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REVIEW

Psychiatry meets pharmacogenetics for the treatment of revolving door patients with psychiatric disorders

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ABSTRACT

Introduction: Therapeutic failures (TFs) and adverse drug reactions (ADRs), together with the recurring nature of the clinical course of psychiatric disorders, mainly bipolar disorders (BDs), strongly contributed to the prevalence and frequency of hospital readmissions observed in these patients. This is the revolving door (RD) condition, dramatically rising costs for the management of these patients in psychiatric settings.

Areas covered: We searched in the medical literature until May 2016 to review the role of functional variants in the cytochrome P450 (CYP) 2D6 gene on observed ADRs and TFs in RD patients with BDs, conferring a different capacity to metabolize psychotropic drugs.

Expert commentary: CYP2D6 functional polymorphisms might directly contributed to the prevalence and frequency of the RD condition, commonly observed in BD patients. Although several environmental and socio-demographic/diagnostic variables such as alcohol/drug abuse, and medication non-compliance accounted for a significant proportion of the ability to predict RD prevalence and frequency, the pharmacogenetics of CYP, particularly CYP2D6, may help to identify BD patients at risk for ADRs and TFs. These patients may be addressed towards alternative treatments, thus improving their quality of life, and reducing RD prevalence and frequency and the overall costs for their management.

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Therapeutic failures; adverse drug reactions; psychiatric disorders; revolving door patients; pharmacogenetics; CYP2D6

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1. Introduction

Psychiatric disorders (PDs), mainly bipolar disorders (BDs), are chronic recurring pathologies typically characterized by sudden alterations in mood. These changes resulted in severe mental and social impairments, rising risk for suicide [1]. PDs affected 3–5% of Caucasian population [2], with BDs accounting for 4.4–10.3 of years lived with disability, with a cost for the health services at about $15B in the United States and in Western countries [3–5]. To treat BDs, evidence-based treatment guidelines included a wide range of medications, such as first- and second-generation antipsychotics, antidepressants, anxiolytics, and in particular mood stabilizers (Table 1), also in multidrug combinations [6–8]. Despite the availability of all these drugs, however, psychiatrists still met great difficulty in treating PDs, since treatment response is often inadequate, and the rate of remission is poor, particularly among BD in the depressive phase [9–12]. This clinical condition is synonymous of a therapeutic failure (TF), i.e. a failure to accomplish the goals of treatment attributable to inadequate therapy resulting in a subtherapeutic level for a drug or medication nonadherence [13]. Elevated comorbidity and concomitant treatments are also responsible for the increased prevalence of TFs in psychiatric clinics. Despite the few epidemiological data available regarding the contribution of TFs to the overall cost of hospital admissions [14], TFs are responsible of 18% of all hospitalizations [15]. Conversely, many drugs are poorly tolerated, and medication side effects like metabolic disturbances, motor effects, and affective switching are common [16]. This clinical condition is synonymous of an adverse drug reaction (ADR), observed in about 30–50% of psychiatric patients regardless of the initial choice of psychiatric medication [17–22]. ADRs are worldwide primary causes of morbidity and mortality in hospital settings, particularly in those settings with elevated comorbidity, and thus increased concomitant drug treatments [23,24]. It was reported that ADRs caused 6.2–6.7% of all hospitalizations and caused death of 0.15–0.3% of all admissions in United States and in Western countries [25,26]. In fact, according to the recent estimate of the US Agency for Healthcare Research and Quality [13,14], the 770,000 people that are

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Table 1. Most common mood stabilizers frequently used in psychiatric settings.

	Class	Summary of main indications (US FDA approved)	Main off-label indications	CYP	
Carbamazepin	Anticonvulsant, voltage-sensitive sodium channel antagonist	Seizures, pain associated with true trigeminal neuralgia, glossopharyngeal neuralgia, acute/ mixed mania	Maintenance of bipolar depression, psychosis, schizophrenia (adjunctive)	CYP1A2 CYP2A6 CYP2B6 CYP2C8 CYP2C9 CYP2C19 CYP3A4 CYP3A5 CYP3A7	S/Inh/Ind Ind S/Ind[1] S/Ind Ind Inh/Ind S/Ind S/Ind[1] S
Lamotrigine	Anticonvulsant, voltage-sensitive sodium channel antagonist	Maintenance treatment of bipolar I disorder, same types of seizures	Bipolar depression, major depressive disorder, bipolar mania and psychosis (adjunctive and second line), neuropathic/chronic pain, other seizure types	No CYP metabolism	
Lithium	Ion	Manic episodes, maintenance treatment of bipolar disorder	Bipolar depression, major depressive disorder (adjunctive), vascular headache, neutropenia	No CYP metabolism	
Oxcarbazepine	Anticonvulsant, voltage-sensitive sodium channel antagonist	Partial seizures	Bipolar disorder	CYP2C19 CYP3A4 CYP3A5	Inh Ind Ind
Valproate	Anticonvulsant, voltage-sensitive sodium channel modulator	Acute mania and mixed episodes, seizures, migraine prophylaxis	Maintenance treatment of bipolar disorder, bipolar depression, psychosis, schizophrenia (adjunctive)	CYP1A2 CYP2A6[2] CYP2B6[3] CYP2C8 CYP2C9 CYP2C18 CYP2C19 CYP3A4 CYP3A5[3] CYP4A11[4]	Inh S S Inh S/Inh Inh S/Inh Inh S Ind

[1]Reported as pure inducer by the DrugBank database [27]; [2]reported as a S/Ind in the DrugBank database [27]; [3]missing in the SuperCYP database [28]; [4]missing in the DrugBank database [27].
CYP: Cytochrome P450; Ind: inducer; Inh: inhibitor; S: substrate.

