European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-025-03835-5

CORRESPONDENCE

Predictive Role of Serotonin Receptor *(5HTR2A)* and Dopamine Receptor *(DRD2)* gene polymorphisms in risperidone-induced weight gain and hyperprolactinemia in patients with schizophrenia

Alladi Charanraj Goud[1,2] · Ravi Philip Rajkumar[3] · Deepak Gopal Shewade[2] · Luxitaa Goenka[4] · Suresh Kumar Srinivasamurthy[5]

Received: 16 December 2024 / Accepted: 27 March 2025

Introduction

Schizophrenia (SCZ) is a chronic psychiatric disorder characterized by a spectrum of symptoms, which can lead to significant social and occupational dysfunction [19]. The management of SCZ typically involves the use of antipsychotic medications, particularly second-generation antipsychotics (SGAs) such as risperidone, which are favoured for their efficacy in alleviating psychotic symptoms along with the relatively lower incidence of extrapyramidal side effects [14]. However, the long-term administration of risperidone is associated with notable adverse effects, including hyperprolactinemia and weight gain. These effects can adversely impact treatment compliance and patient outcomes [17].

Risperidone exerts its therapeutic effects primarily through antagonism of dopamine D2 receptors *(DRD2)* and serotonin 2A receptors *(5HTR2A)* [3, 8]. The blockade of these receptors is crucial in the neurochemical pathways implicated in SCZ and treatment-associated side effects [11]. For instance, hyperprolactinemia, a common consequence of *DRD2* antagonism, can result in sexual dysfunction, menstrual irregularities, and osteoporosis [24]. Concurrently, weight gain associated with risperidone treatment is often linked to the modulation of serotonin receptors, increasing the risk of metabolic disorders such as obesity and cardiovascular diseases [7]. These adverse effects can contribute to non-compliance with treatment regimens, further complicating the long-term management of SCZ.

Recent advancements in pharmacogenetics have highlighted the potential role of genetic variations in neurotransmitter receptors in influencing individual susceptibility to drug-induced side effects [22, 32]. Specifically, polymorphisms in the *5HTR2A* and *DRD2* genes have been implicated in modulating responses to antipsychotic medications [21, 30]. Variations in these genes can alter the pharmacodynamics and receptor sensitivity, contributing to differential impact for adverse outcomes such as hyperprolactinemia and weight gain [13]. Despite the increasing recognition of the influence of genetic factors on antipsychotic drug responses, there remains a limited understanding of the specific genetic polymorphisms that predispose patients to these effects. However, the identification of genetic markers associated with risperidone-induced adverse effects could facilitate more personalized treatment approaches. These advancements would allow clinicians to predict and mitigate potential side effects through tailored medication choices based on an individual's genetic profile.

In the present study, we sought to explore the impact of *5HT2A* and *DRD2* receptor gene polymorphisms on risperidone-induced prolactin elevation and weight gain in patients with SCZ. By conducting this investigation, we aim to deepen our understanding of pharmacogenetic factors influencing antipsychotic adverse effects. More importantly, we strive to use this understanding to develop more effective

✉ Alladi Charanraj Goud
charan.raj002@gmail.com; charanrajgoud.alladi@upol.cz

1 Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Hněvotínská 1333/5, 77900, Olomouc, Czech Republic

2 Department of Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

3 Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India

4 Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India

5 Department of Pharmacology, Ras Al Khaimah Medical and Health Sciences University, P.O. Box 11172, Ras Al Khaimah, United Arab Emirates

Published online: 02 April 2025

and personalized treatment strategies, ultimately improving therapeutic outcomes in the management of SCZ.

