# Risperidone-Induced Hyperprolactinemia in Adolescents: A Case Series

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***Objective:*** To study the effect of risperidone on prolactin levels in 3 adolescent patients.

***Method:*** This is a case study of 3 adolescent patients with DSM-IV diagnosis of schizophreniform disorder, major depressive disorder with psychotic features, or chronic undifferentiated schizophrenia who were treated in inpatient and outpatient psychiatric settings with risperidone. Patients developed hyperprolactinemia with clinical symptoms. Risperidone was discontinued gradually over 2 weeks, and patients were treated with other atypical antipsychotics.

***Results:*** Prolactin levels returned to normal, and clinical symptoms of hyperprolactinemia resolved in all 3 patients after 2 weeks of tapering and discontinuation of risperidone.

***Conclusion:*** Hyperprolactinemia can be a troublesome side effect with potentially serious complications. It is being increasingly reported in younger patients treated with risperidone. Recognition and treatment of this condition including switching to a prolactin-sparing agent are important to prevent this complication.

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The overwhelming majority of cases of drug-induced hyperprolactinemia are secondary to first generation antipsychotics and risperidone. However, hyperprolactinemia has been associated with several other medications like cimetidine, verapamil, alprazolam, and mirtazapine.[1–4] Risperidone-associated hyperprolactinemia is increasingly being reported in recent years.

Recognition of this condition is important, due to its potentially serious short- and long-term effects—hypogonadism with sexual dysfunction, reduced fertility, and possibly high rates of breast cancer.[5] Treatment usually consists of reducing or discontinuing the offending agent and replacing it with another drug with a lesser potential for this side effect.

Published reports of drug-induced hyperprolactinemia with clinical manifestations in adolescents are limited. In this article, we report a case series of 3 adolescents treated with risperidone in a New Zealand outpatient mental health clinic who developed hyperprolactinemia. We then discuss how this agent can be safely discontinued and the patients can be switched to another atypical antipsychotic with good clinical efficacy and resolution of both laboratory and clinical evidence of hyperprolactinemia.

The unit of prolactin measurement used in New Zealand laboratories is mIU/L (milli-International Units per liter) and the reference normal range is 45–362 mIU/L. The U.S. measurement of 1 ng/mL (nanogram per milliliter) is equivalent to 36 mIU/L.

## CASE SERIES

### Case 1

Patient A is a 17-year-old Maori boy with a DSM-IV diagnosis of schizophreniform disorder who was initially treated with risperidone following his first psychotic episode. The patient's first contact with the mental health services was after an arrest, when he exhibited bizarre behavior and was extremely agitated. During his initial assessment, he appeared highly disorganized, reporting auditory hallucinations; he also displayed hypersexual and inappropriate behaviors and was grandiose at times. Further information from his family revealed insidious changes in his behavior over the previous 4 to 5 months, including suspiciousness that gradually progressed to

clear persecutory delusions and responding to internal stimuli. The patient had a strong family history of mental illness—schizophrenia and bipolar disorder. The results of an initial neurologic work-up, including brain imaging, were normal.

The patient was hospitalized and started on a regimen of risperidone, which was gradually titrated to 4 mg daily. Due to improvement in his symptoms, he was discharged after a short inpatient stay. Unfortunately, he stopped taking the antipsychotic and quickly deteriorated, requiring rehospitalization. The patient was restarted on risperidone. During the course of the hospital stay, the patient complained of breast enlargement. A prolactin level at that time was 2100 mIU/L (reference range, 45–362 mIU/L). Risperidone was gradually tapered off over a period of 2 weeks, and the patient was started on olanzapine treatment. He continued to display psychotic symptoms of moderate intensity. After 6 weeks on olanzapine treatment, the patient's psychotic symptoms and gynecomastia resolved. Prolactin levels returned to normal (63 mIU/L).

### Case 2

Patient B is a 15-year-old girl who first presented to the mental health services with severe depression and suicidal thoughts (diagnosed with DSM-IV MDD, single episode with psychotic features), requiring a prolonged inpatient hospitalization. She had a negative family history of mental illness.