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injured or die each year in hospitals from ADRs may cost up to US $5.6 million each year per hospital. Notably, these estimates did not include ADRs causing admissions and National hospital expenses to treat patients who suffer ADRs during hospitalization that are estimated between $1.56 and $5.6 US billion extra costs annually [26].

Thus, although alcohol/drug abuses, medication noncompliance, sociodemographic, and diagnostic variables accounted for a significant proportion of the ability to predict prevalence and frequency of hospital readmissions, genetic factors, such as polymorphisms in genes encoding drug-metabolizing enzymes, may play a pivotal role. Thus, pharmacogenetics of cytochrome P450 (CYP), the most important family of drug metabolizing enzymes in humans, particularly *CYP2D6*, may help to identify BD patients at risk for ADRs and TFs that may be addressed toward alternative treatments. The identification of these patients reduced/ avoided the prevalence and frequency of hospital readmission, so improving the quality of life, and reducing the overall costs for the clinical management of these patients. In the present narrative review article, we underlined the importance that pharmacogenetic data about CYP, particularly *CYP2D6* polymorphisms, may offer for the fingerprinting of the pharmacological treatment of PIs, especially patients with BD, given the relevance of this enzyme in metabolizing psychotropic drugs.

2. The revolving-door condition

Patients' individual 'frailties,' also reflecting demographic characteristics such as individual illness severity as well as individual variations of the treatment process and social situation, could be taken into account for readmission risk and integrated into the phenomenon commonly known as revolving-door (RD) condition [29], to which the recurring nature of the psychopathological course of PDs, together with the TFs and ADRs observed in these patients, strongly contributed, further increasing costs for their clinical management (Figure 1). According to the number of single hospitalizations, time to readmission seems to fall shorter with higher numbers of rehospitalizations in patients with schizophrenic disorders [30], as well as with affective disorders [31]. It is clear that

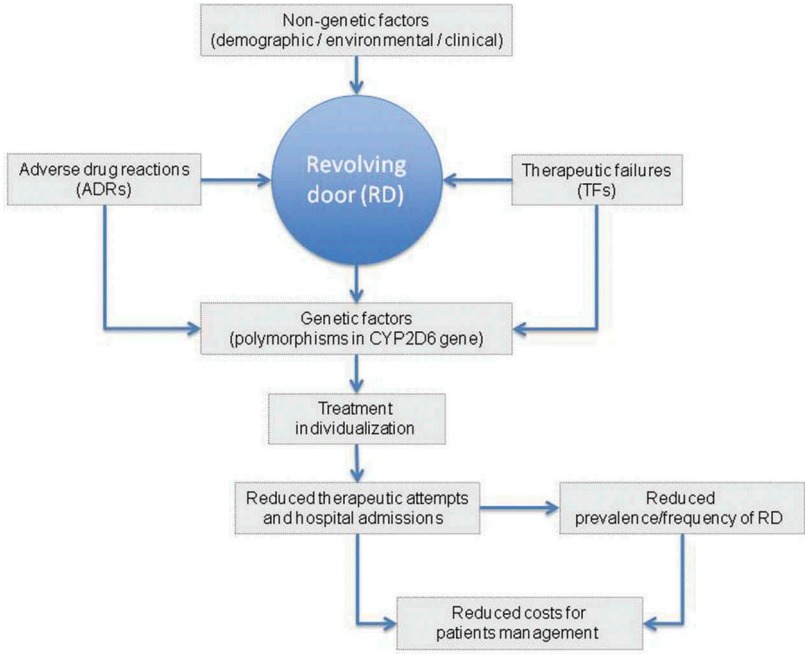

Figure 1. (Full color available online) The recurring nature of the bipolar disorder (BD), together with the patients' individual 'frailties', the high prevalence of therapeutic failures (TFs) and adverse drug reactions (ADRs) observed in these patients, are probable the major responsible of the revolving door condition. We suggested that the pharmacogenetics of CYP2D6 may offer several advantages such as the individualization of the treatment, the reduction of therapeutic attempts and hospital admissions, saving a number of drugs, the identification patients who are at risk of developing affective switching, so improving the quality of life of these patients and reducing the overall costs for the national health systems.

