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# Clinical Significance of Pharmacogenetic Profiling in Akathisia Associated With Obsessive-Compulsive Disorder

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## Abstract

Obsessive-compulsive disorder (OCD) involves involuntary, distressing thoughts and compulsive behaviors. While selective serotonin reuptake inhibitors (SSRIs) are widely used in the treatment of OCD, when administered concomitantly with antipsychotics, they can contribute to akathisia. Drug metabolism and side-effect profiles can be influenced by genetic variations in genes encoding cytochrome P450 (CYP450) enzymes. In this case report, the pharmacogenetic findings and clinical features of a 29-year-old male patient diagnosed with OCD and experiencing akathisia were evaluated. The patient received standard pharmacotherapy prior to the genetic test. However, pharmacogenetic analysis revealed that the patient was an intermediate metabolizer (IM) for CYP2D6, a normal (extensive) metabolizer for other CYP enzymes, and showed increased induction for CYP1A2. Despite beta-blocker therapy, akathisia persisted and subsided following the readjustment of the quetiapine dose. However, the simultaneous use of multiple psychotropic drugs, dose changes, and potential drug-drug interactions limited the interpretation of the pharmacogenetic findings. This case report highlights the potential role of pharmacogenetic tests in clinical practice, but demonstrates that they do not definitively predict treatment response or adverse effects. Larger studies are needed to determine the clinical utility of pharmacogenetic testing in the management of OCD.

**Categories:** Neurology, Psychiatry, Pharmacology
**Keywords:** akathisia, cyp2d6, deep transcranial magnetic stimulation (tms), obsessive-compulsive disorder (ocd), pharmacogenetics, selective serotonin reuptake inhibitors (ssris)

## Introduction

Cytochrome P450 (CYP) is a hemeprotein vital in metabolizing drugs and other xenobiotics. CYP2D6 is a crucial member of this family, metabolizing various substances. However, gene polymorphisms can lead to different phenotypes: poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultrarapid metabolizers (UM). For certain antidepressant and antipsychotic drugs metabolized via CYP2D6, low enzyme activity may lead to slowed drug metabolism and increased drug exposure, thereby elevating the likelihood of adverse effects. Conversely, in UM, the rapid elimination of the active drug can prevent the attainment of adequate therapeutic concentrations at standard doses, leading to reduced treatment response. Therefore, when evaluating the clinical effects of CYP2D6 metabolism phenotypes, the metabolic properties of the drug in question and its reliance on the CYP2D6 pathway must be taken into consideration [1,2].

Moreover, the inhibition of CYP2D6 activity resulting from drug interactions can contribute to elevated levels of certain antipsychotics and the emergence of extrapyramidal symptoms. Akathisia, which may be among these symptoms, is characterized by inner restlessness and a compelling need to move. Therefore, the evaluation of CYP2D6 genetic variations may provide supportive information for understanding individual drug responses and potential adverse effects that may arise during treatment [3]. Importantly, the relationship between CYP2D6 metabolizer status and the development of akathisia may vary depending on the degree to which the drug used is metabolized via the CYP2D6 enzyme. Therefore, CYP2D6 metabolizer status is not a sufficient indicator on its own in evaluating susceptibility to akathisia [4].

OCD is a psychiatric disorder where individuals have recurring involuntary thoughts (obsessions) and engage in repetitive behaviors (compulsions) to prevent them. Examples include fear of contamination, losing control, aggressive behavior, and excessive preoccupation with religion. These behaviors can interfere with daily activities and social interactions. OCD is the fourth most common psychiatric illness, and its cause varies depending on factors such as a neurological precedence and past traumas [5].

Selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT) are evidence-based primary approaches in the treatment of obsessive-compulsive disorder (OCD). CBT is considered one of the most evidence-based psychotherapeutic interventions for OCD [6]. If an SSRI does not work, it is considered

resistant OCD. Clomipramine is a tricyclic antidepressant that is FDA-approved for childhood OCD and can also be used for resistant OCD. Venlafaxine, clonazepam, and monoamine oxidase inhibitors (MAOIs) may be recommended in some cases [7]. Akathisia is a movement disorder characterized by inner restlessness and an irresistible urge to move. Antipsychotics with a particularly potent dopamine D2 receptor blockade are among the common causes of akathisia. Neurodegenerative diseases can also cause akathisia. It is a common side effect of antipsychotic drugs, leading to a feeling of nervousness and an urge to act [8].

