The comparative effects of risperidone long-acting injection and paliperidone palmitate on social function in schizophrenia: a 6-month, open-label, randomized controlled pilot trial.

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Abstract:

Purpose: The aim of this study was to compare risperidone long-acting injection (RLAI) and paliperidone palmitate (PP) on non-acute phase social function in patients with schizophrenia.
**Patients and methods:** In this 6-month pilot, open-label, randomized controlled study, 30 patients with schizophrenia who were treated with RLAI were randomly allocated to the RLAI continuation group or switched to the PP group. Patients were evaluated at baseline and 6 months with the Social Functioning Scale (SFS) as the primary outcome variable and The University of California San Diego Performance-based Skills Assessment Brief (UPSA-B), Social Emotional Cognition Task (SECT), Positive and Negative Syndrome Scale (PANSS), and Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) scores as secondary outcomes. **Results:** At baseline, the two groups did not significantly differ in demographic and clinical features. The two groups did not differ in the total scores changes for the UPSA-B, the SECT, the PANSS and DIEPSS. However, the total scores and the two subscales of SFS, independence-competence and independence-performance, were more improved in the PP group compared to the RLAI group (total scores, p = 0.038; Competence, p = 0.001; Performance, p = 0.007, respectively). **Conclusion:** These results suggest that PP may improve total social function, independent life competence and performance, as compared to the RLAI group. However, results are preliminary and need independent replication in larger samples before any definitive statement.

**Keywords:** social function, risperidone long-acting injection, paliperidone palmitate, schizophrenia, efficacy

**Introduction**

Relapse in schizophrenia carries a heavy burden[1,2]. One of the key factors contributing to this issue is non-adherence[3]. Current guideline for schizophrenia suggest that long-acting injection of antipsychotics (LAI) are one of the optional choices for improving treatment adherence or minimizing non-adherence[4]. In fact, there are many studies about LAI improving psychiatric symptoms and prevent relapse in patients with schizophrenia. Some studies have shown that LAI have improved usability over oral antipsychotics[5,6]. Because LAI reduce the risk of relapse, more attention is now being paid to other daily life factors, such as social function. Social function consists of multiple domains that encompass social[7], vocational[8], and residential[9] aspects. Impairment in social function is one of the central features of the patients with schizophrenia, and this was recognized a century ago in the earliest clinical descriptions of the disorder[10]. Moreover, deficits in social function are present throughout the course of the
disorder[11]. Therefore, social function should be considered as one important target of treatment for patients with schizophrenia.

Interestingly, there is one study that aimed to compare the clinical remission rates, number of hospital readmissions and personal and social functioning between patients with schizophrenia in treatment with risperidone (RIS) LAI (RLAI) and patients receiving oral antipsychotics[12]. This previous study suggested that treatment with RLAI instead of oral antipsychotics in patients might improve clinical symptoms and social functioning. Thus, LAI are expected to improve social function compared to oral antipsychotics. Harvey and colleagues suggested that treatment outcome studies focused on social function should consider using subscales targeted on specific domains of outcome, for example social, residential, and vocational, rather than using total scores[13]. However, previous comparative LAI studies used social function total scores only[14-17]. Therefore, it is deemed necessary to examine how LAIs affect multiple domains of social function.

RLAI and paliperidone (PAL) palmitate (PP) that were used in previous trials consist of LAI of RIS and PAL. Essentially, PAL is an active metabolite of RIS. On the other hand PAL is similar to RIS in its effect. However, they have several different characteristics in terms of formulation and pharmacological features[18]. Due to this, we assumed that RLAI and PP might have a different effect on social function multiplicity. Thus, this study aims to investigate the influence of RLAI and PP on social function using the Social Functioning Scale (SFS) and its subscales as primary outcome.

