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Original article

INFLUENCE OF CYP2D6 POLYMORPHISMS ON CLINICAL OUTCOMES AND QUALITY OF LIFE IN RISPERIDONE-TREATED PATIENTS WITH SCHIZOPHRENIA

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Abstract

Introduction: Schizophrenia is a chronic mental disorder that significantly affects patients' quality of life (QoL), despite antipsychotic treatment. Variability in therapeutic response and frequent adverse effects pose major challenges, making QoL a crucial treatment outcome.

Aim: To assess the impact of CYP2D6 genetic polymorphisms, psychopathology, and adverse drug reactions on subjective QoL in patients with schizophrenia treated with risperidone.

Material and methods: A prospective observational study was conducted at the University Clinic for Psychiatry, Ss. Cyril and Methodius University in Skopje. Ninety-one adult patients (20–63 years; 42 males, 49 females) with ICD-10 F20–F29 psychotic disorders treated with risperidone (1–6 mg/day) were evaluated on admission and discharge using SQLS, PANSS, and BPRS scales. Patients were classified by CYP2D6 metabolic phenotype. Data were analyzed using SPSS v23.0; $p < 0.05$ was considered significant.

Results: CYP2D6 phenotype significantly influenced QoL, with poor metabolizers showing lower scores than moderate and extensive metabolizers (p=0.00003). Psychopathology severity strongly correlated with reduced QoL on discharge. Specific adverse effects, including anxiety (p=0.026), dizziness (p=0.00007), vertigo (p=0.004), suboptimal effect (p=0.00003), and rigor (p = 0.022), were associated with QoL impairment.

Conclusion: CYP2D6 pharmacogenomic profiling can guide personalized risperidone therapy, reducing adverse effects and improving QoL. Optimal control of psychopathology and proactive management of side effects are essential for enhancing patient outcomes.

Keywords: schizophrenia, quality of life (QOL), risperidone, polymorphism, pharmacogenomics

Introduction

Schizophrenia is a serious and complex mental disorder characterized by a combination of positive and negative symptoms that profoundly affect an individual's quality of life and functional capacity[1-3]. It affects millions of people worldwide, with the global number of cases rising from 13.1 million in 1990 to 20.9 million in 2016[4]. Although its prevalence remains

relatively low[4], schizophrenia contributes substantially to the global disease burden, accounting for approximately 13.4 million years of life lived with disability[4]. The disorder typically has an early onset, a chronic course, and is associated with low remission rates, leading to marked functional impairment and a considerable social and financial burden[5]. The economic impact of schizophrenia is significant, with total costs estimated to range between 0.02% and 1.65% of a country's gross domestic product[6]. Indirect costs, primarily due to loss of productivity, represent the largest share of this burden and are consistently reported across national and health system studies[7-9].

Current treatments for schizophrenia primarily rely on antipsychotic medications that modulate neurotransmitter systems, particularly dopamine and serotonin pathways[10]. However, these therapies present significant challenges. There is considerable interindividual variability in both treatment response and tolerability, making it difficult to predict therapeutic outcomes or establish uniform treatment guidelines[11-15]. A substantial proportion of patients continue to experience persistent psychotic symptoms despite ongoing therapy[16], often resulting in a "trial-and-error" approach to medication selection[17]. Moreover, antipsychotic drugs are frequently associated with serious adverse effects, including extrapyramidal symptoms, weight gain, and hyperprolactinemia[18,21]. Such side effects frequently contribute to poor adherence or complete discontinuation of treatment[18].

To address the challenges of variable treatment response and adverse drug reactions, personalized medicine strategies are gaining increasing importance in psychiatry[22,23]. Pharmacogenomics, the study of how genetic variability influences drug response, offers a promising framework for optimizing pharmacotherapy[16,24,25]. By identifying genetic variants associated with drug metabolism, efficacy, and safety, pharmacogenetics research enables more individualized and effective treatment approaches[14,26,27]. Such strategies can help predict which patients are likely to respond favorably to specific medications or develop certain adverse effects[25,28], thereby improving therapeutic outcomes and enhancing overall quality of life[16]. Implementing pharmacogenetics profiling allows clinicians to move beyond the traditional "one-size-fits-all" model toward personalized therapy[27,31].

