Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: A randomized, double-blind, placebo-controlled, dose–response study

Jing-Xu Chen a,1, Yun-Ai Su b,1, Qing-Tao Bian a, Li-He Wei a, Rong-Zhen Zhang a, Yan-Hong Liu a, Christoph Correll c, Jair C. Soares d, Fu-De Yang a, Shao-Li Wang a, Xiang-Yang Zhang a,d,*

a Beijing Hui-Long-Guan Hospital, Peking University, Beijing 100096, China
b Peking University Sixth Hospital/Institute of Mental Health, Key Laboratory of Mental Health, Ministry of Health, Peking University, Beijing, China
c The Zucker Hillside Hospital, Psychiatry Research, North Shore-Long Island Jewish Health System, Glen Oaks, NY, USA
d Department of Psychiatry and Behavioral Sciences, Harris County Psychiatric Center, The University of Texas Health Science Center at Houston, Houston, TX, USA

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KEYWORDS
Risperidone; Aripiprazole; Prolactin; Hyperprolactinemia; Intervention; Placebo controlled trial; Dose effect

Summary Hyperprolactinemia is an unwanted adverse effect associated with several antipsychotics. The addition of partial dopamine receptor agonist aripiprazole may attenuate antipsychotic-induced hyperprolactinemia effectively. However, the ideal dosing regimen for this purpose is unknown. We aimed to evaluate the dose effects of adjunctive treatment with aripiprazole on prolactin levels and hyperprolactinemia in schizophrenia patients. Stable subjects 18–45 years old with schizophrenia and hyperprolactinemia (i.e., >24 ng/ml for females and >20 ng/ml for males) were randomly assigned to receive 8 weeks of placebo (n = 30) or oral aripiprazole 5 mg/day (n = 30), 10 mg/day (n = 29), or 20 mg/day (n = 30) added on to fixed dose risperidone treatment. Serum prolactin levels were measured at baseline and after 2, 4 and 8 weeks; clinical symptoms and side effects were assessed at baseline and week 8 using...
1. Introduction

Prolactin elevating effects of antipsychotics are well-known (Haddad and Wieck, 2004), and hyperprolactinemia is a well-recognized complication of treatment with some of antipsychotic agents, particularly first-generation antipsychotics (FGAs) and many second-generation antipsychotics (Leucht et al., 2013). Prolactin elevation is caused by blocking the dopamine D2 receptors in lactotroph cells in the anterior pituitary gland. Reports indicate that as many as 65% of women of reproductive age and 40–70% of men taking antipsychotics have hyperprolactinemia (Montgomery et al., 2004). Antipsychotic-induced hyperprolactinemia can cause menstrual irregularities, amenorrhea, galactorrhea, gynecomastia, sexual dysfunction and osteoporosis (Ajmal et al., 2014; Kishimoto et al., 2012; La Torre et al., 2013), which in turn can have a negative impact on patient compliance with treatment.

Although antipsychotic dose, duration of treatment, antipsychotic potency, age, and sex contribute to the severity of hyperprolactinemia (Inder and Castle, 2011; Madhusoodanan et al., 2010), the strongest predictor of hyperprolactinemia in patients with schizophrenia is the type of antipsychotic and higher antipsychotic doses (Inder and Castle, 2011). In contrast, the atypical antipsychotics generally are much less likely to increase prolactin levels than conventional antipsychotics, yet there is considerable variation among specific drugs. Among the atypical antipsychotics, risperidone, paliperidone and amisulpride are associated with the highest prolactin increases and rates of hyperprolactinemia (70–100%) (Bushe et al., 2008). Risperidone and its major active metabolite of risperidone, 9-hydroxyrisperidone (paliperidone), have been shown to produce significantly higher prolactin levels compared to some conventional antipsychotics, such as haloperidol (Leucht et al., 2013). Olanzapine causes transient elevations in prolactin levels and is less commonly associated with hyperprolactinemia, while clozapine and quetiapine have very weak affinity for the D2 receptors and rarely elevate prolactin levels (Fragas et al., 2011; Leucht et al., 2013). Among the newest of the atypical antipsychotics, iloperidone and asenapine did not significantly increase prolactin levels compared with placebo (Leucht et al., 2013). Of particular interest is aripiprazole, which is a potent (high-affinity) partial agonist at D2 receptors, partial agonist at serotonin 5-HT1A receptors, and antagonist at 5-HT2A receptors (Kessler, 2007). It acts as an antagonist at D2 receptor in the state of excessive dopaminergic neurotransmission, while it acts as an agonist at D2 receptor in the state of low dopaminergic neurotransmission, and thus can balance dopaminergic neurotransmission. In ex vivo experiments, aripiprazole inhibited spontaneous prolactin release from isolated anterior pituitary slices (Inoue et al., 1996). Because of these unique pharmacological profiles, aripiprazole may ameliorate schizophrenia symptoms without elevating prolactin levels, and even decrease prolactin levels below those expected from placebo (Belgamwar and El-Sayeh, 2011; Findling et al., 2008; Kane et al., 2007; Potkin et al., 2003; Suzuki et al., 2013; Yoo et al., 2013). One well-documented approach to the management of antipsychotic-induced hyperprolactinemia is a switch to aripiprazole (Byerly et al., 2009; Jeong et al., 2012; Newcomer et al., 2013). However, this strategy is not always feasible, especially if the patient has responded well to the antipsychotic causing hyperprolactinemia and since switching can increase the risk of a relapse (Kelly et al., 2013; Kuloglu et al., 2010).