**Methods**

*Study design*

Patients satisfying the inclusion criteria were randomly allocated to the RLAI-continued group (hereafter, the RLAI group) or the PP-switching group (hereafter, the PP group) using the pseudo-random number generation program of the SPSS software, version 21 (IBM SPSS, Tokyo, Japan). Patients in the RLAI group continued their treatment with a uniform dose of RLAI, and then underwent intramuscular injection into the gluteal muscles every two weeks. The daily doses of the drug were individually adjusted according to the patient’s clinical status, with an upper limit of 50 mg/2 weeks. Patients in the PP group started treatment with PP by intramuscular injection into the deltoid or gluteal muscles. Their starting dose was equivalent to twice the dose of RLAI[19]. In the present study, a 4-week PP preparation was used. The dose
was determined depending on each patient’s clinical status, with an upper limit of 150 mg/4 weeks. Included patients were assessed in terms of social function, functional capacity, social emotional cognition, psychopathology and extrapyramidal symptoms at baseline and after 6-months. Patients and raters were not blind to patient’s group because this study had an open-label design.

This open-label, 6-months, randomized controlled pilot trial was conducted at Kansai Medical University Takii Hospital in Osaka, Japan from July 2014 to February 2015, in accordance with the Declaration of Helsinki. The institutional review board at Kansai Medical University approved the trial protocol. After a full description of the study, all participants provided written informed consent prior to entering the study. This trial was registered at UMIN Clinical Trials Registry (UMIN-CTR) on July 2014 (UMIN000014470).

**Subjects**

30 outpatients who were at least 20 years old were included in this study. All patients had been diagnosed with schizophrenia or schizoaffective disorder based on DSM-IV-TR criteria. The inclusion criteria were: 1) being during a non-acute phase of disease; 2) Positive and Negative Syndrome Scale (PANSS) total score of 120 or less; and 3) having received RLAI for two months or longer. The exclusion criteria were: 1) comorbid serious physical disorder; 2) active suicidal ideation; 3) history of attempted suicide; 4) history of drug or alcohol abuse; 5) mental retardation; 6) pregnancy; 7) current treatment with Oral-RIS, Oral-PAL; or 8) current treatment with multiple oral antipsychotics. Because of too low patients’ IQ have possible disturbing to understand the contents of this trial questionnaire, the Japanese Adult Reading Test (JART)[20] was used for assessing the intelligence quotient (IQ).

For the duration of the study, subjects were allowed drugs for concomitant medical conditions that had started before enrollment in the study, such as low-dose sleep-inducing medications as needed, and other drugs considered to have no effect on the outcomes of interest. In the case of patients with schizophrenia that developed new extrapyramidal symptoms, they were allowed to take anticholinergic agents. Additional administration of new antipsychotics, except for RLAI and PP, were not allowed during the study. Moreover, the patients were considered to be dropout in the case that they needed an emergency medical examination except the normal depot treatment owing to worsened their psychotic symptoms.

**Assessment**
The primary outcome measures consisted in the changes in social function in the RLAI group and the PP group from baseline to the endpoint. Social function was assessed with the Social Functioning Scale (SFS)[21,22]. The SFS is an informant-report completed by the patient or a relative. It distinguishes lack of competence (absence/loss) from lack of performance (non-use/disuse) of a skill[23]. It has seven domains: withdrawal, interpersonal, independence-competence (the ability to perform a variety of life skills, such as shopping, washing and so on), independence-performance (the actual performance of these skills), recreation, pro-social and employment. Higher scores indicate better social functioning.

The secondary outcome measures consisted of changes in functional capacity and social emotional cognition. These were assessed with the University of California San Diego (UCSD) Performance-based Skills Assessment Brief (UPSA-B) for functional capacity[24,25] and the Social Emotional Cognition Task (SECT) for emotional cognition[26,27].

