, and increased GAF scores in both groups, but the magnitudes of change were significantly greater in the DSP group relative to the NonDSP group. ESRS scores were also reduced in the DSP group. Responder rates (≥ 20% reduction in BPRS total score) were 62.3% in the DSP group and 21.2% in the NonDSP group.

Conclusions: It is suggested that DSP contributes to the etiology of TRS. Atypical antipsychotic drugs in long-acting forms, such as RLAI, can provide beneficial effects for patients with DSP.

Clinical trials registration: UMIN (UMIN000008487).

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1. Introduction

Antipsychotics are usually effective against the acute symptoms of schizophrenia (Freedman, 2003), especially for the first episode of the
illness (Lieberman et al., 1993; Szymanski et al., 1996). However, most of the patients relapse into psychotic episodes even after attaining amelioration of their preceding episodes (T.S.S.R. Group, 1992; Robinson et al., 1999). This progressive clinical course is thought to be part of the disease process, indicative of continuing brain dysfunction, while other factors, including effects of the antipsychotic medications being used for treatment, are also thought to play a role in this clinical progression (Zipursky et al., 2013).

Dopamine supersensitivity psychosis (DSP) was first identified in the 1970s (Chouinard et al., 1978), and from 22–43% of all patients with schizophrenia suffer from this psychosis (Chouinard et al., 1988; Chouinard, 1991). The features of DSP include development of tolerance to antipsychotic therapeutic effects, such that even high doses of antipsychotics no longer control symptoms, and an acute exacerbation of symptoms on discontinuing antipsychotics or even after minor stress (Kirkpatrick et al., 1992; Moncrieff, 2006; Chouinard and Chouinard, 2008; Fallon and Dursun, 2011). It is thought that these features may be an integral factor in the development of relapse vulnerability and treatment-resistant psychosis. It has been estimated that more than half of treatment-resistant schizophrenia (TRS) cases may be related to DSP (Iyo et al., 2013). The mechanisms underlying DSP are not fully understood yet, but may be closely associated with the increased density of dopamine D2 receptors (DRD2), which increases behavioral sensitivity to dopamine, following chronic treatment with antipsychotics, as reported in animal models (Houe et al., 1997; Samaha et al., 2007, 2008; Tadokoro et al., 2012; Iyo et al., 2013). DSP may be also accelerated more profoundly by first-generation antipsychotics than second-generation antipsychotics (Correll et al., 2004; Li et al., 2009; Iyo et al., 2013). Thus, although up-regulation of dopamine D2 receptors (DRD2), induced by antipsychotic therapy blockade, may underlie DSP, an effective treatment strategy for patients with DSP has yet to be established.

We have recently put forward a hypothesis on the mechanisms and treatment strategy for patients with DSP (Iyo et al., 2013). Briefly, optimal DRD2 occupancy by antipsychotics is higher in patients with DSP, leading to the need for higher doses of antipsychotics to achieve a clinical result. However, in these cases, greater quantities of the drug may be eliminated relative to standard doses, as the elimination half-life of the drug may remain the same, independent of the dose load. This greater level of elimination causes drug concentrations to fluctuate across both upper and lower lines of the optimal therapeutic window, particularly for high-dose oral antipsychotics with a relatively short half-life. Furthermore, endogenous dopamine may bind to larger numbers of DRD2, producing enhanced effects. Therefore, in patients with DSP, antipsychotics administered in a form that will yield stable blood concentrations within optimal therapeutic ranges may be of greater use in improving severe and unstable symptoms than the usual tablet formats.

Risperidone long-acting injection (RLAI) was the only long-acting injectable second-generation antipsychotic drug available in Japan at the start of this study. The width between peak and trough blood concentration of RLAI is 32 to 42% smaller than that of oral-risperidone (RIS) using equivalent doses (Eerdenkens et al., 2004). We recently reported that RLAI treatment successfully ameliorated unstable positive symptoms in two DSP cases with TRS (Kimura et al., 2013). Here, we aim to explore the hypothesis that an atypical long-acting agent can prove clinically efficacious in TRS patients with DSP.

