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Article type : Clinical Conundrum

Pharmacogenetic variants in Bipolar Disorder with elevated treatment resistance and intolerance: towards a personalised pattern of care

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Accepted Article

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bdi.12763
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KEY MESSAGE

Among the goals of personalized medicine, prediction of favourable treatment response and susceptibility to drugs' adverse reactions are of primary interest in psychiatry. Although far from widespread application, pharmacogenetics might represent an extremely useful tool to aim for an individualised therapy, especially in treatment–refractory cases.

Although available treatments for Bipolar Disorder (BD) are effective in reducing the risk of recurrence, over 90% of patients experience relapses and a significant minority have a poor outcome. Among patients who do respond, mild and subthreshold symptoms of the disorder are frequently observed and greatly affect their quality of life.

Interindividual variability in drug response and side effects depends on a variety of non-genetic factors such as gender, ethnicity, age, smoking, diet, psychiatric diagnosis, disease status and concomitant medications, but also genetic ones[1]. As most antipsychotic medications undergo first-pass metabolism, cytochrome (CYP) 450 enzymes play a crucial role in drug response, influencing bioavailability, clearance and, for some antipsychotics like risperidone and clozapine, bioactivation. Furthermore, pharmacodynamic-related gene variants are hypothesised to affect both drug response and susceptibility to side effects. Overall, specific predictor biomarkers of treatment response are still lacking[2].

Despite the difficulty of clearly defining genetic variants that can guide clinicians towards a prediction of individual drug response, retrospective analysis of specific cases is considered useful in the development of a personalised approach to care.

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We report on the case of a patient with a long history of drug resistance and adverse reactions that led to poor compliance and severe chronicity. A retrospective analysis on the patient's pharmacogenetic profile revealed polymorphisms that could explain otherwise puzzling peculiarities of the patient's history.

Case report

EDP is a 48-year-old Caucasian, smoking female with good premorbid social and cognitive functioning and no reported familiar psychiatric history. The only child of a married couple, whose mother described a physiological perinatal period and early-life psychomotor development, EDP had a clinical onset at the age of 28, with a Manic Episode characterised by elevated mood, increased psychomotor activity, persecutory and grandiose delusions with abnormal behaviour and a significant lack of insight. Abuse of neither alcohol nor any other substance was reported. A diagnosis of BD was made according to DSM-IV criteria and a treatment regimen with a first-generation antipsychotic started. The patient soon complained of severe muscular postural rigidity and a switch to a second-generation antipsychotic and a mood stabilizer was initiated with a rapid emergence of similar adverse reactions. During her long clinical history, she was treated with most available antipsychotics, mood stabilizers and antidepressants, showing severe adverse reactions with almost all of them even at the lowest dose. This often limited the possibility of reaching effective doses and jeopardized her compliance.

EDP presented with a severe disorder with continuous hospitalizations and a progressive deterioration of her psychosocial condition. Throughout her life, she was hospitalized 29 times, spending a total of 372 days on a psychiatric ward. The elevated treatment

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refractoriness and the patient's continuous complaint of adverse events, several of which exquisitely subjective, generated elevated frustration in treating clinicians. The patient presented a globally low level of insight and maintained a highly hostile interaction with the operators involved. Personality traits such as intense episodic dysphoria with anger outbursts, self-dramatization and theatricality during depressive or clinically stable phases generated doubts over the influence of a complex personality disorder on clinical outcome. A personality disorder diagnosis was not confirmed by the Structured Clinical Interview for the DSM-IV Axis II disorders (SCID II). The adverse events were – at least in part – suspected by the clinicians to be feigned or exaggerated by the patient in order to avoid medication and sustain her continuous request to interrupt treatment. Due to the relevant burden of adverse events, the patient began to take medication irregularly and presented sub-chronic manic symptoms. She also continuously refused the psychosocial rehabilitative interventions proposed by our outpatient service. The consequent, progressive psychosocial deterioration led to an isolated lifestyle, with limited social interactions and welfare provision as her only income.

