

# Comparison of prolactin level in schizophrenia patients treated with risperidone oral or long-acting injections – preliminary report

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## ABSTRACT

**Introduction:** Hyperprolactinemia is a significant side effect of antipsychotic therapy. Risperidone, commonly used antipsychotics, is available in oral tablets and long-acting injections (LAI). This study aimed to investigate a potential difference in terms of prolactin levels among patients treated with these formulations of risperidone.

**Method:** This was a naturalistic, retrospective, cross-sectional study. 91 patients with schizophrenia treated with risperidone in monotherapy were included into the study. 72 patients were treated with the oral form and 19 patients were treated with LAI form. All subjects had one measurement for prolactin level.

**Results:** Our results showed that a mean dose of prolactin was significantly higher in the RIS- oral group and the difference was significant ( $p=0.019$ ). There was no difference ( $p=0.59$ ) in the percentage of patients with hyperprolactinemia in both study groups but more patients in the RIS-oral group had severe hyperprolactinemia and fewer patients in the RIS-oral group had mild hyperprolactinemia. Hyperprolactinemia was the main reason for discontinuation of treatment in the RIS-LAI group.

**Conclusions:** According to the data from our study two forms of risperidone may differ in terms of impact on prolactin levels. Patients treated with LAI risperidone may have prolactin levels lower than on the oral form.

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**Keywords:** schizophrenia; risperidone; prolactin; long-acting injections

## Introduction

Schizophrenia is a chronic and recurrent psychiatric disorder that requires a long-term treatment with antipsychotics. It is a complex disorder associated with high rates of noncompliance and treatment discontinuation<sup>1</sup>. There are many factors influencing compliance in schizophrenia, such as medication side effects, insight, access to treatment or, social support<sup>2</sup>. The introduction of long-acting injections (LAI) antipsychotics has shown the improvement of compliance, reduction of relapses and hospitalization rates<sup>3,4</sup>. Randomized studies suggest that some LAIs may be also associated with fewer side effects compared with their oral forms<sup>5,6</sup>.

Risperidone is an older (introduced in 1993) second-generation antipsychotics, but due to its good efficacy and safety profile, it remains one of the most frequently prescribed antipsychotics for schizophrenia. Long-acting risperidone was the first long-acting injectable atypical antipsychotic. Experimental studies suggest that treatment with risperidone LAI is more effective than the oral form in improvement in clinical symptoms and functioning, reduction in a number of rehospitalization, and better adherence. The risperidone LAI, like other LAI, ensures a better bioavailability, because the correlation between drug dose and plasma concentrations is more predictable during the

treatment. It provides a better pharmacokinetic profile, which allows to use of lower doses and to reduce the risk of side effects<sup>7-10</sup>. The common side-effects of risperidone LAI, except for an injection site pain, are consistent with those associated with oral risperidone: hyperprolactinemia, extrapyramidal symptoms and sedation. Furthermore, experimental studies have confirmed that risperidone treatment may induced weight gain and disturbed glucose homeostasis, what can result in metabolic syndrome also in children and adolescent population<sup>11,12</sup>. Interestingly, some studies suggest, that the frequency of some side effects may be lower for long-acting risperidone than oral risperidone<sup>10,13</sup>.

Hyperprolactinemia (hPRL) is the elevation of blood prolactin level. It is a significant side effect, which may result in non-compliance and treatment discontinuation. It is due to secondary sexual dysfunctions, which are often unacceptable by the patients. In patients treated with antipsychotics hyperprolactinemia usually results from the blockage of dopamine type 2 receptors (D2) in the anterior pituitary lactotrophic cells. Prolactin (PRL) elevation during antipsychotic treatment is mostly correlated with the affinity of an antipsychotic for dopamine D2 receptors and their blood-brain barrier penetrating ability. Of all second- generation antipsychotics, risperidone has one of the highest potential for PRL elevation<sup>13</sup>. This may potentially limit its use in many patients, especially in women.

Interestingly, recent meta-analyses revealed that breast cancer is probably more common in female patients with schizophrenia than in the general population and there may be a link between antipsychotic-induced hyperprolactinemia and breast cancer risk in women with schizophrenia<sup>14-16</sup>. It is worth noting that several studies on hyperprolactinemia have been conducted in children and adolescents populations with autism spectrum disorder treated with risperidone<sup>17,18</sup>. The results confirmed that risperidone treatment could cause hyperprolactinemia also in this population. The authors have suggested that the effects of risperidone on prolactin were probably dose-related in pediatric patients.

This study was aimed at comparing the prolactin level in schizophrenia patients treated with oral risperidone or long-acting injections risperidone. Although similar studies have already been published, this study provides still valuable clinical data as it indicates the consistent conclusion.

