An Overview of the Clinical Relationship Between Atypical Antipsychotics and Prolactin Levels in Children

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Background

- Prolactin (PRL) is a polypeptide hormone synthesized and secreted primarily by the anterior pituitary. It is involved in more than 300 biological functions, the most important of which is in the preparation of the breast for lactation during pregnancy and subsequent lactogenesis and lactopoiesis. Prolactin also plays a role in endocrine regulation, behavior, development, and immune function.[1]
- Prolactin secretion is highly complex and incompletely understood. Physiological stimuli such as suckling, stress, and increased estrogen levels stimulate prolactin synthesis, the pulsatile secretion of which is further influenced by circadian rhythms. Neurotransmitters play a nuanced role in prolactin secretion and have a profound influence on prolactin levels.[2]
- Dopamine has the strongest and most important inhibitory influence on prolactin secretion.[2] All antipsychotics act via dopamine inhibition in some capacity and the corresponding blockade of D_2 receptors – themselves prolactin inhibitors – caused by antipsychotics results in unmediated prolactin secretion.[3] Antipsychotics with strong dopaminergic inhibition are thought to elicit the greatest increase in prolactin concentrations. Prolactin elevation in pediatric patients treated for psychosis is not considered illness-related and is instead thought to be a result of antipsychotic intervention.[4,5]
- Acceptable serum prolactin concentrations vary with sex, age, stress, time of day, and life stage. No consensus exists on the normal range of prolactin concentration in the literature, though conservative estimates put acceptable values at 20 ng/mL for adult males and 24-25 ng/mL for non-pregnant women.[6] Normal values for children are marginally lower.
- Treatment-emergent hyperprolactinemia is a potential adverse event associated with antipsychotic use in pediatric patients. Prolonged elevation of prolactin can result in galactorrhea, amenorrhea, gynecomastia, decreased bone density, and delayed sexual development. Many of the side effects brought on by elevated prolactin levels are also commonly seen in puberty, presenting a challenge for clinicians.[7]
- Precisely which prolactin concentrations correspond to hyperprolactinemia is unclear. In adults, hyperprolactinemia may be diagnosed in relation to laboratory values or clinical manifestations. PRL ≥100 ng/mL is considered marked and is associated with hypogonadism, galactorrhea, and amenorrhea. Mild hyperprolactinemia (between 30-51 ng/mL) can shorten the luteal phase and may result in decreased libido and infertility. In children, hyperprolactinemia may be considered as two consecutive tests with PRL concentrations ≥20 ng/mL.[8]

History

- Antipsychotics acting via dopamine D_2 receptor inhibition have been the focus of clinical treatment of schizophrenia and related psychosis for more than 50 years. Antipsychotics are divided into 2 groups: First-generation agents (FGAs, or conventional) and second-generation agents (SGAs, or atypical).
- Conventional antipsychotics have been largely replaced by atypical antipsychotics as newer drugs cause fewer extrapyramidal symptoms, have similar efficacy profiles, and address the negative and cognitive symptoms associated with schizophrenia.[9] However, newer compounds are frequently related to metabolic adverse events including weight gain, diabetes, and elevated prolactin levels.[10] The clinical significance of the relationship between atypical antipsychotics, elevated prolactin, and long-term outcomes remains unclear.
- Recent studies show a dramatic rise in off-label and approved prescriptions of atypical antipsychotics in children for a variety of disorders (**Table 1**).[11] Because the efficacy of different atypical antipsychotics is relatively consistent, medication choices for children and adolescents are driven by the compounds' side effect profiles, particularly as they relate to growth, development, adherence, and quality of life.[10]

Table 1. Disorders Treated with Antipsychotics in Adolescents*

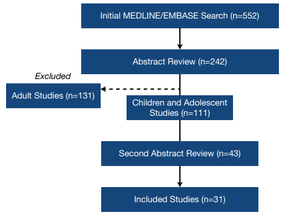
Pervasive Development Disorders, including autism	Anorexia Nervosa
ADHD & Disruptive Behavior Disorders	Schizophrenia and Schizophrenia-related Psychosis
Bipolar Disorder	Tourette Syndrome
	Post-traumatic Stress Disorder