UPSA-B is the measurement of functional capacity in which patients are asked to perform everyday tasks related to communication and finances. Raw scores are converted into a total score ranging from 0 to 100, with higher scores indicating better functional capacity. SECT is a domain of the CogState, which is a computerized cognitive battery. It consists of eight tasks related to verbal learning, speed of processing, attention/vigilance, visual memory, spatial working memory, reasoning and problem solving, and social cognition[26,27]. SECT is a social cognition task where four human facial pictures are presented, one of which is different to the others in facial expression. Subjects should choose the different one as quickly as they can. Stimuli in the SECT were customized to only include faces with a Mongoloid countenance to avoid any other race effects that can occur in tasks that use representations of human faces[28]. The SECT data were uploaded to a secure account on the CogState server (http://www.cogstate.com). Uploaded outcome parameters are calculated using custom software blind to diagnosis. SECT accuracy scores were logarithm and arcsine transformed.

Possible correlations between social function (SFS scores) and psychotic symptoms (Positive and Negative Syndrome Scale (PANSS) [29] scores) and between social function and extrapyramidal symptoms (Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) scores[30]) were also investigated.

Statistical analysis
Analyses were performed with the SPSS software, version 21.0J (SPSS, Tokyo, Japan), only for patients that completed all 6 months of the study. All statistical tests were two-tailed, and a
p-value less than 0.05 was considered to be significant. The raw data collected at baseline and endpoint were used for the analysis. Differences between the RLAI and PP groups in terms of demographic and baseline characteristics were assessed using independent t-tests and Pearson's chi-square test for categorical variables. Analysis of covariance (ANCOVA) was used to assess the change of SFS scores, UPSA-B score and SECT accuracy in each treatment group using baseline score as covariate. Pearson correlation coefficient analysis was used to determine potential associations between SFS scores and PANSS scores. Effect size conventions were determined according to the Cohen method: small effect size $f = 0.10$, medium effect size $f = 0.25$, and large effect size $f = 0.40$. Setting alpha value to 0.01, our sample provided a power of 0.80 to detect an effect size of $f = 0.65$.

**Results**

*Demographic and clinical characteristics*

30 patients were allocated into the two groups (RLAI group, $n = 16$; PP group, $n = 14$) at the beginning of the study. During the study, 5 patients from the RLAI group and 4 from the PP group dropped out (Fig. 1). Thus, the final analysis included the 21 patients who completed the study (11 in the RLAI group and 10 in the PP group). Baseline demographics and clinical characteristics were comparable between treatment groups (Table 1). At baseline, the two groups did not significantly differ in age, age at onset of illness, sex, diagnosis, PANSS total score, DIEPSS total score, presence/absence of anyone living together, prescribed drug dose of each drug (chlorpromazine equivalent), or concomitant medications. At 6 months, no differences in PANSS total or subscale scores and in DIEPSS score between the treatment groups were identified[31]. During the 6 months study period, one patient from the RLAI group and one patient from the PP group were also treated with low-dose ultra short-acting hypnotics for their insomnia, and one patient from the PP group was treated with an anti-hyperlipidemia drug. The patients were not treated with other drugs, including psychotropic drugs.

*Change in SFS*

Comparisons of the changes in the social functions between treatment groups are summarized in Table 2. The PP group showed higher improvement for the SFS total score and two subscales, independence-competence and independence-performance, than the RLAI group (total score, $F = 5.03; \text{df} = 1,18; p = 0.038$; Competence, $F = 14.04; \text{df} = 1,18; p = 0.001$; Performance, $F = 9.14; \text{df} = 1,18; p = 0.007$; respectively).
Change in UPSA-B and SECT

Comparisons of the changes in the functional capacity and social emotional cognition of the treatment groups are summarized in Table 2. There were no significant differences between two groups in UPSA-B total score and SECT accuracy.

Correlations between social function and psychopathology

Correlations between social function and psychopathological outcomes are shown in Table 3. Significant negative correlations were found between negative symptoms assessed with PANSS and two subscales of the SFS, namely recreation and pro-social (recreation, \( r = -0.46, p = 0.036 \); pro-social, \( r = -0.48, p = 0.028 \); respectively). However, there were no associations between psychotic symptoms and the two domains of competence and performance that showed higher improvement in the PP group compared to the RLAI group.