Recently, several studies have shown the reversal or attenuation of antipsychotic-induced hyperprolactinemia with the addition of aripiprazole to some antipsychotics, such as risperidone (Chen et al., 2009; Rainka et al., 2009), risperidone long-acting injection (van Kooten et al., 2011; Ziadi Trives et al., 2013), paliperidone (Basterreche et al., 2012; Rocha et al., 2010) and amisulpride plus ziprasidone (Saitis et al., 2008). Placebo-controlled studies showed improvement in prolactin levels with adjunctive aripiprazole in patients maintained with haloperidol (Shim et al., 2007) or risperidone (Kane et al., 2009; Yasui-Furukori et al., 2010). However, to date, the ideal dosing regimen for this purpose is not known. An open dose-dependent study (Yasui-Furukori et al., 2010) suggested significant improvements in prolactin and prolactin-related symptoms within 4 weeks of adjunctive aripiprazole treatment (3, 6, 9 and 12 mg). Prolactin lowering effects were apparent even at a low dosage of 3 mg/day, and the most robust improvements were seen at the 9 and 12 mg/day dose. By contrast, a meta-analysis reported that the appropriate dose of adjunctive aripiprazole for improving hyperprolactinemia may be as low as 5 mg/day (Li et al., 2013). Therefore, the current randomized, double-blind, placebo-controlled study was designed to compare the dose–response relationship of aripiprazole in the treatment of antipsychotic-induced hyperprolactinemia and to evaluate the time-course of action in patients with schizophrenia experiencing hyperprolactinemia during risperidone treatment.
2. Methods

2.1. Subjects

Eligible subjects were Chinese male and female schizophrenia patients deemed appropriate candidates by their treating physicians who were recruited from the Beijing Hui-Long-Guan hospital, China, between October 2009 to July 2013. The study was approved by the hospital’s ethics committee, and all participants provided written informed consent in accordance with National Health and Medical Research Council guidelines. The diagnosis of schizophrenia was determined by the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (Association AP: Diagnostic and Statistical Manual of Mental Disorders, 1994). To be eligible for the study, patients aged 18–45 years had to be relatively stable during the screening phase, as indicated by a total score <70 on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987); had to be treated with risperidone monotherapy, except for anticholinergics or benzodiazepines, taking the same dosage of risperidone for at least 6 weeks; and had to experience hyperprolactinemia induced by risperidone. Hyperprolactinemia was defined as a morning serum prolactin level of >24 ng/ml for females and >20 ng/ml for males (Shim et al., 2007). All participants had to be under the care of a parent or another adult caregiver who monitored and recorded medication intake during each day of the trial to monitor adherence.

Patients were excluded if there was evidence of significant medical illnesses, such as liver or renal dysfunction, cardiovascular disease, organic brain disorder; if they were pregnant or lactating; if they had a psychiatric diagnosis other than schizophrenia or a current history of substance use disorder; or if they were taking other medications than risperidone, anticholinergics or benzodiazepines, such as other antipsychotics, antidepressants, or mood stabilizers etc., which may alter prolactin levels.

2.2. Study design and procedures

This was an 8-week double-blind, placebo-controlled study of adjunctive aripiprazole for risperidone-induced hyperprolactinemia. Eligible subjects were randomized in a 1:1:1:1 ratio to receive placebo, 5 mg/day of aripiprazole, 10 mg/day of aripiprazole, or 20 mg/day of aripiprazole, taken once daily in the morning. Study medication was prepared by an independent research pharmacy. Placebo and aripiprazole tablets were physically indistinguishable. Aripiprazole was titrated from a starting dose of 5 mg/day, and then increased to the target dose by the end of week 2 if it was clinically tolerated. The dose of risperidone remained fixed throughout the study. Concomitant medications such as anticholinergics and benzodiazepines, which had been prescribed at baseline (prior to study entry), were continued without change during the study period. No concomitant psychotropic medications were permitted during the study, except trihexyphenidyl 2–6 mg/day as needed for extrapyramidal symptoms, lorazepam 0.5–1.0 mg/day for anxiety or insomnia, and propranolol 10–30 mg/day for tachycardia.

