

PERSONALIZED TREATMENT OF SCHIZOPHRENIA IN EVERYDAY CLINICAL PRACTICE: REALITY OR FICTION?

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SUMMARY

Each day clinical practice tries to follow the idea and principles of personalized medicine. Besides predicting an individual's sensibility or predisposition for developing schizophrenia, pharmacogenetic and pharmacogenomic approaches attempt to define and acknowledge important indicators of clinical response to antipsychotics namely their efficacy and adverse effects. The main focus of our article were not facts regarding the role CYP450 liver enzymes have in this; our purpose is introducing other, new genetic and epigenetic factors which could introduce important biomarkers in diagnostics of the disease itself, the efficacy and tolerance for antipsychotics. There is still a huge gap between gathering and collecting information and using them for the personalized treatment of schizophrenia. From the genetic point of view personalized treatment of schizophrenia is the field we need to focus on and successfully incorporate it our everyday clinical practice in the future.

Key words: schizophrenia - personalized medicine – pharmacogenetics – pharmacogenomics - antipsychotics

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INTRODUCTION

The intensive development of pharmacogenetics and pharmacogenomics in the late 1990s enhanced the development of personalized medicine. Claims like "one for every one" or "one size fits all" do not sustain the real clinical practice anymore.

Tailoring the therapy to the individual patient means considering the individual's unique characteristics such as age, genetic factors, endophenotypes, biomarkers and also environmental factors, i.e. trying to predict the individual's susceptibility to disease, determine accurate diagnosis and consequently achieve beneficial treatment and thereby incorporate the notion of creative psychopharmacotherapy (Jakovljević 2013a, Jakovljević 2013b).

Pharmacokinetic genetic studies of antipsychotic drug response are supported by the identification of multiple functional variants with well-defined effects of drug metabolism (Malhotra et al. 2012a) and are not the subject of this review; here we only want to mention the FDA's opinion which approved the use of CYP2D6 enzyme activity in antipsychotic prescribing decisions, providing recommendations to reduce the dosage or avoid prescribing perphenazine, pimozide, thioridazine, aripiprazole, clozapine, iloperidone and risperidone in individuals known to be non extensive metabolizers (U.S. Food and Drug Administration 2014).

CYP2D6 metabolic status could play an important role in determining patients' antipsychotic response but so far no empirical data support the association between this enzyme and antipsychotic efficacy, although studies found significant associations between poor metabolizers and higher rates of tardive dyskinesia and weight gain (Zhang & Malhotra 2013a). But what are other genetic factors in antipsychotic response and adverse effects? Can we tailor them to an individual patient?

CHALLENGES OF PHARMACOGENETICS/ PHARMACOGENOMICS IN ANTIPSYCHOTIC RESPONSE

In the treatment of schizophrenia the focus is on clinical response to treatment and adverse effects as well as trying to include an individual approach or principles of personalized medicine. Variability in clinical response to medications or antipsychotics manifests regardless to the comparable severity of the disease and etiology (Hamilton 2015).

Many obstacles exist in predicting response to the treatment with individual antipsychotic, the major one being the lack of scientific proof (Malhotra et al. 2012a, Ozomaro et al. 2013, Hamilton 2015). Pharmacogenetics as well as pharmacogenomics (PGx) should lead clinicians through personalized approach using genetic information when choosing the appropriate antipsychotic with the intention to maximise therapeutic efficacy and minimize drug-induced side effects (Zhang & Malhotra 2013a).

The majority of pharmacogenetic/pharmacogenomic studies have utilized a candidate gene approach, usually based upon the receptor pharmacology of the psychotropic agent (Zhang et al. 2012). The common mechanism of action of all antipsychotics is the dopamine D2 receptor, therefore it is not unusual that polymorphism in the DRD2 gene has been intensively studied. One polymorphism, -141CIns/Del (rs 1799732) in the promoter region is assumed to reduce D2 density and activity in the brain and significantly influences antipsychotic drug efficacy (Zhang & Malhotra 2013a, Malhotra et al. 2012a, Brandl et al. 2014a).