2. Methods

2.1. Study design

This is a multicenter, observational study, with a prospective design for assessing clinical outcomes in patients with TRS. The primary objective is to verify the effectiveness of RLAI, that is, the percent change in total BPRS during a 12-month follow-up of the patients. We recruited patients with TRS, who had been selected to receive RLAI by their physicians in clinical setting, from May 2010 to September 2011 and divided them into two groups, defined by the presence or absence of DSP. The assessment of DSP in patients was evaluated by two experienced psychiatrists (H.K. and N.K.). Physicians were given no specific instructions for administering RLAI and oral antipsychotics, although they were instructed to give oral antipsychotics for at least 3 weeks following RLAI initiation and to inject RLAI every two weeks, in accordance with the approved labeling. Physicians were allowed to prescribe antiparkinsonism agents, benzodiazepines and mood stabilizers at their own discretion. Briefly, physicians were encouraged to treat participants so as to achieve maximal clinical effect with minimal side effects. This study was approved by the ethics committees of all participating research facilities. Written informed consent was obtained from all participants after providing them with a full explanation of the study.

2.2. Patients

Patients were eligible for study inclusion if they had a diagnosis of schizophrenia or schizoaffective disorder according to the Structured Clinical Interview for DSM-IV (First et al., 1995). We applied the broad eligibility criteria (Juarez-Reyes et al., 1996) for TRS in the present study, as follows. A patient who scored below 60 in the Global Assessment of Functioning (GAF) at least one year before entering this study and who met either or both of the following two criteria. 1) Non-responder criterion: failure to respond to at least two antipsychotics belonging to two different chemical classes, at dosages equivalent to or greater than 600 mg/day chlorpromazine equivalent (CPZeq) for at least 4 weeks. 2) Intolerance to antipsychotics criterion: TD with moderate or greater severity assessed by ESRS, causing profound distress to the patient. Exclusion criteria for this study were: previous treatment with RLAI and/or clozapine, a history of illegal drug use or substance dependence, the presence of any other Axis I disorders except for schizophrenia or schizoaffective disorder, mental retardation, pregnancy or any severe physical disease, and the presence of poor medication adherence.

2.3. Measurements

2.3.1. Dopamine supersensitivity psychosis

Presence of DSP was defined using criteria proposed by Chouinard (1991). That is, 1) withdrawal psychosis: acute relapse or exacerbation of psychosis appearing after a dose reduction or discontinuation of antipsychotics, within 6 weeks for oral medication or 3 months for intramuscular medication. This episode must be observed within the last 5 years. Or 2) developing tolerance to antipsychotic effects: This is defined as when an acute relapse or exacerbation of psychosis occurs, independent of a dose reduction or discontinuation of antipsychotic therapy, which cannot be successfully controlled by a 20% increased titration of drug. Or 3) psychotic symptoms which are new to the patient, or of greater severity, occurring immediately after a decrease in drug dosage. Or 4) a history or presence of TD. Based on available information from medical records and hospital staff, if at least one of the listed items above was present, the participant was diagnosed as having a history of DSP. The inter-rater reliability between the two assessors (H.K. and N.K.) was .88. If non identical diagnoses were reached, a consensus-based judgment by these two assessors was applied to the case.