Pharmacogenetic pattern

In 2017, the clinical team conducted a customized, retrospective laboratory analysis of available CYP450 genes involved in the metabolism of the medications EDP had been prescribed over time. The patient provided written informed consent for every analysis conducted.

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Table 1 summarises all the medications administered, their adverse events and reactions and the enzymes involved in their metabolism.

Genomic DNA was isolated from a whole blood sample, using an automatic DNA extraction system (Maxwell® 16 System, Promega) according to the manufacturer's instructions. DNA concentration and purity were evaluated by absorbance methodology using a NanoDrop 1000 Spectrophotometer V3.7 (Thermo Fisher Scientific). SNPs were determined by Real-Time PCR, using a LightSNiP (assays based on SimpleProbe®, TIB-MolBiol) or TaqMan® assay (Applied Biosystems) on LightCycler 480 (Roche).

Most of the drugs indicated for BD are eliminated by CYP450 enzymes. The major CYP3A4/5, CYP1A2, CYP2C19 and CYP2D6 variants – associated with altered enzymes activity – were analysed (Figure 1). Pharmacogenetic testing revealed this patient to be a poor metabolizer (PM) for both CYP2C19 (*2/*2) and CYP3A (CYP3A4*1/*22 and CYP3A5*3/*3). Moreover, the patient was heterozygous for the CYP1A2*1F allele that is known to influence the inducibility of the enzyme. Finally, EDP had an extensive metabolism for the investigated polymorphisms of CYP2D6. Many antipsychotics and antidepressants are also substrates of P-glycoprotein (P-gp), an ABC transporter protein, encoded by the multidrug resistance 1 gene (MDR1, ABCB1). The SNPs 1236C>T (G412G), 2677G>T (A893S), 3435C>T (I1145I) are the most commonly studied coding region variants of *ABCB1* gene, together defining the two most prevalent haplotypes (*ABCB1*1* 1236C-2677G-3435C; and *ABCB1*13* 1236T-2677T-3435T)[3]. The patient was homozygous for the variant alleles T-T-T, corresponding to ABCB1*13 haplotype (Figure 1).

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Discussion

Genotyping revealed reduced metabolism for CYP3A4/3A5 and CYP2C19, hepatic enzymes mainly involved in the metabolism of psychotropic agents[2]. No case with a combination of these three variants has previously been reported. The intronic SNP CYP3A4*22 (rs35599367 C>T) is associated with decreased hepatic CYP3A4 mRNA expression and enzyme activity, thus explaining some interindividual differences observed in clinical responses to drugs. The CYP3A5 enzyme contribution in the metabolism of psychiatric drugs is not fully elucidated, although evidence suggests its substrate specificity may largely overlap with that of CYP3A4. While 95% of Caucasians are CYP3A5 nonexpressers, homozygosity for the CYP3A5*3 allele results in undetectable enzyme activity. In a CYP3A4*22 and CYP3A5*3 combined allelic status, a genotype with CYP3A4*22 carriers and CYP3A5*3/*3 results in a poor metabolizer CYP3A phenotype, with a frequency of 8% in Caucasians.

CYP2C19 is largely involved in the metabolic pathways of some of the most common antidepressants and variations in CYP2C19 activity may result in altered drug exposure. The splicing variant CYP2C19*2 (rs4244285 G>A) is the main defective allele, accounting for some 75 to 85% of CYP2C19 alleles responsible for the poor metabolizer phenotype in Asians and Caucasians. The frequency of CYP2C19*2 has been reported to be 12-15% in Caucasians. The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends dose reductions in CYP2C19 poor metabolizers, or the selection of an alternative drug that is not extensively metabolized by CYP2C19[4].

