

# Efficacy of low-dose D<sub>2</sub>/D<sub>3</sub> partial agonist pramipexole on neuroleptic-induced extrapyramidal symptoms and symptoms of schizophrenia: a stage-I open-label pilot study

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Jia Jun Weng<sup>1,\*</sup>  
Li Hua Wang<sup>1,\*</sup>  
Hao Zhu<sup>2</sup>  
Wen Rong Xu<sup>1</sup>  
Yu Mei Wei<sup>1</sup>  
Zhi Yang Wang<sup>1</sup>  
Wen Juan Yu<sup>1</sup>  
Hua Fang Li<sup>1,3,4</sup>

<sup>1</sup>Department of Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University of Medicine, Shanghai, People's Republic of China; <sup>2</sup>Department of Anesthesiology, Renji Hospital, Shanghai Jiao Tong University of Medicine, Shanghai, People's Republic of China; <sup>3</sup>Shanghai Key Laboratory of Psychotic Disorders, Shanghai, People's Republic of China; <sup>4</sup>Clinical Research Center, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China

\*These authors contributed equally to this work

**Objective:** Some lines of evidence show that D<sub>2</sub>/D<sub>3</sub> receptor partial agonist pramipexole may be effective in the treatment of extrapyramidal symptoms (EPS) and psychiatric symptoms of schizophrenia. Therefore, we analyzed whether a low dose of pramipexole (0.375–0.75 mg/day) has efficacy on EPS and symptoms of schizophrenia while maintaining tolerability.

**Methods:** Ten subjects with EPS [including drug-induced parkinsonism (DIP) and akathisia] were recruited in a stage-I, open-label pilot study. All the subjects were treated with a low dose of pramipexole. The evaluations were performed at baseline, day 3, week 1, week 2, week 4, week 6, and week 8. The ratings of SAS, BARS, PANSS, CDSS, and CGI-S and adverse effects (AE) were recorded in every visit.

**Results:** SAS total scores decreased significantly during the study in patients with DIP ( $P < 0.001$ ), and mild AEs were detected. Treatments with pramipexole did not show an anti-akathisia effect during the study, while 2 subjects experienced deterioration of akathisia and mood symptoms. The psychiatric symptoms of schizophrenia showed a trend of improvement during the study, but there was no improvement in depressive mood.

**Conclusion:** A low dose of pramipexole can significantly relieve antipsychotic-induced parkinsonism, but not akathisia. Improvements in psychiatric symptoms of schizophrenia were found, but the results of this study need to be validated in a larger sample. No improvement of mood disorder was detected.

**Keywords:** extrapyramidal symptoms, antipsychotics, pramipexole, clinical trial

## Introduction

Drug-induced extrapyramidal symptoms (EPS) is a neurological adverse effect (AE) caused by the over-blockade of D<sub>2</sub> receptor in the substantia nigra-striatum pathway by antipsychotics.<sup>1</sup> Various factors including drug overdose, long-term use of antipsychotics, use of first-generation antipsychotics, age, and gender are correlated with the incidence of EPS.<sup>2,3</sup> Schizophrenia patients with EPS often have more severe psychiatric symptoms and poorer social functions.<sup>4,5</sup> The treatment and prevention of EPS is of great importance in the treatment outcome of patients with schizophrenia.

The current treatment of EPS in China contains anticholinergics including benzoyl.<sup>6,7</sup> However, the side effects of anticholinergics can deteriorate the physical

Correspondence: Wen Juan Yu; Hua Fang Li  
Drug Clinical Trial Institution, Wan Ping Nan Road No. 600, Shanghai Mental Health Center, Shanghai 200300, People's Republic of China  
Tel +86 21-34773122; +86 21-34773128  
Email wenjuanyu2004@163.com; hlh\_5@163.com

condition and cognition of patients with schizophrenia, especially elderly patients, which strongly restrict its clinical application.<sup>8,9</sup> Finding a safer and better-tolerated treatment of EPS is therefore warranted.