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the number of rehospitalizations also strictly depends from the diagnostic profile. Some studies reported a diagnostic profile of schizophrenia, dementia or organic psychoses, personality disorders, and abuse prevalent in males and a profile of BD, brief psychotic disorder, anxiety disorders, somatoform disorders, and dissociative disorders prevalent in female RD patients [32,33]. Furthermore, the average risk of hospital admission recurrence increases with the number of episodes in depressive and in bipolar affective disorders [31]. Among the conditions contributing to increase the prevalence of TFs in BD patients, and thus the RD occurrences, a number of demographic and environmental factors must be considered, such as sex, age at onset in older age, positive family history of depression, higher number of lifetime stressors, medical conditions, comorbid anxiety, substance abuse disorders, different personality and temperament profile, and more regular use of benzodiazepines [34]. Also, the potential for toxic interactions between psychoactive substances of abuse and therapeutic psychoactive agents must be considered as a factor increasing prevalence of ADRs. BD patients were more likely to engage in substance abuse; hence, at least some of these patients may have been admitted frequently but for shorter periods of time [35]. Alternatively, substance abuse may have produced depression in these patients, or they may have turned to alcohol and drugs as a form of self-medication. Further research is needed to clarify this issue. Differently, Swigar and colleagues [36], in a study of readmission to a university-affiliated mental health center, found significant current substance abuse in one-third of non-repeater and repeater groups of patients, except for the most frequently readmitted group. The authors noted that frequent repeaters were not dual-diagnosis patients, and substance abuse was not the cause of their high use of resources. Perhaps this difference among studies could be attributable to the different percentage of patients with primary personality disorders, most notably borderline personality disorder [36]. Overall, the RD condition was defined for patients with a minimum of four admissions and, (1) no admission or discharge period lasting for more than one-fourth of the observation period or, (2) at least four admissions over the first one-fourth of the observation period [33].

3. Genetic factors influencing the RD condition

Molecular genetics offers an opportunity to explain and predict the interindividual variability of drug response patterns. Hypothetically, all genetic factors contributing to TFs and ADRs may strongly affect the RD condition. In fact, otherwise innocuous genetic traits might underlie phenotypes resulted from variations in drug response among individuals [37], in which ADRs and TFs are the two faces of the same coin, an unbalanced drug metabolism, in which common causes are shared. In fact, the better response to a given drug is a phenotype lying in the midpoint of a continuum in which ADRs and TFs are the severe ones [38]. All these findings leaded to the definition of the new term 'pharmacogenetics' [39].

Currently, the concept that interindividual differences in genetic variations may be responsible of differences in drug response is widely accepted and validated in many psychiatric settings [40–42]. In fact, it is commonly accepted that interindividual differences in drug response resulted from the enormous DNA sequence variability in genes encoding drug transporters and receptors, as well as drug-metabolizing

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enzymes [43,44]. Thus, the empirical a-priori evidence for strong genetic forces influencing psychotropic drug effects in individuals is solid, and inherited variants in *CYP* genes, and in particular *CYP2D6*, may play a major role [45–47]. In the United States, phenotyping studies suggested that CYP2D6 deficiency was present in 7% of the population [48]. A pilot study suggested that CYP2D6 deficiency might be overrepresented in Caucasians who are admitted to psychiatric hospitals (14%) [49]. Although a European study suggested that severe mental illness was not related to CYP2D6 genotype [50], other evidences argued that CYP2D6 deficiency may be associated with more medication side effects and subsequently with noncompliance and rehospitalization [51]. Two possible explanations for these controversial results were that CYP2D6 might be associated with severe mental illness or with a greater risk for hospital admissions. Several neurobiological factors have been described associated with mood episode switches in BD [52] and the propensity to mood switch in BD patients has been described to depend on individual differences [53]. In particular, antidepressants have been associated with an increased risk of inducing mania [54] and may increase maniac symptom severity [55] in BD patients, possibly influencing RD condition. However, the literature is controversial. Pharmacogenetics could help to explain this controversy since the resulting metabolizer status likely impacts the response to drugs used in clinical trials.

4. The hepatic system of CYP

It has been clearly demonstrated that plant–animal cohabitation drove the evolution of the CYP gene family [56], and this evolutionary process was the source of the high genetic variability currently observed in the CYP system [57–60]. Overall, 18 CYP gene families and 44 CYP gene subfamilies were described in humans for a total of 9000 CYP named sequences [61–63]. Clearly, this great gene diversity results into a high variability in the activity of the encoded enzymes. Potentially, in this system, the catalytic activity of each enzyme differed from each other [64,65]. Conversely, contemporary pharmacology did not completely take advantage from this variability since more than 90–95% of the CYP reactions with drugs are catalyzed by the same enzymes, i.e. only by 5 (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) of the 44 CYP subfamilies (11.36%), with the CYP3A subfamily accounting for approximately 50% of the total CYP reactions [58].

CYPs are monooxygenases that catalyze an oxidative reaction, typically involving a substrate (the drug), a CYP reductase, and oxygen. This reaction converts the drug, typically a lipophilic chemical compound, into a more polar product readily excreted in stool and urine. Notably, this rate of conversion is the key determinant of duration and intensity of drug efficacy. In fact, a drug administered as an active molecule gave an immediate therapeutic effect, and then it is inactivated by oxidation reaction and excreted. Alternatively, the drug may be administered as an inactive molecule (a prodrug) that is converted by oxidation in a more polar active metabolite, gives the therapeutic effect, and is excreted [66–69].

