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Pharmacogenetics to prevent maniac affective switching with treatment for bipolar disorder: *CYP2D6*

“...potential drug interactions need to be taken into account when selective serotonin reuptake inhibitors or tricyclic antidepressants are combined with other drugs metabolized by *CYP2D6*...”

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Bipolar disorder (BPD), formerly known as manic depression, is a mental illness characterized by periods of depression and periods of mania/hypomania. The main symptoms such as depressed mood, insomnia, paranoid ideation, anxiety and appetite changes are shared with other psychiatric disorders. However, the phenomenon of switching, in other words, a sudden transition from a mood episode to another episode of the opposite polarity, is a critical difference between BPD and other psychiatric disorders [1].

Despite the importance of the switching phenomenon, the exact mechanisms leading to this process are still poorly understood although certain neurobiological factors have been associated with mood episode switches [1]. Switching from depression to mania/hypomania can occur spontaneously over the course of the illness, but can also be precipitated by stress, sleep deprivation or standard treatment for bipolar depression such as electroconvulsive or drug therapy [2].

Nearly all antidepressants have been associated with increased risk for treatment-emergent affective switching (TEAS) [3]. Antidepressant-induced TEAS are observed in 10–70% of patients (depending on study design, concomitant treatment and statistical analyses conducted). In addition, the BPII subtype has been associated with low rates of switching [3].

Antidepressants appear to be associated with an increased risk of mania and the severity of maniac symptoms in bipolar

patients [4], however, the evidence regarding the likelihood that antidepressant treatment in individuals with BPD confers increased risk of TEAS has long been inconclusive. In previous clinical trials, the maniac switch episodes were similar between antidepressant and placebo groups [5]. Furthermore, there is no consensus whether antidepressants may be harmful or beneficial to BPD patients [6]. USA guidelines do not recommend antidepressant use in bipolar depression unless depression is severe, which contrasts European guidelines.

The propensity to mood switching in bipolar patients has been attributed to individual differences in the genetic make-up of patients. Differences in a patient's capacity to metabolize drugs could therefore contribute to some of the observed adverse events. We are therefore assessing the value of utilizing pharmacogenetic information to improve antidepressant drug therapy in BPD patients [7].

Role of *CYP2D6* in response to bipolar disorder treatment

CYP2D6 is a major drug metabolizing enzyme and one of the most studied CYP enzymes. It is involved in the metabolism of approximately 25% of the most commonly used drugs [8]. Regarding drugs used for the treatment of bipolar disorder, *CYP2D6* contributes to approximately half of all the drugs prescribed including antidepressants and antipsychotics. Also, there is evidence from animal models indicating that *CYP2D6* is

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involved in the biosynthesis of dopamine and 5-HT. Of note, CYP2D6 may be inhibited by a number of drugs that may further complicate complex medication schedules. For all these considerations and their involvement in clinical practice, it has been one of the most studied enzymes [9,10].

“...bipolar patients genotyped as CYP2D6 poor metabolizers suffered from maniac episodes after taking a drug that is metabolized by CYP2D6...”

Over 100 allelic variants have been defined for *CYP2D6* to date by the Human Cytochrome P450 Allele Nomenclature Committee [11]. Allele frequencies vary considerably among populations. Overviews of the *CYP2D6* gene locus and phenotype prediction have been published by Gaedigk [12] and Hicks *et al.* [13] and genotype-based dosing guidelines for tricyclic antidepressants and SSRIs have been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [13]. These guidelines also provide extensive information regarding allelic variation and frequency. Additional information regarding predicted phenotype (metabolizer status) has recently been published by Gaedigk *et al.* [14].

There are four defined phenotype categories: poor metabolizers (PMs), intermediate metabolizers (IMs), normal metabolizers (NMs) and ultra-rapid metabolizers (UMs). Based on allele frequencies, the PM phenotype is lowest in Asians and Oceania (0–2%) followed by the Americas (0–8%), Africans and African-Americans (1–6%) and Europeans (2–11%) [15,16]. Ultrarapid metabolism on the other end of the extreme activity distribution also varies among world populations (0–22%) [14].