Materials and methods

Patients and study setting

In this study, newly diagnosed patients with SCZ ($n = 104$) were recruited according to the Diagnostic and Statistical Manual for Mental Disorders-Fifth edition (DSM-V) criteria from the Department of Psychiatry at a tertiary care hospital in South India. The Institute Ethics Committee approved the study (Project No. JIP/IEC/4/2013/189), and after obtaining written informed consent from each patient or patient's legally acceptable representatives, patients were recruited for the study. All the study participants were recruited between December 2013 to August 2015. The study included patients who had not taken any antipsychotic medication for at least 30 days before enrolment and were prescribed risperidone (4–8 mg/day) as their antipsychotic treatment for a minimum of four weeks. Baseline data were collected before starting the therapy and follow-up details were recorded after receiving the risperidone therapy for at least four weeks. Pregnant or nursing women, individuals under the age of 18 years, and patients with a history of other medical conditions such as hypertension or diabetes were excluded from the study. Additionally, other concurrent psychiatric diagnoses, such as mood disorders or substance abuse, were also excluded.

Prolactin measurement and weight assessment

Five ml of venous blood was collected from all the patients at baseline and after four or more weeks of treatment with risperidone between 9 A.M. and 12 P.M. The serum was separated and stored at −80 °C deep freezer until assay. The measurement of Prolactin was done using the standard Advia-Centaurs Chemiluminescence (Advia-Centaur CP, Siemens healthcare diagnostics, Germany) immunoassay method [16].The intra-assay and inter-assay coefficients of variation were less than 7% and 9%, respectively. Patients exhibiting more than a 20% increase in prolactin levels from baseline to follow-up after four weeks of risperidone therapy were classified as having risperidone-induced hyperprolactinemia [5]. Body weight measurement was done at baseline and after six weeks of treatment with risperidone (4–8 mg/day) with a weight gain of greater than 5% considered significant [2, 10, 26].

Co-medication

During the study, Clonazepam (0.5–1 mg/day as required before bedtime) was prescribed for sleep disturbances, and trihexiphenidyl (2–4 mg/day) was administered to manage extrapyramidal symptoms.

Compliance

During the risperidone treatment period, patients who did not receive risperidone medication for five consecutive days were excluded from the study. Treatment compliance was verified through reports from the patient's family members or caregivers of the patients.

DNA extraction & genotyping

Five ml of blood were collected from each patient to analyze the genetic polymorphisms in dopamine *DRD2* rs1800497 (*Taq1A*) and serotonin *5HTR2A* (rs6311, rs6313) receptor genes. DNA extraction was performed using the standard phenol–chloroform method and quantified by NanoDropTM (ThermoFisher). Genotyping for genetic polymorphisms was performed using real-time thermocycler (ABI Prism 7300) with Taqman® SNP probes for *DRD2* gene, rs1800497 Assay ID: C__7486676_10 and *5HTR2A* rs6311 Assay ID: C__8695278_10, and rs6313 Assay ID: C__3042197_1_ from Applied Biosystems (Foster City, CA, USA).

Statistical analysis

The normality of data for continuous variables was checked using the Kolmogorov-Simonov test. Continuous variables were expressed as the median and Interquartile range (IQR). Wilcoxon test was used to compare the baseline prolactin levels and weight change at baseline and post-treatment, and the Kruskal–Wallis test was used to study the individual genotype influence on median prolactin levels and weight changes. GraphPad Prism version 10 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis. Hardy–Weinberg equilibrium was assessed for genotype frequencies. Logistic regression: analyses were performed to evaluate associations between genotype and risperidone-induced prolactin elevation, weight gain, and extrapyramidal symptoms using SNP stats software. All values were two-sided, and $p < 0.05$ was considered statistically significant.

Table 1 Baseline characteristics of study participants

Characteristics	Subjects (*n*=104)
Age (Years)	30 (25 – 37)
Height (Cm)	164 (154.8 - 169.3)
Baseline Weight (Kg)	55 (47 - 67)
Baseline Prolactin levels (ng/ml)	24.40 (11.58 - 46.51)
Risperidone dose (mg/day)	4 (4–6)

Values expressed as median (Inter Quartile Range)

Results

A total of 104 newly diagnosed patients with SCZ were recruited for this study, and 103 patients completed the follow-up assessments. The median age of participants was 30 years, baseline weight was 55 (kgs), and prolactin levels were 24.40 (ng/ml), respectively Table 1. The sample consisted of an unrelated, diverse population, enabling a thorough analysis of genetic polymorphisms associated with risperidone-induced side effects. During the treatment, one patient lost follow-up, 103 patients were included for prolactin levels assessment, and one patient could not turn up for the follow-up after six weeks for weight assessment. Four patients' genotyping data of *5HTR2A* (rs6311, rs6313) and *DRD2* (rs1800497) genetic polymorphisms were excluded from the analysis due to improper amplification signals.