Pramipexole is a novel, highly active, partial dopamine (DA) receptor agonist that acts on the D<sub>2</sub> receptor family with a preferential affinity for the D<sub>3</sub> receptor. Pramipexole is widely used in the treatment of DA-related neurological disorder including Parkinson disease, restless leg syndrome, and EPS. The antiparkinson effect of pramipexole is correlated with its stimulation effect of the postsynaptic D<sub>2</sub> receptor.<sup>10</sup> The incidence of EPS is significantly correlated with the D<sub>2</sub> receptor occupancy in the substantia nigra and striatum areas.<sup>11</sup> Approximately, 75–80% blockade of D<sub>2</sub> receptors by antipsychotics could lead to the induction of EPS.<sup>12</sup> The partial D<sub>2</sub> receptor agonist effect of pramipexole may reverse the over-blockade of D<sub>2</sub> receptor in the substantia nigra and striatum areas and therefore reverse the symptoms of EPS.

Studies have found pramipexole can also relieve mood disorders and anhedonia symptoms of Parkinson disease, which may be related to its partial agonist effect on the D<sub>3</sub> receptors.<sup>13,14</sup> Moreover, pramipexole may be effective in the treatment of schizophrenia considering its modulation effect on DA transmission through partial agonist effect of D<sub>2</sub> and D<sub>3</sub> receptors.<sup>15</sup> Last but not least, pramipexole's efficacy on negative symptoms also deserves to be investigated, depending on the facts antipsychotics with D<sub>2</sub>/D<sub>3</sub> partial agonist effect, such as cariprazine, have better treatment outcome than other atypical antipsychotics.<sup>16</sup> Therefore, symptoms of schizophrenia, especially negative symptoms that are difficult to relieve depending on the current treatment of atypical antipsychotics, might benefit from the use of the D<sub>2</sub>/D<sub>3</sub> receptor partial agonist pramipexole.

The primary outcome of this study is to investigate whether the D<sub>2</sub>/D<sub>3</sub> receptor partial agonist pramipexole could relieve EPS, and the secondary outcome is to evaluate the effect of low-dose pramipexole for the psychiatric and mood symptoms of schizophrenia. We hypothesized that a low dose of pramipexole may be effective in the treatment of EPS and schizophrenia.

## Patients and methods

### Patients

This study is a stage-1 pilot study of a two-stage clinical trial. In the stage-1 study, 10 subjects were recruited to preliminarily explore the efficacy and safety of

pramipexole. All subjects were recruited in Shanghai Mental health center. The inclusion criteria were as follows: 1) 18–65 years of age; 2) met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for drug-induced parkinsonian and akathisia<sup>17</sup>; and 3) a 6-item Simpson–Angus Scale (SAS) total score above 2 or a score of 2 (mild) or above on the global subscale of the Barnes Akathisia Rating Scale (BARS). If any of the following events occurred, the subject was withdrawn from the study: 1) a serious AE (ie, death, rehospitalization, physical disability, etc.) 2) poor compliance, obvious protocol violation, or those who did not take the drugs continuously for 4 days; and 3) scored (mild) on at least two Abnormal Involuntary Movement Scale items or three (moderate) on one of the items that are considered to be tardive dyskinesia. All the subjects did not receive any treatment of EPS before entering the study.

Among the 10 subjects included in this study, 7 of them were diagnosed with schizophrenic disorder according to the DSM-IV; 1 subject was diagnosed with obsessive-compulsive disorder, 1 subject was diagnosed with major depressive disorder (MDD); and 1 was diagnosed with mental retardation. Seven subjects were diagnosed with drug-induced parkinsonism (DIP); 2 subjects were diagnosed with akathisia, and 1 subject fitted both the criteria. Most of the subjects were taking antipsychotic polytherapy. Four subjects were treated with risperidone (mean, 4.3±0.5 mg; range, 4–5 mg); four subjects were treated with aripiprazole (mean, 11.3±6.3; range, 5–20 mg); and three subjects were treated with quetiapine (mean, 366.7±251.7; range, 100–600) and clozapine (mean, 166.7±57.8; range 100–200 mg). Amisulpride (1000 mg), Olanzapine (20 mg), and Fluphenazine injection (25 mg qw) were used in one subject. The demographics and mean scale ratings are shown in Table 1, and clinical variables and drug characteristics of each subject are shown in Table 2. The drug dose of pramipexole and change in antipsychotics of each subject during the trial are shown in Table 3.