2.3. Assessment and outcome measures

Psychopathology was assessed with the PANSS and with the Clinical Global Impressions severity scale (CGI-I) (Branch, 1976). Tolerability was evaluated with the Barnes Akathisia Scale (BAS) (Barnes, 1989), Simpson Angus Scale (SAS) (Simpson and Angus, 1970) and the UKU Side Effects Rating Scale (Lingjaerde et al., 1987). For each patient, the same investigator rated on these scales at baseline and 8 weeks.

Prolactin levels were measured at 6:30–7:00 am following an overnight fast, 12 h after the evening dose of risperidone was taken. The morning dose of medication was administered after blood was drawn. Blood was drawn at baseline and at 2, 4, and 8 weeks after starting adjunctive aripiprazole. The serum prolactin levels were measured by electro-chemiluminescence immunoassay. The assay was performed in accordance with the manufacturer’s instructions (Beckman Coulter, USA). Each assay was run in duplicate. All samples were assayed by the same technician, who was blind to the clinical situation. The sensitivity was 0.25 ng/ml, and intra-assay and inter-assay variation coefficients were 1.87% and 2.5%, respectively.

2.4. Statistical analysis

The primary outcome measure was the weekly change in the prolactin levels from baseline. The key secondary outcome measures were the response rate, defined as a ≥30% reduction in prolactin, and the rate of remission, defined as prolactin levels ≤24 ng/dl for females and ≤20 ng/dl for males, after 8 weeks of treatment. Other secondary outcome measures included the mean change from baseline at the end of the study in PANSS total score and CGI-S, score, as well as side effects measured with the BARS, SAS and UKU.

All analyses were conducted with SPSS, version 11.5 (SPSS, Inc., Chicago), using data from all randomized patients with at least 1 follow-up test (modified intent-to-treat analysis). The principal outcome analysis consisted of repeated-measures multivariate analyses of variance (MANOVAs) for the prolactin levels with a between-subject factor of drug (placebo, 5 mg, 10 mg, 20 mg) and a within-subject factor of time (baseline, week 2, week 4 and week 8). If the drug or drug-by-time interaction effects were significant in the repeated-measures MANOVA, the effects of age, sex, duration of illness, risperidone dosage, duration of risperidone and baseline prolactin levels were tested by adding these variables to the model as covariates. If the overall treatment effect was significant, three planned comparisons for the effects of each dosing level of aripiprazole on the prolactin levels compared with placebo were performed by analysis of covariance (ANCOVA), with baseline score as a covariate. Additional statistical analyses included t tests, analyses of variance (ANOVA) for continuous variables, and chi-square tests for categorical variables.

In order to protect the alpha level at 0.05 when conducting three comparisons of aripiprazole fixed doses vs placebo in the primary efficacy analyses, the statistical testing was carried out using the Hochberg’s sequentially rejective procedure (Hochberg, 1988). Superiority to placebo was proclaimed if all three pairwise comparisons were significant at
Aripiprazole for hyperprolactinemia

3. Results

3.1. Demographic and clinical characteristics

In total, 119 patients were randomly assigned to adjunctive aripiprazole or placebo (placebo, n = 30; aripiprazole 5 mg/day, n = 30; aripiprazole 10 mg/day, n = 29; aripiprazole 20 mg/day, n = 30) (Fig. 1). There were no significant differences in demographic or clinical characteristics between patients who received placebo or aripiprazole (Table 1).

A total of 107 patients (89.9%) completed the trial. There was no significant difference in the study dropout rates between treatment groups, with 86.7% of placebo-treated patients (n = 26), 93.3% of 5 mg/day aripiprazole-treated patients (n = 28), 93.1% of 10 mg/day aripiprazole-treated patients (n = 27), and 86.7% of 20 mg/day aripiprazole-treated patients (n = 27) remaining in the trial at week 8 ($X^2 = 4.67, p = 0.20$). Among the 12 non-completers (10.1%), 4 had been assigned to placebo, 2 to 5 mg/day of aripiprazole, 2 to 10 mg/day of aripiprazole, and 4 to 20 mg/day of aripiprazole. Of these, 7 (5.9%) were lost to follow-up, 2 (1.7%) withdrew consent, 3 (2.5%) withdrew because of adverse event (Fig. 1).