Discussion

In this preliminary trial, the PP group showed a significantly higher improvement in SFS total score, competence and performance subscales, compared to the RLAI group. Two main hypotheses may explain the different effect of these two drugs on social function.

The pharmacological differences between RLAI and PP are the first possible explanation. From the perspective of pharmacokinetics, the two LAIs differ regarding the PAL/RIS drug level ratio in the blood. PP works exactly as PAL in blood. On the other hand, the PAL/RIS drug level ratio of oral RIS is from 11.5 to 13.5 and the ratio of RLAI is from 2.4 to 3.0[32]. Thus, oral RIS works similar to PAL rather than to RLAI in blood. Indeed, RLAI had a lower PAL/RIS ratio compared to PP and oral RIS. One possible reason for such a low PAL/RIS ratio for RLAI is the lack of a first pass effect in the liver. Therefore, RLAI is considered as a drug that more strongly reflects the influence of “risperidone” compared to PP and oral RIS. From a pharmacodynamics viewpoint, PAL and RIS show many similarities in their affinities for receptors. However, their affinities for the alpha2-adrenergic receptor are different, since PAL has a higher affinity than RIS for this receptor[18]. Animal studies have shown that the blockage of alpha2-adrenergic receptors greatly affects the release of dopamine and noradrenaline from the medial prefrontal cortex[33]. It has also been shown that noradrenaline is related to motivation and vigilance[34]. In particular, motivation is one of a number of important factors that mediate social function improvement[35]. Consistently, Kim and colleagues reported that there was significant
improvement of social function in the oral PAL group compared to the oral RIS group [36]. In the present study, the different alpha2-adrenergic receptor affinity between RLAI and PP is emphasized because of the peculiarity of RLAI pharmacokinetics. Thus, assuming that social function may be related to noradrenaline neurotransmission, patients treated with PP may show higher improvement in motivation, vigilance, mood, and consequently higher increase in their competence associated with their independence of life.

The second hypothesis is that the different frequency of treatment administration between the RLAI and PP groups may have affected patients’ psychosocial factors. In this study, subjects were included if they were injected with RLAI at least for more than 2 months. In the PP group, subjects decreased their hospital visits owing to the switch from RLAI to PP, resulting in a possible influence on patients’ self-efficacy. Bandura defined that self-efficacy is the self belief that one has the ability to successfully execute a behavior and outcome [37,38]. Self-efficacy is a concept based on psychological procedures that emphasizes the self perception of one’s expectation for efficacy and outcome [37]. Due to the decrease of the patients’ hospital visit, they may perceive an improvement of their treatment when compared to the past. This may result in confidence and expectations related to their treatment process, with enhanced self-efficacy. In fact, self-reports demonstrated that patients who were prescribed a LAI expected a decrease of their hospital visit frequency to once a month by using LAI [39]. In a previous study, self-efficacy was found to correlate to social function in schizophrenia [40]. Moreover, self-efficacy influenced behavioral choices [37] and it was correlated to performance [38]. Thus, self-efficacy may influence SFS-competence and SFS-performance. On the other hand, we may also hypothesize that the reduced number of contacts could reduce the accuracy of the assessments and thus represent a source of bias.

Some previous reports compared social function measures between RLAI and PP, although no differences were found between the two drugs [14-17]. The most relevant factor influencing the result is the tool used to measure the outcome in our opinion. The present study used the SFS, while the previous ones used the personal and social performance scale (PSP). Although both scales have common domains such as interpersonal functioning and employment they have also different domains. For example, SFS has domains related to withdrawal, competence and performance of independence, recreation and pro-social, whereas PSP has domains about self-care, and disturbing and aggressive behaviors. The SFS competence and performance domains were found associated with the treatment arm by the present study and they are not assessed by the PSP. Moreover, the two scales have different scoring methods. PSP is a
100-point, single-item rating scale, subdivided into ten equal intervals, and four domains are assessed on a six-category severity scale ranging from absent to very severe[41]. On the other hand, SFS has seven domains and assigns point to items on each domain. A sum of these domain scores provides the total score of social functioning[21,22].