### Treatment protocol

Considering that pramipexole was being used for the first time in Chinese patients with schizophrenia, low dose of pramipexole was used for safety considerations (0.375–0.75 mg/day). Subjects took 0.375 mg/day of pramipexole (0.135 mg thrice per day) on week 1, and the dose was increased to 0.75 mg/day (0.25 mg thrice per day) after week 1 depending

**Table 1** Demographics and baseline scale ratings of all subjects

Demographics	
Age (years)	51.4 (14.7)
Gender, men	8 (80%)
Illness duration (years)	20.6 (14.6)
Number of hospitalization	3.1 (3.2)
Rating scores	
SAS	4.8 (3.6)
BARS	0.7 (0.9)
PANSS positive	16.1(1.6)
PANSS negative	27.4(3.1)
PANSS general psychopathology	42.9(3.0)
PANSS total	86.4(6.9)
CDSS	3.7 (1.8)
CGI-S	5.0 (0.3)

**Abbreviations:** SAS, Simpson-Angus Scale; BARS, Barnes Akathisia Rating Scale; AIMS, Abnormal Involuntary Movement Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression Scale.

on the researchers' decision. Treatment protocol was based on the treatment of Parkinson disease by pramipexole.<sup>17</sup>

The evaluations of SAS and BARS were used to assess the severity of EPS. SAS is a 10-item rating scale that is frequently used to assess DIP and muscle rigidity in clinical practice.<sup>18</sup> One item measure gait, 6 items measure stiffness, and 3 items measure tremor, salivation, and palpebral reflex (each item ranging from 0 to 4). BARS is a scale used to assess akathisia, and it consists of 4 items, including

objective symptoms, subjective symptoms, subjective distress, and global evaluations items (the score of each item ranges from 0 to 4).<sup>19</sup> Positive and Negative Syndrome Scale (PANSS) is a 30-item rating scale designed to assess dimensions of schizophrenia symptoms. Its items were originally grouped into scales for Positive Symptoms (7 items), Negative Symptoms (7 items), and General Psychopathology (16 items). Calgary Depression Scale for Schizophrenia (CDSS) is a 9-item rated scale specifically designed to assess depression in patients with schizophrenia with high sensitivity rate and high specificity rate.<sup>20,21</sup> The CGI-S scale is a valid, reliable instrument to evaluate severity and treatment response in schizophrenia, and its score ranges from 0 (no illness) to 7 (severe illness).<sup>22</sup> PANSS, CDSS, and Clinical Global Impression Scale (CGI-S) were used to access the psychiatry symptoms and mood symptoms of schizophrenia. Assessments were conducted at baseline, day 3, week 1, week 2, month 1, week 6, and month 2. The laboratory measurements, vital signs, and electrocardiogram were recorded at baseline and endpoint of the study to see whether pramipexole can deteriorate the physical status of the subjects.

## Ethics approval and informed consent

All subjects and their guardians signed a written informed consent, and all the assessment was conducted by trained psychiatrists who have underwent scale consistency

**Table 2** Clinical and drug characteristics of each subject

Subject	Gender/Age	Diagnosis	Antipsychotics	Additional medicine
1	M/57	SCH/PRA	Risperidone 5 mg Quetiapine 600 mg	
2	M/58	SCH/AKA	Amisapride 1000 mg Clozapine 200 mg	
3	M/60	SCH/AKA	Risperidone 4 mg Clozapine 200 mg	
4	M/60	SCH/PRA	Risperidone 4 mg Olanzapine 20 mg	Sertraline 100 mg
5	M/49	MT/PRA	Aripiprazole 10 mg Quetiapine 100 mg	
6	M/56	SCH/PRA	Risperidone 4 mg Clozapine 100 mg	
7	F/24	SCH/PRA/AKA	Aripiprazole 20 mg	
8	M/62	SCH/PRA	Fluphenazine Decanoate Injection 25 mg qw	
9	F/63	MDD/PRA	Aripiprazole 5 mg	Venlafaxine 300 mg
10	M/25	OCD/BD/PRA	Aripiprazole 10mg Quetiapine 400 mg	Fluvoxamine 300 mg lithium carbonate 500 mg

**Abbreviations:** SCH, schizophrenia; MR, mental retardation; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; BD, bipolar disorder; PRA, drug-induced parkinsonism; AKA, akathisia.