Cytochrome P450 2D6 (CYP2D6) plays a central role in the metabolism of risperidone, and genetic polymorphisms in this enzyme can markedly influence both treatment efficacy and the risk of adverse reactions. These variations may also affect treatment adherence, clinical outcomes, and quality of life. Therefore, this study aimed to investigate the relationship between CYP2D6 metabolic phenotype and quality of life in patients with schizophrenia treated with risperidone, contributing to the advancement of individualized psychiatric care.

Material and methods

This prospective observational study was conducted at the University Clinic for Psychiatry in collaboration with the Institute of Immunobiology and Human Genetics, Faculty of Medicine and the Institute of Pharmaceutical Chemistry, Faculty of Pharmacy Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia. A total of 91 patients diagnosed with psychotic disorders (ICD-10 codes F20–F29) were included. All participants were over 18 years of age, ranging from 20 to 63 years, and the sample comprised 42 males and 49 females. Each patient received oral risperidone therapy at doses ranging from 1 to 6 mg per day. Inclusion criteria were a diagnosis of psychosis based on ICD-10 codes F20–F29, age above 18 years, provision of written informed consent, and initiation of risperidone treatment during the study period. Exclusion criteria included age below 18 years, non-adherence to prescribed antipsychotic therapy, and the presence of significant comorbidities beyond psychotic disorders, such as hepatic or renal impairment or substance abuse.

The study protocol was approved by the Ethics Committee of the Faculty of Pharmacy and the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje. All procedures were carried out in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians, and all clinical and genetic data were anonymized before analysis.

Demographic and clinical variables, including family history, comorbidities, treatment details (dose, duration, co-medications), and lifestyle factors, were collected from patient records at the University Clinic for Psychiatry in Skopje, North Macedonia. Validated psychiatric and quality-of-life scales were administered at baseline (admission, prior to therapy initiation) and after one month of risperidone treatment (discharge). The Positive and Negative Syndrome Scale (PANSS) was used to evaluate positive, negative, and general psychopathology symptoms; the Brief Psychiatric Rating Scale (BPRS) was used to assess overall psychiatric symptom severity and treatment efficacy; and the Schizophrenia Quality of Life Scale (SQLS) was used to evaluate subjective quality of life (scores range from 0 to 100, with higher values indicating poorer quality of life). All clinical assessments were performed by psychiatrists trained and experienced in the use of these instruments.

Peripheral blood samples were collected, and genomic DNA was isolated from lymphocytes using standard proteinase K digestion. DNA samples were stored at -80°C until analysis. *CYP2D6* genotyping was performed using the PGX-CYP2D6 StripAssay®, which detects clinically relevant alleles such as CYP2D6*3, CYP2D6*4, and CYP2D6*6. Based on allele combinations, patients were classified into metabolizer phenotypes according to established pharmacogenetics guidelines: extensive metabolizers (EM, n=49), intermediate metabolizers (IM, n=35), and poor metabolizers (PM, n=6). No ultra-rapid metabolizers (UM) were identified in this cohort.

For statistical analysis, all collected variables were entered into a database and analyzed using the SPSS software, version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics (mean, standard deviation, standard error, median, and interquartile range) were calculated. Parametric and non-parametric tests, including Student's t-test for independent samples, Pearson's χ^2 test, Fisher's exact test, Mann–Whitney U test, analysis of variance (ANOVA), and Kruskal-Wallis test, were applied as appropriate. Data distribution was assessed using the Kolmogorov-Smirnov and Shapiro–Wilk tests. Bivariate analyses were conducted to compare phenotypic groups, while univariate and multivariate logistic regression analyses were performed to identify predictors of therapeutic response, calculating odds ratios (ORs) and 95% confidence intervals (CIs).