2.3.2. Clinical measurements

The patients were evaluated at baseline (T0), and then after three (T1), six (T2), nine (T3), and twelve months (T4). The primary outcome measure was the percent change in the Brief Psychiatric Rating Scale (BPRS: 18 items, 1–7 scale for each item: Overall and Gorham, 1962) score from T0 to T4. The secondary outcome measures were recorded changes every three months in GAF and Clinical Global Impressions—Severity of Illness (CGI-S). For analyses of patient numbers showing a
response on BPRS during the study, responders were defined as patients showing a reduction of greater than 20% from baseline. Extrapyramidal symptoms (EPS) were evaluated using the Extrapyramidal Symptom Rating Scale (ESRS: 0–257 point that is summed from all of the factors including the last four sections of clinical impressions: Chouinard and Margolese, 2005). Compliance with treatment medication was monitored using by both a self-rating visual analog scale for patient and objective observation by their respective physicians, which rated medication administration from 0 to 100% (Garfield et al., 2011). If these measurements differed from each other by no more than 25%, the mean of both values was used as the patient’s adherence rate. To reliably evaluate with these measurements, physicians on the study underwent several rounds of assessment training.

2.4. Statistical analysis

All analyses were conducted using SPSS, version 19.0 (IBM, NY, US). Data analyses were conducted on an intent-to-treat basis including all dropout cases (Fig. 1). Analyses for the primary efficacy measure were performed using a mixed-effects model repeated-measures analysis (Gueorguieva and Krystal, 2004). Treatment group, time and each time-by-group interaction were included as fixed effects, while baseline scale scores and age were included as covariates. The within-subject factor was considered as a random effect. Compound symmetry was used.

Logistic regression analyses was also performed to look at the effect of treatment group on the outcome measure of treatment response or nonresponse at T4, with age, sex, duration of illness, baseline BPRS of treatment group on the outcome measure of treatment response or nonresponse at T4, with age, sex, duration of illness, baseline BPRS, and ESRS scores, treatment adherence and the presence or absence of DSP included as items. Continuous and categorical variables were compared by independent t test and chi-square test, respectively. A P value of .05 was set as the threshold of significance.

3. Results

3.1. Patient characteristics and analysis of drop-out cases

Of the 115 patients screened, 21 patients were excluded due to meeting exclusion criteria, being lost to follow-up or refusing to participate before the evaluation for DSP, yielding a final analytic sample of 94 patients (Fig. 1: DSP group: N = 61, NonDSP group: N = 33).

Baseline demographics and clinical characteristics were similar between the two groups (Table 1). The BPRS positive symptoms score showed no difference between the two groups, whereas the BPRS negative symptoms score and ESRS score in the DSP group were significantly higher than those of the NonDSP group (P < .001). A total of 75 patients (79.8%) completed the 12-month RLAI treatment. There was no significant difference in the dropout rates between the two groups: 14.8% (N = 9) in the DSP group and 30.3% (N = 10) in the NonDSP group (P > .05). Seven DSP and 7 NonDSP patients left the study due to an exacerbation of psychotic symptoms. Two DSP patients discontinued due to dystonia and akathisia, and 3 NonDSP patients discontinued due to constipation, hyperglycemia and dystonia.

3.2. Treatment with RLAI and other oral antipsychotics, medication adherence

The mean daily total CPZeq-dose of oral antipsychotics at baseline was about 1000 mg in both groups (Table 1). The subjects received quite variable types and combinations of antipsychotics with variable dose ranges. The primary types of antipsychotics used in the present patients were risperidone (1–18 mg), olanzapine (4–40 mg) and quetiapine (200–825 mg). Percent rate of RLAI patients receiving dose of 25 mg, 37.5 mg and 50 mg at T4 was 13.5%, 19.2% and 67.3% respectively in the DSP group, and 13.0%, 21.7% and 65.2% respectively in the NonDSP group. For daily oral antipsychotics dosing (CPZeq-dose), the mean (± SD) doses at T4 were 605 (791) mg/day and 471 (421) mg/day in the DSP group and the NonDSP group, respectively. There was a significant main effect for Time (F = 9.70, P < .001), but no main effect for Group (F = 0.37, P > .05) or for an interaction of Time × Group (F = 0.07, P > .05). There was no significant difference in the total amount of daily oral antipsychotics and RLAI dose (CPZeq) at T4, between the two groups nor were there significant time effects during the treatment between the groups (Table 2).