**Table 3** Drug dose of pramipexole and change in antipsychotics of subjects during the trial

Subject	Pramipexole dosage	Whether there is a change of antipsychotics	Change of antipsychotics	Time of the change of antipsychotics	The reason for the change of antipsychotics
1	Baseline: 0.375 mg/day V4: 0.75mg/day	N			
2	Baseline: 0.375 mg/day V4: 0.75mg/day	N			
3	0.375 mg/day	Y	Risperidone: Increased from 4 to 5 mg/day	1W	Deterioration of psychiatric symptoms and mood symptoms
4	0.375 mg/day	N			
5	0.375 mg/day	N			
6	0.375 mg/day	Y	Additional Aripiprazole 10 mg/day were prescribed	6W	Manage side effect of hyperprolactinemia
7	0.375 mg/day	Y	Aripiprazole decreased from 20 to 5 mg/day Additional Quetiapine 600 mg/day were prescribed	2W	Deterioration of psychiatric symptoms and mood symptoms
8	0.375 mg/day	Y	Changed from Fluphenazine Decanoate Injection 25 mg/qw to Amisapride 600 mg/day	4W	Lack of efficacy
9	0.375 mg/day	N			
10	Baseline: 0.375 mg/day V4: 0.75mg/day	N			

training before the first subjects were enrolled. This study was approved by the Shanghai Mental Health Center ethics committees (No. 2017-40), and this trial has been registered in the Clinical Trial website (NCT03430596). This study was conducted in accordance with the Declaration of Helsinki.

## Statistical analysis

All statistical analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as mean  $\pm$  SEM. ANOVA tests with post hoc analyses were used to examine differences in EPS, psychiatric symptoms, and mood symptoms of schizophrenia among the different visits. The Bonferroni correction was used to perform post hoc analysis for the chi-square tests, and statistical significance was set at  $P < 0.007$  (0.05/number of comparisons=0.007).

## Results

### Primary outcome

The ratings of SAS decreased significantly during the visit [5.9 $\pm$ 3.2 vs 1.1 $\pm$ 0.6, respectively,  $F(6,7)=9.46$ ,  $P < 0.007$ ]

among subjects with DIP. The ratings of the BARS global subscale [2.3 $\pm$ 0.3 vs 2.0 $\pm$ 0.7, respectively,  $F(6,3)=0.12$ ,  $P=0.99$ ], objective subscale [1.3 $\pm$ 1.3 vs 0.7 $\pm$ 0.7, respectively,  $F(6,3)=0.16$ ,  $P=0.98$ ], subjective subscale [1.7 $\pm$ 0.3 vs 1.3 $\pm$ 0.9, respectively,  $F(6,3)=0.18$ ,  $P=0.98$ ], and distress subscale [1.3 $\pm$ 0.3 vs 1.3 $\pm$ 0.9, respectively,  $F(6,3)=0.09$ ,  $P=0.99$ ] did not significant change during the visit. The changes in the SAS and BARS scores are shown in Table 4.

### Secondary outcome

The PANSS negative subscale [27.4 $\pm$ 3.1 vs 24.3 $\pm$ 3.5, respectively,  $F(6,7)=0.26$ ,  $P=0.95$ ], PANSS positive subscale [16.1 $\pm$ 1.6 vs 13.7 $\pm$ 1.6, respectively,  $F(6,7)=1.03$ ,  $P=0.49$ ], PANSS general psychopathological subscale [42.9 $\pm$ 3.0 vs 41.6 $\pm$ 5.6, respectively,  $F(6,7)=0.24$ ,  $P=0.96$ ], PANSS total score [86.4 $\pm$ 6.9 vs 79.4 $\pm$ 10.1, respectively,  $F(6,7)=0.38$ ,  $P=0.89$ ], CDSS [3.7 $\pm$ 1.8 vs 5.0 $\pm$ 1.6, respectively,  $F(6,7)=0.08$ ,  $P=0.99$ ], CGI-S [5.0 $\pm$ 0.3 vs 4.9 $\pm$ 0.6, respectively,  $F(6,7)=0.44$ ,  $P=0.85$ ] did not significant change during the study. The changes in psychiatric rating scales of schizophrenia during the study are shown in Figure 1.

