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CYP2D6 genotypes in revolving door patients with bipolar disorders

A case series

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Abstract

Rationale: In psychiatric disorders, interindividual differences in cytochrome P450 (CYP)2D6 (CYP2D6) enzymatic activity could be responsible of adverse drug reactions (ADRs) and therapeutic failures (TFs) for CYP2D6-metabolized drugs, contributing to the periodical hospital readmissions of the revolving door (RD) condition.

Patient concerns: We investigated *CYP2D6* genotypes in a controlled series of 5 consecutive RD patients with Bipolar Disorder (BD).

Diagnoses: Psychiatric patients affected by Bipolar Disorder.

Interventions: We defined TFs as a difference at the Brief Psychiatric Rating Scale score $\Delta BPRS < 25\%$ at each 1-week of stable treatment, and ADRs as the onset of extrapyramidal symptoms and/or metabolic impairment with weight gain.

Outcomes: At 3 months, a mean number of 2.75 ± 1.26 ADR and a mean $\Delta BPRS$ score of $16.07 \pm 0.05\%$ were observed. At 6 months of follow-up, compared to the only patient without BD ($\Delta BPRS < 32.10\%$), BD patients ($n = 4$) showed TFs ($\Delta BPRS < 25\%$). *CYP2D6* genotyping revealed intermediate metabolizer phenotypes for BD patients and an extensive metabolizer phenotype for the patient without BD. In BD patients, the ratio of drugs maintained/discontinued for TFs or ADRs was 1.75 for non-CYP2D6 versus 0.33 for CYP2D6 interacting drugs, while the proportion of ADR:TF was 0:4 versus 6:3.

Lessons: Our findings may suggest that CYP2D6 clinically relevant genotypes may be involved in the unwanted outcomes observed in RD patients with BD.

Abbreviations: ADRs = adverse drug reactions, BD = bipolar disorder, BPRS = Brief Psychiatric Rating Scale, CAN = Camberwell Assessment of Need, CYP = cytochrome P450, DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revised, RD = revolving door, TFs = therapeutic failures.

Keywords: adverse drug reaction, bipolar disorders, CYP2D6 polymorphisms, revolving door, therapeutic failure

1. Introduction

Psychiatric illnesses, mainly bipolar disorder (BD), are chronic and recurrent pathological conditions characterized by repeated and severe changes in mood, leading to significant mental and social impairments with an increased risk for suicide, and thus among the most important causes of death and disability worldwide.[1] Psychiatric diseases affected 3% to 5% of the Caucasian population,[2] with BD accounting for 4.4 to 10.3 of

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years lived with disability,[1] with a cost for the health services at about $15B in the US and in Western countries.[3,4]

Evidenced-based treatment guidelines included a wide range of medications for the clinical management of these patients, such as mood stabilizers, first- and second-generation antipsychotics, antidepressants, and anxiolytics, also in multidrug combinations.[5,6] Despite the availability of this wide range of different drug classes, however, psychiatrists still met great difficult in treating psychiatric illnesses, since treatment response is often inadequate, and the rate of remission is poor, particularly among BD in the depressive phase.[7] Consequently, about 30% to 50% of psychiatric patients showed therapeutic failures (TFs), regardless of the initial choice of psychiatric medication.[8] Finally, many drugs are poorly tolerated, and adverse drug reactions (ADRs), like metabolic disturbances and extrapyramidal symptoms, are common.[9–11]

Previous studies have correlated the length of psychiatric hospitalization with cytochrome P450 (CYP)2D6 (CYP2D6) functional status.[12,13] However, the recurring nature of the psychopathological course of psychiatric illnesses, together with the unwanted outcomes observed in these patients, are probable the major responsible of the revolving door (RD) condition, a periodical hospital readmission without any substantial improvements in psychiatric symptoms,[14] further increasing costs for their clinical management.

