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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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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

* Corresponding author at: Harris County Psychiatric Center, 2800 South MacGregor Way, Houston, TX 77021, USA. Tel.: +1 713 7416047; fax: +1 713 486 2552.
E-mail address: xiang.y.zhang@uth.tmc.edu (X.-Y. Zhang).
[1] Jing-Xu Chen and Yun-Ai Su contributed equally to this work. They should be regarded as Joint First Authors.

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the Positive and Negative Syndrome Scale, Clinical Global Impressions Severity scale, Barnes Akathisia Scale, Simpson-Angus Scale and UKU Side Effects Rating Scale. Of 119 randomized patients, 107 (89.9%) completed the 8-week study. At study end, all three aripiprazole doses resulted in significantly lower prolactin levels (beginning at week 2), higher response rates (≥30% prolactin reduction) and higher prolactin normalization rates than placebo. Effects were significantly greater in the 10 and 20 mg/day groups than the 5 mg/day group. No significant changes were observed in any treatment groups regarding psychopathology and adverse effect ratings. Adjunctive aripiprazole treatment was effective and safe for resolving risperidone-induced hyperprolactinemia, producing significant and almost maximal improvements by week 2 without significant effects on psychopathology and side effects.

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 (Fraguas 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.