## Material and methods

### Data sources

This was a naturalistic, retrospective, cross-sectional study. Data from years 2011-2018 was collected. Our psychiatry clinical hospital electronic database was screened for adult Caucasian patients with schizophrenia, treated with risperidone oral (the RIS-oral group) or long-acting injections (the RIS-LAI group), who had at least one measurement for PRL level. All study subjects were on antipsychotic monotherapy with risperidone.

### Study subjects

All study subjects were diagnosed as paranoid schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). 91 patients with schizophrenia treated with risperidone in monotherapy were included into the study. 72 patients were treated with the oral form and 19 patients were treated with LAI form. All study subjects were taking risperidone as the only antipsychotic drug. Pregnant women, patients with acromegaly and other conditions known to elevate PRL level, and patients taking medications other than risperidone that may affect PRL level (e.g. anticonvulsants, antihistamines, antihypertensives, oestrogens, opiates) were excluded from the study.

### Prolactin level determination

Blood samples for PRL test were drawn for all patients between 8 and 9 a.m. after 12 hours overnight fast. Immediately after collecting blood samples, concentration of PRL (expressed in ng/mL) was determined using the Architect i1000SR Immunoassay Analyzer (Abbott, USA). Normal level of prolactin was defined as 25 ng/mL (19).

### Statistical analysis

Statistical procedures were performed with STATA 15.1 (StataCorp, USA). Simple descriptive statistics (mean  $\pm$  standard deviation) were generated for continuous variables. For discrete variables number of patients and percentages are given. Normality of distribution was tested with Shapiro-Wilk test. Level of prolactin was highly skewed, but after square root transformation it followed normal distribution. For statistical analysis one-way ANOVA and t-test were used. The difference between proportions was analysed with the Fisher's exact test. Associations were tested by Pearson's correlation coefficient. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using logistic regression. The level of significance was set at  $p < 0.05$  (two-sided).

## Ethical standards

The study has been approved by the appropriate ethics. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

## Results

There were 72 patients in the RIS-oral and 19 in the RIS-LAI groups. Summary of the demographic and clinical data is shown in Table 1. There was no difference between age of men and women,  $p = 0.78$ . Daily dose of risperidone LAI was calculated as LAI dose divided by 14 (number of days between consecutive injections). Low dose was defined as 1-2 mg/d for risperidone oral and 25 mg/14 days for risperidone LAI; medium dose: 3-4 mg/d for risperidone oral and 37.5 mg/14 days for risperidone LAI; high dose: 5-6 mg/d for risperidone oral and 50 mg/14 days for risperidone LAI. Detailed risperidone treatment data is also shown in Table 1.

Mean level of prolactin was significantly higher in the RIS-oral group ( $99.63 \pm 69.09$  ng/mL vs.  $62.19 \pm 38.81$  ng/mL) and the difference was significant ( $p = 0.014$ ) with corresponding Cohen's  $d$  effect size of 0.58. When this comparison was adjusted for age and a dose of risperidone, the difference remained significant ( $100.42 \pm 7.49$  vs.  $59.17 \pm 14.70$  ng/mL,  $p = 0.014$ ), see Figure 1. However, as there were more women in the study groups (although there were no differences in the percentage of men and women between the RIS-oral and RIS-LAI groups,  $p = 0.28$ ) we have reanalysed the difference adjusting for age, dose of risperidone and sex. This way adjusted mean level of prolactin was still higher in the RIS-oral group ( $98.21 \pm 6.93$  vs.  $67.56 \pm 13.71$  ng/mL), but the difference was of borderline non-significance ( $p = 0.051$ ). There was no difference ( $p = 0.59$ ) in the percentage of patients with hPRL in both study groups (RIS-oral: 68, 94.4% vs. RIS-LAI: 16, 88.9%). However, significantly more patients in the RIS-oral group had severe hPRL (RIS-oral: 32, 47.1% vs. RIS-LAI: 2, 12.5%) and less patients in the RIS-oral group had mild hPRL (RIS-oral: 13, 19.1% vs. RIS-LAI: 6, 37.5%),  $p = 0.027$ , see Figure 2.

