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Case Report: Pharmacogenetics Applied to Precision Psychiatry Could Explain the Outcome of a Patient With a New *CYP2D6* Genotype

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Precision medicine applied to psychiatry provides new insight into the promising field of precision psychiatry. Psychotic disorders are heterogeneous, complex, chronic, and severe mental disorders. Not only does the prognosis and the course of the disease vary among patients suffering from psychotic disorders, but the treatment response varies as well. Although antipsychotic drugs are the cornerstone of the treatment of schizophrenia, many patients only partially respond to these drugs. Furthermore, patients often experience adverse events which can lead to poor treatment adherence. Interindividual variability in drug response could be related to age, gender, ethnicity, lifestyle factors, pharmacological interactions, obesity, and genetics, all of which influence the process of drug metabolism. Commonly prescribed antipsychotics are metabolized by cytochrome P450 (*CYP450*) enzymes, and *CYP450* genes are highly polymorphic. Pharmacogenetic testing is increasingly being used to predict a patient's drug response and could help to find the most appropriate therapy for an individual patient. In this report, we describe a psychotic patient who did not receive adequate clinical follow-up and subsequently presented adverse events, which could be explained by his pharmacogenetic profile and the drug interactions resulting from the polypharmacy prescribed.

Keywords: antipsychotic agents, pharmacogenetics, cytochrome P450 enzyme system, psychotic disorders, precision medicine

INTRODUCTION

An increasing number of children, adolescents, and adults (1) are being diagnosed with mental illness, including depressive disorder, bipolar disorder, and schizophrenia spectrum disorder (2–7). According to the World Health Organization (8), people with mental disorders experience higher rates of disability and mortality compared to the general population, making these conditions a priority of health systems.

Psychotic disorders are a group of heterogeneous, complex, chronic, and severe mental diseases that manifest through positive (hallucinations, delusions, etc.) and negative (impaired motivation, social withdrawal, etc.) symptoms, affecting approximately 1% of the global population (9, 10). Not only are the prognosis and disease course of psychotic disorders variable among patients, but so is treatment response. Antipsychotic drugs comprise the fundamental treatment of schizophrenia and other psychotic disorders (11, 12), but many patients do not only partially respond to drug therapy (13, 14). Furthermore, patients often experience side effects when taking antipsychotics including sedation, cognitive impairment, weight gain and obesity, metabolic syndrome, cardiovascular and neuromotor side effects, among others, which can lead to poor adherence or discontinuation of treatment (15–19).

Interindividual variability in the hepatic metabolism of these drugs may be impacted by several factors including age, gender, ethnicity, lifestyle factors (e.g., tobacco and alcohol consumption, diet), pharmacological interactions (patients taking multiple drugs), obesity, and variation in the genes contributing to the metabolism of the drugs taken (20–22). Many commonly prescribed antipsychotics are metabolized by cytochrome P450 enzymes, mainly *CYP2C19* and *CYP2D6* (23–26).

CYP genes are highly polymorphic, and patients with extreme phenotypes, i.e., those with no or low activity or increased activity, have been shown to have an increased risk of adverse events or treatment failure due to drug levels that are either too high or too low (27, 28). Thus, pharmacogenetic testing is increasingly utilized to predict a patient's metabolic capacity and utilize this knowledge to inform drug therapy (29–33). Variable enzyme activity can to a large part be explained by the presence of variations on the nucleotide level [i.e., single-nucleotide polymorphisms (SNPs)] but also be caused by gene copy number variation (CNVs), i.e., gene duplications or deletions, and rearrangements (34, 35). Genotype is typically translated into phenotype [i.e., poor metabolizers (PM), intermediate metabolizers (IM), normal metabolizers (NMs), rapid metabolizers (RMs), and ultrarapid metabolizers (UMs)] and therapeutic recommendations based thereof. For *CYP2D6* genotype to phenotype translation, recommendations have been published by the Clinical Pharmacogenetics Implementation Consortium (36). Additional details and translation tables for other *CYPs* can be found on the PharmGKB website at https://www.pharmgkb.org/page/pgxGeneRef.

