patients. Throughout the study period, all patients received RLAI procedures at over 90% of the scheduled visits (once every two weeks).

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 (**Figure 2A** and **Table 2**). Average BPRS total scores in both groups significantly were also decreased after the 12-month treatment period ($P < .05$). Based on percentage changes in BPRS positive and negative symptoms scores, DSP patients showed significantly greater improvements compared with NonDSP patients (**Figure 2B, Figure 2C 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.

3.4. 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 group relative to the NonDSP group. Mean ESRS scores showed no significant difference between the two groups at the end of the study (**Table 2**). However, there were significant reductions in this value from T0 to each subsequent time point in the DSP group, whereas 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, no patients 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 (odds ratio=6.90, $P < .01$: **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 (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 (Sasaki et al., 1995a, 1995b) and an important criteria in the diagnosis of DSP (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 (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 (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.

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 50mg/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 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 (Galderisi 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 blockade 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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Figure legends:

Figure 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).

Figure 2: Percentage Change in BPRS total, positive and negative symptoms scores over time.

The red and blue lines indicate changes in the DSP and the NonDSP group, respectively. Error bars indicate standard error of the mean. Percentage changes in BPRS total, positive and negative symptoms scores were analyzed using mixed effects model repeated-measures analysis. There were significant differences in **A**) total, **B**) positive and **C**) negative symptoms scores between the DSP and NonDSP group ($P < .01$).

* $P < .05$ and ** $P < .01$ represent significant improvement in each group and the percentage change in BPRS score from baseline respectively.

Table 1. Characteristics of eligible participants

	DSP Group N= 61	NonDSP Group N= 33	All Patients N=94	Statistical Value[c]
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	-
: toleranet to antipsychotics	35	-	35	-
: relapse with great severity	27	-	27	-
: tardive dyskinesia	24	-	24	-
Antipsychotics dose (CPZeq : mg) [dose range]	1084.6 (741.4) [0-4512.5]	960.1 (444.1) [200-2050.0]	1040.4 (651.7) [0-4512.5]	N.S.
BPRS: Total score	63.0 (18.6)	58.5 (15.7)	61.4 (17.7)	N.S.
: Positive symptoms score[a]	17.0 (5.5)	16.7 (5.6)	16.9 (5.5)	N.S.
: Negative symptoms score[b]	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.

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

a: The summed scores for conceptual disorganization (#4), suspiciousness (#11), hallucination (#12), and unusual thoughts (#15)

b: The summed scores for emotional withdrawal (#3), motor retardation (#13), blunted affect (#16)

c: Statistical 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.

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.

Table 2. Follow-up Assessment Outcomes over All Time Points up to 12 months

BPRS total score	DSP Group		NonDSP Group		
	Score at T4	Percentage Change in Score	Score at T4	Percentage Change in Score	P value[a]
BPRS total score	42.1 (18.0)[b]	33.0 (19.9)	44.3 (16.5)[b]	17.0 (20.5)	< .01
Positive symptoms score	11.3 (5.5)[b]	33.3 (22.9)	12.1 (5.2)	16.7 (27.7)	< .01
Negative symptoms 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]		< .01
GAF	49.2 (16.9)[b]		42.5 (14.9)[b]		< .01
ESRS	19.2 (23.6)[b]		18.1 (16.7)		N.S.
Antipsychotics dose (CPZeq : mg)	1034.7 (823.4)		870.5 (466.9)		N.S.
Adherence (%)	90.0		88.4		N.S.

Data 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.

[a] P values for the comparison in % change score or each measurement score between the DSP and NonDSP groups. The treatment comparison was a liner 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.

[b] P< .01 comparisons in each score between baseline (T0) and T4 within the group.

Abbreviations: N.S.=not significant.

Table 3. Multiple logistic regression model of factors associated with responders.

	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 symptoms score	0.01	.87	1.01	0.86-1.19
: Negative symptoms 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