No patients in the RIS-LAI and 5 (6.9%) patients in the RIS-oral group were taking bromocriptine due to hPRL ( $p = 0.58$ ). After excluding the patients taking bromocriptine from the analysis, the difference between RIS-oral and RIS-LAI was still significant ( $p = 0.019$ ). No other dopamine-agonists were used by the study patients. Risperidone was discontinued in 6 (33.3%) and 41 (56.9%) of the patients in the RIS-LAI and RIS-oral groups, respectively ( $p =$

Table 1. Summary of the demographic and clinical data.

	risperidone oral (n = 72)	risperidone LAI (n = 19)	p
age [y]	36.7 $\pm$ 10.9	37.8 $\pm$ 8.8	0.69
women	51 (70.8%)	10 (55.6%)	0.26
risperidone mean daily dose [mg]	3.78 $\pm$ 1.50	3.12 $\pm$ 0.55	0.07
risperidone dose: low moderate high	17 (23.6%) 21 (29.2%) 34 (47.2%)	1 (5.6%) 7 (38.9%) 10 (55.6%)	0.08
prolactin [ng/mL]*	99.63 $\pm$ 69.09	62.19 $\pm$ 38.81	0.014
treatment with bromocriptine	0	5 (6.9%)	0.58

Data presented as mean $\pm$ standard deviation or absolute number (percentage).

\* unadjusted

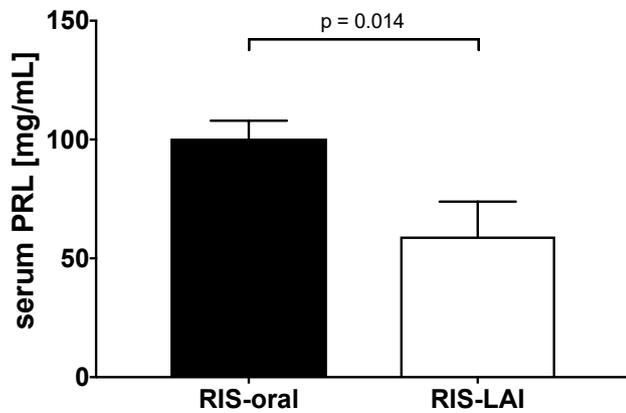


Figure 1. Adjusted (for age and risperidone dose) level of prolactin in the study groups.

PRL: prolactin; RIS-oral: patients taking oral risperidone; RIS-LAI: patients taking long-acting injections of risperidone.

Vertical bars indicate standard deviations.

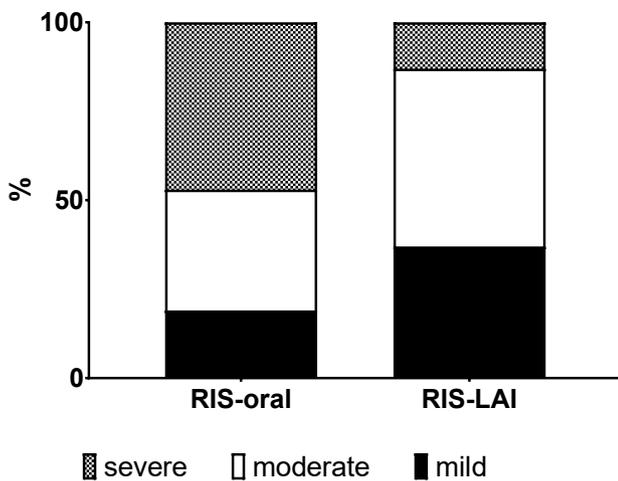


Figure 2. Severity of hyperprolactinemia in the study groups

RIS-oral: patients taking oral risperidone; RIS-LAI: patients taking long-acting injections of risperidone.

0.11). In the RIS-LAI group the major reason for discontinuation was the lack of clinical effectiveness (3, 50.0%), while in the RIS-oral group hPRL was the major reason (25, 61.0%).

In the RIS-LAI group we were able to identify 2 subjects with other potential causes for altered PRL level (past treatment with zuclopenthixol or haloperidol) and 7 subjects in the RIS-oral group (past treatment with amisulpride, haloperidol and post-stroke pituitary insufficiency). When we have excluded these patients from analysis, the difference between both study groups in terms of PRL level remained significant (RIS-oral:  $92.03 \pm 54.77$ , RIS-LAI:  $64.06 \pm 41.25$  ng/mL,  $p = 0.047$ ).

Interestingly, in our study women had lower risk for hPRL (OR 0.2, 95% CI 0.07- 0.59,  $p = 0.003$ ). Compared with the RIS-oral group, in the RIS-LAI group OR for hPRL was 0.5 (95% CI 0.08-2.96), the result was not statistically significant ( $p = 0.44$ ). However, the RIS-LAI group had significantly lower risk of severe hPRL (OR 0.25, 95% CI 0.03-0.68,  $p = 0.015$ ) and there were no differences for risk of mild or moderate hPRL. Medium dose of risperidone was associated with the highest risk of moderate hPRL (OR 5.7, 95% CI 1.36-23.46,  $p = 0.017$ ), while in the high dose of risperidone group the risk of severe hPRL was reduced (OR 0.1, 95% CI 0.03-0.45,  $p = 0.002$ ).

