



Received: 19 December 2016  
Accepted: 05 May 2017  
First Published: 15 May 2017

\*Corresponding author: Bradley Brown, Department of Child and Adolescent Psychiatry, University of Toledo Medical Center, 3000 Arlington Avenue, Toledo, OH 43614, USA  
E-mail: [Bradley.brown2@utoledo.edu](mailto:Bradley.brown2@utoledo.edu)

Reviewing editor:  
Udo Schumacher, University Medical Center Hamburg-Eppendorf, Germany

Additional information is available at the end of the article

## PSYCHIATRY | CASE REPORT

# Risperidone induced amenorrhea and galactorrhea in a case of an adolescent patient

Bradley Brown<sup>1\*</sup>, Navneet Patti<sup>1</sup>, Ryan Rosenberger<sup>2</sup> and Theodor Rais<sup>1</sup>

**Abstract:** Galactorrhea and amenorrhea are known risks of risperidone, given risperidone's blockade of dopamine D2 receptors and subsequent risk of prolactin elevation, and this paper presents the case of an adolescent female patient who developed reversible amenorrhea and galactorrhea after being treated with risperidone 0.25 mg twice a day for three months. Her prolactin levels and pituitary MRI were normal and the patient's menstrual cycles returned to normal after risperidone was discontinued. This case is the sole example found in our literature search regarding an adolescent patient, which raises the unusual and unpredictable responses to psychotropic medications in this population, as most clinical trials are performed with adult patients. This patient was also previously treated with sertraline, which raises the question of a possible drug interaction. Sertraline is known to increase risperidone levels by inhibiting hepatic metabolism, but this does not explain the unusual side effect experiences by this patient: amenorrhea and galactorrhea in the setting of normal prolactin levels.

**Subjects:** Affective Disorders; Child & Adolescent Psychiatry; Psychopharmacology

**Keywords:** prolactin; risperidone; dopamine; amenorrhea; galactorrhea

### 1. Case summary

This patient is a 16-year-old white female in the tenth grade who presents with increasingly severe mood swings and extreme irritability that have dramatically worsened in intensity over the past several weeks. During the past six months, the mood swings have involved increased verbal

### ABOUT THE AUTHORS

Bradley Brown is a PGY-2 psychiatry resident at the University of Toledo College of Medicine.

Navneet Patti is a PGY-1 psychiatry resident at the University of Toledo College of Medicine.

Ryan Rosenberger is a PGY-3 psychiatry resident at the University of Chicago.

Theodor Rais is an attending psychiatrist in Child and Adolescent Psychiatry at the University of Toledo's Koberger Center.

### PUBLIC INTEREST STATEMENT

Risperidone is an atypical antipsychotic medication, originally prescribed for schizophrenia, bipolar disorder, and other severe mental illnesses, but also now commonly prescribed for a wide variety of mood disorders in a diverse patient population, including adolescents and sometimes children. Although many of its side effects are well known, there are still unknowns about its long-term effects and possible drug interactions. One major known side effect of risperidone is that it can increase the levels of a hormone called prolactin, which in males can lead to breast development, or in females to disruption of the menstrual cycle and nipple discharge. In this paper a case of the latter is reported, though with the unusual feature of prolactin levels remaining normal. This strange feature emphasizes the unpredictable nature of the individual's response to psychiatric medications like risperidone, and how much science has yet to learn.

aggression, with decreased energy, anhedonia, and feelings of hopelessness. The patient's past psychiatric history includes a diagnosis of ADHD, inattentive type, and Pervasive Developmental Disorder, not otherwise specified, first diagnosed in the first grade. Past treatment of these conditions included quetiapine, which had no effect, and aripiprazole, which increased the patient's aggression. In addition, pharmacotherapy of ADHD included methylphenidate and amphetamine-dextroamphetamine, which also increased aggressive behaviors in the patient and were subsequently abandoned.

The patient's past medical history is unremarkable. She has no allergies and no history of seizures. Exploration into this patient's social history and development revealed that she did not speak until the age of eighteen months and did not use full sentences until three-and-a-half years. The patient also received occupational therapy for fine motor skill development. However, investigation into the family psychiatric history uncovered no pertinent information.

Mental Status Exam (MSE) described an extremely irritable, non-cooperative patient that was tearful and extremely anxious. She denied any visual or auditory hallucinations or delusions. She did not display any tics or stereotyped movements. Her reality testing was preserved and her cognition was intact. However, she did endorse suicidal ideation without a concrete plan.

Final assessment of the patient was an Axis I diagnosis of Mood Disorder, Not Otherwise Specified, and Pervasive Developmental Disorder Not Otherwise Specified. Axis II was deferred. Axis III: No diagnosis. Axis IV: Past history of education difficulties with an Axis V Global Assessment of Functioning score of 60. As a result of this assessment, the patient was started on sertraline 25 mg three times a day.