The identification of genetic factors underlying drug response is among the most promising areas of research in psychiatric medicine.[15–19] Currently, more than 20 psychotropic drugs have been relabeled by the US Federal Drug Administration adding information on polymorphic drug metabolism and therapeutic recommendations.[15] In particular, CYP2D6 genetic variability has been recently suggested to have a main role in the response to treatment of psychiatric disorders[20–23] and in determining TFs and ADRs to psychotropic drugs.[24–27] Several professional societies have started to develop proper clinical guidelines to maximize the therapeutic effects when minimizing the toxicity in pharmacotherapy including the Clinical Pharmacogenetics Implementation Consortium[28] and the Dutch Pharmacogenetics Working Group.[29] The objective of the present study was to evaluate the contribution of *CYP2D6* genetics to the unwanted outcomes observed in a controlled series of 5 consecutive RD patients with BD attending a psychiatric setting.

2. Methods

2.1. Study design and guidelines

This was a cross-sectional study of a controlled case series, fulfilling the CARE guidelines,[30] Declaration of Helsinki (available at URL http://www.wma.net/en), the guidelines for Good Clinical Practice,[31] the National Institute for Health and Care Excellence,[32] and the Canadian Network for Mood and Anxiety Treatments guidelines.[5] Study design is summarized in Table 1. The research project of the present study has been approved from the Ethics Committees on human experimentation of the IRCCS "Casa Sollievo della Sofferenza," San Giovanni Rotondo, Foggia, Italy and the University of Foggia, Foggia, Italy (Protocol number: 115/CE/2015, October 10, 2015). All the investigated patients gave their informed consent to the publication of the cases in anonymous form.

2.2. Revolving door condition

The RD condition was defined for those patients having a minimum of 4 admissions, and no admission or discharge period lasting for more than 1/4 of the observation period or at least 4 admissions over the first 1/4 of the observation period.[13] The time lapse in which the RD condition was defined is summarized in Table 1. To avoid bias in RD evaluation, that is, any clinical or social needs that aggravate the disease or to explain disease exacerbation, possibly miming/exacerbating the RD condition, the Camberwell Assessment of Need (CAN) rating scale[33] was administered to each patient. A CAN score < 10 is the threshold for a patient to be considered as having no significant clinical/social needs.

2.3. Patient's recruitment and inclusion/exclusion criteria

The study included all the RD patients that consecutively admitted from January 1 to June 30, 2015 to the Psychiatric Unit of the University of Foggia (Foggia, Italy). Written informed consent for research was obtained from each patient's relatives before the enrollment. Inclusion criteria were: Caucasians race, with Italian ancestry living in Italy for at least 2 generations, a diagnosis of psychiatric illnesses according to the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revised (DSM-IV-TR),[34] a RD condition identified in the past 3 years (2013–2015), and a CAN score < 10. Patients were excluded if they have physical complications, history of seizure disorder, dementia, and diabetes mellitus or abused psychoactive in the last 2 years. Subjects older than 70 years, or with intelligence quotient < 70, and women who were pregnant or breastfeeding, were also excluded from the study.

2.4. Therapeutic failures (TFs) and adverse drug reactions (ADRs) assessment criteria

Psychiatric symptoms evaluation was conducted using the 24-item Italian version of the Brief Psychiatric Rating Scale Expanded Version 4.0 (BPRS).[35] According to Leucht et al,[36] the response to treatment was defined by a change in BPRS score $\geq 25\%$ as evaluated at the beginning of (T_0) and at 1 week (T_1) of stable treatment (100% of medications adherence) according to the following formula: $\Delta BPRS = (BPRSt_1 - BPRSt_0)/BPRSt_0 \times 100$. A ΔBPRS score $< 25\%$ suggested a TF. Drug-induced extrapyramidal symptoms were evaluated by means of the Simpson Angus Scale (SAS).[37] An SAS score > 0.3 and/or an early drug-induced metabolic impairment with weight gain according to percent change in body mass index (BMI)[38] were considered as ADRs. An SAS score ≤ 0.3 is considered within the normal range. Both TFs and ADRs were evaluated by at least two 6-years experienced treating psychiatrists in blinded fashion.