## Discussion

In this preliminary study two forms of risperidone (LAI and oral) differed in terms of impact on prolactin levels. Although the frequency of hyperprolactinemia was similar in both groups, the mean dose of prolactin (in blood) was significantly higher in patients taking the oral form of risperidone. Moreover, a higher number of patients in this group had severe hyperprolactinaemia. Significantly, hyperprolactinemia was the major reason for discontinuation of treatment in the RIS-oral group. It is worth noting that the high prolactin levels can trigger clinically significant symptoms like: oligomenorrhea, amenorrhea, galactorrhoea, decreased libido in women and erectile dysfunction, decreased libido, infertility and gynecomastia in men, which can be unacceptable for some patients<sup>20</sup>. An augmentation with a dopamine agonist (such as bromocriptine) may be considered in patients without severe symptomatic hyperprolactinemia and with stable control of psychotic symptoms. It is worth pointing out that in our study no patient in the RIS-LAI group and only 5 (6.9%) patients in the RIS-oral were taking bromocriptine due to hyperprolactinemia. This data would seem to suggest that the prescribing of bromocriptine is still rare in clinical practice, at least among in-hospital subjects.

The differences in prolactin levels between RIS-oral and RIS-LAI group reported in our results are congruent with reported in other studies<sup>21-24</sup>. The difference in prolactin levels for these two forms of administration may be explained by the differences in pharmacokinetics of these two forms of risperidone. Firstly, during treatment with long-acting risperidone peak-trough fluctuations are reduced compared to oral risperidone, what can suggest a correlation between changes in prolactin levels and peak-trough fluctuations of risperidone. Secondly, the long-acting and oral risperidone differ in serum concentrations of risperidone and its major metabolite 9-OH risperidone (paliperidone)<sup>25</sup>. It is possible, that it is the metabolite 9-hydroxyrisperidone which is the main reason for the increased serum prolactin level, what was suggested in some studies<sup>26,27</sup>. The study results showed that the plasma concentration of 9-hydroxy-risperidone, but not of risperidone were significantly correlated with increases prolactin level in plasma<sup>26,27</sup>. Our finding that patients taking a medium dose of risperidone has the highest increase in the risk of hPRL indicates that this sub-population should be particularly carefully monitored for hPRL, even though they may present no hPRL symptoms. In our study women had a lower risk for hPRL. This is interesting because it is found that hyperprolactinemia secondary to antipsychotic medication is greater in females than in males and it is due to the ability of the estrogens to elevate PRL levels<sup>28</sup>. The potential cause of these differences can be a high mean age of women in our study (39.7 years). It is known that postmenopausal women experience pharmacologically induced hyperprolactinemia less frequently than women of reproductive age<sup>29</sup>. Moreover, some studies have also showed that in women using hormonal contraception the increase in prolactin was significantly greater than in those without estrogen supply<sup>30</sup>.

In recent years, some studies have pointed out that polymorphism in dopamine and serotonin receptors could be associated with reduced receptor density what can be essential for drug efficacy and drug-induced side effects like hyperprolactinemia<sup>31,32</sup>. Furthermore, the few studies have also identified specific variants of the DRD2 gene which could be useful in predicting the development of hyperprolactinemia during risperidone treatment both in adults and children populations<sup>33,34</sup>.

As mentioned, this is a preliminary study, hence it has some potential limitations. First of all, the number of the RIS-LAI

subjects is low thus limiting the power of statistical tests. Also, there is a potential risk of selection bias, i.e. patients with confirmed hPRL while on oral risperidone would be unlikely switched to LAI risperidone. However, PRL tests are not done on a routine basis in the hospital unit the study patients were hospitalized in, therefore this would apply mostly to patients with symptomatic hPRL. Secondly, the serum prolactin levels were assessed only once, we did not analyze longitudinal changes of plasma prolactin levels before initiating the treatment with risperidone and in the course of switching from oral risperidone to LAI risperidone. This serious limitation has to be taken into consideration. Thirdly, patients were on antipsychotic monotherapy, but some of them received other psychopharmacological treatments like antidepressants or mood stabilizers, though these should not affect prolactin levels significantly. Finally, there was a discrepancy in number of subjects in both groups (the LAI group was significantly smaller), which reflects that LAI risperidone (as well as other LAI antipsychotics) is still infrequently prescribed to schizophrenia patients.

Despite these limitations, the findings of this study demonstrate the possible relationship between prolactin level and the form of risperidone. Considering its preliminary character the results must be interpreted with caution, but they indicate that patients with schizophrenia that are treated with LAI risperidone may have serum prolactin levels lower compared with patients treated with the oral form. Therefore, taking LAI risperidone may be more advantageous than the oral form in terms of impact on prolactin levels. This observation may be highly useful in clinical practice. Further and more detailed follow-up studies ought to be conducted to confirm our results.

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