5. The CYP2D6

Despite the major number of drugs metabolized by CYP3A4, many central nervous system drugs, including 80% of antidepressants and antipsychotics, are metabolized by the CYP2D6, that is, also is the most polymorphic CYP. Thus, although it was the less prevalent CYP enzyme in the liver [70], CYP2D6 appears to be the first candidate for a genetic analysis, in particular in patients with PDs. Multiple allelic variants of the *CYP2D6* gene have been identified, which are associated with a range of enzymatic activities (EAs) resulting in a series of metabolizer phenotypes.

Epidemiological studies demonstrated a great CYP2D6 enzyme variability in humans. Generally, for European Caucasians and their descendants, the functional group of alleles is predominant with a frequency of 71% and nonfunctional alleles representing 26% of the variability, mainly CYP2D6*4 [71–74]. Overall, the observed EA may be broadly classified into five metabolic phenotypes. It was commonly accepted that subjects with a normal EA, mainly because they carried two functional gene copies, exhibited an extensive metabolizer (EM) phenotype. Together with the wild type, these subjects were the most common in the populations. As compared with EM, subjects lacking of functional enzymes, usually because they were homozygotes for a defective allele, exhibit a poor metabolizer (PM) phenotype. Similarly, subjects with a reduced EA, especially because they were heterozygotes for a defective allele, exhibited an intermediate metabolizer (IM) phenotype. Conversely, subjects with an increased EA, mainly because they carried more than two functional gene copies or carried mutations inducing an increased gene expression, exhibited a ultrarapid metabolizer (UM) phenotype [75,76]. However, the advent of high-throughput genetic analyses revealed a number of nonfunctional/slow-functional alleles [77–80] as well as hyper-functional alleles resulting from gene amplification [81] demonstrating the genetic complexity of *CYP2D6* [82] and the complication in the EA to be associated with [83], thus suggesting a revision of this classification. Nonetheless, it remains true that different metabolizer phenotypes may be at different risk for ADRs and TFs.

CYP2D6 is involved in the metabolism of more than 70 drugs, including many antidepressants and antipsychotics, the most common of which were reported in Table 2. Notably, despite the same CYP–substrate interaction, in several drugs, recommendations were missing. For example, FDA reported a precaution for CYP2D6 PMs when they underwent amitryptiline administration that was reported from SuperCYP and DrugBank databases [27,28] to interact with CYP2D6 as a substrate/inhibitor. However, this kind of interaction is also reported for CYP1A2, CYP2C8, CYP2C19, CYP2E1, and CYP3A4. However, for these CYPs, FDA annotations are missing. As summarized in Table 2, this is true for a number of drugs commonly used in psychiatric settings. Notably, in presence of functional alleles reducing CYP2D6 EA, the coadministration of CYP2D6 inhibitors may play a major role in the onset of ADRs or TFs. According to FDA recommendations [84], the most common CYP2D6 inhibitors are reported in Table 3. Notably, CYP2D6 genotypes have been shown to be associated with antidepressant outcomes across several

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Table 2. FDA-approved cytochrome P450 (CYP) labeling of the most common psychotropic drugs.

	CYP metabolism			
Drug	Enzyme	Interaction[1,2]	At-risk phenotype	Labeled sections
Amitriptyline	CYP1A2	Substrate (inhibitor)[3]	Poor metabolizer ?	Missing
	CYP2B6	Substrate	–	–
	CYP2C8	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2C9	Substrate	–	–
	CYP2C19	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Precautions
	CYP2E1	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP3A4	Substrate (inhibitor)[3]	Poor metabolizer ?	Missing
	CYP3A5	Substrate	–	–
Aripiprazole	CYP2D6	Substrate (inhibitor/inducer)	Poor metabolizer	Dosage and administration Clinical pharmacology
	CYP3A4	Substrate	–	–
	CYP3A5	Substrate	–	–
	CYP3A7	Substrate	–	–
Atomoxetine	CYP2C19	Substrate	–	–
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Dosage and administration Warnings and precautions Drug interactions Clinical pharmacology
	CYP3A4	Inhibitor	–	–
Citalopram	CYP1A2	Inhibitor	–	–
	CYP2B6	Inhibitor	–	–
	CYP2C19	Substrate (inhibitor)	Poor metabolizer	Clinical pharmacology Warnings Dosage and administration
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Clinical pharmacology
	CYP2E1	Substrate	–	–
	CYP3A4	Substrate	–	–
Clomipramine	CYP1A2	Substrate	–	–
	CYP2C19	Substrate	–	–
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Precautions
	CYP3A4	Substrate	–	–
Clozapine	CYP1A1	Inducer	–	–
	CYP1A2	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP1B1	Inducer	–	–
	CYP2A6	Substrate	–	–
	CYP2C8	Substrate	–	–
	CYP2C9	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2C19	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Dosage and administration Use in specific populations Clinical pharmacology
	CYP2E1	Inhibitor	–	–
	CYP3A4	Substrate (inhibitor/inducer)	–	–
Desipramine	CYP1A2	Substrate	–	–
	CYP2A6	Inhibitor	–	–
	CYP2B6	Inhibitor	–	–
	CYP2C18[4]	Substrate	–	–
	CYP2C19	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Precautions
	CYP2E1	Inhibitor	–	–
	CYP3A4	Inhibitor	–	–
Diazepam	CYP1A2	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2B6	Substrate	–	–
	CYP2C8	Substrate	–	–
	CYP2C9	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2C18	Substrate	–	–
	CYP2C19	Substrate (inhibitor)	Poor metabolizer	Clinical pharmacology
	CYP2E1	Inducer[5]	–	–
	CYP3A4	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP3A5	Substrate	–	–
	CYP3A7	Substrate	–	–
Doxepin	CYP1A2	Substrate	Poor metabolizer ?	Missing
	CYP2C9	Substrate	Poor metabolizer ?	Missing
	CYP2C19	Substrate	Poor metabolizer	Clinical pharmacology
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Clinical pharmacology
	CYP3A4	Substrate	Poor metabolizer ?	Missing
Fluoxetine	CYP1A2	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2B6	Substrate (inhibitor)[3]	Poor metabolizer ?	Missing
	CYP2C8[6]	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2C9	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2C19	Substrate (inhibitor)	Poor metabolizer ?	Missing

