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Guiding treatment in obsessive compulsive disorders by a pharmacogenetic approach

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ABSTRACT

Obsessive-compulsive disorder (OCD) is a common and often enduring neuropsychiatric disorder that results in significant impairments in quality of life. Mostly commonly, its pharmacological management entails a course of a selective serotonin reuptake inhibitors (SSRIs) for ten to twelve weeks, but at higher doses than are typical for treating major depression disorder (MDD). However, the relatively high SSRI doses bring a significant risk for dropout due to side effects in the highly anxious OCD population. We now illustrate through a clinical case study how the use of pharmacogenetics (PGx) in an OCD patient enabled a personalized pharmacological strategy giving better therapeutic response along with lesser risk of untoward side effects. In our case, the patient's poor clinical responses to initial trials with fluoxetine and escitalopram led us to undertake her pharmacogenetic profiling, which correctly predicted that high dose sertraline would obtain effective management of OCD symptoms. This case report illustrates how PGx assessment can enable physicians to make a more confident and personalized choice of SSRI and dosage, leading to improved patient compliance and a stronger therapeutic response, along with lesser side effects. Pharmacogenetic testing presents an emerging tool for guiding SSRI prescription for OCD, considerably improving the management of these difficult-to-treat patients.

1. Introduction

Obsessive-compulsive disorder (OCD) is a common and often enduring neuropsychiatric disorder (Fineberg et al., 2015). Contemporary recommendations for pharmacological first-line treatments involve a trial of a selective serotonin reuptake inhibitor (SSRI) for ten to twelve weeks at higher doses than those typically recommended for patients with major depressive disorder (MDD) (Lambert, 2008). Although controlled trials with serotonin reuptake inhibitors (SRIs) have demonstrated selective efficacy in obsessive-compulsive disorder (OCD), up to 40–60 % of patients do not achieve a satisfactory outcome (Pallanti et al., 2002). Symptom resolution in OCD patients treated with SSRIs shows a correlation with blood levels of the active compound (Hiemke et al., 2018). However, prescription of the relatively high SSRI doses in this vulnerable population brings a significantly greater proportion of drops-outs due to untoward side effects (Bloch et al., 2010). The experience of uncomfortable side-effects in conjunction with a prolonged response latency in these highly anxious patients adversely affects their compliance.

Pharmacogenetics (PGx) is a personalized therapeutic approach for assessing how an individual's germline genetic variations influences the response to drug treatments in terms of efficacy, tolerance, and toxicity (Bousman et al., 2023). In this brief account, we illustrate through a clinical case study how the use of PGx in an OCD patient enabled a personalized pharmacotherapeutic approach through the pre-emptive selection of an SSRI likely to provide an optimal therapeutic response with improved tolerability regarding side effects and toxicity. The tailored preemptive selection of sertraline led to improved patient compliance and good clinical response.

2. Case report

Mrs. T, a Caucasian patient currently aged 26 years, had first consulted PdT for severe OCD and pervasive anxiety symptoms at 24 years of age, in June 2023. PdT is a senior psychiatrist, Head of the Department of Psychiatry at the Cliniques Universitaires Saint-Luc, with extensive experience in the treatment of OCD. The center has experience in treating OCD patients, using both CBT and psychodynamic

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approaches, and has also developed a Deep Brain Stimulation program for treatment-resistant cases.

She reported obsessions of contamination (waste, dirt, pathogens, and fear of falling ill or infecting others) and obsessions with hoarding and symmetry, not accompanied by magical thinking. Her compulsions mainly focused on washing and tidying: own (and others') hand and body hygiene, along with cleaning and tidying up living spaces.

The patient's Y-BOCS scale score was 39/40 in January 2023. Her obsessions and compulsions brought her extreme levels of distress; she was quite unable to disengage from them and gave in to all her compulsions. These symptoms led to social withdrawal and significant financial difficulties: she was spending an excessive amount of money on cleaning and hygiene products, had extremely costly water bills, and visited the dry cleaner approximately once a week for recleaning of her coats. She worked in the administrative staff of a state institution but had been on extended medical leave that followed by a period of unemployment. She retained good insight into her condition, and did not present with any depressive or psychotic symptoms.

Mrs.T lived on her own and developed uncontrollable compulsive symptoms at home, which lessened slightly at her partner's house and in the company of her partner's children. She seemed well supported by her parents and partner.