*Including off-label

Methods

- A systematic literature search of MEDLINE, Embase, and OVID was undertaken to investigate the risk of hyperprolactinemia associated with atypical antipsychotic use in pediatric patients. Search terms included "antipsychotics (conventional and atypical)," "prolactin," "hyperprolactinemia," "schizophrenia," "bipolar disorder," "autism (and autism spectrum disorders)," "aripiprazole," "risperidone," "olanzapine," "quetiapine," "paliperidone/paliperidone ER" and "ziprasidone"
- Initial searches included adults and children. These results were narrowed by the authors (**Figure 1**) to include only children (ages 5-18). After two rounds of abstract review 31 studies were identified and reviewed

Figure 1. Methods for Literature Search



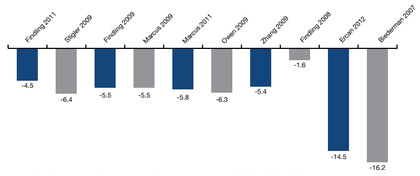
Results

Aripiprazole

Aripiprazole is unique among atypical antipsychotics as it lowers prolactin levels elevated by previous antipsychotic treatment (both traditional and atypical).

- This effect is evident in children and adults.[12,13] Aripiprazole may be administered to normalize prolactin levels elevated by antipsychotic therapy.[13]
- Aripiprazole administration in children can drop serum prolactin levels below baseline in a dose-dependent manner (**Figure 2**). After aripiprazole treatment, 60% of children and 30-32% of adolescents reported subnormal prolactin concentrations.[14]
- Aripiprazole is shown to decrease prolactin concentrations in pediatric patients with Tourette's syndrome.[12]
- Systematic reviews have demonstrated little significant evidence of serum prolactin elevations in children treated with aripiprazole.[15]

Figure 2. Mean Change from Baseline in Serum Prolactin Concentrations in Children & Adolescents Treated with Aripiprazole (ng/mL).



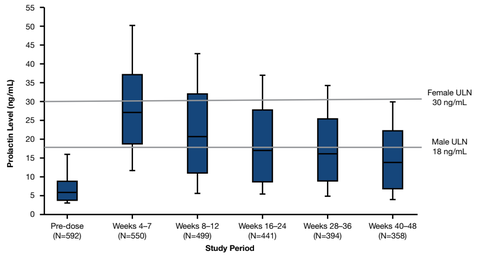
Adapted from Safer DJ, et al. *J Child Adolesc Psychopharmacol*. 2013;23(4):282-289.

Risperidone

Risperidone elevates prolactin levels in the short term, but these concentrations normalize after several weeks or months without dosage augmentation. The adverse events associated with the transitory prolactin elevations are not considered significant.

- Children and adolescents receiving long-term risperidone treatment can expect prolactin concentrations to rise initially but these levels stabilize to normal or upper limit of normal after several weeks without dose augmentation.[7] (**Figure 3**)
- Gradual reduction in serum prolactin concentrations is present in adult patients undergoing long term risperidone therapy, with highly significant linear reduction in prolactin levels throughout treatment.[16]
  - The clinical effects of these risperidone-induced prolactin elevation were not clear and no sexual side effects were reported in the long-term adult trial.[16]
- An analysis of 8 short-term studies of Risperidone in children reported a mean prolactin concentration increase from 7.9 ng/mL to 27.6 ng/mL at endpoint.[4] These levels decreased to a mean of 17.7 ng/mL after one year of treatment.[4]
- Mean prolactin levels rose modestly in a 48-week open label study of risperidone in children.[17] At week 4, the mean was 27.6 ng/mL in boys (ULN = 18 ng/mL) and 23.9 ng/mL in girls (ULN = 30 ng/mL). At endpoint, levels for boys (15.6 ng/mL) and girls (16.9 ng/mL) were within the normal range, suggesting a normalization of prolactin levels after long-term exposure.[17]
  - Migliardi et al., found adjusted mean prolactin levels at month 3 greater than at month 1, but significantly lower than month 1 levels at month 12, suggesting prolactin tolerance over time.[18]
  - This study found prolactin levels 10.3 times higher in patients treated with risperidone than olanzapine.[18]
- Prolactin tolerance is likely a long-term consequence of risperidone treatment. An 8-week study of young children (mean age 42.4 months) found a statistically significant 7-fold increase in prolactin levels after 8 weeks. The mean change in prolactin concentration was 33.9 ± 23.5 ng/mL at endpoint, though no participant reported clinical signs of hyperprolactinemia.[19]

Figure 3. Prolactin Levels in Children Taking Risperidone Normalize to Upper Limit of Normal (ULN) After 8 Weeks Without Dosage Augmentation



Adapted from Findling RL, et al. *J Clin Psychiatry*. 2003;64(11):1362–1369.