3.2. Efficacy

The serum prolactin levels did not differ between treatment groups at baseline ($p > 0.05$) (Table 2). During the 8-week study, there was a statistically significant drug-by-time effect ($F = 18.75, df = 9, 345, p < 0.001$) in the repeated-measures MANOVA (Fig. 2, Table 2). All 3 active treatment groups demonstrated rapid onset of efficacy with statistically significant prolactin lowering effects evident from

![Flowchart of participation in a study of aripiprazole for treatment of risperidone-induced hyperprolactinemia.](image-url)
Table 1  Baseline demographic and clinical characteristics (intent-to-treat population).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 30)</th>
<th>Aripiprazole 5 mg (n = 30)</th>
<th>Aripiprazole 10 mg (n = 29)</th>
<th>Aripiprazole 20 mg (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Men</td>
<td>15</td>
<td>14</td>
<td>14</td>
<td>15</td>
<td>0.99</td>
</tr>
<tr>
<td>Women</td>
<td>15</td>
<td>16</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>In/out-patient status</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13/17</td>
<td>12/18</td>
<td>13/16</td>
<td>11/19</td>
<td>0.92</td>
</tr>
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<td>Co-medications</td>
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</tr>
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<td>Anticholinergics</td>
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<td>5</td>
<td>2</td>
<td>3</td>
<td>0.81</td>
</tr>
<tr>
<td>Benzodiazepines</td>
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<td>1</td>
<td>4</td>
<td>3</td>
<td>0.49</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td>Age</td>
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<td>32.52</td>
<td>33.21</td>
<td>34.50</td>
<td>0.84</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.50</td>
<td>12.00</td>
<td>12.01</td>
<td>12.57</td>
<td>0.64</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>10.77</td>
<td>10.33</td>
<td>11.40</td>
<td>9.45</td>
<td>0.75</td>
</tr>
<tr>
<td>Risperidone dosage (mg/day)</td>
<td>4.93</td>
<td>4.63</td>
<td>4.79</td>
<td>5.07</td>
<td>0.44</td>
</tr>
<tr>
<td>Duration of risperidone (weeks)</td>
<td>9.67</td>
<td>8.57</td>
<td>9.20</td>
<td>9.13</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Fig. 2  Mean serum prolactin levels from baseline over 8 weeks of treatment with aripiprazole (5 mg/day, 10 mg/day or 20 mg/day) or placebo.

week 2, but without significant differences in prolactin levels between week 2, week 4, and week 8. Conversely, no significant effect was observed in the placebo group over time (Fig. 2). When the effects of age, sex, duration of illness, risperidone dosage and duration of risperidone were examined by adding them into the repeated-measures MANOVA as covariates, there was still a significant drug-by-time effect for prolactin levels (F = 21.05, df = 9, 330, p < 0.001).

ANCova analyses showed that after 8 weeks of treatment, the prolactin levels between treatment groups were significantly different (F = 19.96, df = 3, 115, p < 0.001). The prolactin levels were significantly lower in the 20 mg group (p < 0.001; effect size = 1.83), 10 mg (p < 0.001; effect size = 1.63), and 5 mg (p < 0.001; effect size = 0.89) aripiprazole groups than in the placebo group. There was a significant difference between the 5 mg and 10 mg group (p = 0.03), and the 5 mg and 20 mg group (p = 0.003), but no

Table 2  Efficacy data for hyperprolactinemia after treatment in a placebo-controlled trial of aripiprazole.

<table>
<thead>
<tr>
<th>Prolactin levels (ng/ml)</th>
<th>Placebo (n = 30)</th>
<th>Aripiprazole 5 mg (n = 30)</th>
<th>Aripiprazole 10 mg (n = 29)</th>
<th>Aripiprazole 20 mg (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>91.61</td>
<td>89.92</td>
<td>93.63</td>
<td>87.59</td>
<td>0.98</td>
</tr>
<tr>
<td>SD</td>
<td>57.88</td>
<td>53.60</td>
<td>46.57</td>
<td>50.38</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>88.62</td>
<td>50.71</td>
<td>34.02</td>
<td>21.27</td>
<td>0.0001</td>
</tr>
<tr>
<td>Change at week 2</td>
<td>−2.98</td>
<td>−39.21</td>
<td>−39.61</td>
<td>−66.32</td>
<td>0.0001</td>
</tr>
<tr>
<td>Week 4</td>
<td>90.55</td>
<td>50.59</td>
<td>29.32</td>
<td>20.50</td>
<td>0.0001</td>
</tr>
<tr>
<td>Change at week 4</td>
<td>−1.05</td>
<td>−39.33</td>
<td>−64.31</td>
<td>−67.09</td>
<td>0.0001</td>
</tr>
<tr>
<td>Week 8</td>
<td>87.72</td>
<td>49.54</td>
<td>28.50</td>
<td>20.55</td>
<td>0.0001</td>
</tr>
<tr>
<td>Change at week 8</td>
<td>−3.89</td>
<td>−40.38</td>
<td>−65.13</td>
<td>−67.03</td>
<td>0.0001</td>
</tr>
<tr>
<td>Respondera</td>
<td>N</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Normalizationb</td>
<td>3</td>
<td>24</td>
<td>28</td>
<td>30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1</td>
<td>3.3</td>
<td>80.0</td>
<td>96.6</td>
<td>100</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

a Patients with the reduction of ≥30% in prolactin levels at week 8.

