Is there a role for pharmacogenetics in the treatment of panic disorder?

“To date, little research is available on the pharmacogenetics of panic disorder, with inconsistent results.”

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Pharmacogenetics & personalized psychiatry

The ultimate goal of a personalized approach to pharmacotherapy is discovering reliable predictors of psychotropic drug response/tolerability to tailor pharmacotherapy according to each patient's unique features. The interest in this area emerged for several reasons.

First, the evidence-based pharmacological guidelines for psychiatric disorders, including panic disorder (PD), are mainly based on the results of randomized clinical trials (RCTs). They are carried out in highly selected populations of patients and refer to the ‘average’ ideal patient who does not represent real-life patients with their unique characteristics. Consequently, in clinical practice we still proceed by a ‘trial-error’ approach without any evidence-based predictor or test to guide the choice.

Second, while antidepressant drugs are recommended for depressive and anxiety disorders, their clinical outcomes are unsatisfying. The interindividual variability in antidepressant efficacy and induced side effects is high, with many patients not obtaining beneficial responses and/or discontinuing treatments due to adverse side effects.

PD is not an exception. It is a common (lifetime prevalence 3–4%), disabling anxiety disorder including unexpected panic attacks (PAs), anticipatory anxiety and phobic behaviors. Recommended drugs do not achieve full remission in 20–40% of patients and additional cognitive behavioral therapy does not fill this gap. The rate of relapses within 6 months after drug discontinuation is 25–50% and the picture is not better for

the rate of patients with residual panic-phobic symptoms (up to 50%) [1] or who discontinue treatments for side effects (20–30%) [2].

Among multiple factors affecting pharmacotherapy efficacy/tolerability, genetic variability plays a relevant role. Familial and twin studies supported a significant genetic contribution to antidepressants' efficacy and metabolism/distribution [3]. Recently, 42% of individual divergences in antidepressant response was attributed to genetic variations [4]. Pharmacogenetics, in other words, the study of how inherited genetic variations affect an individual's response to medications or tolerability, may contribute to the development of personalized treatments, as already well established in oncology [5]. So far, pharmacogenetics were mainly studied in depression and, despite some inconsistencies, polymorphisms of serotonergic and nonserotonergic (brain-derived neurotrophic factor; P-glycoprotein) genes seemed to be involved in selective serotonin reuptake inhibitors (SSRIs) efficacy/tolerability [4]. Several kits for pharmacogenetic tests are commercially available, but official guidelines for their use are still lacking. Recently, US FDA approved Roche AmpliCyp CYP450 test as a tool to assess functional genetic polymorphisms of the cytochrome P450 *CYP2D6/CYP2C19* genes, involved in antidepressants metabolism, since dose adjustments according to metabolizer phenotype may contribute to reduce the side effects of antidepressants [5]. Though clinical applications are still limited, preliminary studies showed advantageous cost–benefit ratio of genetic-guided antidepressant treatments [4].

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Where are we now in PD?

Compared to depression, anxiety disorders received less attention. To date, little research is available on the pharmacogenetics of PD, with inconsistent results. Pharmacogenetic approach investigates genetic variants selected on the basis of ‘*a priori*’ hypotheses derived from preclinical/clinical findings [3]. A link between serotonin (5-HT) system and PD has been repeatedly supported: SSRIs are the first-line pharmacological intervention [1]; experimental manipulations of 5-HT system influenced the laboratory-induced PAs in subjects with PD [1]; susceptibility for PD was associated with polymorphisms of serotonin transporter (*SLC6A4*) [6] and 5-HT_{2A}/5-HT_{1A} receptors [7] genes; panic symptoms severity was associated with 5-HT_{2A} receptor and serotonin transporter promoter (*5-HTTLPR*) polymorphisms [7,8]. Thus, pharmacogenetic studies in PD focused on serotonergic candidate genes. We investigated the functional polymorphisms of the *5-HTTLPR* in Caucasian patients with PD. Females homozygotes for the long variant (*l/l*) and heterozygotes (*l/s*) had greater decrease of PAs after 12-weeks paroxetine treatment than female homozygotes for the short variant (*s/s*), whereas the groups did not differ in the improvement of anticipatory anxiety/phobic avoidance [9]. Conversely, in Japanese patients, the homozygotes (*s/s*) reported greater reduction of panic-phobic symptoms than heterozygotes (*l/s*), without gender differences, after 2-week paroxetine treatment [10]. In a different Japanese sample, heterozygotes (*l/s*) showed a higher tendency to discontinue therapy for adverse side effects than homozygotes (*s/s*), within the first 2 weeks of paroxetine treatment [2]. In two other Asian samples, no effects of *5-HTTLPR* polymorphisms were found on panic-phobic symptoms or clinical global improvement after 4 weeks or 10-week paroxetine treatment, respectively [11,12]. In these studies, no effects of tryptophan hydroxylase (a rate-limiting enzyme in 5-HT biosynthesis) polymorphisms were also found [12], while patients with the 1019C/C genotype in the regulatory region of the 5-HT_{1A} receptor gene showed a better clinical outcome than those with the C/G or G/G genotype [11]. Similarly, in a Caucasian sample, the G/G genotype was associated with a minimal decrease of PAs after 6-weeks paroxetine/sertraline treatment, while no relationship with *5-HTTLPR* polymorphisms was found [13]. Finally, preliminary results of our group did not show association between 12-weeks paroxetine treatment response and functional polymorphisms of COMT (an enzyme involved in 5-HT/other monoamines catabolism) [14], while Korean patients with *L/L* COMT genotype had poorer clinical global improvement after 12-week paroxetine treatment [15]. These findings are insufficient to draw conclusions. The studies are few, with short-term follow-

