

# Using aripiprazole to resolve antipsychotic-induced symptomatic hyperprolactinemia: A pilot study

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## Abstract

**Objective:** To assess the effectiveness of substituting aripiprazole for other antipsychotic drugs taken by stable schizophrenic patients suffering from antipsychotic agent-induced symptomatic hyperprolactinemia.

**Methods:** Seven female schizophrenic patients with symptomatic hyperprolactinemia ( $167.6 \pm 58.0 \mu\text{g/L}$ ) were recruited to take part in an 8-week open label trial of aripiprazole (10–20mg/day) as a replacement for amisulpride or risperidone. Efficacy was assessed via PANSS and CGI-I scores. Serum prolactin levels were measured at baseline, week 4, and week 8. Data were collected from November, 2004 to May, 2005.

**Results:** At the end of weeks 4, serum prolactin levels were normalized ( $8.8 \pm 5.5 \mu\text{g/L}$ ) and hyperprolactinemic symptoms were resolved in all patients. However, aripiprazole treatment was discontinued within 6 weeks for 2 of the 7 subjects due to aggravated auditory hallucinations.

**Conclusion:** Results from this admittedly small-scale open-label study indicate that switching to aripiprazole may be useful for resolving antipsychotic-induced hyperprolactinemia and associated symptoms.

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**Keywords:** Amisulpride; Aripiprazole; Hyperprolactinemia; Risperidone

## 1. Introduction

Some antipsychotic agents elevate serum prolactin levels by blocking the dopamine 2 ( $D_2$ ) receptor on lactotroph cells in the anterior pituitary. Antipsychotic-induced hyperprolactinemia can cause menstrual irregularities, amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction (Maguire, 2002). Hyperprolactinemia is associated with typical antipsychotic agents and atypical antipsychotics such as risperidone and amisulpride (Haddad and Wieck, 2004; Maguire, 2002). Olanzapine is believed to cause a modest increase in prolactin levels (David et al., 2000). Clozapine, quetiapine and ziprasidone are not usually associated with hyperprolactinemia (Haddad and Wieck, 2004; Maguire, 2002). However, some case reports described ziprasidone-induced

hyperprolactinemia (Angheliescu and Wolf, 2004; Lusskin et al., 2004).

Aripiprazole is a potent partial agonist at  $D_2$  receptors, a partial agonist at serotonin 1A ( $5\text{-HT}_{1A}$ ) receptors, and antagonist at  $5\text{-HT}_{2A}$  receptors (Burris et al., 2002; Jordan et al., 2002; McGavin and Goa, 2002). Aripiprazole blocks  $D_2$  receptors under hyperdopaminergic conditions, and expresses agonist properties under hypodopaminergic conditions (Burris et al., 2002; Kikuchi et al., 1995). Aripiprazole is believed to stabilize the dopaminergic system and ameliorate schizophrenic symptoms without elevating serum prolactin levels (Goodnick et al., 2002; Potkin et al., 2003).

To assess the effectiveness of substituting aripiprazole for other antipsychotic drugs on schizophrenic patients with antipsychotic agent-induced symptomatic hyperprolactinemia, we conducted an 8-week open-label pilot trial of aripiprazole as a replacement for other antipsychotic agents in female schizophrenic patients suffering from symptomatic hyperprolactinemia. Assessments were made in terms of psychiatric symptoms, hyperprolactinemic symptoms, and serum prolactin levels.

**Abbreviations:** CGI-I, Clinical Global Impressions-Improvement Scale;  $D_2$ , dopamine 2; PANSS, Positive and Negative Syndrome Scale; PRL, prolactin;  $5\text{-HT}_{1A}$ , serotonin 1A;  $5\text{-HT}_{2A}$ , serotonin 2A.

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## 2. Methods

### 2.1. Subjects

Female schizophrenic outpatients who developed symptomatic hyperprolactinemia while taking atypical antipsychotic drugs were recruited from the Ansan Hospital Department of Psychiatry, which is associated with Korea University's College of Medicine. Inclusion criteria were (a) female patients of reproductive age (18–45 years) with DSM-IV schizophrenia; (b) having a stable psychiatric condition, defined as taking a stabilized dose of an atypical antipsychotic (amisulpride or risperidone) for at least 8 weeks; and (c) expressing symptomatic hyperprolactinemia associated with antipsychotic treatments, which is prolactin elevation with simultaneous causing menstrual irregularities, amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction. Females with other medical maladies (e.g., thyroid or gynecological diseases) were excluded. The final sample consisted of seven women. All subjects gave written informed consent to participate. The study was approved by the Ansan Hospital, Korea University Institutional Review Board. Data were collected from November 2004 to May 2005.