b Patients with prolactin levels in normal range (i.e., ≤24 ng/dl for females and ≤20 ng/dl for males) at week 8.
A significant difference was noted among the three aripiprazole groups (p < 0.05). For the high PRL level subgroup, the PRL levels were lower in all three aripiprazole groups compared with placebo (all p < 0.01), while no significant difference was noted among the three aripiprazole groups (p = 0.05). For the very high PRL level subgroup, at 8-week post-treatment, the PRL levels were lower in all three aripiprazole groups compared with placebo (p = 0.000). Further, there was a significant difference between 5 mg and 10 mg groups (p < 0.006) or between 5 mg and 20 mg groups (p = 0.002), but no significant difference between the 10 mg and 20 mg groups (p = 0.72). These results suggest that for those who had only slightly higher PRL level than normal range, aripiprazole dose to normalize PRL level were lower, with 5 mg being as effective as 10 mg or 20 mg.

At week 8, response rates between treatment groups were significantly different (X² = 77.87, df = 3, p < 0.001). Response rates were highest for all three aripiprazole groups (80–100%) compared with placebo (10%) (5 mg: X² = 29.70, p < 0.001; 10 mg: X² = 44.30, p < 0.001; 20 mg: X² = 49.09, p < 0.001) (Table 2). Moreover, response rates were significantly lower in the 5 mg group compared to the 10 mg group, and the 20 mg group (X² = 4.25, p = 0.04; X² = 8.99, p = 0.003, respectively), without a significant difference between 10 mg and 20 mg group (X² = 1.35, p = 0.23). At the end of the study, 6 of 30 (20.0%) in 5 mg group, 15 of 29 (51.7%) in 10 mg group, 20 of 30 (66.7%) in 20 mg group were within normal range, whereas only one of 30 (3.3%) in the placebo group had normalized prolactin levels that was decreased from original 267.3 ng/ml to 17.57 ng/ml (X² = 35.34, df = 3, p < 0.001). Further analysis showed that the normalization rate between each of the four treatment groups were significantly different (10 mg vs 20 mg group: p = 0.24; 5 mg vs 10 mg group: p = 0.01, all others: p < 0.001).

When men and women analyzed separately, the mean baseline was significantly higher in women than men in every treatment group (all p < 0.001). However, the percent change in prolactin levels from baseline to week 8 was not significantly different between male and female patients in any of the treatment groups (all p > 0.05).

### 3.3. Psychopathology

The PANSS total and CGI-S score did not differ between treatment groups at baseline (all p > 0.05). Repeated-measures MANOVA on psychopathology showed no statistically significant drug-by-time effect in the PANSS total (F = 0.49, df = 3, 115, p = 0.69) or CGI-S score (F = 0.22, df = 3, 115, p = 0.88) (Table 3). No patient withdrew from the study because of worsening in symptoms.

### 3.4. Adverse effects

The overall incidence of adverse events and of specific adverse events during the study measured with the UKU was similar between the four treatment groups (χ² = 0.88, df = 3, p = 0.86). Treatment-emergent adverse events occurred in 20.0% of patients in the placebo group, 23.3% of patients in the aripiprazole 5 mg group, 24.1% of patients in the aripiprazole 10 mg group, and 30.0% of patients in the aripiprazole 20 mg group. Dry mouth was the adverse event with the highest incidence, both in the total aripiprazole groups (3.3–6.9%) and placebo group (3.3%) (all p > 0.05).

No patient had worsening of extrapyramidal symptoms or akathisia after adjunctive aripiprazole treatment as measured by the SAS and BARS. There were no statistically significant time or group by time interaction effects for BAS or SAS scores (F = 0.27, df = 3, 115, p = 0.99; and F = 0.09, df = 3, 115, p = 0.97, respectively) (Table 3). No clinically relevant changes from baseline were observed in body weight.
laboratory evaluations, or QTc interval occurred in either group (Table 4; all $p > 0.05$).