Mood stabilizers were prescribed for 19 of 61 DSP patients and 14 of 33 NonDSP patients. Among them, 13 DSP patients and 9 NonDSP patients took sodium valproate at T0: their distributions and their mean doses did not differ between the two groups. These doses tended to be lower during the study, though not significantly, in both groups (data not shown). Regarding benzodiazepine and antiparkinsonism agents, none of the groups showed any significant differences either in baseline doses or in dose changes between T0 and T4.

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**Fig. 1.** Overview of participant flow. Initially, 115 patients were screened. Of these, 21 were lost to the study due to meeting the exclusion criteria, being lost to follow-up, or a withdrawal of consent before evaluation of DSP status, yielding a final analytic sample of 94 patients (DSP group: N = 61, NonDSP group: N = 33).
Adherence to treatment medication, which was measured by a self-administered visual analog scale at T0, T2, and T4, was 89.2%, 92.2% and 90.0% in the DSP group and 88.4%, 86.8%, and 88.4% in the NonDSP group during the 12-month treatment period (P < .05). Based on percentage changes in BPRS positive and negative symptom scores, DSP patients showed significantly greater improvements compared with NonDSP patients (Fig. 2B, C and Table 2).

Furthermore, we analyzed the percentage BPRS changes only among inpatients with DSP (N = 32) whose adherence was approximately 100%, because they took their medication under staff observation. The results revealed that BPRS scores at T0 and T4 were 68.1 ± 20.3 and 53.6 ± 25.2, respectively, indicating change of more than 20%, suggesting that amelioration in the DSP group was not caused simply by improvement of medication adherence.

### 3.3. Primary outcome measures

Mixed-model analysis of the percentage change in BPRS total scores from baseline to 12 months showed significant improvement in DSP relative to NonDSP patients. This difference was observed from T1 to T4 at each time point analysis (Fig. 2A and Table 2). Average BPRS total scores in both groups were also significantly decreased after the 12-month treatment period (P < .05). Based on percentage changes in

### 3.4. Secondary outcome measures

The mean CGI and GAF scores significantly improved in both groups. The CGI and GAF scores significantly decreased and increased respectively, in each DSP and NonDSP group (P < .05). The improvements during treatment were significantly more pronounced in the DSP

### Table 1

Characteristics of eligible participants.

|                      | DSP group | NonDSP group | All patients | Statistical valuea |
|----------------------|-----------|--------------|--------------|--------------------|
|                      | N = 61    | N = 33       | N = 94       |                    |
| Age (years)          | 43.6 (14.7) | 48.5 (11.1) | 45.4 (13.7) | N.S.               |
| [Age range]          | [18–69]   | [26–69]      | [18–69]      |                    |
| Sex (male/female)    | 30/31     | 17/16        | 47/47        | N.S.               |
| Duration of illness (years) | 20.4 (12.5) | 21.2 (11.9) | 20.7 (12.3) | N.S.               |
| Inpatient/outpatient | 32/29     | 14/19        | 46/48        | N.S.               |
| Non-responder/intolerance to antipsychotics | 57/4 | 33/0 | 90/4 | N.S. |
| Diagnosis            | Schizophrenia 58 | 29 | 87 |                    |
|                      | Schizoaffective disorder 3 | 4 | 7 |                    |
| DSP type             | Withdrawal psychosis 41 | – | 41 | – |
|                      | Tolerant to antipsychotics 35 | – | 35 | – |
|                      | Relapse with great severity 27 | – | 27 | – |
|                      | Tardive dyskinesia 24 | – | 24 | – |
| Antipsychotics dose (CPZeq: mg) | 1084(714.4) | 960.1(444.1) | 1040.4(651.7) | N.S. |
| [Dose range]         | [0–4512.5] | [200–2050.0] | [0–4512.5] |                    |
| BPRS                 | Total score | 63.0 (18.6) | 58.5 (15.7) | 61.4 (17.7) | N.S. |
|                      | Positive symptom scorea | 17.0 (5.5) | 16.7 (5.6) | 16.9 (5.5) | N.S. |
|                      | Negative symptom scoreb | 13.0 (3.8) | 10.8 (3.1) | 12.2 (3.7) | P = .004 |
| CGI-S                | 5.5 (1.1) | 5.3 (1.0) | 5.4 (1.0) | N.S. |
| GAF                  | 30.9 (13.1) | 32.7 (11.4) | 31.5 (12.5) | N.S. |
| ESRS                 | 34.2 (32.4) | 17.8 (17.5) | 28.5 (29.1) | P = .001 |
| Adherence            | 89.2 | 80.6 | 86.3 | N.S. |