Pharmacogenetic tests, which allow the identification of genetic variations affecting drug metabolism and response to treatment, stand out as one of the important components of personalized medicine practices. During the psychiatric treatment process, pharmacogenetic tests can help identify individuals at risk of altered drug exposure and contribute to the individualized planning of drug selection and dose adjustment. On the other hand, genetic variations are only one of numerous factors determining drug response. Concomitant medication use, interactions that alter enzyme activity, drug-specific metabolic characteristics, and individual clinical variables can also be decisive. However, the clinical contribution of pharmacogenetic tests in psychiatric treatment varies depending on the drug and the available level of evidence. Consequently, the results obtained from these tests should be considered not as standalone indicators determining treatment response or adverse effects, but rather as data supporting clinical evaluation [9].

In this case report, we present a patient with OCD and akathisia whose medication regimen was revised based on the results of a pharmacogenetic panel assessing variants in CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19.

## Case Presentation

A 29-year-old male patient presented to our psychiatry outpatient clinic with severe anxiety and refractory, distressing obsessive thoughts featuring themes of theft, sexual content, and harming young children that had persisted for approximately 5 years and severely disrupted his daily functioning. Due to marked impairment in daily functioning and symptom exacerbation, the patient was admitted to the inpatient psychiatry service for treatment. This marked the patient's second psychiatric hospitalization; however, as this was his first admission to our facility, detailed information regarding prior treatment courses could not be obtained. The duration of use and treatment adherence for the psychotropic medications he used prior to admission could not be reliably determined.

Upon admission, the patient's medication regimen consisted of a combination of fluvoxamine (200 mg/day), paliperidone (9 mg/day), and quetiapine (200 mg/day). Fluvoxamine treatment was maintained at 200 mg/day throughout the hospitalization. During the first week of admission, amisulpride (400 mg/day), which exerts a potent antagonistic effect on dopamine D2/D3 receptors, was added to the regimen to optimize the clinical response [10]. Following the addition of amisulpride (400 mg/day) to the treatment, the doses of paliperidone (from 9 mg/day to 6 mg/day) and quetiapine (from 200 mg/day to 100 mg/day) were reduced to minimize potential dose-dependent side effects and the overall pharmacological burden associated with adding a new antipsychotic medication. Both dosage reductions were performed simultaneously. Furthermore, as part of the antidepressant management, fluoxetine (40 mg/day) was initiated on the third day of admission, and clonazepam (1.2 mg/day for 7 days) was administered starting from the third day of treatment.

On the fifteenth day of treatment, the patient developed symptoms of akathisia, characterized by an inability to remain still, persistent restlessness, and an inner sense of unease. This evaluation was conducted based on the patient's self-reported symptoms and clinical observation; however, because the Barnes Akathisia Rating Scale (BARS) was not utilized, symptom severity was not evaluated using a standardized method. Paliperidone was discontinued, considering it a potential contributing factor. Nevertheless, it was noted that potential withdrawal effects resulting from the quetiapine dose reduction, as well as the possible contribution of fluoxetine initiated on the third day of hospitalization, should also be taken into account in the emergence of akathisia. Pharmacogenetic genotyping analysis was performed to guide further treatment decisions, identify potential genetic differences in drug metabolism, and perform patient-specific dose adjustments. In addition, deep transcranial magnetic stimulation (dTMS) was administered to the patient.

To evaluate the patient's drug metabolism and potential genetic variations, targeted polymorphisms were analyzed using real-time PCR (Thermo Fisher Scientific, QuantStudio 3 Real-Time PCR, USA). The alleles of the analyzed genes are presented in Table *1*.

| Gene | Alleles |
|---|---|
| CYP2D6 | *1, *2, *3, *4, *6, *7, *8, *9, 10*, *12, *14, *17, *41 |
| CYP2C9 | *1, *2, *3, *4, *5, *6, *11 |
| CYP2C19 | *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *17 |
| CYP1A2 | 1A, 1F, 1C |
| CYP3A4 | *1, *1B, *2, *3, *12, *17, *22 |

**TABLE 1: Cytochrome P450 genes and their corresponding allele variants analyzed in the study**

CYP: Cytochrome P450; *: Star allele nomenclature used to designate specific genetic variants of CYP genes.