(*Continued*)

Table 2. (Continued).

Drug	CYP metabolism			Labeled sections
	Enzyme	Interaction[1,2]	At-risk phenotype	
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Clinical pharmacology Warnings Precautions
	CYP2E1[6]	Substrate	–	–
	CYP3A4	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP3A5 (4)	Substrate	–	–
Fluvoxamine	CYP1A1	Inhibitor	–	–
	CYP1A2	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2B6	Inhibitor	–	–
	CYP2C8[6]	Inhibitor	–	–
	CYP2C9	Inhibitor	–	–
	CYP2C19	Inhibitor	–	–
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Drug interactions
	CYP2E1	Substrate	–	–
	CYP3A4	Inhibitor	–	–
	CYP3A5	Inhibitor	–	–
	CYP3A7	Inhibitor	–	–
Iloperidone[8]	CYP1A2	Substrate	Poor metabolizer ?	Missing
	CYP2E1	Substrate	Poor metabolizer ?	Missing
	CYP2D6	Substrate	Poor metabolizer	Dosage and administration Warnings and precautions Drug interactions Clinical pharmacology
	CYP3A4	Substrate	Poor metabolizer ?	Missing
	CYP3A5	Substrate	Poor metabolizer ?	Missing
	CYP3A7	Substrate	Poor metabolizer ?	Missing
Imipramine	CYP1A2	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2B6	Substrate	–	–
	CYP2C18	Substrate	–	–
	CYP2C19	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Precautions
	CYP2E1	Inhibitor	–	–
	CYP3A4	Substrate	–	–
	CYP3A7	Substrate	–	–
Nefazodone[5]	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Precautions
	CYP3A4	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP3A5	Inhibitor	–	–
	CYP3A7	Inhibitor	–	–
Nortriptyline	CYP1A2	Substrate	–	–
	CYP2C9[4]	Substrate	–	–
	CYP2C19[4]	Substrate	–	–
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Precautions
	CYP2E1	Inhibitor	–	–
	CYP3A4	Substrate	–	–
	CYP3A5[4]	Substrate	–	–
Paroxetine	CYP1A2[6]	Inhibitor	–	–
	CYP2B6	Inhibitor	–	–
	CYP2C8	Inhibitor	–	–
	CYP2C9	Inhibitor	–	–
	CYP2C19[6]	Inhibitor	–	–
	CYP2D6	Substrate (inhibitor)	Extensive metabolizer	Drug interactions
	CYP3A4 (6)	Inhibitor	–	–
Perphenazine	CYP1A2	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2B6	Substrate	–	–
	CYP2C8	Substrate	–	–
	CYP2C9	Substrate	–	–
	CYP2C18	Substrate	–	–
	CYP2C19	Substrate	–	–
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Clinical pharmacology Precautions
	CYP3A4	Substrate	–	–
Pimozide	CYP1A2	Substrate	–	–
	CYP2C19	Inhibitor	Poor metabolizer ?	Missing
	CYP2D6	Inhibitor	Poor metabolizer	Precautions Dosage and administration
	CYP2E1	Inhibitor	Poor metabolizer ?	Missing
	CYP3A4	Substrate (inhibitor)	–	–
	CYP3A5	Substrate	–	–
	CYP3A7	Substrate	–	–
Protriptyline	CYP2D6	Substrate	Poor metabolizer	Precautions
Risperidone	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Clinical pharmacology
	CYP3A4	Substrate (inhibitor)	Poor metabolizer ?	Missing

(*Continued*)

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Table 2. (Continued).