**Table 4** The change in rating score in subjects with drug-induced parkinsonian and akathisia

	SAS <sup>#</sup>	BARS objective	BARS subjective	BARS distress	BARS global
Baseline	5.9(3.2)	1.3(0.3)	1.7(0.3)	1.3(0.3)	2.3(0.3)
3D	3.8(1.8)	0.7(0.7)	2.0(0.6)	2.0(1.0)	2.7(0.3)
1W	2.1(0.6)	0.7(0.7)	2.0(0.6)	1.7(0.7)	2.7(0.7)
2W	1.5(1.4)	0.7(0.7)	1.7(0.7)	1.7(1.2)	2.3(0.9)
4W	1.5(0.9)	0.7(0.7)	1.3(0.9)	1.3(0.9)	2.0(1.2)
6W	1.4(1.0)	0.7(0.7)	1.3(0.9)	1.3(0.9)	2.0(1.2)
8W	1.1(0.6)	0.7(0.7)	1.3(0.9)	1.3(0.9)	2.0(1.2)

Note: <sup>#</sup> $P < 0.007$ .

Abbreviations: SAS, Simpson Angus Scale; BARS, Barnes Akathisia Rating Scale.

## Adverse effect

The main AEs of pramipexole in this study include depressed mood (2 subjects), suicidal ideation (2 subjects), drowsiness (1 subject), and nausea (1 subject). Depressed mood occurred in two subjects with akathisia. Both of them showed the deterioration of psychiatric symptoms and mood symptoms. One of them withdrew from the study, and in other patient, drug switch and MECT were performed to manage AEs. Drowsiness and nausea occurred in two subjects with DIP. Two other subjects withdrew from the study: one subject discontinued the drug intake because of nausea, and the other one withdrew the consent. All the side effects were relieved after the measurements. The adverse events that occurred during the study are shown in Table 5. The laboratory measurements, vital signs, and electrocardiogram did not change significantly during the trial.