## 2. Clinical course

After one month of sertraline treatment, the patient returned for evaluation. The patient displayed increased energy, but no anhedonia and no feelings of hopelessness. However, the patient's irritability and aggressiveness towards others had increased. The patient was also extremely suspicious of her environment and felt that the teachers at school were plotting to fail her. Thus, risperidone 0.25 mg twice a day was added to the patient's treatment plan to help reduce her irritability, aggressive behavior and her suspicious attitude in school.

Three months after the addition of risperidone to the patient's treatment regimen, she developed amenorrhea and galactorrhea. Risperidone therapy was immediately discontinued and prolactin levels were ordered, which were later reported to be within normal limits. In addition, an MRI without contrast was ordered to rule out pituitary adenoma with referral to her primary care physician for a neurologic and endocrine assessment. The MRI results showed no evidence of adenoma, and both neurologic and endocrine assessments revealed no further abnormalities.

Due to the patient's irritability and aggression, treatment with a mood stabilizer such as lamotrigine was discussed with the patient's family. However, the family refused. Three weeks after discontinuing risperidone treatment the patient's galactorrhea resolved and within two months the patient's menstrual cycle returned to normal.

## 3. Discussion

Since the late 1970s it has been known that neuroleptics can raise prolactin levels due to their dopamine antagonist action (Sachar, Gruen, Altman, & Frantz, 1976). Although this patient did not have elevated levels of prolactin, her case must be placed in the context of the available literature of risperidone's effect on the tuberoinfundibular pathway and associated side effects. Patients who are taking risperidone have higher prolactin serum levels than patients on haloperidol and it is hypothesized that this may be due to the higher affinity of risperidone's 9-OH metabolite for the D2 post synaptic receptors (Kleinberg, Davis, De Coster, Van Baelen, & Brecher, 1999). Women have higher

levels of prolactin but the side effects attributable to this have been found to be the same in groups receiving risperidone compared to haloperidol (Kleinberg et al., 1999).

Hyperprolactinemia-related side effects of risperidone do not appear to be dose related: amenorrhea or galactorrhea appears in approximately ten percent of the female patients receiving risperidone or haloperidol (Kleinberg et al., 1999). If risperidone levels do not correlate to risk of side effects, then it is unlikely that the use of sertraline, which can increase risperidone levels, was a major factor in this case (Spina et al., 2004). Prolactin sparing antipsychotic medications are reported to be the following: clozapine, olanzapine, quetiapine, and aripiprazole (Mallikaarjun, Salazar, & Bramer, 2004). With the possible exception of aripiprazole, which is known to have dopamine agonist properties, it remains unclear what distinguishes these medication's dopamine antagonism from risperidone's such that they avoid prolactin-related side effects (Mallikaarjun et al., 2004). This further highlights how much remains to be discovered about the diverse effects of these medications in humans.

A pilot study with sixteen female patients with amenorrhea found that after treatment with risperidone for more than three months fourteen of the patients had elevated blood levels of prolactin (Lee, Han, Kim, & Kim, 2005). Nine of the patients had their risperidone dosage reduced and the remaining seven patients were switched to a different antipsychotic medication such as olanzapine and quetiapine (Lee et al., 2005). The study concluded that stopping risperidone or switching to a prolactin sparing antipsychotic were both effective treatment strategies for risperidone induced amenorrhea. In this study the risperidone dosages were between 0.5 and 8 mg with most of the patients taking more than 2 mg (Lee et al., 2005). This was an adult group of patients with ages ranging from 28 to 43 years old, and all of the patients except one had higher than normal prolactin levels (Lee et al., 2005). The authors question why amenorrhea develops with dosages of risperidone lower than 2 mg. They quote PET studies showing that, in schizophrenic patients, dosages of risperidone between 3 and 4 mg daily cause up to a ninety percent blockade of D2 receptors (Nyberg, Eriksson, Oxenstierna, Halldin, & Farde, 1999).

The effect of risperidone on the 5-HT<sub>2</sub> receptors does not interfere with the dopamine pathways involved in the regulation of prolactin release *in vivo* (Nyberg et al., 1999). In the study by Bun-Hee Lee's group there were two patients who had amenorrhea with normal prolactin blood levels, and the authors address the issue of individual differences in prolactin blood levels in patients who receive similar doses of risperidone (Lee et al., 2005). Patients who have a polymorphism in the A1 allele of D2 receptor are reported to have higher prolactin levels at similar risperidone dosages (Mihara et al., 2001; Young et al., 2004). Prolactin has to pass through the blood brain barrier after it is released by the pituitary gland, which is another area of possible individual variability among patients. A 1999 case series of patients taking risperidone in moderate and low doses and developing amenorrhea showed that risperidone dosages ranging from 1 to 8 mg daily resulted in elevated prolactin levels (Kim, Kim, & Lee, 1999). This study also used an adult patient population.

The case presented in this paper is significant because it occurred in an adolescent 16-year-old and the dose of risperidone was remarkably low compared with other reports: only 0.25 mg twice a day. Also, in this case brain MRI and prolactin levels were normal. This patient was on risperidone for a short period: only three months before the amenorrhea and galactorrhea occurred. Although one cannot generalize to the entire adolescent female population from this case, the unusual and physiologically unexplained nature of this patient's amenorrhea and galactorrhea emphasizes how much more there is to understand about the atypical antipsychotics, especially in the adolescent population. This report is meant to draw attention to a unique clinical response to risperidone and place it in the context of the available literature on risperidone and its effects on the tuberoinfundibular pathway.