Drug	CYP metabolism			
	Enzyme	Interaction[1,2]	At-risk phenotype	Labeled sections
	CYP3A5	Substrate	–	–
	CYP3A7	Substrate	–	–
Tetrabenazin	CYP1A1[6]	Inducer	–	–
	CYP1A2[6]	Inducer	–	–
	CYP2C8[6]	Inducer	–	–
	CYP2C9[6]	Inducer	–	–
	CYP2C19[6]	Inducer	–	–
	CYP2D6	Substrate[9]	Poor metabolizer	Dosage and administration Warnings and precautions Use in specific populations Clinical pharmacology
Thioridazine	CYP1A2	Substrate (inhibitor)	Poor metabolizer ?	Missing
	CYP2C8	Inhibitor	–	–
	CYP2C9	Inhibitor	–	–
	CYP2C19	Substrate	–	–
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Contraindications Warnings Precautions
	CYP2E1	Inhibitor		
Trimipramine	CYP2D6	Substrate	Poor metabolizer	Precautions
	CYP2C9	Substrate	Poor metabolizer ?	Missing
	CYP2C19	Substrate	Poor metabolizer ?	Missing
	CYP3A4	Substrate	Poor metabolizer ?	Missing
Venlafaxine	CYP2B6	Inhibitor	–	–
	CYP2C9	Substrate	–	–
	CYP2C19	Substrate	–	–
	CYP2D6	Substrate (inhibitor)	Poor metabolizer	Precautions
	CYP3A4	Substrate (inhibitor)	Poor metabolizer ?	Missing
Vortioxetine[3]	CYP2D6	Not available	Poor metabolizer	Dosage and administration Clinical pharmacology

[1]According to the SuperCYP database [28]; [2]according to the DrugBank database [27]; [3]reported as a substrate in the DrugBank database [27]; [4]Missing in the SuperCYP database [28]; [5]reported as an inhibitor in the DrugBank database [27]; [6]missing in the DrugBank database [27]; [7]missing CYP metabolism in the SuperCYP database [28]; [8]reported as inhibitor in the SuperCYP database [28]; [9]reported as a substrate (inhibitor) in the SuperCYP database [28].
CYP: Cytochrome P450.

Table 3. Most common inhibitors of CYP2D6 according to FDA [84].

Strong inhibitors[1]	Moderate inhibitors[2]	Weak inhibitors[3]
Bupropion	Cinacalcet	Amiodarone
Fluoxetine	Duloxetine	Celecoxib
Paroxetine	Terbinafine	Cimetidine
Quinidine		Desvenlafaxine
		Diltiazem
		Diphenhydramine
		Echinacea
		Escitalopram
		Febuxostat
		Gefitinib
		Hydralazine
		Hydroxychloroquine
		Imatinib
		Methadone
		Oral contraceptives
		Propafenone
		Ranitidine
		Ritonavir
		Sertraline
		Telithromycin
		Verapamil

[1]≥Fivefold increase in AUC or >80% decrease in CL; [2]≥two- but <fivefold increase in AUC or 50–80% decrease in CL; [3]≥1.25- but <twofold increase in AUC or 20–50% decrease in CL.
AUC: Area under curve; CL: clearance; CYP: cytochrome P450.

dimensions [85–87]. Response to venlafaxine was significantly greater in CYP2D6 EM subjects who metabolize the drug normally compared to IM subjects who require lower doses [88]. Major depressive disorder patients showed higher rates of remission among CYP2D6 IMs compared to PMs, after 8 weeks of escitalopram treatment [89]. CYP2D6 UM status contributed to nonresponse by increasing early dropout rates [90,91], and CYP2D6 UM status was associated with a higher risk of suicide [92–94]. The majority of serious ADRs occurring in clinical routine with treatment when prescribing CYP2D6-dependent selective serotonin reuptake inhibitors (SSRIs) can retrospectively be traced back to functionally inactive or overactive genetic CYP2D6 variants in naturalistic clinical settings [95]. Several SSRIs inhibit CYP2D6 (particularly strong inhibitors are fluoxetine and paroxetine) (Table 3) [84]; thus, coadministration of one of these drugs might change a person with the status of UM, IM, or EM into a PM status independent of the individual genotype [45]. All BD patients with PM status could experience a maniac episode after introducing a substrate of CYP2D6 such as paroxetine or fluoxetine to their treatment regimes, but there is uncertainty regarding the potential harm or benefit associated to antidepressants used in BD [16]. Recent data suggest absent or very weak efficacy data for paroxetine in bipolar treatment [96]. Although, European guidelines exert a more allowing attitude, US guidelines do not recommend antidepressants in bipolar depression, unless depression is severe. As previously commented, many factors have been involved in antidepressant-induced affective side effects, including comorbidities, a history of mania, early beginning, psychotic features, or even the type of BD. According to recent study, BD II subtype has been