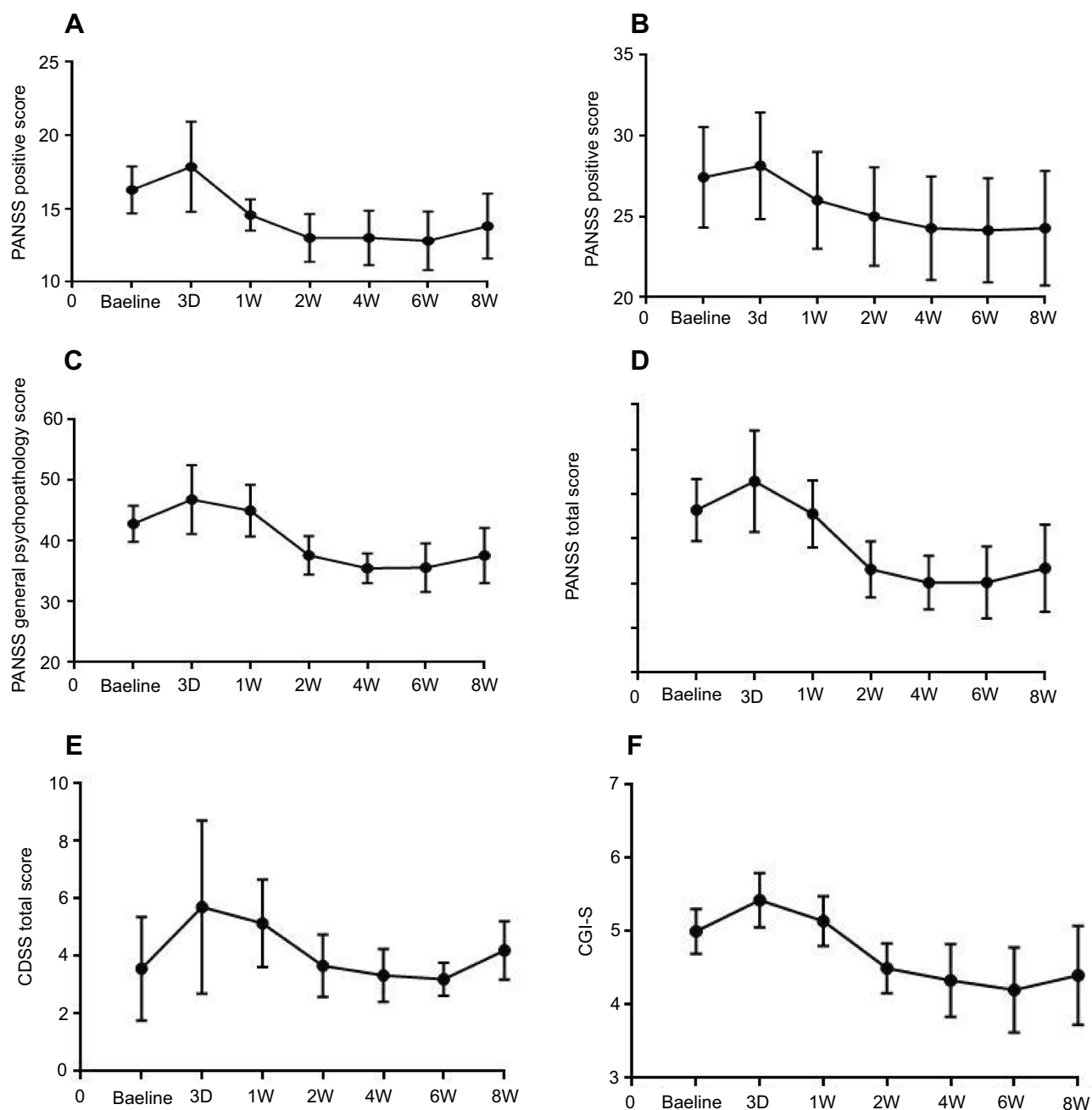
## Discussion

Our study has shown that low doses of D<sub>2</sub> and D<sub>3</sub> receptor partial agonists, ranging from 0.375 to 0.75 mg/day, may be beneficial in the treatment of DIP. SAS score decreased over 80% during the visit, without worsening of psychiatric symptoms and with low dropout rate (14.2%, 1 of 7). Pramipexole was well tolerated among subjects with DIP, and side effects, primarily drowsiness and nausea, were reported. A previous study showed that the D<sub>3</sub>/D<sub>2</sub> receptor partial agonist rotigotine in low doses is safe and effective in patients with EPS including antipsychotic-induced parkinsonism and akathisia.<sup>23</sup> Rotigotine significantly decreased the ratings of Unified Parkinson's Disease Rating Scale total (a scale used to evaluate the symptoms of Parkinson disease), SAS total score, and BARS global subscale. One study showed that pramipexole can relieve haloperidol-induced catalepsy and tremor in mice.<sup>24</sup>

Haloperidol-induced catalepsy is used as an animal model of extrapyramidal side effects. This relief of catalepsy by pramipexole confirmed that it may be beneficial in symptoms of antipsychotic-induced parkinsonism including dystonia, akinesia, and slowness of movement.

The mechanisms underlying the antiparkinson effect of pramipexole are complicated. Despite its partial agonistic effect on the postsynaptic D<sub>2</sub> receptor, pramipexole can also reduce DA uptake and increase DA neurotransmission through its long-term interaction of the presynaptic D<sub>3</sub> autoreceptor.<sup>25</sup> The agonism of the postsynaptic D<sub>2</sub> receptor and increase in the DA neurotransmission may reverse the phenomenon of "dopamine-acetylcholine" imbalance caused by the blockade of D<sub>2</sub> receptor which is the key phenomenon of DIP.<sup>26</sup> Furthermore, the neuroprotective and antioxidant effects of pramipexole can also explain its efficacy.<sup>27,28</sup> Overall, the mechanisms of pramipexole in its treatment effect of DIP merit further investigation.

Treatments with pramipexole did not show an anti-akathisia effect during the study, regardless of subjective pain, distress, or objective observation symptoms of akathisia. Nevertheless, two subjects (four subjects with akathisia in total) experienced an AE during the study. One subject (No. 3) had a depressed mood and suicidal ideation, with a deterioration of the akathisia syndrome. Another subject (No. 7) experienced a recurrence of her psychiatric symptoms, consisting of auditory hallucination and delusional thoughts. After the MECT treatment, No. 3 patients' symptoms were immediately relieved. After a slow exchange of antipsychotics from Aripiprazole 20 mg/day to Quetiapine 600 mg/day combined with aripiprazole 5 mg/day polytherapy, symptoms of No.7's psychiatric syndromes are stabilized and akathisia syndromes disappeared. In general, pramipexole did not show efficacy and safety in subjects with akathisia in the step 1 trial.