2.5. CYP2D6 genotype analysis

Genomic DNA was purified from frozen blood samples following the salting-out method.[39] As previously reported,[40] the analysis of the 16 clinical relevant polymorphisms *CYP2D6*2*, *CYP2D6*2A*, *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*6*, *CYP2D6*7*, *CYP2D6*8*, *CYP2D6*9*, *CYP2D6*10*, *CYP2D6*12*, *CYP2D6*14*, *CYP2D6*17*, *CYP2D6*29*, *CYP2D6*41*, *CYP2D6*XN* in the CYP2D6 gene was made in blinded fashion by means of the INFINITI Analyzer (AutoGenomics, Inc., Carlsbad, CA) using the INFINITI CYP4502D6-I Assay according to manufacturer instructions. All the *CYP2D6* genotypes were interpreted according to the Home Page of The Human Cytochrome P450 (CYP) Allele Nomenclature Committee.[41] Indications about the metabolizer phenotypes resulting from *CYP2D6* genetics were reported as already described.[42,43]

Table 1

Time lapse in which the revolving door (RD) condition was defined in our case series of patients with psychiatric illnesses.

					Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Time lapse defining the RD condition		Retrospective	2013	January					
				February		Admission	Admission		
				March	Admission				
				April					
				May					
				June					
				July					
				August					
				September					
				October					
				November					
				December	Admission				Admission
			2014	January					
				February		Admission		Admission	
				March					
				April				Admission	
				May					
				June					
				July					Admission
				August					
				September				Admission	
				October	Admission		Admission		
				November					
				December					
	Recruitment	Perspective	2015	January	Outpatient				Admission
				February		Admission[‡]	Admission		
				March	Admission[*,†]			Admission	
				April		Admission	Admission		
				May					Admission[§]
				June					
	Follow-up			July					
				August					
				September					
				October	Outpatient				Outpatient
				November				Outpatient	
				December					Admission

[*] Transfer from intensive care unit after attempted suicide.
[†] Voluntary discharge after 2 weeks.
[‡] Transfer from Emergency Surgery Care Unit after attempted suicide.
[§] Voluntary discharge after 1 week.

3. Results

In the 6 months of recruitment, 5 consecutive psychiatric RD patients (4 females and 1 male, mean age 44.40 ± 7.23 years, range from 37 to 54 years) were enrolled in the study. Three of these patients received a diagnosis of type-II BD, whereas 1 patient received a diagnosis of type-I BD, and 1 patient a diagnosis of bipolar-type schizoaffective disorder. Two patients smoke $n \geq 20$ cigarettes/daily. In each patient, no neurological or cognitive deficits were observed, with a computed tomography (CT) scan image within normal limits. For each patient, a detailed clinical history is reported in Supporting Document 1, and summarized in Table 1, http://links.lww.com/MD/.

Patient 1 was a 44 years old female. Since 1995, the patient received a diagnosis of chronic type-I BD. With a previous history of attempted suicides, the patient was frequently admitted to the Psychiatric Unit of the University of Foggia for recurrent mixed mood states and obsessive–compulsive symptoms, frequently associated with sexual and aggressive urges. Overall, a total of 8 drugs were administered to this patient. Across 4 hospital readmissions 7 of these drugs were discontinued because to ADR or TF (Table 2, Fig. 1A). At the analysis of the CYP2D6 genotype, the patient resulted *CYP2D6*2A/CYP2D6*5*. In detail, the allele *CYP2D6*2A* is associated to a minimal increased enzymatic activity because of an higher promoter activity in vivo associated with the A allele of the polymorphism $G^{2,988} \rightarrow A$ (rs28371725), always in linkage disequilibrium with the G allele of rs1080985,[44] the single nucleotide polymorphisms (SNP) labeling *CYP2D6*2A*. On the other hand, the allele *CYP2D6*5*, consisting in a gene deletion, is representative of a missing enzymatic activity (The Human Cytochrome P450 (CYP) Allele Nomenclature Database). Thus, genotype *CYP2D6*2A/CYP2D6*5* was indicative of a reduced enzymatic activity that can be assigned to the intermediate metabolizers (IMs).