There were no significant differences between the RLAI and PP groups in UPSA-B total score and SECT accuracy. In previous trials, second-generation antipsychotics (SGAs) showed higher improvement in functional capacity compared to placebo, however there was no significant difference between different SGAs[42,43]. Thus, functional capacity and emotional cognition are probably not differently affected by different SGAs, consistently with the present findings.

We hypothesize that the lack of difference between the treatment groups as measured by the UPSA-B while a higher improvement in the PP group when considering the SFS independence-competence subscales is probably due to the different psychometric characteristics of the two scales. Indeed, the concept of “competency” measured by the UPSA-B and that of independence-competence measured by the SFS should be considered as different. Accordingly to a previous review [44], the UPSA-B assesses competency related to one’s life skills while the SFS assesses a self concept, i.e. one’s perception about his/her social function. Thus, the effect on self-efficacy in the PP group might reflect inner factors such as one’s self concepts but it might not affect outer factors such as acquisition/possession of actual skills.

Besides, the UPSA-B requires to pass some appraisal standard for getting higher scores. Independence-performance as calculated by the SFS is based on the number of times one is capable to perform an activity such as housework and not on the quality of life skills. In conclusion, the SFS may represent a valid tool to detect changes of performance within relatively brief periods such after the beginning of a treatment. The difference between the two treatment groups in SFS total score was due to effect on the independence-competence subscales.

The present study found negative correlations between negative symptoms assessed with the PANSS and two subscales of the SFS. A previous trial reported social function improvement alongside the improvement of psychotic symptoms[45]. Particularly, negative symptom severity was associated with social function[46] and improvement of negative symptoms also improved social function[47].

There are several limitations in this study. The major limitation is the relatively low number of patients, which should have been at least 26 in each group as calculated by a power analysis with G*Power Version 3.1.7 (effect size = 0.4, alpha error = 0.05, Power = 0.8). Thus, some of the non-significant differences observed between the two groups may be due to type II error.
Given the preliminary nature of this study, no correction for multiple testing was applied. However we reported our findings as they may be of broad interest for clinicians facing new LAI treatment options. Second, due to the open-label trial nature, raters and patients were not blind to each subject's medication. Therefore, expectation bias when raters measured each assessment cannot be excluded. Third, the follow up period of 6 months may be short for assessing social function. Therefore, these preliminary results should be interpreted cautiously. A confirmatory study should be a double blind trial on a larger sample and with a longer follow-up period. Finally, Harvey et al.[48] suggested that self-report is a problematic way to assess functioning, because patients with schizophrenia often show reduced awareness of their psychotic symptoms. On the other hand, Sumiyoshi et al.[22] reported that patients' SFS data are highly correlated with informants' data and with informant-based objective measures.

To the best of our knowledge, this is the first study that compared the influence of RLAI and PP on social function assessed with the SFS. Compared to continuation of the RLAI treatment, switching to PP might have favorable effects on general social function, life independence domain and performance (according to the SFS scale). However, these results are preliminary and need independent replication in larger samples before any definitive statement.

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References


19 Drug information of paliperidone palmitate: Interview form of xeplion®: Aqueous Suspension for IM Injection 5th edition, 2014,