CYP2D6 is one of the most important and extensively studied *CYP450* enzymes (34, 37). It has been shown to contribute to the metabolism of over 20% of commonly prescribed medications (38) including atypical antipsychotics such as aripiprazole, asenapine, clozapine, olanzapine, quetiapine, and risperidone. To date, the Pharmacogene Variation Consortium (39, 40) has described over 140 variant alleles (star alleles) (41). Approximately 5–10% of the European population are poor metabolizers due to having two nonfunctional alleles (42). Additional information regarding allele and genotype frequencies can be found on the PharmGKB website.

In this report, we describe a psychotic patient who did not receive adequate clinical follow-up and presented with side effects, which could have been prevented considering pharmacogenetic test results, complex history, and polypharmacy.

CASE DESCRIPTION

The following report describes the situation of a male European patient, who gave us consent to publish his situation, who was born in 1956, and who had been receiving mental health care since 1993, initially under private care, with a diagnosis of schizotypal personality disorder (DSM-V, F21). Regarding the psychiatric family history, his father suffered from bipolar disorder (DSM-V, F31), and his brothers suffered from major depressive disorder (DSM-V, F33). The review of the family history also revealed a psychotic disorder in a second-degree relative (niece). Somatic personal history included hemorrhoids and an anal fissure. The patient did not smoke, drink alcohol, or have a history of substance abuse. During the routine clinical analysis performed throughout the study, there were no ionic, metabolic, or hematological alterations found. In 1994, during his first admission at the University Hospital of Salamanca, he was diagnosed with schizoaffective disorder bipolar type (DSM-V, F25.0). From 1994 to 2015, follow-up treatment was carried out with no hospital admissions and no documented adverse events (AE). In the months following his mother's death and the admission of this father into a care facility, the patient overdosed on lithium with autolytic intention, which required a 3-day stay in intensive care. After this event, the patient clinically deteriorated, and his treatment was changed in seven phases (see **Figure 1A**):

1st treatment plan (1994–18/01/2016): The first admission was triggered by hypomanic symptoms (expansive mood, ideo-fleeting speech, decreased sleep needs, and maniform symptomatology), after which he was diagnosed with schizoaffective disorder. The treatment prescribed when he was described was as follows: lithium, amisulpride, escitalopram, trazodone, and clobazam. No documented AE. After a sudden change in his familiar environment, the patient overdosed on lithium, with autolytic intention, which required a 3-day stay in intensive care, and was hospitalized for 43 days (6/12/2015–18/01/2016), presenting with rudeness, inappropriate sexual behavior, childish utterances, emotional coldness, and antagonistic behavior. Previous treatment was continued with minor extrapyramidal effects. For pharmacogenetic interactions (see **Figure 1B**).

2nd treatment plan (18/01/2016–13/06/2016): Based on the adverse effect referred by the patient and taking into account his poor clinical progress during the last hospitalization, the prescriber adjusted the drug treatment upon the patient's release to only include lithium and amisulpride, neither of which is metabolized by a *CYP* enzyme. Although this adjustment reduced adverse effects, the patient's clinical condition did not improve, and he was readmitted for 49

days (25/04/2016–13/06/2016) due to disturbed behavior with neither depressive nor psychotic symptomatology whereupon he was treated with amisulpride, lorazepam, lormetazepam, quetiapine, and fluoxetine with deep venous thrombosis and gastrointestinal bleeding (melena) as AE.