Patient 2 was a 37 years old male. Since 2005, the patient received a diagnosis of chronic bipolar-type schizoaffective disorder, and was repeatedly admitted to the Psychiatric Unit of the University of Foggia for psychotic exacerbation. The patient presented auditory disturbances in the form of mandatory hallucinations, ideas of reference and not-bizarre ideas with suspiciousness, accompanied with a significant drop in social and

Table 2

Drug treatments in our case series of revolving door (RD) patients with psychiatric illnesses.

	Amisul-pride	Aripip-razole*	Asena-pine*	Clona-zepam	Chlorpro-mazine*	Cloza-pine*	Delora-zepam	Diaze-pam	Escita-lopram*	Halope-ridol*	Lamo-trigine	Lithium	Loraze-pam	Metfo-rmin	Olanza-pine*	Orphena-drine*	Oxcarba-zepine	Palipe-ridone	Paro-xetine*	Quetia-pine*	Risperi-done*	Trazo-done*	Valp-roate	Venla-faxine*
Patient 1		ADR†							TF		OK	TF			ADR‡			TF§		ADR			TF	
(BD-I)		(D)							(D)		(M)	(D)			(D)			(D)		(D)			(D)	
Patient 2	OK					OK				TF		TF			TF								TF	
(non-BD)	(M)					(M)				(D)		(D)			(D)								(D)	
Patient 3		ADR		OK					TF												TF	OK	TF	
(BD-II)		(D)		(M)					(D)												(D)	(M)	(D)	
Patient 4								OK		ADR				OK	ADR	OK			OK	ADR	TF		OK	
(BD-II)								(M)		(D)				(M)	(D)	(M)			(M)	(D)	(D)		(M)	
Patient 5		ADR	ADR		TF		TF						OK				OK			ADR		OK	TF	ADR
(BD-II)		(D)	(D)		(D)		(D)						(M)				(M)			(D)		(M)	(D)	(D)
ADR/TF		ADR	ADR		TF		TF		TF	ADR/TF		TF			ADR/TF			TF		ADR	TF		TF	ADR
Disc/maint	M	D	D	M	D	M	D	M	D	D	M	D	M	M	D	M	M	D	M	D	D	M	D/M	D

ADR = adverse drug reaction, BD = bipolar disorder, D = discontinued, M = maintained, OK = no ADR no TF, TF = therapeutic failure.

* CYP2D6 metabolism.

† Reintroduced to one-half dosage with no ADR.

‡ Introduced twice, and discontinued twice for ADR.

§ The introduction of paliperidone pamoate resulted in an ADR.

occupational functioning and 4 cruel suicide attempts for caustics and drug ingestion and injection. Overall, a total of 6 drugs were administered to this patient. Across 4 hospital readmissions 4 of these drugs were discontinued because to TF (Table 2, Fig. 1B). No ADR were observed in this patient. At the analysis of the CYP2D6 genotype, the patient resulted *CYP2D6*1/CYP2D6*2A*. In detail, in this patient the allele *CYP2D6*2A* (described for patient 1) is combined with *CYP2D6*1*, the wild-type allele (The Human Cytochrome P450 (CYP) Allele Nomenclature Database). Thus, genotype *CYP2D6*1/CYP2D6*2A* is indicative of a normal enzymatic activity that can be assigned to the extensive metabolizers (EMs).