Meta-analysis of Zhang and co-workers which includes 687 patients showed that patients who carry 1 or 2 alleles have significantly poorer response to antipsychotic drugs than patients with the Ins/Ins genotype (Zhang et al. 2010). Polymorphism in Tag1A has been associated with treatment response to aripiprazole, risperi-

done and haloperidol in Arranz and co-workers review of candidate genes studies (Arranz et al. 2011).

Contradictory results were found for other DRD2 polymorphisms, such as TaqIB, Ser311Cys, A-241G (Brandl et al. 2014a). Some studies were focused on the DRD3, the Gly9 variant of the Ser9Gly polymorphism (substitution of Glycine for Serine) in coding region with contradictory findings according to the treatment response (Reynolds et al. 2006, Huang et al. 2010, Arranz et al. 2011, Reynolds et al. 2013).

Due to the mechanism of action second generation antipsychotics (SGAs) genes in the serotonergic neurotransmitter system are at the centre of studying antipsychotic treatment response, particularly polymorphisms in HTR2A, the gene encoding 5-HT_{2A} receptor. The most commonly researched genetic polymorphisms are the 102T/C region SNP and -1438A/G, a promoter SNP that is in complete lineage with 102T/C (Brandl et al. 2014a, Moore et al. 2014). Some associated studies indicated poorer response in G alleles carriers of the -1438A/G SNP; but not all (Arranz et al. 1998, Ellingrod et al. 2003, Schafer et al. 2001). Inconsistent were also in PGx studies focused on HTR2C, encoding 5-HT_{2C} receptor.

Meta-analysis supports the role of -759C/T promoter polymorphism and weight gain (De Luca et al. 2007), but not the treatment response. On the other hand, the association of the 44 bp Ins/Del polymorphism in the promoter region of 5-HTT gene (5-HTTLPR) and poorer response to the antipsychotics has consistently been demonstrated (Dolžan et al. 2008, Vazquez-Bourgon et al. 2011). New data suggest that HT1A rs6295 and 5-HTTLPR polymorphisms can influence some clinical symptoms in schizophrenia (Terzič et al. 2015). Some positive results (improvement of symptoms) were associated with the HTR1A-1019C/G SNP (Reynolds et al. 2006).

Therapeutic response to antipsychotics can include also other gene candidates such as COMT gene (encodes catechol-o-methyltransferase), genes encoding brain-derived neurotrophic factor, TNF (tumor necrosis factor- α) and others (Brandl et al. 2014a), as well as a new candidate, a zinc-finger domain-containing protein (ZNF804A), which appears to play a role in neurodevelopment and has been implicated in the risk for schizophrenia (Riley et al. 2010).

A lot of studies lack adequate sensitivity and specificity to reliably guide clinical practice (Malhotra et al. 2012a). Although studies are promising, validations in larger samples are necessary; moreover, enough reliable results should be obtained, since the effect size of genetic variants associated with antipsychotic response is relatively small and as such is not adequate as a predictor of clinical value. Investigations of polymorphisms in the whole genome, though GWAs association with treatment response held more consistent data, have higher predictable value, however facing serious challenge - large samples are necessary for a higher statistical power (signal) which means several thousand or ten

thousand individuals needed for such prospective PGx trial (Zhang & Malhotra 2013a, Brandl et al. 2014a).

One example is the CATIE study, where examining several GWASs of antipsychotic drug responses on a larger sample (738 subjects) did not find any genetic markers for antipsychotic treatment response that can be used in clinical practice or will have a genome-wide significance (McClay et al. 2011). In the future it will be necessary to focus on the early stages of disease and consider treatment adherence among psychiatric patients (Malhotra et al. 2012a).

ANTIPSYCHOTIC-INDUCED ADVERSE EFFECTS

Some progress has been made in the studies of genetic markers of antipsychotic-induced adverse effects, especially clozapine-induced agranulocytosis (CIA), weight gain (AIWG) and tardive dyskinesia (TD). Data for adverse effects are more robust than for antipsychotic response, because of their more objective measures or their more specific evaluation and are not dependent on a patient's evaluation or on raters sensitivity.