**Abbreviations:** DSP = dopamine supersensitivity psychosis, CPZeq = chlorpromazine equivalent, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impression Severity, GAF = Global Assessment of Functioning, ESRS = Extrapyramidal Symptom Rating Scale.

aData are mean (SD) [absolute range]. Unless otherwise noted, differences between the DSP and NonDSP groups were not statistically significant (P > .05).

bThe summed scores for conceptual disorganization (#4), suspiciousness (#11), hallucination (#12), and unusual thoughts (#15).

bThe summed scores for emotional withdrawal (#3), motor retardation (#13), and blunted affect (#16).

cStatistical result of each comparison between the DSP and NonDSP groups. Student’s t test is applied for continuous variables and the chi-square test is applied for categorical variables.

### Table 2

Follow-up assessment outcomes over all time points up to 12 months.

| BPRS total score | DSP group | NonDSP group | P valuea |
|------------------|-----------|--------------|----------|
| Score at T4      | Percentage change in score | Score at T4 | Percentage change in score |
| BPRS total score | 42.1 (18.0)b | 33.0 (19.9) | 44.3 (16.5)b | 17.0 (20.5) | <.01 |
| Positive symptom score | 11.3 (5.5)b | 33.3 (22.9) | 12.1 (5.2) | 16.7 (27.7) | <.01 |
| Negative symptom score | 8.8 (3.9)b | 31.7 (24.0) | 8.6 (2.7)b | 16.6 (22.2) | <.01 |
| CGI-S            | 3.8 (1.4)b | 4.3 (1.3)b | 42.5 (14.9)b | N.S. |
| GAF              | 49.2 (169)b | 42.5 (14.9)b | N.S. |
| ESRS             | 19.2 (236)b | 18.1 (16.7) | N.S. |
| Antipsychotics dose (CPZeq: mg) | 103.4 (823.4) | 870.5 (466.9) | N.S. |
| Adherence (%)    | 90.0 | 88.4 | N.S. |

aData are mean (SD). T4 indicate time points at 12 months. The numbers of patients at T4 were 52 in the DSP group and 23 in the NonDSP group.

**Abbreviations:** N.S. = not significant.

aP values for the comparison in % change score or each measurement score between the DSP and NonDSP groups. The treatment comparison was a linear contrast based on a mixed-effects model with three fixed effects (time, treatment group, and time–treatment group interaction). The within-subject factor was considered as a random effect.

bP < .01 comparisons in each score between baseline (T0) and T4 within the group.
and the percentage change in BPRS score from baseline respectively. Multiple logistic regression model of factors associated with responders. Table 3 show significant differences in A) total, B) positive and C) negative symptom scores between the DSP and NonDSP group \( (P < .01) \). Significance of increases in A) total, B) positive and C) negative symptom scores respectively. Error bars indicate standard error of the mean. Percentage changes in time. The red and blue lines indicate changes in the DSP and the NonDSP group, respectively. There was no change in the NonDSP group. Furthermore, the TD score of ESRS was significantly lower in the completers of the DSP group. On the other hand, there was no change in the NonDSP group exhibited new TD during the study period.

Responder rates were 62.3\% \((N = 38)\) in the DSP group and 21.2\% \((N = 7)\) in the NonDSP group, indicating a significant difference \( (\chi^2 = 14.5, P < .001) \) between the two groups.