21 Sumiyoshi C, Sumiyoshi T: Social function scale (matreics-pass)-japanese version. 2011


26 Pietrzak RH, Olver J, Norman T, Piskulic D, Maruff P, Snyder PJ: A comparison of the
cogstate schizophrenia battery and the measurement and treatment research to improve
cognition in schizophrenia (matrics) battery in assessing cognitive impairment in chronic
Ishikawa M, Higuchi Y, Seo T, Ueoka Y, Tomotake M, Kaneda Y, Darby D, Maruff P, Iyo M,
Kasai K, Higuchi T, Sumiyoshi T, Ohmori T, Takahashi K, Hashimoto K: Criterion and construct
validity of the cogstate schizophrenia battery in japanese patients with schizophrenia. PLoS One
2011;6:e20469.
other-race effect in face rocessing among african american and caucasian individuals with
schizophrenia. Am J Psychiatry 2008;165
29 Kay SR, Flszbeln A, Opler LA: The positive and negative syndrome scale (panss) for
30 Inada T: Evaluation and diagnosis of drug-induced extrapyramidal symptoms:
Commentary on the diepss and guide to its usage. Tokyo, Seiwa Shoten, 1996.
31 Takekita Y, Koshikawa Y, Fabbri C, Sakai S, Sunada N, Onohara A, Nishida K,
Yoshimura M, Kato M, Serretti A, Kinoshita T: Cognitive function associated with risperidone
long acting injection vs. Paliperidone palmitate in schizophrenia: A 6-month, open-label,
randomized, pilot trial. in submission
32 Nesvag R, Hendset M, Refsum H, Tanum L: Serum concentrations of risperidone and
9-oh risperidone following intramuscular injection of long-acting risperidone compared with oral
33 Franberg O, Marcus MM, Svensson TH: Involvement of 5-hl2a receptor and
alpha2-adrenoceptor blockade in the asenapine-induced elevation of prefrontal cortical
34 Sara SJ: The locus coeruleus and noradrenergic modulation of cognition. Nat Rev
35 Nakagami E, Xie B, Hoe M, Brekke JS: Intrinsic motivation, neurocognition and
psychosocial functioning in schizophrenia: Testing mediator and moderator effects. Schizophren


Npo zenseinet: The state of the prescription to be able to see from statistics-comparison between schizophrenia and depression-. Fukuoka, Incorporated nonprofit organization Wendy, 2014.


Ciudad A, Olivares JM, Bousono M, Gomez JC, Alvarez E: Improvement in social functioning in outpatients with schizophrenia with prominent negative symptoms treated with
olanzapine or risperidone in a 1 year randomized, open-label trial. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1515-1522.

Table 1 Demographic and Clinical Characteristics of the Patient Sample at Baseline

<table>
<thead>
<tr>
<th></th>
<th>RLAI (n = 11)</th>
<th>PP (n = 10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.43 ± 10.38</td>
<td>43.50 ± 11.76</td>
<td>n.s.</td>
</tr>
<tr>
<td>Onset (years)</td>
<td>29.46 ± 11.90</td>
<td>32.98 ± 11.75</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex (Male / Female)</td>
<td>7/4</td>
<td>4/6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diagnosis (schizophrenia / schizoaffective disorder)</td>
<td>11/0</td>
<td>9/1</td>
<td>n.s.</td>
</tr>
<tr>
<td>PANSS total score</td>
<td>83.00 ± 19.88</td>
<td>78.10 ± 21.01</td>
<td>n.s.</td>
</tr>
<tr>
<td>DIEPSS total score</td>
<td>3.09 ± 3.08</td>
<td>1.10 ± 1.66</td>
<td>n.s.</td>
</tr>
<tr>
<td>Anyone living together (presence / absence)</td>
<td>4/7</td>
<td>3/7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total antipsychotic drug a</td>
<td>431.91 ± 112.55</td>
<td>342.30 ± 94.70</td>
<td>n.s.</td>
</tr>
<tr>
<td>Concomitant medication, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Anticholinergic drugs</td>
<td>1 (9.1)</td>
<td>0 (0)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

**Note:** a: Chlorpromazine-equivalent dose. Independent t-tests and Pearson’s chi-square test for categorical variables were performed.