Compulsive symptoms had emerged at the age of ten, first characterized by an excessive need to tidy up her room. At secondary school (aged 12–15 years), she described feeling herself to be unhygienic. She reported having felt unwell at school, finding the classroom environment too impersonal, and with too many pupils. Her symptoms had eased slightly when she reached lycée (high school) at 16 years of age, whereupon she had continued her education by correspondence. At 18 years of age, she enrolled at university, but was unable to continue her studies because of her intrusive compulsions.

She had no other personal psychiatric or medical history, and does not consume alcohol, tobacco, or any toxic substances. Her family history included maternal OCD, paternal alcohol-use-disorder marked by episodes of violence, and a maternal grandmother with chronic depression.

Mrs. T. had consulted a psychiatrist for the first time at 21 years of age, in 2020. He prescribed fluoxetine (120 mg per day), and provided a course of cognitive-behavioral therapy (CBT). With the medication, she reported side-effects such as a feeling of euphoria and physical and mental hyperactivity which she described as 'like being an electric battery', but experienced no alleviation of her OCD symptoms. The patient follows this combined pharmacological and CBT treatment for eighteen months, with sudden discontinuation of the CBT therapy in 2021 due to the COVID pandemic. A few weeks later, she decided to stop her medications and subsequently experienced withdrawal symptoms such as significant irritability, sadness, and impulsivity. She ceased follow-up consultations and treatment for eight months. Due to her OCD symptoms, in 2022 she underwent hospitalization for ten days in another country, where she received R-TMS treatment combined with escitalopram at a dose of 20 mg per day, but without follow-up. She continued escitalopram at 20 mg per day for six months, with no beneficial effects on her OCD symptoms and no reported side effects. She decided to stop the medication on her own.

Few months later, in June 2023, Mrs. T had her first consultation at our clinic, when she expressed her dissatisfaction with the various therapies she had received, and further conveyed her impression that health care professionals were not listening to or taking seriously her health concerns. At the time, she was not taking any medications apart from prazepam 5 mg, when necessary for anxiety.

Given the failure of two lines of SSRI treatment combined with appropriate psychotherapy, we offered the patient PGx analysis of the main cytochromes involved in SSRI metabolism. The patient proved to have the following genetic profile: *CYP2C19×1/*17* (corresponding to CYP2C19 rapid metabolizer), *CYP2D6×4/*41* (corresponding to CYP2D6 intermediate metabolizer, with a very low activity score of 0.25), and *CYP2B6×1/*1* (corresponding to CYP2B6 normal metabolizer). Based on these PGx results and according to Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations, the PGx consultant (VH) proposed a switch to sertraline (CYP2C19 and CYP2B6 substrate), which was introduced in July 2023 at a dose of 50 mg per day. and then increased to 100 mg after one week. An initial assessment in August 2023 after one month on sertraline showed a possible improvement in symptoms: the patient then agreed to lower slightly her hygiene standards. After three months of sertraline treatment at this dose (October 2023), there was a clear improvement in symptoms which she described as "miraculous": she went on holidays with her partner and his children, and reported a significant improvement in her OCD symptoms, along with better management of her anxiety. Given this response, she was considering to start a new CBT treatment. Aiming to improve further her symptoms, we gradually increased sertraline to a dose of 300 mg per day. In December 2023, she had considerable further improvement of her OCD symptoms as compared to 100 mg, with a clear reduction in the obsessions and compulsions: rather than cleaning her desk for several hours before starting work, a simple wipe was now enough. She then resumed CBT, moved in with her partner, and allowed him to do house cleaning. However, she remains sensitive to excessive demands on her time, especially during premenstrual periods. For this reason, she takes lorazepam 0.5 mg when necessary.

Mrs. T describes being in a stable condition lasting for the past eighteen months, with her last evaluation in February 2025. She remains on maintenance treatment dose of sertraline 300 mg as monotherapy (except for lorazepam) and follows her CBT therapy. Her Y-BOCS scale score was evaluated at 10/40 in January 2025, as compared to 39/40 at baseline, indicating nearly complete remission.

3. Discussion

With a 2 to 3 % prevalence in adults, OCD is a common mental illness which can be severe in many patients (Fineberg et al., 2015) to the great detriment of their quality of life (Katzman et al., 2014). SSRIs are recommended as first-line pharmacological treatment (Fineberg et al., 2015; Lambert, 2008; Katzman et al., 2014), but approximately 50 % of patients do not respond to their initial treatment (Zai, 2021), which calls for adaptation of their therapeutic strategy (Lambert, 2008; Katzman et al., 2014). According to consensus opinion, OCD patients enjoy a therapeutic response at SSRI doses higher than are typically applied in patients with MDD (Lambert, 2008; Katzman et al., 2014; Jenike, 2004) and with the expectation of a 10–12 weeks delay before significant improvement in their symptoms (Lambert, 2008; Katzman et al., 2014; Zai, 2021).