Paliperidone

- Paliperidone ER elevates prolactin in adults, similar to risperidone.[20] Data from a randomized, placebo-controlled study in adults shows prolactin levels to increase from 16.5 ± 17.5 ng/mL to 42.9 ± 29.1 ng/mL in males and from 36.6 ± 68.8 ng/mL to 120.2 ± 89.6 ng/mL in females.[21] In adults, plasma prolactin concentrations are more elevated in females treated with paliperidone and are likely to remain elevated throughout treatment.[22]
- A prospective 8-week open label study of young adults with autism found mean serum prolactin increased from 5.3 to 41.4 ng/mL.[23]
- Young patients switching from long-acting injectable risperidone to injectable paliperidone palmitate reported significant decreases in serum prolactin levels.[24]

Olanzapine

Olanzapine is associated with prolonged and statistically significant increases in prolactin concentrations in pediatric and adolescent patients, though long-term data in this population is limited.[4,25]

- Olanzapine exhibits more pronounced effect on prolactin levels in children than in adults.[26]
- A placebo-controlled study of olanzapine in adolescents reported statistically significant prolactin elevations after 6 weeks.[27]
- Prolactin tolerance may develop with olanzapine. Adolescent patients receiving long-term treatment reported elevated prolactin levels at 3 and 6 months, though concentrations fell below baseline after 12 months of continuous treatment.[18]

Quetiapine

Quetiapine has a muted effect on prolactin levels in children, though limited data underscores the need for further study.

- A 3-week placebo-controlled study found elevations of 2.84 ng/mL and 1.86 ng/mL for 400 mg/day and 600 mg/day, respectively, though the brevity of the trial is a limitation for long-term outcomes.[28]
- A retrospective study found 20% of patients treated with quetiapine had prolactin in the upper limit of normal after 6 weeks. The elevation was not dose dependent.[29]
- Prolactin increases from 11.3 ng/mL to 14.4 ng/mL was documented in a study of 13-17 year old boys, though the effect was transient and not statistically significant.[30]

Ziprasidone

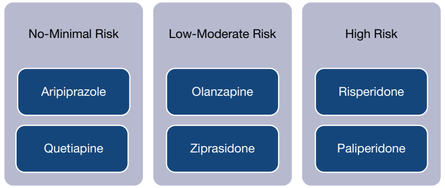
Ziprasidone's effect on QTc prolongation and the need for ongoing electrocardiograms in young patients makes the compound a second or third-line therapy in this population.[31] As such, clinical data on its use in children is scarce.

- Prolactin changes in child and adolescent patients are small, transient, and dose dependent.[32]
- Prolactin elevations are lower in children administered ziprasidone than olanzapine or risperidone.[4]
- No sexual or developmental side effects in adolescent patients taking ziprasidone have been published.

Conclusion

- Antipsychotic-induced adverse events may be especially significant in children and adolescents, who are prescribed these drugs at increasing rates.
- Prolactin-related adverse events represent particular challenges in this patient population. Significant increases in prolactin concentration may result in delayed sexual development, bone formation, and growth.
- Therapeutic choices in young patients administered antipsychotics are frequently driven by adverse event profiles of available compounds.
- The risk of hyperprolactinemia in pediatric patients taking antipsychotics varies between compounds (**Figure 4**).
- Atypical antipsychotics have a limited effect on prolactin concentrations in children. However, there is limited long-term evidence on incidence and outcomes in pediatric patients undergoing antipsychotic treatment. More research is required to determine the long-term relationship between these compounds and prolactin side effects.

Figure 4. Relative Risk of Antipsychotics to Induce Hyperprolactinemia in Pediatric Patients



Adapted from Peuskens J, et al. *CNS Drugs* 2014 Mar 28.

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