4. Discussion

The current study is, to our knowledge, the first randomized, double-blind, placebo-controlled, dose–response study to evaluate more than 2 fixed doses of aripiprazole in the treatment antipsychotic-induced hyperprolactinemia. We found that the prolactin levels significantly decreased from baseline in all 3 aripiprazole groups (5 mg, 10 mg or 20 mg), whereas there were no significant changes in prolactin levels in the placebo group. Furthermore, 20.0–66.7% of patients in the aripiprazole groups had normal prolactin levels at 8 weeks despite continued risperidone treatment at pre-baseline doses, compared only 3.3% in the placebo. In our previous open study (Chen et al., 2009), we found that 10 mg/day aripiprazole could attenuate risperidone-induced hyperprolactinemia and related symptoms. Similar reductions in prolactin levels were seen following adjunctive use of aripiprazole in haloperidol-treated patients with hyperprolactinemia (Shim et al., 2007). Moreover, our results generalized across males and females and were robust even after adjusting for potential confounders and the aripiprazole augmentation was very well tolerated. Taken together, these results suggest that the addition of oral aripiprazole is a safe and effective strategy in patients with risperidone or haloperidol-induced hyperprolactinemia. However, it is worthy of mentioning that the addition of aripiprazole does not seem to be as effective for other antipsychotics such as amisulpride (Chen et al., 2010), suggesting that the effect of aripiprazole treatment on prolactin reduction may differ from the mechanism of action of the prolactin-inducing antipsychotics.

Interestingly, aripiprazole at dosage of 5 mg, 10 mg, and 20 mg produced statistically significant improvements as early as week 2 and achieved almost all of its effects in reducing risperidone-induced hyperprolactinemia by week 2. A couple of other reports have also found the onset and time trends of adjunctive aripiprazole relieving antipsychotic-induced hyperprolactinemia. For example, Byerly et al. (2009) examined three switching strategies and followed up PRL levels, finding that following aripiprazole initiation, mean prolactin levels decreased significantly at week-1 and were maintained to week-8 in all groups irrespective of prior treatment or switching strategy. Taken together, these studies suggest that rapid decreases of

| Table 4 Body weight, laboratory evaluations, and QTc interval among patients with schizophrenia receiving placebo or aripiprazole for 8 weeks. |
| Variable                          | Placebo (n = 30) | Aripiprazole | p |
|                                  | Mean (SD)       | 5 mg (n = 30) | 10 mg (n = 29) | 20 mg (n = 30) |
|                                  | Mean (SD)       | Mean (SD)     | Mean (SD)      | Mean (SD)      | Mean (SD)      | Mean (SD)      |
| Body weight (kg)                 | 68.24 (9.50)    | 68.90 (14.21) | 67.61 (13.36) | 70.37 (14.15) | 0.88          |
| Waist circumference              | 87.94 (9.07)    | 88.97 (10.41) | 86.93 (12.36) | 89.30 (10.99) | 0.85          |
| Hip circumference                | 97.63 (7.89)    | 100.37 (8.43) | 94.93 (11.22) | 98.30 (8.40)  | 0.17          |
| Fasting glucose                 | 5.06 (0.92)     | 5.62 (1.66)   | 5.13 (0.60)   | 5.18 (0.56)   | 0.23          |
| Triglycerides                   | 1.40 (0.46)     | 1.62 (0.84)   | 1.66 (0.72)   | 1.79 (1.07)   | 0.53          |
| Total cholesterol               | 4.52 (0.94)     | 4.99 (0.98)   | 4.55 (0.87)   | 4.81 (1.00)   | 0.26          |
| LDL cholesterol                 | 2.48 (0.82)     | 2.99 (1.59)   | 2.44 (0.80)   | 2.76 (1.01)   | 0.28          |
| HDL cholesterol                 | 2.82 (0.95)     | 2.67 (0.94)   | 2.70 (0.63)   | 2.80 (0.77)   | 0.95          |
| QTc interval                    | 378.73 (27.74)  | 378.85 (24.26)| 386.35 (25.42)| 378.05 (30.28)| 0.70          |
|                                  | 374.56 (26.01)  | 374.53 (39.31)| 388.14 (33.34)| 381.00 (35.84)| 0.72          |
prolactin levels could be achieved with adjunctive aripipra-
zole treatment.