A p-value <0.05 was considered statistically significant, and $p<0.01$ was considered highly significant.

Results

Psychopathology was assessed using the PANSS and BPRS, while subjective quality of life was evaluated with the SQLS. Correlation analyses showed clear positive links among the three scales. This means that patients with more severe psychopathology reported poorer quality of life. Patients who responded less well to risperidone treatment tended to have higher SQLS scores, reflecting lower well-being.

All patients were evaluated with the SQLS scale on admission and discharge to assess their quality of life before and after treatment. Before the start of therapy, no statistically significant difference in the SQLS scale score was identified between the three *CYP2D6* groups, i.e., patients from the three groups did not have significantly different quality of life ($p=0.16$).

On discharge, after treatment, poor metabolizers had the highest mean SQLS score (81.0 ± 9.8), moderate and extensive metabolizers had similar mean scores for the scale (58.94 ± 10.8, 58.98 ± 10.8, respectively). The difference in SQLS score between the three groups was statistically significant (p=0.00003). Post-hoc analysis with between-group comparisons showed that this overall significance was due to the significant difference between poor and moderate metabolizers (p=0.00014), and between poor and extensive metabolizers (p=0.00014). These results indicate that after completing antipsychotic treatment, moderate and extensive metabolizers rated their quality of life significantly better than poor metabolizers (Table 1).

Table 1. *CYP2D6* classification of patients according to SQLS-scale score on admission and discharge of patients diagnosed with psychosis

Variables	CYP2D6 Slow	Moderate Metabolizers	Extensive	p value
SQLS Reception (mean ±SD)	91.67 ± 10.2	90.25 ± 8.4	93.94 ± 8.9	F=1.85 p=0.16
SQLS Iscopy (mean ±SD)	81.0 ± 9.8	58.94 ± 10.8	58.98 ± 10.8	F=11.8 p=0.00003 $^{ap=}$0.00014 $^{bp=}$0.00013

F (Analysis of Variance) post-hoc ^{ap}(Analysis of Variance), ^{bp}(Analysis of Variance), ^{cp}(Moderate *vs*. Extensive)

We analyzed the correlation between the SQLS scale and the two psychiatric scales PANSS and BPRS, in order to see the connection between the quality of life of patients with schizophrenia and the therapeutic effect of antipsychotic therapy. The results showed a statistically significant correlation between the SQLS scale and the PANSS scale for negative schizophrenic symptomatology (p<0.0001), with the PANSS scale for general psychopathology (p=0.003), and with the BPRS scale (p=0.002) (Table 2). All these correlations were observed on discharge, after completion of antipsychotic treatment. The Pearson's correlation coefficient value of r=0.391 for the relationship between SQLS and the PANSS negative schizophrenic symptomatology scale, r=0.309 with the PANSS general psychopathology scale, and r=0.323with the BPRS scale showed that all three correlations were positive, i.e. direct. This means that with an increase in the score on the psychiatric scales, the SQLS scale score also increased, *and vice versa*: patients with lower scores on the PANSS negative and general schizophrenic symptomatology scale also had a lower score on the SQLS scale. Patients with a worse therapeutic response to antipsychotic therapy had a worse quality of life, and *vice versa*. The results are presented in Figures 1, 2, and 3.