Patient 3 was a 49 years old female. Since 1996, the patient was diagnosed as obsessive–compulsive disorders and, from 2013, as type-II BD with psychotic behavior and recurrent depressive episodes. At the first admission to the Psychiatric Unit of the University of Foggia, the patient presented symptoms of sad mood, social withdrawal, reduced speech output, forgetfulness, motor movement and vocal sounds-like tics. The patient also expressed death wishes and refuted to carry out even basic activities of daily living. Overall a total of 6 drugs were administered to this patient. Across 4 hospital readmissions 4 of these drugs were discontinued because to ADRs or TFs overall TF (Table 2, Fig. 1C). At the analysis of the CYP2D6 genotype, the patient resulted *CYP2D6*2A/CYP2D6*4*. In detail, allele *CYP2D6*2A* (described for patient 1) was combined with allele *CYP2D6*4*, identified by a splicing defect associated to a not-functional protein, responsible of a missing enzymatic activity (The Human Cytochrome P450 (CYP) Allele Nomenclature Database). Thus, genotype *CYP2D6*2A/CYP2D6*4* was indicative of a reduced enzymatic activity that can be assigned to the IMs.

Patient 4 was a 54 years old female. Since 1984, she was diagnosed as enduring type-II BD. Monthly admitted to the Psychiatric Unit of the University of Foggia, the patient presented perceptual disturbances in the form of content calling the patient's name, psychotic behavior with recurrent depressive episodes frequently expressing death wishes with several previous suicide attempts. A successive attempted suicide episode caused a minor head injury. Overall a total of 9 drugs were administered to this patient. Across 4 hospital readmissions, 4 of these drugs were discontinued because to ADR or TF (Table 2, Fig. 1D). At the analysis of the CYP2D6 genotype, the patient resulted *CYP2D6*4/CYP2D6*17*. In detail, the allele *CYP2D6*4* (described for patient 3) in this patient was combined with allele *CYP2D6*17*. This allele is identified by the amino acid changes T107I (rs28371706) and R296C (rs16947), causing a reduced CYP2D6 EA. Thus, genotype *CYP2D6*4/CYP2D6*17* was indicative of a reduced enzymatic activity (The Human Cytochrome P450 (CYP) Allele Nomenclature Database) that can be assigned to the IMs.

Patient 5 was a 38 years old female. Since 2005, she was diagnosed as borderline personality disorders and, from 2013, as type-II BD with recurrent depressive episodes. The patient was frequently admitted to the Psychiatric Unit of the University of Foggia because to increased anxiety, depression, irritability, impulsivity, and suicidal ideation. Overall a total of 10 drugs were administered to these patient. In particular, across 4 hospital readmissions, 7 of these drugs were discontinued because to ADR or TF (Table 2, Fig. 1E). At the analysis of the CYP2D6 genotype, the patient resulted *CYP2D6*1/CYP2D6*4*. In detail, the allele *CYP2D6*1* (already described for patient 2) and the allele *CYP2D6*4* (already described for patients 3 and 4) were combined in this genotype to give a reduced enzymatic activity that can be assigned to the IMs.

At follow-up (Fig. 1), TFs were observed in the 3 patients diagnosed as type-II BD (ΔBPRS% = 11.50%, 11.11%, and 21.74% respectively for patients 3, 4, and 5), a probable response was observed in patient 1, diagnosed as type-I BD (ΔBPRS% = 25.40%), and a response to treatment was observed in patient without BD (ΔBPRS% = 32.10%). In the BD patients, resulting IMs, a comparison of non-CYP2D6 versus CYP2D6 interacting drugs is summarized in Fig. 2. Overall, about one-half of the administered drugs interact with CYP2D6 (45.45% vs 54.55%). The ratio of drugs maintained versus discontinued resulted 1.75 versus 0.33. Among discontinued drugs, the ratio TF/ADR was 0/4 versus 6/3 ($P = .070$).

4. Discussion

In the present case-series study, we investigated the genetics of CYP2D6 in RD patients with psychiatric illnesses, mainly BD. The analysis of CYP2D6 clinical relevant polymorphisms revealed that 4 patients, each affected by a diagnosis of BD,