We observed a dose effect of aripiprazole on the reduc-
tion in the serum prolactin levels. Our analysis suggested 
that serum prolactin levels during risperidone treatment 
were significantly decreased with 5 mg/day of aripipra-
zole co-administration. However, it seems that a threshold 
of approximately 10 mg/day for treatment of risperidone-
induced hyperprolactinemia, and doses above 10 mg/day 
are likely, at best, to provide no further therapeutic ben-
efit. This finding is not consistent with previous studies 
that found similar effects at lower as well as higher doses, 
with 5 mg/day seemingly producing almost maximum bene-
fit (Kane et al., 2009; Li et al., 2013). However, our study 
was larger than prior studies. Moreover, while differences 
between the 5 mg/day and 10 mg/day dose groups were 
already apparent in the analysis of change in prolactin 
levels and response status (i.e., 30% reduction in pro-
lactin levels), differences were mostly pronounced 
and even separated significantly the 10 mg/day and 20 mg/day arip-
iprazole dose groups when requiring normalized prolactin 
levels. It is widely accepted that dopamine is the predomi-
nant prolactin-inhibiting factor in humans. Dopamine D2 
agonists, such as risperidone, bind to D2 receptors in 
the pituitary gland and lead to the release of prolactin 
by the lactotroph cells. Aripiprazole, a potent partial ago-
nist of the dopamine D2 receptors (Kessler, 2007), has 
a greater affinity for the D2 receptor than risperidone 
with central D2 receptor occupancy of approximately 70% at 
a dose of 2 mg/day (Kegeles et al., 2008; Kim et al., 2012).

The partial agonist property means that, in the presence of 
dopamine hypoactivity, as induced by risperidone, aripipra-
zole will function as a dopamine agonist with roughly 30% 
intrinsic activity at postsynaptic receptors, restoring tonic 
inhibition to anterior pituitary lactotroph cells (Grunder et al., 2003), thereby decreasing serum prolactin levels. 
PET studies have established the dose-dopamine occupancy 
relationship for aripiprazole in vivo. One study found a 
hyperbolic concentration between aripiprazole dose and 
plasma levels with striatal dopamine D2/D3 receptor occu-
pancy. Almost complete saturation was found at peak plasma 
levels above 100–200 ng/ml (Yokoi et al., 2002). It has 
been shown that there is no significant difference in recep-
tor occupancy across different brain regions. At plasma 
levels above the range 100–150 ng/ml, D2 receptor occu-
pancy approached 100%. A systematic review evaluated 
the relationship between aripiprazole dose, plasma level, 
pharmacologic activity, and clinical outcome, finding that 
a concentration range of 150–200 ng/ml corresponds to an 
approximate dose of 10–15 mg/day aripiprazole (Sparschatt et al., 2010). Even at low doses, dopamine receptor occu-
pancy was high with aripiprazole and almost complete 
saturation occurred above 10 mg/day (Sparschatt et al., 2010). Nevertheless, inside of the CNS, the net effect of 
ariipiprazole is dopamine blockade. Our results suggest in 
the pituitary gland even partial D2 agonism of about 30% 
suffices to act at the lactotroph cells as a full agonist.

Antipsychotic polypharmacy has been scrutinized, mainly 
because of a lacking evidence base for its efficacy and 
for fear of enhanced adverse effects (Correll et al., 2011; 
Gallego et al., 2012a,b). In the present study, adjunctive 
ariipiprazole treatment to risperidone did not produce any 
significant changes in overall psychopathology as measured 
by PANSS total and CGI-severity scale scores. This finding is 
not surprising, as we selected patients who were not very 
symptomatic at baseline and clinically stable. In fact, the 
scores indicated a mean mild or lower symptom and global 
illiness severity, creating a ceiling effect for symptomatic 
improvement.

Although antipsychotic polypharmacy can induce 
increased adverse effects, the combination of the partial 
agonist aripiprazole has been associated with a reduction in 
certain adverse effects, including hyperprolactinemia and 
related sexual/reproductive dysfunction, weight gain and 
metabolic effects and sedation (Gallego et al., 2012a,b). 
However, weight gain and metabolic related adverse effects 
only seem to be reduced when combining aripiprazole with 
olanzapine or clozapine (Wang et al., 2013; Fleischhacker 
et al., 2010), but not when combining it with risperidone or 
quetiapine (Kane et al., 2009; Wang et al., 2013). We found 
the same in our study in which aripiprazole was added to 
risperidone. Although aripiprazole has been associated 
with akathisia more than other atypical antipsychotics 
(Kane et al., 2010), the addition of aripiprazole to risperi-
done did not increase either akathisia or EPS ratings or 
complaints compared to the placebo group monotherapy. 
These findings are concordant with the aforementioned 
study results (Kane et al., 2009) and suggest that at least 
some of the restlessness observed with aripiprazole is due 
to dopamine D2 stimulation when the partial agonist is 
initiated, but this effect is mitigated when D2 receptors 
are already blocked by risperidone treatment. On the other 
hand, a prior study found that the addition of aripiprazole 
 improved extrapyramidal side effects induced by the 
highly antipodaminergic agent haloperidol (Shim et al., 2007). 
Different from that study, patients in our study had low 
baseline SAS and BAS scores, which may have limited the 
opportunity to detect potential improvements.