Our study findings show that 87% of participants experienced hyperprolactinemia after four weeks of risperidone therapy, which underscores the clinical significance of these side effects. Similarly, 52% of weight gain and 45% of drug-induced extrapyramidal symptoms were documented in the study.

Weight gain assessment

The baseline median weight and median weight change from baseline to six weeks of risperidone treatment were reported in Supplementary Table S1. In terms of weight gain, the results indicated that the *5HTR2A* gene polymorphisms *5HTR2A* rs6313 ($n = 98$, GG = 31, GA = 53, AA = 14, $p = 0.007$) and rs6311 ($n = 98$, GG = 33, GA = 51, AA = 14, $p = 0.026$) and were significantly associated with risperidone-induced weight gain whereas *DRD2 rs1800497* ($n = 98$, GG = 43, GA = 46, AA = 9, $p = 0.14$) genetic variants were not associated with risperidone induced weight gain (Table 2). The individual genotype influence on baseline weight and median difference of weight change from baseline to six weeks of risperidone treatment was reported

Table 2 Serotonin (*5HTR2A* rs6311 and rs6313) and Dopamine receptor *(DRD2* rs1800497*)* gene polymorphism influence on risperidone-induced weight gain

Genotype	Patients with <5% increase in weight gain (*n*=47)	Patients with ≥5% increase in weight gain (*n*=51)	Odds ratio (95%CI)	*p*-value
5HTR2A rs6311 (*n*=98)				
G/G (*n*=33)	21(44.7%)	12 (23.5%)	1.00	0.026*
G/A+A/A (*n*=65)	17+9 (55.3%)	34+5 (76.5%)	2.62 (1.10–6.24)	
5HTR2A rs6313 (*n*=98)				
G/G (*n*=31)	21(44.7%)	10 (19.6 %)	1.00	0.007*
G/A+A/A (*n*=67)	17+9 (55.3%)	36+5 (80.4%)	3.31 (1.35–8.14)	
DRD2 rs1800497 (*n*=98)				
G/G (*n*=43)	17 (36.2%)	26 (51%)	1.0	0.14
A/G+A/A (*n*=55)	24+6 (63.8%)	22+3 (49%)	0.54 (0.24–1.22)	

Logistic regression $p < 0.05$ is considered significant

Table 3 Serotonin receptor *(5HTR2A* rs6311 and rs6313*)* gene polymorphisms influence on risperidone-induced prolactin levels

Genotype	≤20% increase in prolactin levels (*n*=12)	>20% increase in prolactin levels (*n*=87)	Odds ratio (95%CI)	*p*-value
5HTR2A rs6311 (n=99)				
G/G (*n*=33)	4 (33.3%)	29 (33.3%)	1.00	1.0
G/A+AA (*n*=66)	6+2 (66.7%)	45+13 (66.7%)	1.0 (0.28–3.6)	
5HTR2A rs6313 (*n*=99)				
G/G (*n*=31)	3 (25%)	28 (32.2%)	1.00	0.61
G/A+A/A (*n*=68)	7+2 (75%)	47+12 (67.8%)	0.70 (0.18–2.80)	

Logistic regression $p < 0.05$ is considered significant

in Supplementary Table S2. The logistic regression analysis with genotype–phenotype confirmed that these associations were statistically significant ($p < 0.05$) (Table 3).