A pharmacogenetic test [AmpliChip *CYP450* Test (43), the Antigenomics platform, MassARRAY 4.2 (Agena), and probed-based assays using the Light-Cycler platform] was performed while the patient was hospitalized. The following allelic variants were tested: *CYP2B6* (*6), *CYP2C9* (*2 and *3), *CYP2C19* (*2, *3, and *17), *CYP2D6* (*2, *3, *4, *5, *6, *7, *8, *9, *10, *12, *14, *17, *29, *41, and presence of gene duplication), *CYP3A4* (−392 G>A), *CYP3A5* (*3), and *MDR1* (3435C>T) (**Table 1**). Allele nomenclature was per the Pharmacogenetic Variation (PharmVar) Consortium

(41). The *CYP2D6* genotype, however, was returned as a "no call". Subsequent gene resequencing revealed that the patient had a novel allele, which was submitted to PharmVar (41) and designated *CYP2D6*119*. The genotype of the patient was revised to *CYP2D6*4/*119*. The *CYP2D6*119* allele shares many sequence variants with the decreased function *CYP2D6*41* allele but lacks 2851C>T (p.R296C). Due to the presence of 2989G>A which has been shown to impact splicing, the *CYP2D6*119* allele may have decreased function (PMID 33043448); thus we classified the patient as an IM (it is noted though that CPIC classified this alleles as "unknown function"). PM status for *CYP3A5* and decreased expression of the *MDR1* drug transporter were also discovered.

3rd treatment plan (13/06/2016–04/10/2016): Upon discharge, a treatment readjustment was made, as the
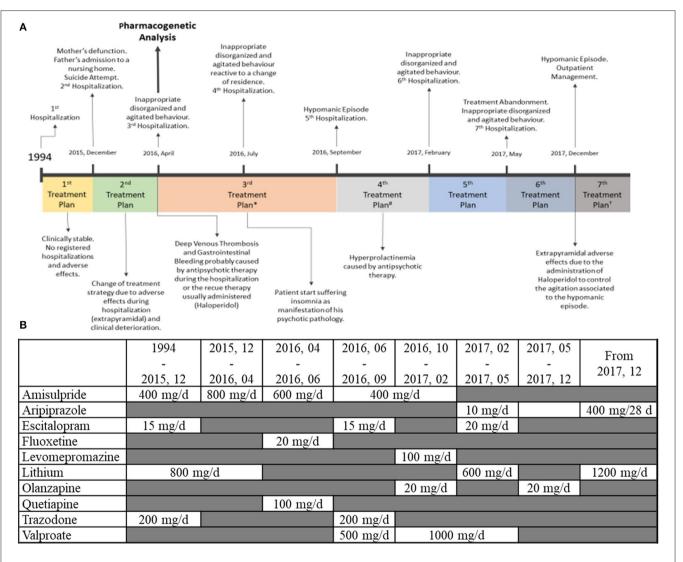

FIGURE 1 | (A) Clinical history of the patient from 1994 to the end of the case study. *Therapeutic plan is slightly modified due to the patient's complaints of insomnia. #One of the antipsychotics used is discontinued due to the appearance of hyperprolactinemia. †After stabilizing a hypomanic episode, olanzapine (oral) is substituted by aripiprazole (LAI), and therapy is readjusted to control insomnia. **(B)** Pharmacotherapy doses. Daily doses administered through the different stages of the patient clinical evolution. Mg, milligram; D, day.

	1994 - 2015, 12	2015, 12 - 2016, 04	2016, 04 - 2016, 06	2016, 06 - 2016, 09	2016, 10 - 2017, 02	2017, 02 - 2017, 05	2017, 05 - 2017, 12	From 2017, 12
Amisulpride	400 mg/d	800 mg/d	600 mg/d	400 mg/d				
Aripiprazole						10 mg/d		400 mg/28 d
Escitalopram	15 mg/d			15 mg/d		20 mg/d		
Fluoxetine			20 mg/d					
Levomepromazine					100 mg/d			
Lithium	800 mg/d				600 mg/d			1200 mg/d
Olanzapine					20 mg/d		20 mg/d	
Quetiapine			100 mg/d					
Trazodone	200 mg/d			200 mg/d				
Valproate				500 mg/d	1000 mg/d			