Tardive dyskinesia – TD

Tardive dyskinesia is an unpleasant and uncomfortable motoric dysfunction characterized by hyperkinetic and periodic involuntary movements and is present in 25 % to 30 % of all patients treated with antipsychotics, predominantly those with long history of mental illness and many years of treatment with antipsychotics, mostly of first generation (Ozomaro et al. 2013).

Clinical risk factors include age, antipsychotics dosage, gender and the overall time of treatment. In some families TD is more common which brought it in the focus of genetic researches/studies. Pharmacokinetic as well as pharmacodynamic factors are significant, i.e. poor CYP2D6 metabolizers are at high risk for extrapyramidal side effects as shown in several studies (Brandl et al. 2014a). An increased risk for the development of TD was linked with the DRD2 gene or for the carriers of the A2 allele of the TaqIA polymorphism (Zai et al. 2008, Steen et al. 1997, Lerer et al. 2002).

Several studies have investigated the role of DRD3 gene in tardive dyskinesia. Some of them found that Sr9Gly polymorphism was associated with tardive dyskinesia (Steen et al 1997, Basile et al. 1999), but meta-analysis of Bakker and co-workers did not show any overall effects of Ser9Gly genotype on the development of TD (Bakker et al 2006). However, there are hypothesis and assumptions that DRD3 has some specific part in the development of TD.

Other genetic variants positively associated with TD have been identified for the serotonin 2A receptor gene (HTR2A), especially C allele of the T102C (rs6313) polymorphism, for the COMT Val108/158Met, where Val allele has shown some association with increased risk for TD; and for MnSOD-Ala9Val (manganese

superoxide dismutase) with a protective effect for Val carriers (Ozomaro et al. 2013). In a GWAS of Japanese ancestry schizophrenia patients the association between variants in heparan sulfate proteoglycan 2, perlecan (HSPG2) and tardive dyskinesia was replicated in two independent samples (Greebaum et al. 2012). These results show possible usage of GWAS in well-defined phenotypes to identify novel candidate genes.

The most robust evidence have linked tardive dyskinesia and dopaminergic genes yet we still do not have reliable data on the genetic of tardive dyskinesia especially regarding development of predictive tests that could be used in clinical practice.

Clozapine-induced agranulocytosis – CIA

Clozapine is the most effective antipsychotic, especially in the treatment of refractory schizophrenia patients. Its use is limited mainly due to adverse side effects, the most problematic and most serious being agranulocytosis. The cumulative incidence is 0.8 % to 1.5 % within the first year of treatment (Alvir et al. 1993). This fear from developing agranulocytosis in particular limits its use despite its good efficacy. Prognosis of genetic predictors of CIA could improve frequency of using clozapine since the identification of patients with high risk of CIA would be enabled.

Precise polymorphism of CIA is unknown; maybe it is the result of toxicity of metabolites for neutrophils or some immunological processes damaging neutrophils are involved in CIA and their bone marrow precursors (Utrecht et al. 1997, Gerson et Meltzer 1992). A number of classical human leucocyte antigen (HLA) alleles have shown association with CIA in small samples, but without replications in independent samples (Zhang & Malhotra 2013b).

In some studies HLA-DQB1 variant G6672C (rs 13332494) showed strong association with CIA (Dettling et al. 2001, Amar et al. 1998). The C allele of G6672 showed very strong association in the study made by Althanasiou and co-workers (Athansiou et al. 2011). HLA-DQB1 G 6672 C was involved in the commercially available PGx Predict: Clozapine pharmacogenetic test (Pouget et al. 2014).

However, the sensitivity was merely 21%, indicating that most individuals developing CIA are not carriers of the risk allele and presumably have other genetic risk factors (Zhang & Malhotra 2013b). The test was taken off the market. Recently, the first whole-exome sequencing study was undertaken in CIA identifying several non-HLA candidate genes such as PPF1A4, ACTN1, PODNL1 and SATS1 (Tiwari et al. 2013). However, these results need additional replications in independent samples.