Table 2. Correlation between SQLS scale with PANSS scale for negative schizophrenic symptomatology, PANSS scale for general psychopathology, and BPRS scale

Correlation	Pearson r	p - level
SQLS reception & PANSS positive reception	-0.159	0.133 ns
SQLS Print & PANSS Positive Print	0.191	0.070 ns
SQLS Reception & PANSS Negative Reception	0.166	0.23 ns
SQLS Print & PANSS Negative Print	0.391	0.000 sig
SQLS Reception & PANSS Reception	0.109	0.300 ns
SQLS Print & PANSS General Print	0.309	0.003 sig
SQLS Reception & BPRS Reception	-0.009	0.929 ns

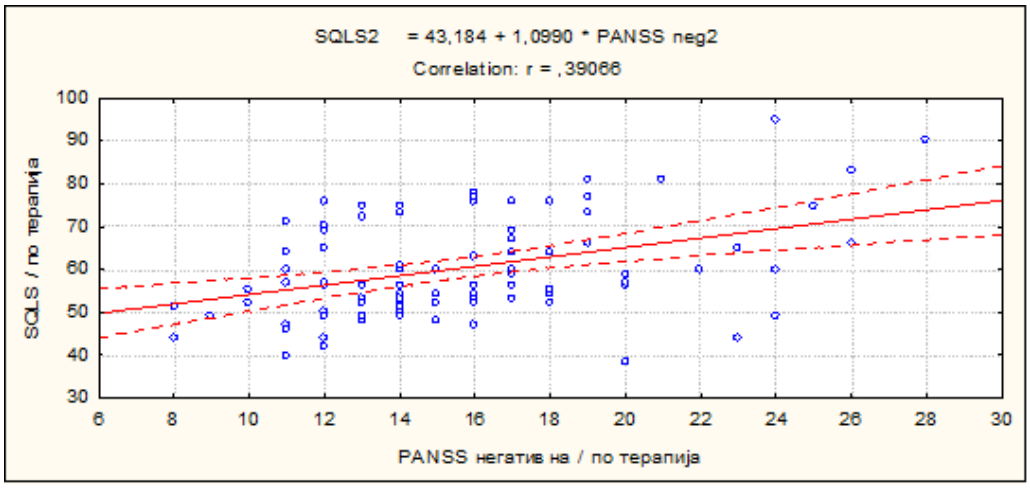

Fig. 1. Correlation between SQLS scale and PANSS scale for negative schizophrenic symptomatology

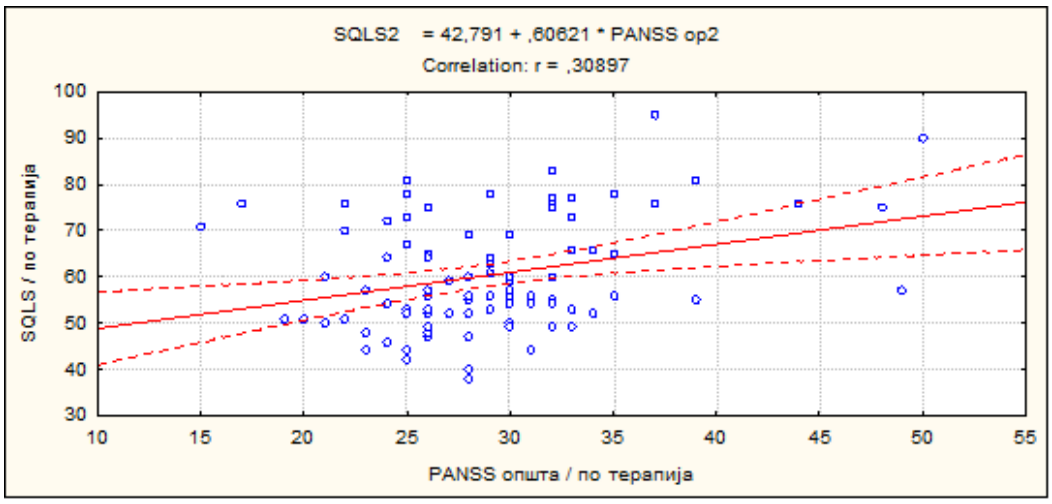

Fig. 2. Correlation between SQLS scale and PANSS scale for general psychopathology