Extrapyramidal symptoms

Furthermore, the study examined the association between *5HTR2A* (rs6313, rs6311) and *DRD2* rs1800497 gene polymorphisms and risperidone-induced extrapyramidal symptoms after 4 weeks of risperidone therapy. *5HTR2A* rs6313 genetic polymorphism ($n = 99$, GG = 33, GA = 51, AA = 14, $p = 0.089$), rs6311 ($n = 99$, GG = 31, GA = 54, AA = 14, $p = 0.2$) and *DRD2* rs1800497 ($n = 99$, GG = 43, GA = 47, AA = 9, $p = 0.82$) genetic variants were not associated risperidone induced extrapyramidal symptoms. The results demonstrated that the *5HTR2A rs6313* polymorphism was associated with an increased risk of developing extrapyramidal symptoms during treatment (Table 4). However, these findings were not statistically significant.

Genetic polymorphisms and prolactin levels

The baseline median prolactin levels after four weeks of risperidone treatment were reported in Supplementary Table 1. The analysis of genetic polymorphisms revealed that the *5HTR2A* rs6313 ($n = 99$, GG = 31, GA = 54, AA = 14, $p = 0.61$) and rs6311 ($n = 99$, GG = 33, GA = 51, AA = 15, $p = 1.0$) did not significantly impact risperidone-induced hyperprolactinemia (Table 3). The baseline median prolactin levels and individual genotype influence on the median difference of prolactin levels from baseline to four weeks of risperidone treatment was reported in Supplementary Table 3. These findings indicate that *5HTR2A* rs6313 and rs6311 genetic variations may not serve as predictive markers for elevated prolactin levels in the studied population.

Discussion

The present study investigated the influence of *5HTR2A* (rs6311, rs6313*)* and *DRD2* (rs1800497) gene polymorphisms on risperidone-induced weight gain and hyperprolactinemia in patients with SCZ from the South Indian population. Our findings indicate a significant association between specific *5HTR2A* (rs6313, rs6311) gene polymorphisms and weight gain, while no such associations were observed for *DRD2* rs1800497 polymorphism regarding risperidone-induced weight gain, prolactin elevation, and extrapyramidal symptoms in the studied population. These results contribute to the existing literature examining the pharmacogenetic factors that may predispose individuals to the adverse effects of antipsychotic medications, which is specific to understanding the importance of *5HTR2A* gene polymorphisms with weight gain. In the present study, the allele frequencies of *5HTR2A* (rs6311 & rs6313) and *DRD2* (rs1800497) polymorphisms in the study population were consistent with the reported previous studies of the Indian population. The *DRD2* rs1800497 polymorphism, G allele frequency (0.67) was consistent with Vijayan et al. (0.69) and Kaur et al. (0.68) studies reported in the Indian population [12, 28]. Similarly, *5HTR2A* gene rs6311 (G-0.59; A-0.41) and rs6313 (G-0.59; A-0.41) allele frequencies were consistent with a study by Sujitha et al. of 5*HTR2A* rs6311 (G-0.56; A-0.44); rs6313 (G-0.58; A-0.42) in patients with SCZ from South Indian populations [25]. Similarly, allele frequencies also consistent with another study by Kaur et al. rs6311 (G-0.59; A-0.41), and rs6313 (G-0.56; A-0.44) reported in patients with SCZ from North Indian populations [12].

The present study found a significant association between the *5HTR2A* rs6311 and rs6313 gene polymorphisms and risperidone-induced weight gain, supporting previous studies highlighting the role of serotonin pathways in metabolic

Table 4 Serotonin (*5HTR2A* rs6311 and rs6313) and Dopamine receptor *(DRD2* rs1800497*)* gene polymorphisms influence on risperidone-induced extrapyramidal symptoms

Genotype	Patients without EPS (*n*=54)	Patients with EPS (*n*=45)	Odds ratio (95%CI)	*p*-value
5HTR2A rs6311 (*n*=99)				
G/G (*n*=33)	15 (27.8%)	18 (40%)	1.00	0.2
G/A+A/A (*n*=66)	32+7 (72.2%)	19+8 (60%)	0.58 (0.25–1.34)	
5HTR2A rs6313 (*n*=99)				
G/G (*n*=31)	13 (20.4%)	18 (40%)	1.00	0.089
G/A+A/A (*n*= 68)	35 +6 (79.6%)	19+8 (60%)	0.38 (0.16–0.94)	
DRD2 rs1800497 (*n*=99)				
G/G (*n*=43)	24 (44.4%)	19 (42.2%)	1.0	0.82
A/G+A/A (*n*=56)	25+5 (55.6%)	22+4 (57.8%)	1.09(0.49–2.43)	