Patients with bipolar disorders present with a maniac (or hypomaniac) episode or depressive episodes. Switching is a major risk factor during the treatment of bipolar depression. Recently, it has been reported that bipolar patients genotyped as *CYP2D6* PMs suffered from maniac episodes after taking a drug that is metabolized by CYP2D6 such as the selective serotonin reuptake inhibitors (SSRI) paroxetine or fluoxetine [7].

Moreover, it is also important to consider interactions with other drugs. In the case of patients with bipolar disorder, the majority is treated for other conditions as well and will likely take numerous drugs of which some may be CYP2D6 substrates or inhibitors and may lead to undesirable plasma levels in poor metabolizers [17]. Consequently, potential drug interactions need to be taken into account when SSRIs or tricyclic antidepressants are combined with other drugs metabolized by CYP2D6 [18]. Examples are paroxetine and fluoxetine, antidepressant inhibiting CYP2D6

with the potential to turn genotypic normal and intermediate metabolizers into PMs (a process also known as phenocopying) [19].

Clinical application of CYP2D6 pharmacogenetic testing

One of the main applications in clinical practice of pre-emptive *CYP2D6* genotyping is the identification of psychiatric patients with an increased risk of developing adverse effects. Patients with genotypes predicting poor or intermediate metabolizer status receiving CYP2D6-mediated drugs may develop an exaggerated response or toxicity. On the other end of the extreme, ultra-rapid metabolizers may not favorably respond, because they do not reach the target drug level.

Individualizing drug therapy (choice of drug and/or dosage) has the prospect of reaching target drug levels within a shorter period of time and avoiding potentially interfering drug combinations. Pharmacogenetic testing provides highly valuable information to guide initial treatment regimens as well as treatment adjustments of patients whose drugs ‘did not work’. For BPD patients, genotype analysis could identify those patients with an increased risk of suffering a switching episode after initiating certain SSRI treatment. For patients with known genotype, the CPIC guideline recommends reducing the dose for SSRIs metabolized by CYP2D6 for PMs [13]. In our experience alternative antidepressants whose metabolism does not depend on CYP2D6 such as escitalopram, sertraline or mirtazapine are alternative options. Of note, many SSRIs are metabolized by CYP2C19, another polymorphic enzyme. *CYP2C19* genotype should therefore also be taken into consideration when choosing an appropriate alternative (see CPIC SSRI guideline).

Implementing pharmacogenetic testing into routine clinical practice may be challenging due to the cost of the test especially if not covered by insurance. However, the cost of pharmacogenetic testing may easily outweigh financial burden of repeat patient visits, adverse events, hospitalizations as well as patient safety, loss of quality of life of the patient and his/her family, loss of earnings, among others.

Other factors are without doubt contributing to drug response in BPD patients. However, the utilization of genotype-guided drug therapy, albeit not perfect, constitutes an important first step in the adoption of individualized drug therapy in this complex patient population.

Conclusion & future perspective

Personalized medicine is opening important perspectives [20] and is increasingly embraced by clinicians. Information regarding its utility is urgently needed [21].

The determination of metabolizer status before treatment initiation would be most valuable to individualize therapy. Unfortunately, most of times genotyping is sought retrospectively ‘*a posteriori*’ to help explain adverse events or therapeutic failure. This approach, however, disadvantages patients with extreme phenotypes of receiving optimal care.

For these reasons, we consider that *CYP2D6* genotyping could be very useful in the psychiatric setting especially in BPD treated with antidepressant. It provides important benefits in drug safety by identifying patients at risk to develop affective switching when

treated with SSRIs, especially fluoxetine or paroxetine, or other *CYP2D6* substrates and inhibitors.

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