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CYP1A2 genotyping during antipsychotic treatment contributes to the assessment of both drug efficacy and adverse drug reactions. Across studies, the CYP1A2*1F haplotype has been associated with an altered phenotype, with the A allele leading to lower serum drug concentrations and higher risk of non-response and the C allele leading to higher plasma drug levels and greater risk of adverse reactions. The patient presented a minor-inducible CA genotype at CYP1A2 rs762551 that could represent a 'slower' metabolizer phenotype compared to AA genotype. Yet a significant impact of environmental factors, mostly smoking status, on CYP1A2 activity has been reported. This suggests that pharmacogenetic testing, in this specific case, has to be complemented by other clinical tools, such as therapeutic drug monitoring (TDM), an action we could not do here extensively due to the retrospective nature of our analysis.

Variability in drug response is also a function of drug distribution throughout the body, and particularly to the brain. Many CNS drugs are substrates of transmembrane transporter P-glycoprotein 1 (P-gp), encoded by ABCB1 gene in humans, that plays a crucial role in their distribution. It functions as a drug efflux pump with a protective and excretory role; it influences the permeability limitation of drugs, especially for complex organs, such as the brain. Consensus on the association between ABCB1 SNPs and drug response has been lacking, due to their unclear effect on protein expression and activity, with no established clinical indication for analysis of variants. Despite this, in a recent study, Papazisis and colleagues conclude that an interaction between ABCB1 and CYP2D6 might affect patients' response to antipsychotic treatments[5]. Indeed, patients carrying a combination of a loss of function (LOF) CYP2D6 allele and an ABCB1 rs2032582 TT genotype presented a significantly worse response to antipsychotic drug treatment compared to non-carriers. According to these results and considering that P-gp and some drug-metabolizing enzymes share the

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same substrates of centrally active drugs, treatment resistance might be influenced by an association of LOF alleles other than CYP2D6 with homozygous recessive ABCB1 rs2032582 genotypes (TT).

In the case presented, several adverse reactions might have developed due to an elevated vulnerability at the lowest doses.

Complex patients with severe psychopathology are known to reduce their compliance due to an elevated burden of adverse reactions. Low compliance is highly correlated with worse outcomes and recurrent hospitalizations. In the case presented, most of the drugs metabolized by hepatic enzymes, with a poor metabolizer genotype-phenotype association, failed because of adverse reactions. Strikingly, a recent introduction of Paliperidone – which is largely excreted unmetabolized – led to a progressive reduction of symptoms within a period of 4 weeks from its titration. The patient entered a stable remission, during which she has accepted a long-acting monthly injection and a trial with Lithium Sulphate 124.5 mgs/day. Paliperidone Palmitate was tapered to suspension after 12 months and the patient remained stable on a Lithium monotherapy for a further 6 months.

So far, the use of pharmacogenetics has been limited by the lack of evidence on improved clinical outcomes. Although not every patient is likely to benefit from a prospective approach, patients with marked resistance or intolerance to conventional treatment might in future gain a relevant benefit from early pharmacogenetics screening and the consequent choice of a tailored medication regimen.

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LEARNING POINTS

- Treatment-refractory BD cases deserve a more comprehensive and thorough assessment in order to investigate the possible alternatives for unsatisfactory response to medications
- Pharmacogenetics analyses on CYP450 enzymes might be of extreme help for patients who show high susceptibility to severe and multiple adverse reactions to common medications
- Selected patients with rare genetic variants of CYP450 enzymes might benefit from the choice of a treatment based on its metabolism and possibly a dose adjustment.

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Table 1. Summary of the adverse reactions and metabolic profile of each drug taken