Logistic regression $p < 0.05$ is considered significant

regulation. Our study findings, in line with [6] reported in patients with SCZ ($n = 25$) using post-mortem brain samples. This study also demonstrated the *5HTR2A* gene (rs6314, $p = 0.008$, rs6313, $p = 0.026$) polymorphisms impact on the *5HTR2A* gene methylation and *5HTR2A* mRNA expression [6]. For instance, Wan et al. [29] illustrated that risperidone increases energy intake via the 5HT2C receptor-NPY pathway through serotonin receptors in weight gain and appetite control [29]. Furthermore Li et al. [15] confirmed that risperidone modulates hypothalamic melanocortin-4 receptors (MC4R) and causing hyperphagia, and obesity implying a complex interplay between serotonin signaling and metabolic regulation [15]. Our results also confirm those of Qiu et al. [23], established metabolic biomarkers of risperidone-induced weight gain among drug-naïve patients. This study proved α-aminobutyric acid levels, and phosphatidylcholine were predictive biomarkers of weight gain [23]. Similarly, Vanwong et al. [32] demonstrated that long-term risperidone treatment had a significant correlation with an increased rate of overweight and obesity in children and adolescents with autism spectrum disorder (ASD) compared to healthy controls. The study also reported that *5HTR2C* and the *ABCB1* genetic variants were not associated with obesity risk. Another case–control study by Genis-Mendoza et al. [33] reported the possible role of the *5-HTR2A* rs6311 polymorphism in the genetic vulnerability to eating disorders in the Mexican population. Our results align with this study observation, which involves the *5HTR2A* gene in appetite, mood, and behavior regulation, and indicate that *5HTR2A* genetic variants of the serotonin signaling pathway could be one of the etiologic determinants of such disorders. Furthermore, the study reported an association between the rs6311 GG genotype and increased risk of suicide attempts, highlighting the interplay between genetic factors and psychiatric comorbidities in eating disorders. The genetic mechanisms underpinning weight gain caused by antipsychotic drugs revolve around polymorphic loci in dopamine and serotonin receptors. The *5HTR2A* rs6311 is thought to contribute to weight gain by modulating serotonin signaling pathways that regulate appetite and feeding, while rs6313 may influence weight gain indirectly due to its linkage disequilibrium with rs6311. Additionally, *DRD2* rs1800497 polymorphisms have also been related to weight gain, probably through increased reward-related eating by decreased dopamine receptor availability. However, our study findings of *DRD2* rs1800497 polymorphism association with weight gain are consistent with recently reported meta-analysis [31].