**Figure 1** Changes in (A) PANSS positive score, (B) PANSS negative score, (C) PANSS general psychopathological score, (D) PANSS total score, (E) CDSS total score and (F) CGI-S. **Abbreviations:** PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression Scale.

The immediate deterioration of akathisia and mood symptoms indicates that the partial agonist effect of the DA receptor does no good in treating the symptoms of akathisia. A previous study showed that antipsychotics with a partial DA receptor agonistic effect (ie, aripiprazole, brexpiprazole, and cariprazine) and high  $D_2$  receptor antagonist effect (ie, risperidone and haloperidol) are more risky for inducing akathisia than antipsychotics (ie, olanzapine and quetiapine).<sup>29</sup> The relation between the partial

DA receptor agonist effect and akathisia is complicated and remains unknown, especially considering the relatively high  $D_2$  receptor binding ability and both partial agonist and antagonist effect on the  $D_2$  receptor of this kind of antipsychotics.<sup>30,31</sup> Besides, the short-term administration of pramipexole can spontaneously decrease the synaptic release of DA and firing rate of DA and norepinephrine (NE) neurons.<sup>32</sup> The decrease of the firing rate of DA, NE neurons, and DA release may account for the

**Table 5** Adverse effects

Subject no.	Adverse effects	Withdrawn from the study due to AE	Switch to other medication or MECT due to AE	AE recovered hereafter
3	Depressed mood/suicidal ideation	Y	Y	Y
6	Drowsiness	N	N	Y
7	Symptoms deterioration/ depressed mood	N	Y	Y
9	Nausea	Y	N	Y

**Notes:** Y means yes and the event occurred; N means no and the event did not occur.

**Abbreviations:** MECT, Modified Electra convulsive Therapy; AE, adverse effect.

spontaneous deterioration of mood symptoms and akathisia. Nevertheless, considering the relatively small sample of subjects with akathisia in step 1, this phenomenon will be observed, monitored, and validated in the step 2 study.

All the psychiatric rating scales including PANSS, CDSS, and CGI-S did not change significantly during the trial. All the psychiatric rating scales showed an increasing trend on day 3 and at 1 week, which is due to the immediate deterioration of the symptoms in two subjects with akathisia. After one subjects' withdrawal and management of another subjects' AE, the PANSS positive score, PANSS negative score, PANSS general psychopathology score, PANSS total score, and CGI-S all showed a trend of improvement during the remaining follow-up. The mild improvement of positive symptoms, negative symptoms, and general psychopathology symptoms of patients proved that pramipexole may be beneficial to the psychiatric symptoms of schizophrenia. The results of our trial are consistent with those of a previous study, with a higher dose range and higher rating improvement of the PANSS rating scale.<sup>15,33</sup> Unexpectedly, we did not see improvement of mood symptoms of patients with schizophrenia in this trial. After the management of akathisia symptoms, the CDSS total score slowly decreased but remained higher than the baseline score until the endpoint. Pramipexole has shown efficacy on mood symptoms of MDD, bipolar disorder, and Parkinson disease.<sup>34–36</sup> But the dose of pramipexole in these studies is relatively higher, ranging from 1.0 to 3.0 mg/day. The lack of efficacy on depression mood may be due to low drug dose and relatively mild depression mood of our subjects. Considering the complicated mechanism of depression mood of schizophrenia patients, whether a low dose of pramipexole can be effective in mood symptoms will be further validated in the step 2 study.

## Limitations and further study

The limitations of the study are small sample size (n=10), wide age range (18–65 years), and the open-label design. Depending on the preliminary results of the current study, we will enlarge the sample size and make a single-blind study design in Phase II study, which will further validate pramipexole's efficacy on EPS and symptoms of schizophrenia.

## Conclusion

In conclusion, a low dose of pramipexole is efficacious in the treatment of antipsychotic-induced parkinsonism, but it did not show efficacy on akathisia. Our study also demonstrated that co-medication with pramipexole may be effective on psychiatric symptoms of schizophrenia, although the improvements are not very significant probably due to the low dose. The symptoms of mood are not improved after combining with the treatment of pramipexole. In general, the findings of this study suggest that the usage of the D<sub>2</sub>/D<sub>3</sub> partial agonist pramipexole could be beneficial in the treatment of neuroleptic-induced EPS, especially DIP, and show a trend of improvement of schizophrenia symptoms. The results of this study need to be validated in a larger sample.

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## Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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