Adjuvant aripiprazole was generally well tolerated. 
Except for very low rates of mild dry mouth, headache, 
insomnia, sedation, akathisia and tachycardia constipation, 
ariipiprazole augmentation was not associated with any 
additional adverse effects.

The results of this study must be interpreted within its 
limitations. First, the optimum dose for aripiprazole in our 
present study appears to be 10 mg/day, which is somewhat 
different from previous studies. For example, in the recent 
meta-analysis, the efficacy of adjunctive aripiprazole dose 
could be 5 mg/day (Li et al., 2013). Several factors, such 
as differences in sample size, the gender ratio and age 
of the patients, ethnicities, different illness courses, origin-
ial prolactin level, exposure for different type, dosage 
and length of antipsychotics being taken, the subtypes of 
schizophrenia patients recruited, samples of patients in 
different stages of disease progression (acute vs chronic or 
active phase vs remission) and study conduct may be respon-
sible for the discrepancy. Of note, the original prolactin 
level could be the key, together with antipsychotic dose 
that is associated with prolactin level directly. For example, 
the baseline prolactin levels were 94.6 ± 38.1 ng/ml for 
women and 56.9 ± 24.3 ng/ml in a previous study by 
Shim et al. (2007), with haloperidal monotherapy at the average 
dose of 22.8 mg/day. However, the average baseline pro-
lactin levels were 12.0 ng/ml for the olanzapine group and
40.6 ng/ml for risperidone group in the study by Byerly et al. (2009), which are significantly lower than those reported in Shim’s study. In our present study, with the average dose of risperidone of 4.86 mg/day, the baseline prolactin levels for men were 56.1 ± 30.6 ng/ml, which are similar to that in Shim’s study; however, the PRL levels for women were 123.5 ± 30.6 ng/ml, which were markedly higher than that in Shim’s study. Therefore, the adjunctive aripiprazole treatment as the management of antipsychotic-induced hyperprolactinemia warrants further investigation in first-episode and drug-naïve patients with schizophrenia, with the minimum effect of relevant moderator and mediator variables. Second, all participants in our current study were Chinese. As discussed above, the baseline prolactin levels varied significantly in the previous studies performed in different ethnic or geographical populations (Shim et al., 2007; Byerly et al., 2009), suggesting that the differential baseline prolactin levels may be associated with different ethnic populations. Hence, whether our findings may be generalized to other ethnic or geographical populations warrants further investigation. Also, future studies from different ethnicities will be needed to confirm the external validity of our results. Third, although larger than most studies in its kind, the individual study groups were still not large, which may have introduced bias in the estimation of the treatment effects. Fourth, the dose of aripiprazole was fixed at 5, 10, and 20 mg/day. It is possible that below 5 mg/day or above 20 mg/day could also be effective and safe for resolving antipsychotic-induced hyperprolactinemia (Kane et al., 2009; Li et al., 2013). However, we did observe a dose–response relationship with 10–20 mg achieving the greatest benefit. Fifth, the duration of 8 weeks was short and we cannot comment on the long-term effects, but generally emergence or reduction in adverse effects and efficacy are seen early in the treatment course. Sixth, the stable psychopathology and lack of enrichment for overweight/obese individuals limited our ability to assess the efficacy of aripiprazole augmentation of risperidone for the improvement of psychopathology and cardiometabolic burden. Finally, sexual and reproductive side effects of hyperprolactinemia induced by risperidone were not evaluated in this trial. Nevertheless, this study clearly demonstrated that aripiprazole augmentation of risperidone is well tolerated and effective for the reduction and reversal of risperidone induced hyperprolactinemia, that effects occur early, and that 10–20 mg/day are more effective than 5 mg/day.

In summary, adjunctive aripiprazole treatment reversed effectively hyperprolactinemia induced by risperidone in a Chinese population. Moreover, adjunctive aripiprazole was generally well tolerated, with a low rate of discontinuation due to adverse events and a high completion rate in reducing elevated prolactin levels. These results provide support for adjunctive aripiprazole use in risperidone-induced hyperprolactinemia at a starting dose of 5 mg/day, and the optimum dose for aripiprazole appears to be 10 mg/day, with some expected additional benefit at 20 mg/day if lower doses do not fully normalize prolactin levels. However, these findings remain preliminary due to a limited sample size of solely Chinese chronic patients and to a short treatment duration of only three doses of aripiprazole, and requires replication in larger, first-episode and drug-naïve schizophrenic patients in different ethnicities treated with lower and higher doses of aripiprazole for a long-term.

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Conflict of interest statement

The authors have no conflicts to disclose.

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