Logistic regression analysis revealed DSP as the only factor significantly related to RLAI response \( (\text{odds ratio} = 6.90, P < .01: \text{Table 3}) \).

4. Discussion

To our knowledge, this is the first study to investigate the efficacy of a 12-month RLAI treatment regime in patients with TRS and DSP. The treatment yielded significantly greater improvement in psychiatric symptoms and global functioning in DSP patients compared with DSP-free patients. DSP patients also showed a higher response rate \( (62\%) \) relative to those without DSP \( (21\%) \). Multiple logistic regression analyses revealed that the presence of DSP greatly contributed to clinical improvements in this study. Furthermore, at the end of the study, patients who received high antipsychotic doses \( (\text{both oral antipsychotics and RLAI}) \), took comparable daily oral antipsychotic doses at baseline prior to RLAI initiation. These results imply that adjunctive RLAI treatment with a gradual reduction of oral antipsychotics can help to promote a remarkable improvement in DSP patients. Unsurprisingly, DSP patients showed severer EPS at baseline, including TD, a neurological DRD2 supersensitivity \( (\text{Sasaki et al., 1995a, 1995b}) \) and an important criteria in the diagnosis of DSP \( (\text{Chouinard, 1991; Fallon and Dursun, 2011}) \). In the DSP group, the possibility that RLAI treatment lessens severe EPS was observed. Taken together, our findings suggest that achieving and maintaining stable therapeutic blood levels of antipsychotics could improve symptoms in patients with severe and treatment-resistant DSP, supporting our original hypothesis \( (\text{Iyo et al., 2013}) \). In addition, the development of other long acting injectable antipsychotics, such as other classes of atypical antipsychotics or longer-acting forms, may be desirable for the treatment of DSP.

The ESRS score and the TD score were lower overall in the DSP group, whereas no change was observed in the NonDSP group. When we consider that the mean of the total chlorpromazine equivalent doses was not different between the entry \( (T0) \) and the end \( (T4) \) of this study, we can infer that the reduced fluctuation of plasma antipsychotic levels contributes not only to the stabilization of psychosis but also to the reduction in antipsychotic-induced EPS and TD, which can be considered neurological manifestations of dopamine supersensitivity.

In this study, DSP patients exhibited significant negative symptoms at baseline, which improved remarkably during treatment. Antipsychotics are capable of improving negative and depressive symptoms, depending on the extent to which positive symptoms and EPS are reduced \( (\text{Tandon, 2011}) \). In DSP patients, the dramatic improvement in positive symptoms and EPS plays a contributory role in the improved negative symptoms and general functioning.

Table 3

| Partial regression coefficient | \( P \) value | Odds ratio | 95\% confidence intervals |
|-------------------------------|-------------|-----------|--------------------------|
| Presence of DSP | 1.93 | \(< .01\) | 6.90 | 2.19–21.80 |
| BPRS at baseline | | | | |
| Total score | \(-0.02\) | .45 | 0.98 | 0.92–1.04 |
| Positive symptom score | 0.01 | .87 | 1.01 | 0.86–1.19 |
| Negative symptom score | 0.07 | .46 | 1.07 | 0.90–1.28 |
| ESRS | \(< -0.01\) | .79 | 1.00 | 0.98–1.02 |
| Sex | -0.23 | .63 | 0.95 | 0.31–2.05 |
| Age | -0.02 | .58 | 0.99 | 0.94–1.04 |
| Duration of illness | -0.01 | .94 | 1.00 | 0.94–1.06 |
| Adherence | 0.19 | .38 | 1.20 | 0.80–1.82 |
One part of DSP patients didn’t respond to the treatment. One possible reason may be sub-optimal dosing, with the combined RLAI and oral antipsychotic treatment. If the total dosages were too low to achieve optimal receptor occupancy, or if the elimination half-life of the oral drugs was too short to maintain optimal occupancy, RLAI therapy may not be sufficient to control disease symptoms. In Japan, the maximum dose of RLAI is limited to 50 mg/2-week, which is estimated to produce an occupancy range of 65.4 to 74.4% (Remington et al., 2006), corresponding to the optimal range for patients with a cupancy range of 65.4 to 74.4% (Remington et al., 2006), corresponding to the optimal range for patients with a first schizophrenic episode (Kapur et al., 2000). Further studies are needed to clarify the accuracy of this data and its validity for subsequent episodes.