The prolonged delay in improvement is taxing for patients (Fineberg et al., 2015), such that the physician may feel compelled to increase doses or change treatments prematurely, thereby increasing the risk of side effects or therapeutic failure. Furthermore, therapeutic responses and emergence of side effects and toxicity (e.g., increased QTc) are influenced by individual differences in the activity of the cytochrome P450 (CYP) enzymes that metabolize SSRI (Bousman et al., 2023; Helton and Lohoff, 2015; Lazaridis, 2017). The long latency before drug efficacy and the possible side effects can negatively impact upon treatment adherence. Identifying CYP variants through PGx analysis can help to improve the prediction of treatment response by personalizing the choice of antidepressant for a given patient (Zai, 2021). Ultimately, this should reduce the number of therapeutic trials, minimize exposure to side-effects, and improve patients' overall quality of life, while reducing the patients as well as the health services cost of OCD (Zai, 2021). The main CYP enzymes involved in the metabolism of antidepressants are CYP2D6, CYP2C19, CYP3A4, CYP2B6 and CYP1A2 (Helton and Lohoff, 2015), most of which have genetic polymorphisms (PharmVar, n.d.), which can influence the rate of drug metabolism and blood levels.

The first psychiatrist consulted by Mrs. T initiated treatment with fluoxetine, which is mainly metabolized by CYP2D6 to the active

metabolite S-norfluoxetine (Bousman et al., 2023).

Both fluoxetine and its active metabolite, norfluoxetine, exhibit comparable activity in inhibiting serotonin reuptake (Bousman et al., 2023). However, in that study, CYP2D6 metabolic variability significantly affected the parent-to-metabolite ratio in plasma. Moreover, there is insufficient evidence to determine whether CYP2D6 phenotype–related imbalances between fluoxetine and norfluoxetine concentrations impact the pharmacodynamic effects of fluoxetine. Consequently, genotype-based dose adjustments for fluoxetine are not currently recommended.

Mrs. T proved to carry a CYP2D6×4/*41 genotype, which corresponds to intermediate metabolic activity, with a notably low predicted activity score (0.25 compared to 2.0 in a homozygous wild-type individual). She reported significant side effects with fluoxetine treatment, including both physical and mental hyperactivity, and did not observe any improvement in her OCD symptoms. We hypothesize that her unique metabolic profile (intermediate CYP2D6 metabolizer at the lower end of the intermediate range 0.25–1) could have reduced her metabolite-to-parent compound ratio due to a slower conversion of fluoxetine to norfluoxetine (Hiemke et al., 2018). This potentially altered ratio may have impacted the pharmacodynamic effects of the drug (Bousman et al., 2023), potentially increasing toxicity while diminishing therapeutic efficacy. Given the lack of conclusive data regarding the relative efficacy or toxicity of fluoxetine versus norfluoxetine (Bousman et al., 2023), no definitive conclusions can be drawn to explain the effects reported by the patient. However, the atypical response she described, combined with the fact that she was receiving a high dose of fluoxetine (120 mg), suggests that this altered ratio may have played a role in her poor response. Unfortunately, there was no therapeutic drug monitoring (TDM) of the plasma fluoxetine concentration and metabolite ratio), which represents a significant limitation of this case report. Given the lack of accepted recommendations for genotype-based dose adjustments for fluoxetine, it would seem advisable to orient treatment towards a compound that is not primarily metabolized by this pathway (e.g., escitalopram or sertraline) for patients with poor or very low CYP2D6 metabolic activity (Bousman et al., 2023; Zai, 2021).

A second psychiatrist treated Mrs. T with escitalopram, an SSRI medication mainly metabolized by CYP2C19 (Bousman et al., 2023). Her *CYP2C19×1/*17* genotype corresponds to a CYP2C19 rapid metabolizer (RM) profile, which predicts faster metabolism of escitalopram to less active compounds when compared with CYP2C19 normal metabolizers (Bousman et al., 2023; Rudberg et al., 2008). Lower escitalopram plasma concentrations at a given dose would decrease the probability of clinical benefits (Bousman et al., 2023). Indeed, the patient described an absence of any effects (therapeutic or iatrogenic) from this drug at a dose of 20 mg per day, The CPIC has issued optional recommendations for this CYP2C19 RM profile (Bousman et al., 2023), suggesting initiation of escitalopram at the manufacturer's recommended starting doses, and (in the event of insufficient response), a dosage increase or switching to a medication that is not primarily metabolized by CYP2C19. Mrs. T did not have a trial with higher escitalopram dose, and she spontaneously stopped the drug after six months of futile treatment.