Integrating genetic factors with metabolic biomarkers may enhance our understanding of individual susceptibility to weight gain during antipsychotic treatment. The results concerning hyperprolactinemia and *DRD2* variants contradict our hypothesis, as no significant association was found between *DRD2* rs1800497 and risperidone-induced hyperprolactinemia [5]. However, this is consistent with conflicting findings in the literature regarding the role of *DRD2* variants in prolactin elevation; some studies have reported positive associations between *DRD2* polymorphisms and increased prolactin levels, while others have not found such an association. [1, 4, 5, 18, 20, 33] The discrepancies between our study findings and previous studies with respect to *DRD2* rs1800497 gene polymorphism lack of association with prolactin levels may be attributed to differences in study design, population characteristics, sample sizes, treatment duration, baseline prolactin levels, dietary intake, and physical activity highlighting the need for further investigation into the genetic determinants influencing prolactin levels on antipsychotic treatment. A study by Li et al. reported that the melanocortin-4 receptor (Mc4r) in the hypothalamus is a key mediator of risperidone-associated hyperphagia and weight gain. In this study, risperidone modulated gene expression and neural activity in the hypothalamus, leading to increased appetite. Mc4r activity plays a key role in regulating food intake, suggesting that Mc4r receptor antagonism significantly contributes to risperidone-induced weight gain. Furthermore, the study highlights the need for future research on Mc4r-mediated pathways as potential therapeutic targets to minimize metabolic side effects of antipsychotic medications [15]. The present study offers valuable insights into the genetic factors underlying risperidone-induced side effects, particularly concerning *5HTR2A* and *DRD2* genetic polymorphisms. However, our findings were restricted to the cohort group of SCZ patients ($n = 99$) recruited from a single tertiary care hospital, with four to six weeks of treatment with risperidone as an antipsychotic medication. The evaluation of weight changes was restricted to pre and post-treatment measurements, without accounting for dietary habits or physical activity, which are critical factors influencing weight outcomes. Future research should consider employing a longitudinal design with larger, more diverse cohorts to address these limitations. This approach will contribute to a better understanding of the complex interactions between lifestyle factors, genetic predispositions, and adverse effects of antipsychotic medications. Analysis of other gene polymorphisms apart from *5HTR2A* and *DRD2* may provide a more detailed understanding of individual susceptibility toward side effects of antipsychotics. Exploring other neurotransmitter systems involved in appetite and metabolic regulation could provide further insights into mitigating these common side effects. Future studies are required to incorporate risperidone levels to account for pharmacokinetic and drug compliance factors in assessing the role of *5HTR2A* and *DRD2* receptor genetic polymorphisms.

In conclusion, our findings highlight that the *5HTR2A* (rs6311 and rs6313) genetic variants are significantly

associated with risperidone-induced weight gain, while *DRD2* rs1800497 and other *5HTR2A* (rs 6311, rs6313) genetic variants are not linked to risperidone-induced hyperprolactinemia or extrapyramidal symptoms. These results illustrate the potential genetic factors to assess the individuals at risk of developing antipsychotic-induced adverse effects. Implementation of these genetic markers into clinical practice may enable personalized treatment strategies that improve therapeutic outcomes and minimize adverse effects for individuals with schizophrenia. Future studies are required to validate these findings and explore additional genetic predictors to optimize antipsychotic therapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-025-03835-5.

Acknowledgements The study was supported by Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) Intramural Research Grant (Grant No. JIP/Res/Intra-PhD/01/2014) and Indo-French Centre for the Promotion of Advanced Research (IFCPAR/CEFIPRA) for promoting the collaboration (Grant No. IFC/4098/RCF2016/853) between JIPMER and University of Sorbonne universities, Paris, France.

Author contribution A.C. Goud drafted the manuscript and performed biochemical and molecular experiments. R.P. RajKumar was involved in the screening and recruitment of patients, as well as their treatment and follow-up. D.G. Shewade contributed to the planning and execution of the study. L. Goenka conducted the statistical analysis of the data and assisted in improving the manuscript. S.K. S was responsible for assessing adverse drug reactions and enhancing the manuscript.