#### Funding

The authors received no direct funding for this research.

#### Competing Interests

The authors declare no competing interest.

#### Author details

Bradley Brown<sup>1</sup>

E-mail: [Bradley.brown2@utoledo.edu](mailto:Bradley.brown2@utoledo.edu)

Navneet Patti<sup>1</sup>

E-mail: [Navneet.Patti@utoledo.edu](mailto:Navneet.Patti@utoledo.edu)

Ryan Rosenberger<sup>2</sup>

E-mail: [Ryan.Rosenberger@uchospitals.edu](mailto:Ryan.Rosenberger@uchospitals.edu)

Theodor Rais<sup>1</sup>

E-mail: [Theodor.Rais@utoledo.edu](mailto:Theodor.Rais@utoledo.edu)

<sup>1</sup> Department of Child and Adolescent Psychiatry, University of Toledo Medical Center, 3000 Arlington Avenue, Toledo, OH 43614, USA.

<sup>2</sup> Department of Psychiatry and Behavioral Neuroscience, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, USA.

<sup>†</sup> Address: The Kobacker Center, 1400 E. Medical Loop, Toledo, OH 43614, USA.

#### Citation information

Cite this article as: Risperidone induced amenorrhea and galactorrhea in a case of an adolescent patient, Bradley Brown, Navneet Patti, Ryan Rosenberger & Theodor Rais, *Cogent Medicine* (2017), 4: 1328819.

#### References

- Kim, Y.-K., Kim, L., & Lee, M. S. (1999). Risperidone and associated amenorrhea: A report of 5 cases. *The Journal of Clinical Psychiatry*, 60, 315–317. <https://doi.org/10.4088/JCP.v60n0509>
- Kleinberg, D. L., Davis, J. M., De Coster, R., Van Baelen, B., & Brecher, M. (1999). Prolactin levels and adverse events in

- patients treated with risperidone. *Journal of Clinical Psychopharmacology*, 19, 57–61.
- Lee, B.-H., Han, C.-S., Kim, K. H., & Kim, Y. K. (2005). Treatment in risperidone-induced amenorrhoea. *International Journal of Psychiatry in Clinical Practice*, 9, 29–34. <https://doi.org/10.1080/13651500510014747>
- Mallikaarjun, S., Salazar, D. E., & Bramer, S. L. (2004). Pharmacokinetics, tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers. *The Journal of Clinical Pharmacology*, 44, 179–187. <https://doi.org/10.1177/0091270003261901>
- Mihara, K., Suzuki, A., Kondo, T., Yasui-Furukori, N., Ono, S., Otani, K., ... Inoue, Y. (2001). Relationship between Taq1 A dopamine D2 receptor (DRD2) polymorphism and prolactin response to bromperidol. *American Journal of Medical Genetics*, 105, 271–274. [https://doi.org/10.1002/\(ISSN\)1096-8628](https://doi.org/10.1002/(ISSN)1096-8628)
- Nyberg, S., Eriksson, B., Oxenstierna, G., Halldin, C., & Farde, L. (1999). Suggested minimal effective dose of risperidone based on PET-measured D2 and 5-HT2A receptor occupancy in schizophrenic patients. *American Journal of Psychiatry*, 156, 869–875.
- Sachar, E. J., Gruen, P. H., Altman, N., Halpern, F. S., & Frantz, A. G. (1976). Use of neuroendocrine techniques in psychopharmacological research. In E. J. Sachar (Ed.), *Hormones, behavior, and psychopathology* (pp. 161–161). New York, NY: Raven Press.
- Spina, E., D'Arrigo, C., Migliardi, G., Morgante, L., Zoccali, R., Ancione, M., & Madia, A. (2004). Plasma risperidone concentrations during combined treatment with sertraline. *Therapeutic Drug Monitoring*, 26, 386–390. <https://doi.org/10.1097/00007691-200408000-00008>
- Young, R. M., Lawford, B. R., Barnes, M. Burton, S. C. Ritchie, T. Ward, W. K., & Noble, E. P. (2004). Prolactin levels in antipsychotic treatment of patients with schizophrenia carrying the DRD2\*A1 allele. *The British Journal of Psychiatry*, 185, 147–151. <https://doi.org/10.1192/bjp.185.2.147>



© 2017 The Author(s). This open access article is distributed under a Creative Commons Attribution (CC-BY) 4.0 license.

You are free to:

Share — copy and redistribute the material in any medium or format

Adapt — remix, transform, and build upon the material for any purpose, even commercially.

The licensor cannot revoke these freedoms as long as you follow the license terms.

Under the following terms:

Attribution — You must give appropriate credit, provide a link to the license, and indicate if changes were made.

You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use.

No additional restrictions

You may not apply legal terms or technological measures that legally restrict others from doing anything the license permits.