The clinical information for each patient is presented in Table 1. Mean age was  $35.0 \pm 7.4$  years, and illness duration was  $31.4 \pm 27.5$  months. All of the patients had been taking amisulpride (200–800 mg/day) or risperidone (6 mg/day) for the preceding  $6.1 \pm 1.8$  months. Mean prolactin level was  $167.6 \pm 58.0$   $\mu$ g/L (baseline). All seven patients suffered from amenorrhea and/or galactorrhea, both of which are associated with hyperprolactinemia. All subjects had histories of regular menstruation prior to taking the current antipsychotic agents. None of the subjects reported having problems with thyroid function, gynecological problems, or other general illnesses.

Two subjects were taking benztropine (2 mg/day) to treat extrapyramidal symptoms; one subject was taking lorazepam (0.5 mg/day) for sleep disturbance.

### 2.2. Study design

The study consisted of an 8-week, open-label, flexible dose trial of aripiprazole as a replacement for amisulpride or risperidone. Subjects were started on aripiprazole at 10 mg/day following spontaneous discontinuation of their current drug; dosage was increased to 30 mg/day at the clinician's discretion. Efficacy assessments included the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) at baseline and the end of week 8 and the Clinical Global Impressions-Improvement Scale (CGI-I) (NIMH, 1985) at the end of the trial. Serum prolactin levels were measured and hyperprolactinemia-associated symptoms were evaluated at baseline and the end of weeks 4 and 8. Serum prolactin levels (fasting blood) were measured between 8 and 9 in the morning. The normal range of serum prolactin in fertile females is 2.7 to 19.7  $\mu$ g/L.

### 2.3. Statistical analysis

Statistical analyses of efficacy measures, serum prolactin levels, and other parameters were performed using the Wilcoxon signed rank test with statistical significance achieved at  $p < 0.05$ . All statistical analyses were performed with SPSS version 12.0 for Windows.

## 3. Results

Of these 7 subjects, 2 had to stop taking aripiprazole after 6 weeks due to worsening auditory hallucinations. The remaining

Table 1  
Data on study subjects and efficacy of switching to aripiprazole

Patient number	Age (years)	Duration of illness (months)	Current antipsychotic	Prolactin-elevating antipsychotic agent				Aripiprazole dosage (mg)	Data after switching to aripiprazole			
				Length of prescription (months)	PANSS at 0 week	PRL at 0 week ( $\mu$ g/L)	Hyperprolactinemic symptoms		PANSS at 8 weeks	CGI-I at 8 weeks	PRL at 4 weeks ( $\mu$ g/L)	PRL at 8 weeks ( $\mu$ g/L)
1	39	6	Amisulpride 400mg	6	37	113.7	Amenorrhea	20	35	4	7.8	7.9
2	37	5	Amisulpride 400mg	5	56	147.0	Amenorrhea galactorrhea	10	50	3	6.5	6.8
3	40	24	Amisulpride 200mg	5	45	170.0	Amenorrhea	15	41	4	8.9	9.0
4	40	60	Amisulpride 800mg	6	34	230.0	Amenorrhea	15	31	4	18.0	14.0
5	36	60	Amisulpride 200mg	6	43	240.0	Amenorrhea galactorrhea	20	40	4	24.0	14.0
6	34	60	Amisulpride 800mg	10	42	190.0	Amenorrhea	20	51	6	4.0	*
7	19	5	Risperidone 6mg	5	58	82.8	Amenorrhea galactorrhea	15	64	6	2.4	*

PRL, serum prolactin level; PANSS, Positive and Negative Syndrome Scale; CGI-I, Clinical Global Impressions-Improvement Scale.

Approximately 4 weeks after switching to aripiprazole, all 7 patients reported having regular menstrual cycles; 3 patients reported improvement in their galactorrhea as their serum prolactin levels were normalized.

\*Serum prolactin level at end of week 8 not available due to aripiprazole discontinuation.

The normal range of serum prolactin in fertile females is 2.7 to 19.7  $\mu$ g/L.

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