The listed alleles represent the genetic variants analyzed for each CYP gene.

The genotypes and predicted phenotypes identified as a result of the pharmacogenetic test are listed in Table 2.

| Gene | Genotype | Predicted Phenotype |
|---|---|---|
| CYP2D6 | *4/*10 | Intermediate metabolizer (IM) |
| CYP2C9 | *1/*1 | Normal metabolizer (NM) |
| CYP2C19 | *1/*1 | Normal metabolizer (NM) |
| CYP3A4 | *1/*1 | Normal metabolizer (NM) |
| CYP1A2 | *1A/*1F | Increased induction |

**TABLE 2: Identified gene genotypes and their corresponding predicted phenotypes**

CYP, cytochrome P450

Genotypes are expressed using star-allele nomenclature, with the two alleles separated by a forward slash (/). “Increased induction” refers to predicted increased CYP1A2 inducibility in response to inducing exposures, rather than a direct measurement of enzyme activity.

Despite the initiation of beta-blocker therapy, the patient's akathisia symptoms persisted. A 30% reduction in obsessions was recorded following 14 sessions of deep transcranial magnetic stimulation (dTMS) therapy administered to target obsessive symptoms. It was considered that the reduction in the quetiapine dose might have played a role in the development of akathisia symptoms due to potential withdrawal effects. A reduction in akathisia symptoms was observed following the readjustment of the dose back to 200 mg/day. Discharged with partial clinical benefit at the end of a one-month treatment period, the patient's medication regimen was arranged as fluvoxamine (200 mg/day), quetiapine (200 mg/day), and fluoxetine (10 mg/day).

## Discussion

This case report presented a 29-year-old male patient with a diagnosis of OCD who developed akathisia symptoms.

Psychopharmacological drugs metabolized by CYP2D6 have recommended doses based on the most common genotype (EM type) [11]. However, genotype affects plasma levels, with PM and IM resulting in higher levels and UM resulting in lower levels than EM. Plasma level affects drug efficacy and side-effect risk, and patients with PM and UM profiles have longer hospital stays and higher costs when prescribed CYP2D6-metabolized drugs [12].

Genetic variations in the CYP2D6 gene may contribute to interindividual differences in drug metabolism and systemic drug exposure. The systematic review and meta-analysis by Milosavljevic et al. [13] demonstrated that individuals classified as IM or PM may have higher exposure to certain antidepressant and antipsychotic medications compared with normal metabolizers. However, the magnitude of this effect varies depending on the medication and its metabolic pathway. Therefore, these findings cannot be generalized to all

psychotropic medications [13].

In the present case, pharmacogenetic analysis identified the CYP2D6 *4/*10 genotype, consistent with an intermediate metabolizer (IM) phenotype. The clinical implications of this finding should be evaluated in the context of the metabolic capacity of CYP2D6, the pharmacokinetic properties of the medications used, and potential drug-drug interactions [13]. As plasma drug concentrations were not measured in this patient, the extent to which the CYP2D6 genotype contributed to drug exposure or the development of akathisia remains uncertain.

Considering the metabolic pathways of the antipsychotics used in this case, the clinical significance of the CYP2D6 IM phenotype may be limited; amisulpride and paliperidone are primarily eliminated via renal excretion, whereas quetiapine is metabolized via CYP3A4 [14,15].

First-generation antipsychotics with potent D2 receptor antagonism, such as haloperidol and fluphenazine, carry a higher risk for the development of akathisia [16]. The prevalence of akathisia is not necessarily higher in moderate and low-potency first-generation antipsychotics or second-generation antipsychotics like quetiapine and olanzapine, but recent studies suggest a higher prevalence with some second-generation antipsychotics like ziprasidone, asenapine, and aripiprazole. Even clozapine, which has a different mechanism of action, has been associated with akathisia. SSRIs and buspirone have also been reported to cause akathisia through mechanisms involving dopamine reduction [17].