The patient was treated with citalopram in combination with risperidone, increased up to 6 mg daily because of persistent psychotic symptoms in the form of mood-congruent auditory hallucinations of a command nature. After 6 weeks of treatment, she complained of amenorrhea and galactorrhea. The prolactin level was 1670 mIU/L. Risperidone was gradually reduced over 10 days and eventually discontinued. The patient was started on quetiapine treatment, and she improved gradually. The voices became less frequent and less intrusive and finally resolved completely. A repeat prolactin level after 2 months showed a value of 90 mIU/L (within normal limits). After 3 months, the patient's menstrual cycles regularized and the galactorrhea resolved.

### Case 3

Patient C is an 18-year-old boy with DSM-IV chronic undifferentiated schizophrenia, who presented with increased thought disorganization, auditory hallucinations, persecutory delusions, and social withdrawal. The patient stopped attending school and eventually spent the whole day in the house, refusing to even accompany his mother to the supermarket and avoiding any interactions with family members. His family history was positive—his father had been diagnosed with a psychotic disorder. An initial neurologic work-up was negative.

The patient did not respond to quetiapine or olanzapine, both of which were discontinued after a short period of time. He agreed to try risperidone, which was gradually titrated up to 5 mg daily, with minimal effect on his symptoms. After 5 weeks of treatment, he complained of breast enlargement and was also noted to have galactorrhea. A prolactin level was significantly elevated (1990 mIU/L). Risperidone was gradually tapered over a period of 2 weeks and discontinued, and the patient was hospitalized due to severe, unremitting symptoms. The patient was treated with clozapine with excellent results—dramatic reduction and eventual resolution of symptoms. The gynecomastia cleared up as well. The prolactin level dropped to 191 mIU/L (within normal range).

## DISCUSSION

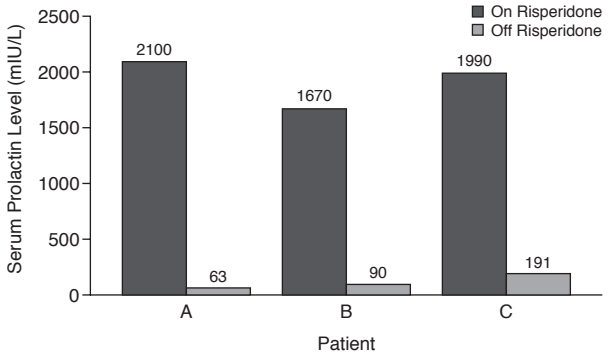
The increase in prolactin secretion results from blockade of the inhibitory actions of dopamine on the lactotrophic cells in the anterior pituitary.[5,6] As the pituitary is outside the blood-brain barrier and risperidone crosses the barrier with relative difficulty, risperidone may have a greater propensity to elevate prolactin levels in comparison to first generation antipsychotics[6] (usually by occupying receptors in the pituitary in higher concentrations than in other areas of the brain).

Hyperprolactinemia occurs frequently with first generation antipsychotics and some second generation antipsychotics (risperidone and amisulpride)—also called prolactin-raising agents—and is rare with other (prolactin-sparing) second generation antipsychotics. When used in combination, the prolactin-raising agents exerted effects that overwhelmed the effects of prolactin-sparing medications.[6] Prevalence rates of hyperprolactinemia associated with antipsychotics vary between 27% to 83% for typical agents, 88% to 100% for risperidone, and 18% to 25% for clozapine, with the condition developing more often in women than in men.[5,7–9] Age appears to have an influence in women, given that women of reproductive age are more susceptible to hyperprolactinemia than postmenopausal females.[7–9] Higher antipsychotic dosages, and not duration of treatment, were found to be directly correlated with prolactin levels.[8]

Clinical manifestations of prolactin elevation include breast enlargement, tenderness, and galactorrhea. Prolactin regulates gonadal function as well; therefore, hyperprolactinemia leads to decreased production of gonadal hormones, manifested by oligomenorrhea or amenorrhea in females with erratic or absent ovulation, and decreased libido with impaired sexual performance in both sexes.[10] Even minimal hyperprolactinemia can impair libido and potency, and hyperprolactinemia associated with antipsychotics may sometimes be of considerable magnitude particularly in some patients taking risperidone. Long-term hyperprolactinemia may lead to an increased risk