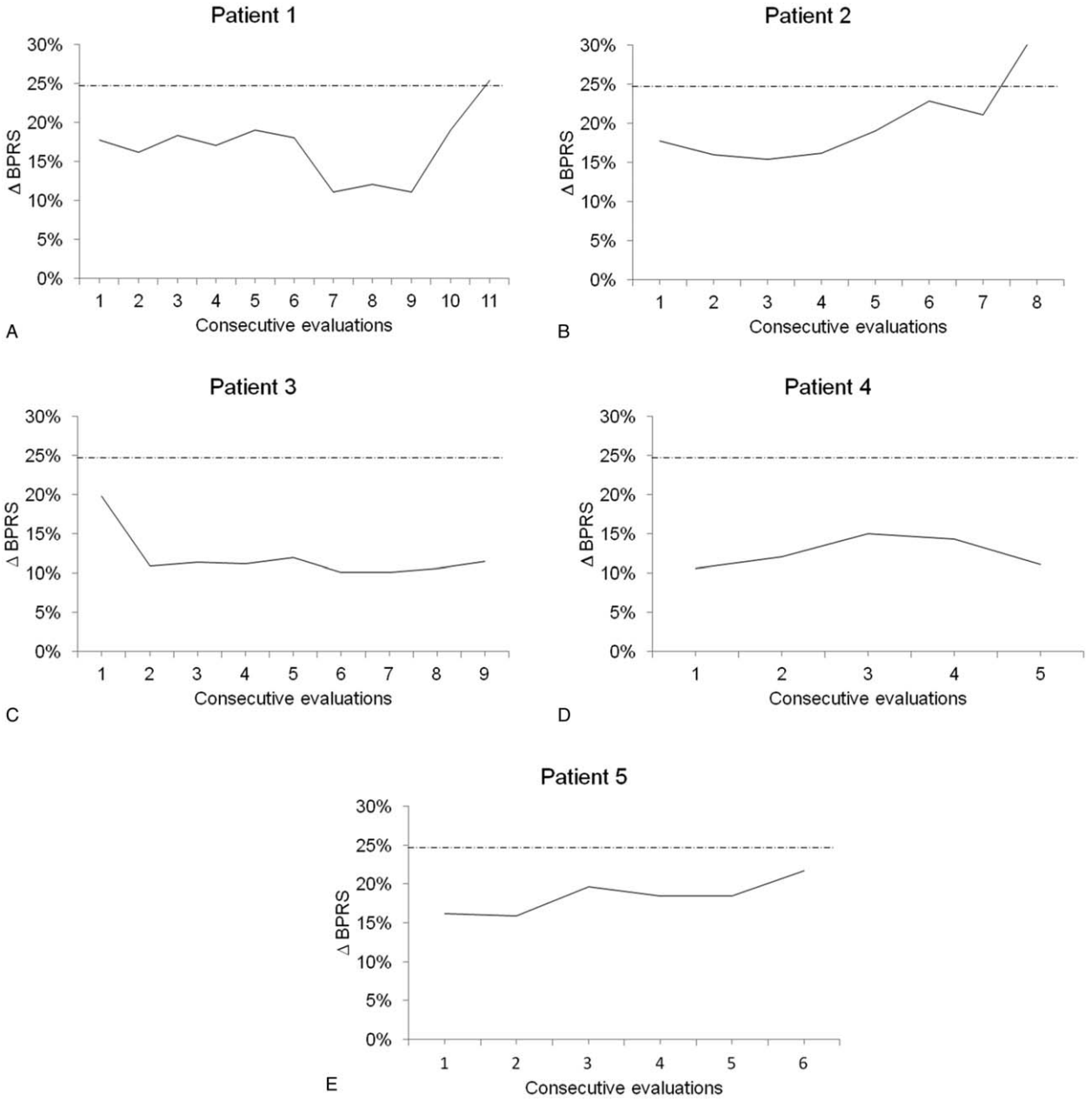

Figure 1. (A–E) Unwanted outcomes to treatment of revolving door (RD) patients with psychiatric illnesses according to interaction of drugs with the cytochrome P450 (CYP)2D6 (CYP2D6) enzyme. BPRS = Brief Psychiatric Rating Scale Expanded Version 4.0.

resulted IMs. Although the limited number of patients, we can confirm that *CYP2D6*4* was the most common variant of nonfunctional allele (3/5 of our patients), leading to the poor metabolizer (PM) phenotype in Caucasians.[45] In the present study, patients heterozygous for the *CYP2D6*4* allele have slower rates of metabolism than EMs and are then classified as IMs, although translation from this genotype to phenotype is rather complex.[46] The only patient without BD diagnosis resulted EM, and he was also the only one responding to drug treatment and not showing ADR. The observed TFs in this latter patient (4 drugs discontinued, 2 of which interacting with CYP2D6) did not depend from the CYP2D6 genotypes, as well as the good response to treatment at the end of the study.