potential increase in quetiapine plasma levels due to the quetiapine-fluoxetine pharmacokinetic interaction was thought to be related to the emergence of the deep venous thrombosis, combined with the fact that the hospital stay was prolonged, and the patient could have been bedridden longer than usual. The new prescription consisted of lorazepam, amisulpride, valproate, escitalopram, and trazodone. There were no documented AE, but required two hospitalizations of 9 days (04/07/2016–13/07/2016), due to behavioral disturbances in response to a change of residence, and 21 days (13/09/2016–04/10/2016), due to an exacerbation of the hypomanic symptomatology. Previous treatment was continued with minor extrapyramidal effects and insomnia.

4th treatment plan (October 2016–February 2017): Given the profile of adverse effects reported by the patient (excessive morning sedation and extrapyramidal symptoms) and the fact that the patient was not receiving a satisfactory therapeutic benefit, the pharmacological treatment was readjusted to amisulpride, olanzapine, valproate, and levomepromazine. Hyperprolactinemia was found in a routine clinical analysis,

and amisulpride was suspended. The patient was hospitalized for 9 days (22/02/2017–03/03/2017) because of behavioral disturbances and depressed mood with delusions of guilt and harm, exhibiting mutism and a catatonic attitude. Treatment was continued with extrapyramidal effects during the hospitalization.

5th treatment plant (February 2017–May 2017): The patient was discharged with aripiprazole, lithium, clonazepam, lormetazepam, and citalopram. Minor extrapyramidal effects. Hospitalized for 12 days (06/05/2017–18/05/2017), due to disorganized behavior and refusal to take medication, with olanzapine, citalopram, lithium, clonazepam, and lormetazepam.

6th treatment plant (May 2017–December 2017): At discharge, the patient continued with olanzapine, clonazepam, lormetazepam, and lorazepam. The patient presented extrapyramidal symptoms after administration of haloperidol due to a manic episode managed as an outpatient.

7th treatment plant (from December 2017): Given the need to control the patient's sleep pattern and in light of the sedative effects of olanzapine, olanzapine was replaced with aripiprazole, eventually a long-acting injectable (LAI), to ensure adherence and simplify the absorption variables, complementing the therapy with lithium, clonazepam, lormetazepam, and pregabalin. From this point, the patient did not present AE, nor needed hospitalization.

DISCUSSION

We present a patient with a novel *CYP2D6* allele, *CYP2D6*119*, which was paired with a known non-functional allele. Since the novel allele and *CYP2D6*41*, a known decreased function allele, essentially only differ by an SNP that is believed to not alter the enzymatic activity, we classified the patient as IM. This phenotype (i.e., decreased *CYP2D6* activity) may have contributed to the extrapyramidal AE presented after administration of levomepromazine and haloperidol, and the

TABLE 1 | Pharmacogenetic analysis.

Gene	Alleles tested	Genotype	Predicted phenotype
CYP2C19	*2, *3, *17	*1/*1	Normal metabolizer
CYP2D6	2-*10, *12, *14, *17, *29, *41, XN	*4/*119	Intermediate metabolizer
CYP2C9	*2, *3	*1/*1	Normal metabolizer
CYP2B6	*6	*1/*1	Normal metabolizer
CYP3A4	−392 G>A	A/A	Normal metabolizer
CYP3A5	*3	*3/*3	Poor metabolizer
MDR1	3435C>T	C/T	Decreased expression

*Alleles listed using the PharmVar Haplotype nomenclature. *Allele.*
Phenotype predictions are according to those recommend by CPIC which are summarized by respective "diplotype to phenotype translation" tables (available at: https://www.pharmgkb.org/page/pgxGeneRef).

TABLE 2 | Pharmacogenetic interaction of all treatment of the patient.