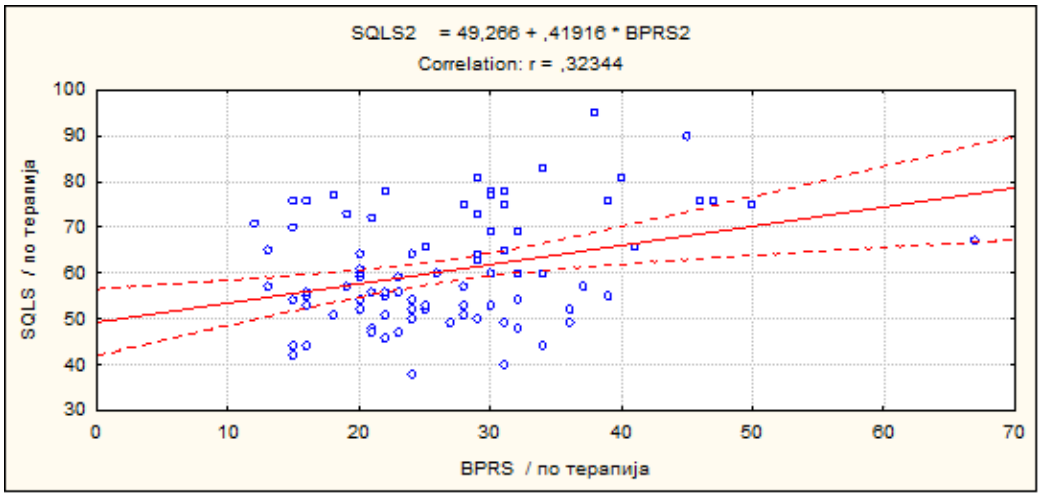

Fig. 3. Correlation between SQLS-scale and BPRS scale

Patients who experienced side effects during antipsychotic treatment had higher SQLS scores than patients without side effects, but a statistically significant difference was identified for the following side effects: anxiety (p=0.026), dizziness (p=0.00007), vertigo (p=0.004), suboptimal therapeutic effect (p=0.00003), and rigors (p=0.022). Patients with anxiety had a mean SQLS score of 65.72 ± 13.7, patients without this side effect 58.81 ± 10.9. The mean SQLS score in patients with dizziness was 73.36 ± 12.9, in patients without dizziness 58.64 ± 10.8. Patients with and without dizziness had a mean SQLS score of 72.43 ± 15.6 and 59.16 ± 10.9, respectively. The mean SQLS score in patients with and without suboptimal treatment effect was 74.09 ± 12.2 and 74.09 ± 12.2, respectively. Patients with rigor had a mean SQLS score of 64.81 ± 14.1, patients without this side effect 58.56 ± 10.5. The occurrence of anxiety, lightheadedness, dizziness, suboptimal treatment effect and rigor during antipsychotic therapy in patients with schizophrenia significantly worsens their quality of life, as presented in Table 3.

Table 3. Impact of side effects on SQLS scale score

Descriptive statistics (SQLS printout)					
Variables	**n**	**yes (mean ±SD)**	**n**	**not (mean ±SD)**	**p value**
Agitation	5	66.80 ± 14.4	85	59.80 ± 11.6	t=1.29 p=0.201 ns
Anxiety	18	65.72 ± 13.7	72	58.81 ± 10.9	t=2.27 p=0.026 sig
Drowsiness	27	64.18 ± 13.9	64	58.83 ± 10.8	t=1.98 p=0.051 ns
Stunned	11	73.36 ± 12.9	80	58.64 ± 10.8	t=4.16 p=0.00007
Dizziness	7	72.43 ± 15.6	83	59.16 ± 10.9	t=2.97 p=0.004 sig
Subefect	11	74.09 ± 12.2	80	58.54 ± 10.7	t=4.44 p=0.00003
Rigor	27	64.81 ± 14.1	64	58.56 ± 10.5	t=2.33 p=0.022 sig
Gain weight	8	65.75 ± 17.7	81	59.78 ± 11.1	t=1.37 p=0.17 ns

In our study, we did not find a significant correlation between the scores on the SQLS scale, i.e. the quality of life, and the number of adverse events that occurred during antipsychotic treatment. However, we observed an association with the occurrence of certain adverse events (R=0.174, p=0.23), as presented in Table 4.