After two unsuccessful SSRI trials, we offered her CYP genotyping via a next-generation sequencing (NGS) panel (SOPHiA genetics pharmacogenomic community panel). Results informed the initiation of sertraline, which is mainly metabolized by CYP2B6 and CYP2C19 (Bousman et al., 2023). Her *CYP2B6×1/*1* genotype corresponds to a CYP2B6 normal metabolizer profile, calling for initiation of sertraline at usual doses (Bousman et al., 2023). Her rapid CYP2C19 metabolizer profile likely induces a slight increase in sertraline metabolism to less active compounds, compared to normal CYP2C19 metabolizers, with no requirement for dose adjustment (Bousman et al., 2023).

Altogether, after six months of sertraline treatment, with a Y-BOCS score of only 10, Mrs. T. had obtained remission, as defined by the threshold score of $< 16/40$ (Pallanti et al., 2002). We note a limitation of this case report is relation to the lacking repeated standardized Y-BOCS scoring during follow-up. Although we recorded her baseline and final Y-BOCS scores, we do not have intermediate assessments. Future clinical follow-up in similar cases would benefit from more systematic longitudinal evaluations.

The clinical description presented above suggests that decisions informed by PGx testing largely contributed to the patients' remarkable remission. In general, the physician's confident and informed choice of a drug tailored to the genetic profile of an individual OCD patient increases the likelihood of long-term patient adherence. The patient's genetic analyses were least indicative of fluoxetine among the three SSRIs tested, which was confirmed clinically by her rapid development of side effects. While escitalopram was not a poor choice, its rapid CYP2C19 metabolism profile likely interfered in attaining sufficient plasma levels.

Her subjective experience of being 'misunderstood' and 'not taken seriously' by previous clinicians probably had a negative impact on her drug adherence. PGx testing and counselling initially reassured Mrs T that her case was indeed being taken seriously, and that the choice of SSRI had empirical support. Furthermore, her sertraline prescription could be safely increased above 200 mg, the maximum dose usually recommended for MDD (2), and the physician could be assertive in supporting continuation long enough to see the beneficial effects on OCD symptoms (starting at about 4 to 6 weeks in this patient).

4. Conclusions

Genetic factors influencing treatment response in OCD remain poorly understood. However, from a pharmacokinetic perspective, genetic variations in cytochrome P450 enzymes offer promising insights (Zai, 2021). While SSRIs are considered the first-line treatment for OCD (Lambert, 2008), their use is often associated with significant challenges, including delayed onset of action, the need for high doses, side effects, and consequently poor treatment adherence. With this in mind, the CPIC has provided validated recommendations for pharmacogenetic (PGx) testing for SSRI administration (Bousman et al., 2023), which may substantially reduce the number of therapeutic trials, dose-related adverse effects, and overall societal costs (Skokou et al., 2024; Swen et al., 2023). Although current evidence does not yet support the broad, preemptive use of PGx testing in OCD (Zai, 2021; Brandl et al., 2014), this tool should be viewed as an emerging strategy for guiding SSRI selection. Finally, genetic factors influencing treatment response, particularly regarding pharmacodynamic mechanisms involving the serotonergic and glutamatergic systems in the central nervous system, remain poorly understood, and further research is needed to refine our understanding of these dimensions in OCD patients (Zai, 2021).

Informed consent

Mrs. T gave her written inform consent for this work.

Fundings

None.

Data availability

All the original data are presented in the article., Further inquiries can be directed to the corresponding author.

Patient consent statement

I hereby certify that I have personally obtained informed consent from the patient described in this clinical case report. The patient has reviewed the information presented and has explicitly agreed to the

publication of all relevant clinical details, provided that her identity remains fully anonymized.

CRediT authorship contribution statement

Avigaelle Amory: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Aurelie Casterman:** Conceptualization. **Philippe de Timary:** Writing – review & editing, Project administration, Methodology. **Vincent Haufroid:** Writing – review & editing, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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