On the other hand, we observed some differences between non-CYP2D6 and CYP2D6 interacting drugs in the 4 BD patients, whom observed genotypes resulted in IM phenotypes. First of all, the ratio of drugs maintained/discontinued was about 5-fold in the first group; secondly, drugs discontinued for ADR were 6-fold in the second groups, since no drugs discontinued for ADR were observed among not-CYP2D6 interacting drugs. Notably, only 1 patient with a diagnosis of type I BD at the end of the time lapse defining the RD condition, showed a trend toward a response to treatment.

At present, pharmacogenetic studies analyzing CYP2D6 activity are among the main aims in the field of psychiatry. The majority of pharmacogenetic warnings in drug labeling for psychiatric medications were related to variations at the *CYP2D6* gene, the most polymorphic gene of the CYP superfamily.[41] To date, pharmacogenetic studies have shown a significant correlation between genotype and adverse effects associated with

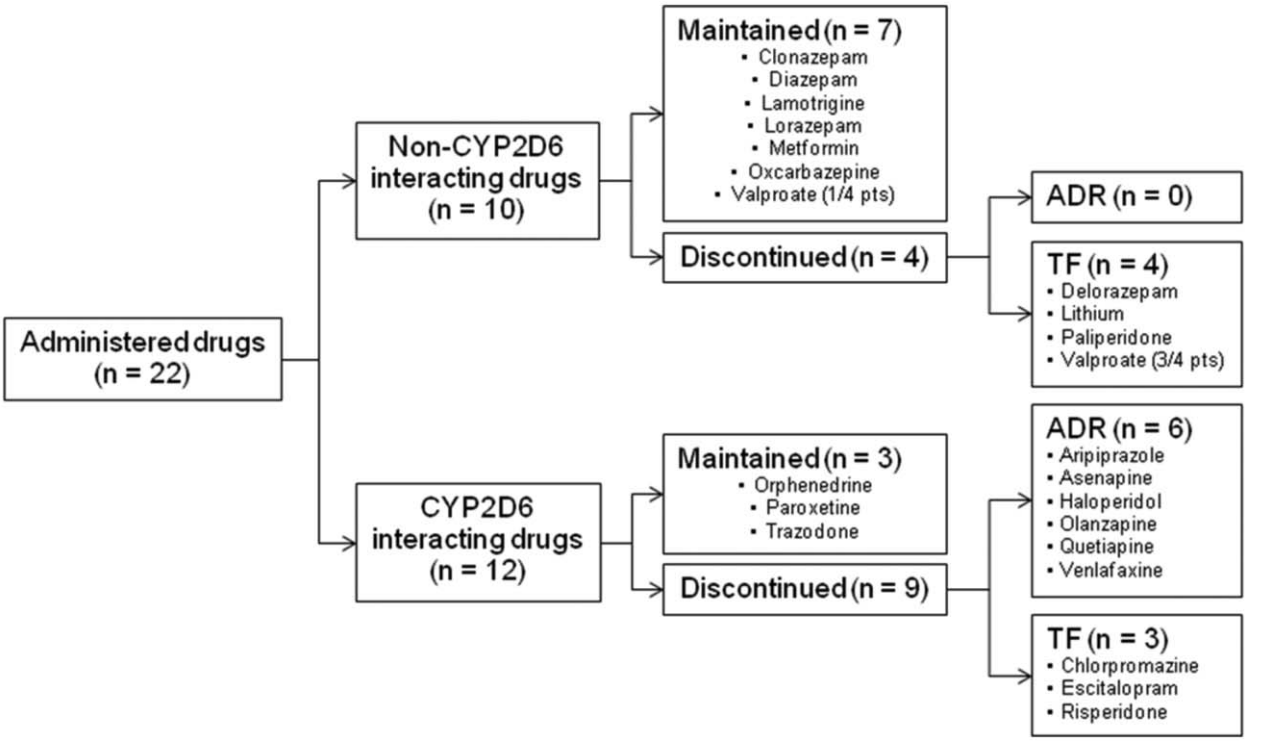

Figure 2. Response to treatment of patients with psychiatric illnesses according to consecutive evaluations in the time lapse defining the revolving door (RD) condition. ADR = adverse drug reaction, CYP2D6 = cytochrome P450 (CYP)2D6, TF = therapeutic failure.

antipsychotics, justifying once again the importance of assessing SNPs in patients treated with antipsychotics.[47] Despite these evidences, the utility of CYP2D6 genotyping in predicting TFs and ADRs in antipsychotic treatments was relatively unexplored. In fact, notwithstanding the FDA approval of CYP450 testing for 27 alleles in CYP2D6.[48] the introduction of CYP2D6 genotyping in clinical practice is still difficult. Furthermore, previous studies evaluated that cytochrome P450 PM polymorphisms of CYP2D6 and CYP2C19 are relevant for the outcome (measured by length of hospitalization) during treatment with psychotropic medications in psychiatric inpatients.[12] In particular, few data supported the possible involvement of CYP2D6-defective drug metabolism in the RD condition of psychiatric patients.[49] According to previous findings, about 50% of drugs we used in the treatments of the patients cases series study, showed interactions with CYP2D6.