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associated with low switch rates, and a patient's CYP2D6 metabolic profile contributes to maniac switching in BD I subtype patients [16]. Finally, CYP2D6 genotype predicts the risk of ADRs as shown among PMs treated with venlafaxine and tricyclic antidepressants [97,98]. Most dramatically, PM cases has been reported to be link to fatal responses to antidepressants [99,100] or at risk to develop affective switching in BD treated with SSRIs [16]. While compelling evidence links functional CYP2D6 haplotypes to drug levels [101], other studies failed to determine an association between CYP2D6 polymorphisms and treatment response [102–104]. This contradictory has led to the formation of the Evaluation of Genomic Applications in Practice and Prevention group to conclude that the evidence in support of CYP2D6 genotyping for guiding antidepressant treatment is inconclusive and recommending implementation clinical trials in order to show the benefits from CYP450 genotyping [105]. Furthermore, CYP2D6 mediates the metabolism of many antipsychotics, making the use of genetic information about this locus a rational strategy for personalized medicine [106–108]. However, the utility of CYP2D6 genotyping in predicting clinical response to antipsychotics is relatively unexplored. CYP2D6 genotype did predict tolerability to risperidone with a higher risk of adverse effects among PMs [109,110]. Several reports also demonstrated extrapyramidal motor symptoms and drowsiness emerging under classical CYP2D6-dependent neuroleptic drugs, as haloperidol, thioridazine, or perphenazine, also associated with PM status [111]. In summary, genetic variation in CYP genes seems to exert a stronger influence on the occurrence of adverse effects than on medication response. Furthermore, there is still a paucity of studies assessing the cost-effectiveness of CYP genotyping in daily practice [21].

In addition to the metabolism of many drugs of relevance to psychiatry, neurology, and addiction medicine such as antidepressants, antipsychotics, and opioids [112,113], CYP2D6 has also been shown to contribute to endogenous metabolism of neuroactive substrates, which can explain the associations up to date observed with human behavior and human disease susceptibility (e.g. personality, neurocognition, and neuropsychiatric disorders) [114,115]. CYP2D6 was identified in human brain in the late 1980s [116], and in the late 1990s, dextromethorphan-to-dextrorphan metabolism was demonstrated in human brain microsomes, of which ratio was later used to properly measure CYP2D6 EA *in vivo* [117]. CYPD6 has been described in neurons in the human cerebral cortex, hippocampus and cerebellum, basal ganglia, and mid-brain [118–120]. Other studies have provided additional evidence of CYP2D6 expression in these brain regions and the thalamus as well as in glial cells in those brain areas [121,122]. This enzyme has also been involved in the metabolism of tyramine to dopamine (DA) *in vitro* [123,124] and in the regeneration of serotonin 5-hydroxytryptamine (5-HT) from 5-methoxytryptamine [125,126]. Interestingly, *in vivo* studies have shown that UMs display higher 5-HT concentrations in platelets than EMs and PMs [127]. A potential influence of CYP2D6 polymorphism in the balanced functioning and physiological crosstalk of the DA and 5-HT endogenous systems has been also proposed [128,129]. Recently, it has been proposed that a potential mechanism for the interaction of the 5-HT and DA system would be the synthesis of 5-HT in DA neurons [130]. Additionally, CYP2D6 has been implicated in the endogenous metabolism of the ligand for the cannabinoid receptor CB1, anandamide [131]. The possibility that CYP2D6 may be involved in the regulation of endogenous neuroactive steroids, such as progesterone and its derivatives in brain tissues, has been suggested [132,133]. Taken together, the relationships observed between CYP2D6 variation and behavior/personality could be mediated by the influence of this EA in the serotonergic/dopaminergic tone plus other neurotransmitters or neuromodulators. Recently, CYP2D6 variability have been related with personality in both healthy volunteers and clinical settings, neurocognitive function in healthy volunteers, vulnerability to psychopathology in schizophrenia, anxiety, depression, eating disorders, and suicide in clinical settings [134].

6. Conclusion

In a possible CYP2D6-driven strategy to the treatment of RD patients with PIs, particularly BD, on the basis of the CYP2D6 EA associated to the identified mutations, several approaches may be hypothesized. Some commonly used drugs CYP2D6 inhibitors can dramatically lower a patient's EA and thereby shift the patient metabolic capacity toward the low end of the activity distribution. In presence of a PM phenotype, i.e. mutations strongly reducing CYP2D6 EA ($50\% < EA \leq 0$), the choice of non-CYP2D6 metabolized drugs is strongly suggested and pharmacogenetic testing are useful to explain severe adverse events in CYP2D6 PMs diagnosed with BD [13]. In presence of an IM phenotype, i.e. mutations slightly reducing CYP2D6 EA ($100\% < EA < 50\%$), a conservative approach pointing to the optimization of the available residual EA suggests to avoid the administration of concomitant CYP2D6 substrates and substrates with a concomitant inhibitory CYP2D6 action. Conversely, in presence of a RM/UM phenotype, i.e. mutations inducing CYP2D6 EA ($EA > 100\%$), a reduction of drug dosage is needed. Otherwise, it may be useful to take advantage form the inhibitory action showed by some drugs' CYP2D6 substrate. The same result may be obtained by using concomitant substrates. Notably, all these approaches tend to reduce ADR, and TFs, possibly resulting in saving drugs and in a reduction of hospital admissions. Thus, among the psychiatric setting, CYP2D6 genotype information has been very useful in BD, as an intervention for analyzing the treatment of bipolar patients. It is clear that PIs are complex diseases, and the concept of pharmacogenetics of CYPs directly translated in PIs is restrictive, since the outcome in these patients is probably the result of the interplay among a number of genes, not even directly responsible of drug metabolism. Nevertheless, the RD condition selected patients with a high prevalence of ADRs/TFs and high prevalence of variations in drug-metabolizing enzymes, particularly CYPs.