Table 4. Correlation of side effects on SQLS scale score

Correlation	**n**	**Spearman - R**	**p-level**
SQLS2 & Number of Side Effects	49	0.174	0.232 ns

Discussion

This study demonstrated a significant impact of CYP2D6 metabolic phenotype on quality of life in patients with schizophrenia treated with risperidone. Poor metabolizers exhibited markedly worse outcomes compared to intermediate and extensive metabolizers, supporting the growing evidence that pharmacogenomics can optimize antipsychotic therapy. These findings are consistent with prior studies showing that CYP2D6 polymorphisms influence risperidone plasma concentrations, therapeutic efficacy, and the risk of adverse drug reactions[32-35]. Poor metabolizers are likely to experience higher plasma drug levels, which may contribute to more severe side effects and diminished treatment tolerability, ultimately affecting subjective quality of life.

Beyond genetic variability, the severity of psychopathology emerged as a critical determinant of quality of life. Patients with higher PANSS and BPRS scores on discharge also had higher SQLS scores, reflecting poorer subjective well-being. This underscores that

effective symptom control remains a central goal of treatment, and improving quality of life requires both optimal pharmacotherapy and comprehensive psychiatric care[36,37].

Interestingly, while the total number of adverse drug reactions did not correlate with quality of life, specific side effects-including anxiety, dizziness, vertigo, rigors, and suboptimal therapeutic response-were strongly associated with poorer outcomes. This aligns with previous reports highlighting that particular adverse effects, rather than overall side-effect burden, drive patient dissatisfaction and impact daily functioning[38,39]. Targeted management of these burdensome side effects may therefore improve treatment adherence, functioning, and overall well-being more effectively than a generalized approach focused solely on minimizing the total number of adverse events[40].

From a clinical perspective, these results highlight the potential value of integrating pharmacogenomics testing into routine psychiatric practice. Identifying poor metabolizers in advance could allow clinicians to adjust risperidone dosing, consider alternative antipsychotics, or implement closer monitoring for side effects, thereby improving adherence and therapeutic outcomes. Personalized therapy approaches can address both biological factors (genetic variability) and clinical factors (symptom severity, adverse effects) that contribute to reduced quality of life.

This study has several limitations. The sample size was modest, and all patients were recruited from a single center, which may limit generalizability. Moreover, the short follow-up period did not allow assessment of long-term trajectories of quality of life. Future studies should include larger, multi-center cohorts and extend follow-up to explore the stability of these findings. In addition, pharmacoeconomic analyses could clarify the cost-effectiveness of routine CYP2D6 testing in psychiatric care.

Conclusion

CYP2D6 genetic polymorphisms, the severity of psychopathology, and the occurrence of specific adverse drug reactions are significant determinants of quality of life in patients with schizophrenia treated with risperidone. Poor metabolizers are particularly vulnerable to reduced well-being due to higher risk of side effects and suboptimal therapeutic outcomes. These findings underscore the importance of integrating pharmacogenomics testing into clinical practice to guide individualized antipsychotic therapy. Personalized treatment strategies, informed by CYP2D6 genotype, symptom severity, and side-effect profiles, have the potential to optimize dosing, improve treatment adherence, minimize adverse events, and enhance overall quality of life.

Moreover, incorporating pharmacogenomic profiling into routine psychiatric care may contribute to more efficient resource utilization and better long-term patient outcomes. Future research should focus on validating these results in larger, multicenter cohorts, exploring the longitudinal effects of personalized treatment, and evaluating the cost-effectiveness of pharmacogenomics-guided therapy. Collectively, these approaches could help move psychiatric care toward a precision medicine model, where treatment is tailored to the unique genetic and clinical profile of each patient, ultimately improving both clinical outcomes and daily functioning.

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