Drug		Adverse reactions	Enzymes*
Antipsychotics	Aripiprazole	Dizziness, stomach pain and acidity	**CYP2D6, CYP3A4**
	Chlorpromazine	EPS, hyperprolactinemia, menstrual disorders	**CYP1A2, CYP2D6**,
	Clozapine	Important sedation, weight gain	**CYP1A2** CYP2D6, CYP3A4
	Fluphenazine Decanoate	EPS (muscular rigidity, bradykinesia, diffused tremors)	**CYP2D6**
	Haloperidol	EPS (muscular rigidity, tremors)	CYP2D6, **CYP3A4**
	Levomepromazine	Swelling of eyelids and ankles, diffuse itching	**CYP3A4**,CYP1A2
	Olanzapine	Conjunctivitis, diffused tremor, constipation, oligomenorrhea	**CYP1A2,** CYP2D6
	Paliperidone	None relevant	60% excreted unmetabolized (minor role for CYP2D6 and CYP3A4)
	Risperidone	EPS (muscular rigidity, tremors), sedation	**CYP2D6,** CYP3A4
	Ziprasidone	Dizziness, vertigo	CYP3A4
	Zuclopenthixole	EPS (muscular rigidity)	CYP2D6
Mood stabilizers	Carbamazepine	Unknown to authors	**CYP3A4**, CYP2C8, CYP1A2, CYP2B6
	Lithium Carbonate	Dermatological problems (dorsal acne)	renal clearance
	Oxcarbazepine	Unknown to authors	renal clearance
	Valproic Acid	Weight gain, menstrual disorders	**UGTs,** CYP2C9, CYP2A6, CYP2B6
Antidepressants	Citalopram	Unknown to authors	**CYP2C19**, CYP3A4, CYP2D6
	Clomipramine	Dry mouth, constipation	**CYP2C19, CYP2D6** CYP3A4, CYP1A2
	Fluoxetine	Dry mouth, constipation	**CYP2D6, CYP2C9,** CYP2C19, CYP2B6, CYP1A2, CYP3A4
	Mirtazapine	Unknown to authors	**CYP2D6**, CYP1A2, **CYP3A4**
	Sertraline	Dry mouth, constipation	**CYP2C19, CYP2B6** CYP2D6, CYP2C9, CYP3A4

The major metabolic pathway **in bold.*

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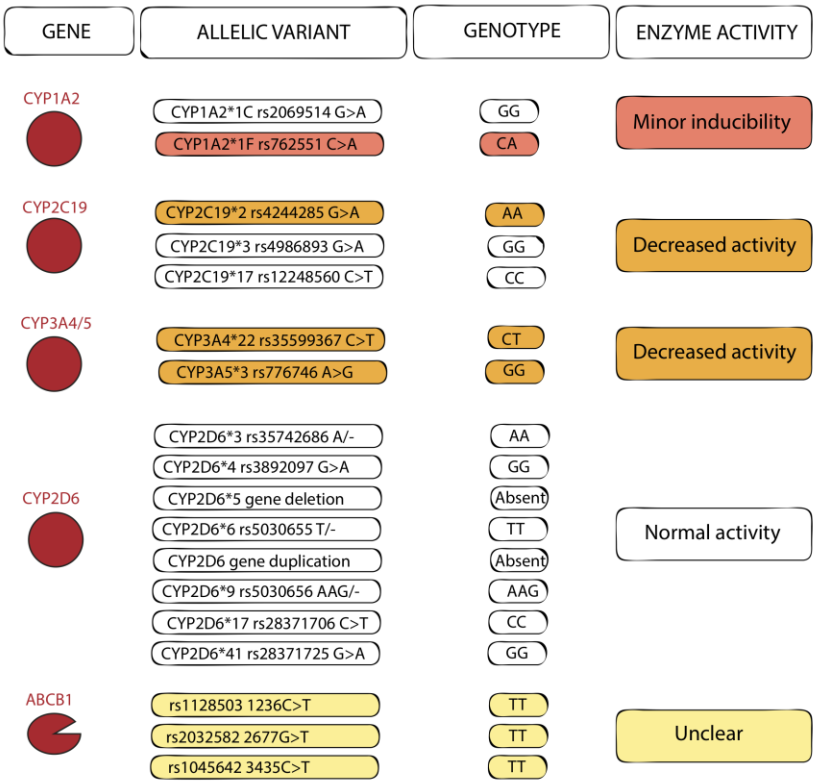
Figure 1. Customized genotyping analysis



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