7. Expert commentary

The course of illness in unipolar and BD patients is heterogeneous, and the effect of previous episodes as well as their

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interaction with other known and unknown risk factors greatly affects the risk of RD, thus needing additional research. Preventing alcohol/drug problems and noncompliance with medication through patient education may also reduce RD [35]. Similarly, ADRs and TFs could be prevented throughout the analysis of CYP2D6 [16], of which the main role in the metabolism of psychotropic drugs has been well documented [18,135], thus making CYP2D6 the first choice to investigate the genetic components to prevent ADRs and TFs in RD patients. Notably, genetic analysis warrants safety, since plasma levels of drugs or active metabolites are widely and controversial studied as phenotypes [136], while the use of genetic information about CYP2D6, mediating the metabolism of many antipsychotics and antidepressants, may be a rational strategy for personalized medicine [18,106,107]. However, the utility of CYP2D6 genotyping in predicting clinical response to antipsychotics and antidepressants is relatively unexplored. In fact, despite the FDA approval of CYP450 testing for 27 alleles in CYP2D6 [137,138], the introduction of CYP2D6 genotyping in clinical practice is still difficult. Unfortunately, despite the wide range of drug classes available for PIs and BD, all these drugs frequently share a common CYP metabolism, thus making impossible a choice of clinicians to avoid substrate overlapping or to skip CYP2D6 metabolism. These must be good reasons to stimulate pharmaceutical companies to improve their research toward patient-driven psychotropic drugs' development. Nonetheless, we suggested that the knowledge of CYP2D6 genotype may be useful for the reduction of therapeutic attempt during patient clinical history, thus reducing admission time and costs, and to guide clinicians toward a better patient management.

8. Five-year view

Evidence-based guidelines included a wide range of medications for BD treatment, mainly crossing CYP2D6 as well as CYP2C9, CYP2C19, and CYP3A4 [139], and the advent of genomic era, together with high-throughput technology, lets us to improve at low cost our knowledge on these CYPs. Accordingly, the next-generation sequence (NGS) analysis of CYP2D6, as well as the other main CYP2C9, CYP2C19, and CYP3A4, in a couple of hours at 150 US$ for each patient let us to have a fingerprint of the patient metabolic status. This let us to decide a priori the better therapeutic strategy to avoid the administration of a number of worthless drugs possibly causing TFs or ADRs, thus reducing hospital readmission, and prevalence and frequencies of RD, improving the quality of life in these patients. However, specific recommendations for the treatment of RD patients are missing despite the concept of RD directly resulting from a high prevalence of ADRs and TFs in these patients, thus disregarding the current pharmacogenetic knowledge permitting the identification of subjects more prone to develop ADRs and TFs. This is true for CYP2D6 as well as the main CYP2C9, 2C19, and 3A4. It is clear that genetic variant in non-CYP drug-metabolizing enzymes as well as drug transporters and receptors may have a role in the response to treatment in these patients despite the limited polymorphic levels of the genes encoding these proteins [15,46,59,60]. However, the expected translation of this knowledge in clinical practice by both clinicians and companies is still missing. This is a strong limitation to the patient's quality of life, to the development of new drugs, and mainly to the management of expenses from the National Health System. Thus, in the next years, besides the complete sequencing of the known 57 functional CYP genes by NGS technologies to give the fingerprint of each patient, the clinical translation of these knowledge is expected to better manage RD patients in psychiatric settings.

Key issues

- Among patients with psychiatric illness, particularly those with bipolar disorder (BD) exist a form of clinical frailty inducing hospital re-admissions.
- The revolving door (RD) condition is defined as a minimum of four admissions and 1) no admission or discharge period lasting for more than 1/4 of the observation period or 2) at least four admissions over the first 1/4 of the observation period.
- Therapeutic failures (TFs) and adverse drug reactions (ADRs), two clinical conditions commonly observed in patients with BD, strongly contributed to the prevalence and frequency of RD in these patients.
- More than 80% of the available psychotropic drugs commonly used in the treatment of BD patients are metabolized by cytochrome P450 (CYP) 2D6.
- Polymorphic variations in the CYP2D6-encoding genes are responsible of interindividual differences in drug metabolism, and thus of the prevalence of TFs and ADRs in the population.
- Among psychiatric settings, CYP2D6 genotype information may be useful in identifying BD patients at risk for TFs and ADRs. These patients may be addressed towards alternative treatments.
- The reduction of TFs and ADRs will result in a decrease of hospital readmission, and thus in the prevalence and frequency of RD.
- As a main consequence, the number of administered drugs will be decreased.
- Overall, the knowledge of CYP2D6 genotype will improve the clinical management and the quality of life of BD patients, resulting in a reduction in the expenses from the National Health System.
- The use of pharmacogenetic information in the management of RD patients attending a psychiatric setting, despite is still limited, is strongly suggested.
- Further studies of pharmacoeconomics proving the clinical and economic benefits of using pharmacogenetic information to improve efficacy and safety of antipsychotic treatment in RD patients, still missing, are welcome.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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