**Abbreviations:** n.s.: no significant difference; RLAI: risperidone long-acting injection; PP: paliperidone palmitate; PANSS: the Positive and Negative Syndrome Scale; DIEPSS: the Drug-Induced Extrapyramidal Symptoms Scale.
### Table 2. Change of outcome measures from baseline to endpoint in risperidone long acting injection and paliperidone palmitate groups

<table>
<thead>
<tr>
<th></th>
<th>RLAI group</th>
<th>PP group</th>
<th>Difference in change between groups</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
<td>Baseline</td>
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<tr>
<td><strong>SFS</strong></td>
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<tr>
<td>Withdrawal</td>
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<tr>
<td>Interpersonal</td>
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<td>Competence</td>
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<tr>
<td>Performance</td>
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<tr>
<td>Recreation</td>
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<td></td>
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<tr>
<td>Pro-social</td>
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<td></td>
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<tr>
<td>Employment</td>
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<td></td>
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<tr>
<td>Total</td>
<td></td>
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<tr>
<td><strong>UPSA-B</strong></td>
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<td></td>
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<tr>
<td><strong>SECT</strong></td>
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</table>

**Note:** *p < 0.05, **p<0.01. An analysis of covariance (ANCOVA) was performed for each score, with baseline data as covariance.

**Abbreviations:** RLAI: risperidone long-acting injection; PP: paliperidone palmitate; SFS: Social Functioning Scale; UPSA: University of California San Diego Performance-Based Skills Assessment-Brief; SECT: Social Emotional Cognitive Task.
Table 3 Interaction between social functioning change and symptoms

<table>
<thead>
<tr>
<th>PANSS</th>
<th>Wit</th>
<th>Int</th>
<th>Comp</th>
<th>Per</th>
<th>Rec</th>
<th>Pro</th>
<th>Emp</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>-0.28</td>
<td>-0.15</td>
<td>0.32</td>
<td>0.15</td>
<td>-0.07</td>
<td>0.15</td>
<td>-0.32</td>
<td>0.09</td>
</tr>
<tr>
<td>Positive</td>
<td>-0.16</td>
<td>-0.05</td>
<td>0.42</td>
<td>0.32</td>
<td>-0.01</td>
<td>0.11</td>
<td>-0.41</td>
<td>0.21</td>
</tr>
<tr>
<td>Negative</td>
<td>-0.08</td>
<td>-0.35</td>
<td>0.03</td>
<td>0.01</td>
<td>-0.46*</td>
<td>-0.48*</td>
<td>-0.03</td>
<td>-0.32</td>
</tr>
<tr>
<td>General</td>
<td>-0.34</td>
<td>-0.10</td>
<td>0.26</td>
<td>0.06</td>
<td>-0.04</td>
<td>0.04</td>
<td>0.35</td>
<td>0.14</td>
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</tbody>
</table>

Notes: *p<0.05, Pearson’s correlation coefficient between changes in Social Functioning Scale scores and changes in the Positive and Negative Syndrome Scale.

Abbreviations: SFS: Social Functioning Scale; PANSS: the Positive and Negative Syndrome Scale. Wit: Withdrawal; Int: Interpersonal; Comp: Competence; Per: Performance; Rec: Recreation; Pro: Pro-social; Emp: Employment
Assessed for eligibility (n = 33)

Randomized (n = 30)

Allocated to intervention: Risperidone long acting injection (n = 16)

Lost at follow-up (n = 0)

Discontinued intervention (n = 5)
  • Insufficient clinical response (n = 4)
  • Complicating disease (n = 1)

Allocated to intervention: Paliperidone palmitate (n = 14)

Lost at follow-up (n = 0)

Discontinued intervention (n = 4)
  • Refusal of treatment (n = 1)
  • Adverse events (n = 2)
  • Insufficient clinical response (n = 1)

Allocated to intervention: Risperidone long acting injection (n = 16)

Lost at follow-up (n = 0)

Discontinued intervention (n = 5)
  • Insufficient clinical response (n = 4)
  • Complicating disease (n = 1)

Allocated to intervention: Paliperidone palmitate (n = 14)

Lost at follow-up (n = 0)

Discontinued intervention (n = 4)
  • Refusal of treatment (n = 1)
  • Adverse events (n = 2)
  • Insufficient clinical response (n = 1)

Analyzed (n = 11)
  • Excluded from analysis (n = 5)

Excluded (n= 3)
Declined to participate (n = 3)

Analyzed (n= 10)
  • Excluded from analysis (n = 4)

Figure 1. Flow chart for study selection.