Some major limitations to the present study must be acknowledged. First of all, we cannot exclude a major role of the other major CYPs in determining the outcomes observed in our findings. In fact, evidence-based treatment guidelines reported a wide range of medications for BD treatment, involving a number of CYPs. Thus, it is clear that a further improvement in understanding TFs and ADRs, and thus their contribution to the RD condition, may result from the knowledge of the other main CYP2C9, 2C19, and 3A4 variants, thus also explaining the TF/ADR to drugs that shows alternative CYP2D6-metabolism. Nevertheless, the main role of CYP2D6, the most polymorphic CYP across this enzymatic system, in the metabolism of psychotropic drugs has been well documented, thus making CYP2D6 the first choice to investigate the genetic components determining the response in psychiatric patients, and the use of this genetic information a rational strategy for personalized medicine.[15,32] Otherwise, the exclusion of CYP2D6 as the main responsible of the observed outcomes can be useful to address the analysis towards the other CYP-encoding genes. Furthermore, the limited number of patients that were investigated was another major limitation. It is clear that no statistical inference can be made on 5 patients. But it is also clear that studies ad personam or in a very limited number of patients are needed to promote tailored medicine. Such studies did not need of statistical associations, but of consideration on the single patients, that must be treated individually on the basis of their genetic patterns. These studies may be also useful to reduce prevent TFs and/or ADRs, resulting in a reduction of therapeutic attempts, with a reduction in the number of the administered drugs, and of hospital readmission, overall improving the clinical management of these patients. Accordingly, a reduction in the overall expenses of the national health system is also expected. The usefulness of case series in psychiatric translational research has been recently reported.[50] Thus, more studies on wider case series are needed to definitively assess the contribution of CYP2D6 genetics and metabolism to TFs and ADRs observed in RD patients attending psychiatric settings.

Author contributions

Davide Seripa and Madia Lozupone conceived and designed the study, interpreted the data, and wrote the manuscript. Francesco Panza, Antonio Greco, Giancarlo Logroscino, and Antonello Bellomo assisted in literature search, interpretation of data and manuscript preparation and are the guarantors for the study. Giuseppe Miscio, Eleonora Stella, Carolina Gravina, Maria Urbano, and Lazzaro di Mauro assisted in study design and in data interpretation, performed the genetic analysis, and had full

access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The funding agencies had no role in design or conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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