Funding The study was supported by Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) Intramural Research Grant (Grant No. JIP/Res/Intra-PhD/01/2014) and Indo-French Centre for the Promotion of Advanced Research (IFCPAR/ CEFIPRA) for promoting the collaboration (Grant No. IFC/4098/RCF2016/853) between JIPMER and University of Sorbonne universities, Paris, France.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Alladi CG, Mohan A, Shewade DG et al (2017) Risperidone-Induced Adverse Drug Reactions and Role of DRD2 (-141 C Ins/Del) and 5HTR2C (-759 C>T) Genetic Polymorphisms in Patients with Schizophrenia. J Pharmacol Pharmacother 8:28–32. https://doi.org/10.4103/jpp.JPP_197_16
2. Alladi CG, RajKumar RP, Adithan S et al (2019) Dopamine (DRD2) and Serotonin (HTR2A, 2C) Receptor Gene Polymorphisms do not influence early response to Risperidone in South Indian Patients with Schizophrenia. Fundam Clin Pharmacol 33:355–364. https://doi.org/10.1111/fcp.12424
3. Alvarez-Herrera S, Rosel Vales M, Pérez-Sánchez G et al (2024) Risperidone decreases expression of serotonin receptor-2A (5-HT2A) and Serotonin Transporter (SERT) but Not Dopamine Receptors and Dopamine Transporter (DAT) in PBMCs from patients with schizophrenia. Pharmaceuticals 17:167. https://doi.org/10.3390/ph17020167
4. Calarge CA, Ellingrod VL, Acion L et al (2009) Variants of the dopamine D2 receptor and risperidone-induced hyperprolactinemia in children and adolescents. Pharmacog Genom 19:373. https://doi.org/10.1097/FPC.0b013e328329a60f
5. Charan A, Shewade DG, Rajkumar RP, Chandrasekaran A (2016) Relation between serum prolactin levels and antipsychotic response to risperidone in patients with schizophrenia. Psychiatry Res 240:209–213. https://doi.org/10.1016/j.psychres.2016.04.001
6. Cheah S-Y, Lawford BR, Young RM et al (2017) mRNA Expression and DNA methylation analysis of serotonin receptor 2A (HTR2A) in the human schizophrenic brain. Genes 8:14. https://doi.org/10.3390/genes8010014
7. Freyberg Z, Aslanoglou D, Shah R, Ballon JS (2017) Intrinsic and antipsychotic drug-induced metabolic dysfunction in schizophrenia. Front Neurosci 11:432. https://doi.org/10.3389/fnins.2017.00432
8. Gener T, Tauste Campo A, Alemany-González M et al (2019) Serotonin 5-HT1A, 5-HT2A and dopamine D2 receptors strongly influence prefronto-hippocampal neural networks in alert mice: Contribution to the actions of risperidone. Neuropharmacology 158:107743. https://doi.org/10.1016/j.neuropharm.2019.107743
9. Genis-Mendoza AD, Ruiz-Ramos D, López-Narvaez ML et al (2019) Genetic association analysis of 5-HTR2A gene variants in eating disorders in a Mexican population. Brain Behav 9:e01286. https://doi.org/10.1002/brb3.1286
10. Goeb J-L, Marco S, Duhamel A et al (2010) Metabolic side effects of risperidone in early onset schizophrenia. L'Encephale 36:242–252. https://doi.org/10.1016/j.encep.2009.10.008
11. Howes OD, Egerton A, Allan V et al (2009) Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. Curr Pharm Des 15:2550. https://doi.org/10.2174/138161209788957528
12. Kaur G, Gupta D, Chavan BS et al (2017) Identification of genetic correlates of response to Risperidone: Findings of a multicentric schizophrenia study from India. Asian J Psychiatry 29:174–182. https://doi.org/10.1016/j.ajp.2017.07.026
13. Lencz T, Malhotra AK (2009) Pharmacogenetics of antipsychotic-induced side effects. Dialogues Clin Neurosci 11:405. https://doi.org/10.31887/DCNS.2009.11.4/tlencz
14. Leucht S, Corves C, Arbter D et al (2009) Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet Lond Engl 373:31–41. https://doi.org/10.1016/S0140-6736(08)61764-X
15. Li L, Yoo E-S, Li X et al (2021) The atypical antipsychotic risperidone targets hypothalamic melanocortin 4 receptors to cause weight gain. J Exp Med 218:e20202484. https://doi.org/10.1084/jem.20202484
16. Margari L, Matera E, Petruzzelli MG et al (2015) Prolactin variations during risperidone therapy in a sample of drug-naive children and adolescents. Int Clin Psychopharmacol 30:103. https://doi.org/10.1097/YIC.0000000000000063
17. Meyer JS, Quenzer LF (2013) Psychopharmacology: Drugs, the brain, and behavior, 2nd edn. Sinauer Associates, Sunderland, MA, US
18. Miura I, Zhang J-P, Hagi K et al (2016) Variants in the DRD2 locus and antipsychotic-related prolactin levels: a meta-analysis. Psychoneuroendocrinology 72:1–10. https://doi.org/10.1016/j.psyneuen.2016.06.002
19. Muench J, Hamer AM (2010) Adverse effects of antipsychotic medications. Am Fam Physician 81:617–622