	Cytochrome P450										
	1A2	2B6	2C8	2C9	2C19	2D6 (*)	2E1	3A4	3A5 (†)	3A7	*MDR1* (‡)
Amisulpride											S
Aripiprazole						S (+), Ih Id		S (+)	S (-)	S (-)	S
Escitalopram					S (+)	S (-) Ih		S (-)			S
Fluoxetine	S, Ih	S, Ih	S, Ih	S (+) Ih	S (+) Ih	S (+) Ih	S	S (+) Ih			S
Levomepromazine						Ih, S (+)	Ih				
Lithium											
Olanzapine	S (+)			Ih	Ih	S (±) Ih		Ih			S
Quetiapine						S (-)	S (±) Ih	S (+)	S (-)	S (-)	
Trazodone						S (+)		S (+)	S (-)	S (-)	
Valproate			Ih	S (+) Ih	S (-) Ih			Ih			Id

*CYP2D6*4/*119, CYP2D6 predicted intermediate metabolizer (IM) phenotype. †CYP3A5*3/*3 predicted poor metabolizer (PM) phenotype. ‡MDR1 3435C/3435T predicted decreased expression.
Id (Inducer). Ih (Inhibitor). S (Substrate). + (Major Metabolic Pathway), ± (Minor Metabolic Pathway), - (Minor Metabolic Pathway likely not clinically relevant).

sedation associated with olanzapine. *CYP2D6* has also been described to contribute to the metabolism of quetiapine and aripiprazole. Furthermore, the patient's *ABCB1* genotype may have contributed to the hyperprolactinemia associated with amisulpride, to the deep venous thrombosis related to quetiapine, and, together with *CYP2D6*, to the sedation due to olanzapine. While *CYP2D6* and *CYP3A5* are not always the major metabolic pathway of drugs associated with AE presented by the patient, there could be a phenocopy effect related to drugs metabolized by these pathways.

This complex case illustrates how AE can impact patient compliance (44), as shown in two hospitalizations (February 2017, May 2017) caused by the patient refusing to continue the treatment. The patient was prescribed antipsychotics, which appeared to have repeatedly caused AE. Pharmacogenetic testing helped to partially understand the origin of his AE; it was possibly caused by a combination of his pharmacokinetic phenotype (reduced *CYP2D6* and *CYP3A5* enzymatic activity and *MDR1* expression) and the phenocopy effect related to pharmacokinetic interactions (**Table 2**). A treatment plan that was guided by the patient's pharmacogenetic profile and knowledge about the pharmacokinetics of drugs prescribed drastically improved his medical condition. The patient ultimately reported no AE and continued to evolve favorably underscoring the utility of pharmacogenetic testing to guide pharmacotherapy. The application of this methodology could ensure a significant reduction in both pharmaceutical (fewer exacerbations hence less rescue medication, lower dosages, etc.) and hospitalization-related (fewer hospitalizations required to manage adverse effects or achieving better treatment adherence due to the reduction in the emergence of these adverse effects) economical costs. Although the evolution of the patient is not certain, the clinical intervention applied has a lifelong nature, and the results obtained by the pharmacogenetic analysis could be used by other medical areas. These conclusions should be considered taking into account the limitations of this study. Being this case report based on the application of a recently implemented approach to our service, we could not make use of all the possible variables that could be helpful when managing these patients

(i.e., antipsychotic plasma levels). Moreover, this methodology was introduced, concurring with the increasing use of LAI presentations, which facilitate therapeutic adherence, and it could be a possible confounder. One of the strong points of this approach is that the decisions concerning the pharmacotherapy of the patient were agreed to by a multidisciplinary team (in which psychiatrists and clinical biochemists, among other clinical specialties, participated), which permitted a more profound knowledge about the drug metabolism and the factors influencing drug varying factors and promoted education on this subject for the bio-sanitary personnel (including psychiatric, nurses, psychologist, etc.).

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University Hospital of Salamanca (CEIC ref.: 107/ 12/2016). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

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