**Figure 1. Serum Prolactin Levels[a] On and Off Risperidone Treatment in 3 Adolescent Patients**




[a]Normal range, 45–362 mIU/L (1 ng/mL is equivalent to 36 mIU/L).

of breast cancer in postmenopausal women, although evidence is conflicting.[5] Chronic hypogonadal states may also lead to osteopenia and osteoporosis.[6,10–13] While bone disorders were not initially believed to happen with antipsychotic-induced hyperprolactinemia, recent case reports describe reduced mineral bone density in patients treated with antipsychotics.[12] Other studies fail to demonstrate an association between sustained hyperprolactinemia and bone mineral loss over a 12-month period, but do acknowledge higher rates of bone formation and resorption.[13]

While most studies focus on hyperprolactinemia in adults, it is clear that children and adolescents are very susceptible, with postpubertal females the most at risk for prolactin elevation and its associated adverse effects.[14]

The first step in management of hyperprolactinemia is identifying patients with clinical manifestations of prolactin elevation through detailed inquiries into sexual dysfunction, menstrual disturbances, galactorrhea, and gynecomastia, both before starting treatment and regularly thereafter.[9,15] Since these side effects are important reasons for nonadherence in younger patients, these should be explored further in all nonadherent patients. Management is tailored to each individual patient. Most common options include reducing the dose or switching to a prolactin-sparing agent. If the antipsychotic has to be maintained, a dopamine receptor agonist can be added. Bromocriptine (dose: 5–15 mg/day) and amantadine (dose: 100 mg twice daily) are widely used. Studies on cabergoline,[16] a dopamine $D_2$ agonist, suggest it to be safe and effective in risperidone-induced hyperprolactinemia, leading to remission of clinical signs and normalization of prolactin levels. Cabergoline has also been found to be effective in children with this condition, leading even to improvement in bone density and pubertal stage after 12 months.[16–18] Newer dopamine agonists like pramipexole and ropinirole hydrochloride may be of potential benefit, however, there is no published literature to support their use at the time of this writing. Hormone replacement (estrogen/progesterone in hypoestrogenic females and testosterone in males) has also been suggested for management of hyperprolactinemia, although it has not been well investigated and appears controversial.[5,19]

All 3 patients described in our case series exhibited characteristic clinical features of hyperprolactinemia, including gynecomastia in the 2 male patients and amenorrhea and galactorrhea in the female patient. In addition, all patients had laboratory evidence of high levels of serum prolactin—5 to 6 times the upper level of normal range for prolactin (Figure 1). Risperidone appears to be the causative factor in all the above cases since the prolactin levels returned to normal after the discontinuation of risperidone. Pre- and postmarketing studies of risperidone did show evidence of hyperprolactinemia—primarily, the higher serum levels, but to a lesser degree than reported in our case series.[20–22] In adolescents, the degree of prolactin level increase appears to be much higher than in adults[20,21,23] and the elderly.[22] A meta-analysis of 2 multinational studies of schizophrenia in an adult population treated with risperidone found no correlation between treatment-induced hyperprolactinemia and the emergence of prolactin-related side effects.[24] A recent prospective comparative study of the change of prolactin levels associated with the use of risperidone, olanzapine, and quetiapine in children and adolescents indicates that the end point prolactin levels were significantly higher with risperidone compared to olanzapine ($p = .027$) or quetiapine ($p = .008$). The duration of the prolactin elevation and its long-term effects in children and adolescents are unknown.[25]

We did not assess pretreatment levels of prolactin, which would have assisted in further confirmation of the etiology of hyperprolactinemia.

## CONCLUSION

Hyperprolactinemia can be a troublesome side effect that has potentially serious complications. It is being increasingly reported in younger patients treated with risperidone. Recognition and treatment of this condition including switching to a prolactin-sparing agent are very important to prevent this complication.

*Drug names:* alprazolam (Xanax, Niravam, and others), amantadine (Symmetrel and others), bromocriptine (Parlodel and others), cabergoline (Dostinex and other), cimetidine (Tagamet and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), pramipexole (Mirapex), quetiapine (Seroquel), risperidone (Risperdal), ropinirole (Requip), verapamil (Verelan, Isoptin, and others).

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