The study treatment provided only limited efficacy for NonDSP patients. In this group, positive symptoms failed to show significant improvement, while the negative symptoms showed only slight significant improvement. Reports highlight that patients with deficit syndrome (Gelderis and Maj, 2009) respond poorly to antipsychotic treatment and show profound continued negative symptoms. It is possible that there were a significant number of patients with deficit syndrome within our NonDSP cohort. That said, there may be patients with other types of confounding factors, as schizophrenia is known to be a heterogeneous disease (Tandon et al., 2009; Insel, 2010; Kanahara et al., 2013). Clozapine is known to improve symptoms in deficit syndrome (Rosenheck et al., 1999; Kelly et al., 2010). It is highly possible that in these patients, the mechanistic action is not via blockage of DRD2, but by modulation of other sites, such as the N-methyl-D-aspartate receptor, a candidate target of clozapine in the treatment of schizophrenia (Hashimoto, 2011; Miyamoto et al., 2012). However, further studies are needed to fully explore this point.

To date, there are two previous reports on clinical trials using RLAI in TRS (Procyshyn et al., 2010; Volonteri et al., 2010), although in these studies, patients were switched from other antipsychotics to RLAI. This differs from our study where RLAI was used adjunctively. In one study, a 6-month RLAI treatment achieved a 60% response rate in treatment-resistant patients with severe symptoms (Volonteri et al., 2010). The other study failed to show an advantage for RLAI (Procyshyn et al., 2010). Neither of these studies made special reference to DSP, nor did they report on the dosages of antipsychotics in use before patients entered the study. Therefore, it is unknown what percentage, if any of their study participants suffered from DSP and whether the doses of RLAI were high enough to improve symptoms in these studies.

As with all reports of this nature, there are some limitations to this study. First, this was a relatively short term observational study, because our aim was to maximize efficacy of the RLAI regime to effect improved conditions for TRS patients. A randomized, controlled study with a longer follow-up duration is needed to confirm our observation. Second, we didn’t directly measure D2 receptor occupancy or the fluctuation of plasma levels of antipsychotics. Therefore, further studies, including direct measurements of these parameters, are needed to confirm our hypothesis on the mechanisms underlying DSP and treatment of patients with DSP. Third, the medication adherence level may affect the results to some extent in this study, since it has been suggested that most patients actually are under partial adherence (Oehl et al., 2000), especially patients with TRS, like our participants. Therefore, we evaluated our patients’ adherence using self-reported data and the observations of their physicians. The results confirmed no differences between these two reports, although we didn’t use pill-count methods. Furthermore, we analyzed BPRS scores and their changes only among the inpatients with DSP, whose adherence rates could be considered almost 100%, and the results were similar to those obtained by the analysis of all patients with DSP. In this light, we consider that the present results on the improvement of symptoms were not likely attained simply by improvements in medication adherence alone.

In conclusion, our study demonstrated that adjunctive RLAI treatment significantly improved psychotic symptoms and global functioning in TRS patients with DSP. While clozapine is considered the standard antipsychotic drug of choice for TRS (Kane et al., 1988), it is associated with serious adverse events, such as agranulocytosis and diabetes mellitus (Fakra and Azorin, 2012). This study suggests that therapeutic regimes using antipsychotics with long elimination half-lives may prove suitable alternatives to clozapine for this cohort of patients.

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Study supervision: Iyo.

Conflict of interest
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