up, and the sample sizes are small with poor statistical power. Ethnicity of the samples may partly explain discrepancies in results, as shown in previous studies where the same allele of *5-HTTLPR* was predictor of different SSRIs outcome/tolerability in Caucasian or Asian depressed patients [4]. Dose and duration of pharmacotherapy were heterogeneous as well as the inclusion criteria, evaluation time points and measures of outcome, thus making the findings hardly comparable. Finally, some studies used inappropriate outcome measures for PD, such as clinical global improvement, or total panic-phobic symptoms score that does not disentangle drug effects on different clinical features of PD.

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Future perspective

Much more efforts are clearly required in pharmacogenetics of PD and many challenging issues need to be considered. The candidate gene approach has the advantage to be based on putative neurobiological relevance of selected genes, but has some critical points:

- The neurobiology of PD is not fully understood and probably involves an interplay between genetic (half of the variance) and environmental factors [16];
- The mechanisms of actions of antipanic drugs are not fully clarified;
- The antipanic effects are probably influenced by multiple genetic variants with small effect size and potential additive/interactive effects that are not captured by studies with single or few candidate genes in small samples, as those conducted so far;
- Genetic variations are unlikely to completely explain divergences in individual responses to antidepressants. Environmental factors and gene–environment interactions may influence the pharmacological phenotypes [17];
- PD is a heterogeneous condition that includes different clinical phenomena probably resulting from distinct neurobiological mechanisms. Standard diagnostic criteria for PD do not reflect this complexity and the lack of biomarkers/endophenotypes in pharmacogenetic studies may significantly affect the results [1];
- The lack of standardized methodological criteria and the use of unsuitable measures of outcome may influence the reliability of the findings and mask potential promising results [18].

Future strategies to fill the gaps include:

- Multicenter collaborations for large prospective studies with standardized designs, higher statistical power and careful consideration of stratification factors (e.g., age, gender, ethnicity, previous pharmacological treatment);
- Expanding the investigated genes and studying the gene x gene interactions. Connections between multiple polymorphisms of the serotonin system genes as well as between serotonergic genes and novel candidate genes may be relevant to the SSRIs antipanic effects. In animal models, pharmacological modulation of orexin and glutamatergic receptors may influence the occurrence of PAs and preliminary associations between human PD and genes of orexin/glutamatergic systems were found [1]. Since connections between serotonin and orexin/glutamatergic systems exist, the joined genetic investigation of these systems may produce more informative results on the individual response to SSRIs. Finally, the use of inbred strains with different genetic background in animal models of panic may suggest allelic variations of interest that could be tested in human pharmacogenetic studies;
- Implementation of a biomarker/endophenotype approach to decrease the variability within the nosographic diagnosis of PD. Hypersensitivity to hypercapnia is thought to be an endophenotype of panic, is strongly influenced by genetic factors and is associated with respiratory symptoms, higher frequency of PAs and familiarity for PD, possibly typifying a respiratory-panic subtype. Several abnormalities in respiratory/autonomic/balance system functions were found in patients with PD, that may result in different clinical symptoms and outcomes [1]. Incorporating the respiratory endophenotype or patterns of neurobiological functions in pharmacogenetic studies may help to select truly homogeneous patients, to identify more appropriate outcome measures and unravel specific pharmacogenetic associations;
- Connecting genome-wide association studies (GWAS) with pharmacological investigations (pharmacogenomics). GWAS are 'hypothesis free' and

simultaneously genotype many hundred thousands of polymorphisms across the genome, allowing to surmount the need of an *a priori* hypothesis of the candidate genes approach. To date, no published pharmacogenomics studies in PD are available. Since this approach also has limitations [3,17], the opportunity of combining GWAS with complementary strategies may be considered in designing future studies in PD. As GWAS identify genetic regions of interest, resequencing these regions taking into account the results from candidate genes studies may help to validate more relevant variants. The application of pathway analyses (i.e., the analyses of a set of variants within genes implicated in the same biological process) may increase the possibility to investigate the interactions between multiple genetic variants and to identify polymorphisms with single small effects that do not reach genome-wide significance threshold. Finally, incorporating endophenotypes/neurobiological functions in pharmacogenomic studies may produce more reliable results;

- Considering stressful life events/early trauma. Interactions between serotonergic genes and adverse experiences in modulating antidepressant outcome of depressed patients were found, partly related to epigenetic mechanisms [19]. Since childhood maltreatment was significantly reported in patients with PD [20], gene–environment interactions may play a relevant role in pharmacogenetics of PD.

In conclusion, pharmacogenetics of PD is at a very early stage but methodological improvements and promising innovative strategies may produce reliable advances in this field.

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