Antipsychotic-induced weight gain – AIWG

Antipsychotic-induced weight gain is evident in one third of all patients treated with second generation antipsychotics (mostly with olanzapine, clozapine and

quetiapine) as well as in those treated with first generation antipsychotics. Increased body weight along with the metabolic syndrome represents high morbidity as well as mortality risk; furthermore, it can stigmatize patients and consequently leads to poor cooperation in treatment. AIWG and metabolic syndrome can increase the risk of type 2 diabetes and cardiovascular disease.

We do not know good clinical predictors for increasing body weight likewise pathophysiological mechanisms of body weight increase are not well-defined. Numerous pharmacogenetic studies have focused on identifying genetic variants predictive of severe AIWG. The serotonin 2C receptor is involved in the regulation of food intake, with HTR2C antagonists causing increased food intake and weight gain. An association between polymorphism of the HTR2C gene and AIWG is one of the most promising genetic findings (Brandl et al. 2013a).

The functional polymorphism -759C/T, especially C allele was significantly associated with increased risk of weight gain in different clinical studies (Sicard et al. 2010, Reynolds et al. 2002, Miller et al. 2005), and this appears to be a significant risk factor for AIWG, particularly for weight gain early in the treatment (Shams & Müller 2014). Other HTR2C polymorphisms associated with weight gain have also been reported (-995G/A, -1165A/G and Cys23Ser) (Da Luca et al. 2007, Sicard et al. 2010).

Leptin is a peptide hormone secreted by adipose tissue and plays a major role in energy homeostasis. The -2548A/G polymorphism in the encoding gene leptine (LEP) was associated with weight gain (Nurmi et al. 2011). The G allele has been associated with increased weight gain also in the study of Brandl and co-workers (Brandl et al. 2012b). The melanocortin -4 receptor (MCR4) in the receptor for melanocyte-stimulating hormones, which regulate appetite and energy expenditure is now under research (Shams & Müller 2014).

A GWAS of AIWG in a drug-naive pediatric population discovered a single peak signal, located on chromosome 18q21, with the A/A genotype of rs489693, a variant 190 kb downstream of the MC4R gene, to be associated with increased weight gain following treatment with second generation antipsychotics (Malhotra et al. 2012b). In another independent sample A allele of rs489693 was associated with greater weight gain following antipsychotic treatment (Czerwensky et al. 2013a, Czerwensky et al. 2013b). The consistency of HTR2C and MC4R results represents the highest possibilities for further research.

PHARMACOGENETIC TESTING IN CLINICAL PRACTICE

In recent years several commercial pharmacogenetic tests with higher or lower clinical usage have been developed. The first one approved by the FDA in 2005 was the AmpliChip™CYP450 Test, which genotypes up to 33 alleles in CYP2D2 and three alleles in CYP2C19 associated with different metabolizing phenotypes. Many laboratories as well as psychiatrists use it as a

decision-making tool. However, its clinical use is not yet scientifically proven in larger studies.

The DMET (Drug-Metabolizing Enzymes and Transporters)™Plus Solution is an extensive pharmacogenetic test covering 1936 genetic variants in 231 genes in one assay. It is used by several laboratories but has not yet been assessed regarding clinical efficiency. Genecept™Assay is a panel test for various genetic variants however its part in clinical practice is not well-defined. It is still not clear whether clinical benefit of pharmacogenetic testing outweighs their costs, however, it can be expected that pharmacogenetic testing will be included in diagnostic and therapeutic guidelines for schizophrenia.

CONCLUSION

First of all, clinical implications of pharmacogenetic data are limited. Preliminary efforts to translate the most promising pharmacogenetic findings into clinical practice are now under way, but it is still premature to attempt the genetic values to help diagnose schizophrenia or other psychiatric disorders.

At the moment there are no specific pharmacogenetic tests with the introductory value of antipsychotic response. Using pharmacokinetic variants, especially CYP2D6, can be clinically useful in prescribing the proper dosage of antipsychotics and is already used in everyday clinical practice whereas pharmacodynamic variants are still an enigma especially their value for predicting antipsychotic response.

Additional clinical studies are necessary to define utility and cost-effectiveness pharmacogenetic testing. In personalized treatment of schizophrenia we need to include other, especially individual and well established approaches and wait for the results. We can say that in the field of personalized treatment of schizophrenia there are some promising times ahead.

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