20. Nagai G, Mihara K, Nakamura A et al (2012) Prolactin concentrations during aripiprazole treatment in relation to sex, plasma drugs concentrations and genetic polymorphisms of dopamine 2 receptor and cytochrome 450 26 in Japanese patients with schizophrenia. Psychiat Clin Neurosci 66:518–524. https://doi.org/10.1111/j.1440-1819.2012.02391.x
21. Paderina DZ, Boiko AS, Pozhidaev IV et al (2021) Genetic polymorphisms of 5-HT receptors and antipsychotic-induced metabolic dysfunction in patients with schizophrenia. J Pers Med 11:181. https://doi.org/10.3390/jpm11030181
22. Pouget JG, Shams TA, Tiwari AK, Müller DJ (2014) Pharmacogenetics and outcome with antipsychotic drugs. Dialogues Clin Neurosci 16:555. https://doi.org/10.31887/DCNS.2014.16.4/jpouget
23. Qiu Y, Dong Y, Sun W et al (2023) Metabolic biomarkers of risperidone-induced weight gain in drug-naïve patients with schizophrenia. Front Psychiatry 14:1144873. https://doi.org/10.3389/fpsyt.2023.1144873
24. Stroup TS, Gray N (2018) Management of common adverse effects of antipsychotic medications. World Psychiatry 17:341. https://doi.org/10.1002/wps.20567
25. Sujitha SP, Nair A, Banerjee M et al (2014) 5-Hydroxytryptamine (serotonin) 2A receptor gene polymorphism is associated with schizophrenia. Indian J Med Res 140:736
26. Vandenberghe F, Gholam-Rezaee M, Saigí-Morgui N et al (2015) Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment. J Clin Psychiatry 76:e1417-1423. https://doi.org/10.4088/JCP.14m09358
27. Vanwong N, Ngamsamut N, Nuntamool N et al (2020) Risperidone-induced obesity in children and adolescents with autism spectrum disorder: genetic and clinical risk factors. Front Pharmacol 11. https://doi.org/10.3389/fphar.2020.565074
28. Vijayan NN, Bhaskaran S, Koshy LV et al (2007) Association of dopamine receptor polymorphisms with schizophrenia and antipsychotic response in a South Indian population. Behav Brain Funct BBF 3:34. https://doi.org/10.1186/1744-9081-3-34
29. Wan X-Q, Zeng F, Huang X-F et al (2020) Risperidone stimulates food intake and induces body weight gain via the hypothalamic arcuate nucleus 5-HT2c receptor-NPY pathway. CNS Neurosci Ther 26:558–566. https://doi.org/10.1111/cns.13281
30. Zhang J-P, Lencz T, Malhotra AK (2010) Dopamine D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. Am J Psychiatry 167:763. https://doi.org/10.1176/appi.ajp.2009.09040598
31. Zhang J-P, Lencz T, Zhang RX et al (2016) Pharmacogenetic associations of antipsychotic drug-related weight gain: a systematic review and meta-analysis. Schizophr Bull 42:1418–1437. https://doi.org/10.1093/schbul/sbw058
32. Zhang J-P, Malhotra AK (2011) Pharmacogenetics and antipsychotics: therapeutic efficacy and side effects prediction. Expert Opin Drug Metab Toxicol 7:9. https://doi.org/10.1517/17425255.2011.532787
33. Zhang XR, Zhang ZJ, Zhu RX et al (2011) Sexual dysfunction in male schizophrenia: influence of antipsychotic drugs, prolactin and polymorphisms of the dopamine D2 receptor genes. Pharmacogenomics 12:1127–1136. https://doi.org/10.2217/pgs.11.46