The status of fluoxetine as a potent CYP2D6 inhibitor raises the possibility of pharmacokinetic interactions with concurrent drugs metabolized via this enzyme. The concurrent use of multiple antipsychotics and an SSRI during the treatment course complicates the differentiation of the underlying causes of akathisia [18,19]. In the clinical evaluation of akathisia, it is important to consider conditions such as anxiety, restless legs syndrome, and psychomotor agitation, which may present with similar clinical features. Therefore, distinguishing akathisia from other potential causes of restlessness requires a careful clinical evaluation [18].

The persistence of akathisia symptoms despite the discontinuation of paliperidone on the fifteenth day and the initiation of beta-blocker therapy complicates the assessment of paliperidone as the sole causative agent. Nevertheless, it has been reported that akathisia symptoms may persist even after the withdrawal of antipsychotic treatment or may emerge following a dose reduction [16,18]. Although a regression of symptoms was observed following the re-increase of the quetiapine dose to 200 mg/day, this finding alone does not prove that quetiapine treated the akathisia or that the dose reduction caused it. Indeed, the emergence of quetiapine-induced akathisia has also been reported in the literature [19].

Lay and Spisla [20] reported a case of a 28-year-old female patient with OCD who developed rabbit syndrome and akathisia while taking risperidone, quetiapine, and venlafaxine. The patient's akathisia symptoms disappeared after stopping risperidone and increasing the dose of quetiapine. The authors suggest that the patient may be a CYP2D6 poor metabolizer, leading to high levels of risperidone and venlafaxine in the bloodstream. Polypharmacy increases the risk of extrapyramidal symptoms, particularly when combining antipsychotics with SSRI or SNRI. However, the patient was not tested for pharmacogenetics, and drug blood levels were not monitored in this case report [20].

While genetic testing was not performed in similar cases reported in the literature [20], genetic analysis was conducted in the present case, confirming the presence of the CYP2D6 *4/*10 genotype in our patient. Furthermore, the persistence of restlessness despite treatments administered to suppress akathisia symptoms suggests that the patient's pharmacokinetic characteristics may have influenced the clinical presentation. The available data are insufficient to definitively establish a causal relationship between the identified CYP2D6 genotype and the development of akathisia.

Furthermore, pharmacogenetic tests can contribute to understanding individual differences in drug metabolism and evaluating potential drug interactions that may arise during the treatment process. Therefore, considering pharmacogenetic findings alongside clinical evaluation can help tailor treatment approaches to the individual characteristics of the patient [9].

## Conclusions

This case highlights the importance of integrating clinical evaluation and pharmacogenetic data when assessing treatment-emergent akathisia in patients diagnosed with obsessive-compulsive disorder (OCD). Although the identified CYP2D6 genotype and the predicted intermediate metabolizer (IM) phenotype were concordant, no proven direct correlation was demonstrated between these genetic findings and the development of akathisia. When evaluating the clinical presentation, dose adjustments during the treatment course and potential drug-drug interactions with concomitantly administered medications must be taken into account. While a reduction in obsessive symptoms was observed following deep transcranial magnetic stimulation (dTMS), and akathisia symptoms resolved after readjustment of the quetiapine dose, these outcomes cannot be definitively attributed to a single specific intervention. Furthermore, potential drug

interactions and simultaneous medication changes limit the interpretation and generalizability of findings derived from this single case.

In conclusion, therapeutic drug monitoring (TDM) and pharmacogenetic analyses may be considered as adjunctive tools supporting personalized treatment planning in the management of obsessive-compulsive disorder (OCD); however, they cannot be regarded as established strategies for the prevention or management of akathisia. In this case, due to the lack of measurements of drug plasma concentrations, the potential clinical contribution of therapeutic drug monitoring could not be evaluated. Further comprehensive studies are warranted to establish the clinical utility of therapeutic drug monitoring and pharmacogenetic analyses in OCD treatment.

# Additional Information

## Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Acquisition, analysis, or interpretation of data:** Parvin Abdullayev, Tayfun Gözler

**Drafting of the manuscript:** Parvin Abdullayev

**Critical review of the manuscript for important intellectual content:** Parvin Abdullayev, Tayfun Gözler, Korkut Ulucan, Nevzat Tarhan

**Supervision:** Parvin Abdullayev, Korkut Ulucan, Nevzat Tarhan

**Concept and design:** Korkut Ulucan, Nevzat Tarhan

## Disclosures

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