Psychiatria Danubina, 2010; Vol. 22, No. 2, pp 329–334 *Conference paper*

PERSONALIZED ANTIPSYCHOTIC TREATMENT: THE ADVERSE EFFECTS PERSPECTIVES

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SUMMARY

Antipsychotics are the lodestar in the treatment of schizophrenia despite the variability of the therapeutic response and drug-induced adverse effects (especially extrapyramidal symptoms, gain weight, and metabolic disturbances). More and more data are supporting the notion that genetic factors - as well as often overlooked personal and environmental factors - that define the inter-individual differences in pharmacokinetic and pharmacodynamic treatment response. At present, there are no practical pharmakogenetic tests that could be used in everyday clinical practice; however, in the field of psychiatry they are expected within a few years. Pharmacogenetic tests will indubitably become an important tool for personalized prescription.

Key words: *pharmacogenetics – pharmacogenomics – pharmacokinetics – pharmacodynamics - genetic testing - personalized prescription – antipsychotics - adverse effects*

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INTRODUCTION

Antipsychotic drugs are widely prescribed for different psychiatric disorders; they are also the cornerstones of acute and long-term treatment of schizophrenia. Despite different antipsychotics, treatment response in schizophrenia remains heterogeneous and many patients with schizophrenia either do not improve or relapse frequently. Patients who receive antipsychotic drugs differ also with respect to drug-induced adverse reactions or side effects. There are significant risks associated with first- and second-generation antipsychotics like movement disorders, weight gain, diabetes, hyperlipidemia, and cardiovascular events. More than 70% of patients with chronic schizophrenia discontinued their antipsychotics, owing to poor effectiveness or tolerability (Lieberman et al. 2005).

Pharmacogenetic research has expanded over most fields in medicine in the last 20 years with great expectations for the "tailored" or "personalized" treatment for each patient. But over the last ten years a more realistic picture prevailed (Arranz & Slide 2008). The importance of epigenetic is increasing also in psychiatry, but at the moment it is not known how epigenetic changes could be tested in the clinical practice (de Leon 2009a).

PHARMACOGENETICS, PHARMACOGENOMICS AND BIOMARKERS

Pharmacogenetics explores the role of genetic factors in predicting drug response and potential adverse drug reactions, while pharmacogenomics explores the relationship between whole genome factors (genome-wide scans), drug response and potential adverse drug reactions (Foster et al. 2007, Malhotra et al. 2004). Roses proposed two types of pharmacogenetics: one is safety pharmacoogenetics which is aimed at avoiding adverse drug reactions, and the other one is efficacy pharmacogenetics, meant to predict response to medications (Roses 2004, de Leon 2009b). Wagner defines a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions (Wagner 2002). In 2005 the Food and Drug Administration (FDA) established CYP 2D6 and thiopurine S-methyltransferaze (TPMT) as valid biomarkers (de Leon 2009a, de Leon 2009b).

Environmental and personal factors influencing adverse effects of antipsychotic drugs

Most of the pharmacogenetic research has been conducted blind to environmental influences despite the fact that several external environmental factors, such as diet, substance abuse, smoking, co-medication, and herb supplements significantly affect therapeutic dose, response and drug adverse effects (Arranz & Kapur 2008). Caffeine and grapefruit inhibit CYP1A2 and CYP3A4 enzymes and compete for these enzymes with clozapine and risperidone (Spina & de Leon 2007). Cigarette smoking induces CYP activity and rapid clearance of drug substrates, and has a direct effect on drug dose requirements (olanzapine, clozapine) (Haslem et al. 2006). Concomitant therapy can inhibit stimulated CYP enzymes, for example anticonvulsant drugs can induce activity of CYP1A2 and increase the metabolic rate of clozapine, olanzapine and risperidone (Arrant & de Leon 2007).

Personal factors, such as age, gender, medical illness, duration of untreated psychosis, and symptoms' severity may play an important role in response and side-effects fluctuations (Arranz & Kapur 2008).

Pharmacokinetic factors influencing adverse effects of antipsychotic drugs

Pharmacokinetic genes contribute to the differences in the plasma level or tissue distribution of drugs. Examples of very well known pharmacokinetic genes are those coding for cythochrome P450 enzymes (involved in phase 1 metabolism). Some of the CYP 450 genes are highly polymorphic and their variations may contribute to the adverse effects of antipsychotics.

The two most important polymorphic CYPs are cytochrome P450 2D6 (CYP2D6) and cytochrome P450 2C19 (CYP2C19); cytochrome P450 1A2 (CYP1A2) and cytochrome P450 3A (CYP3A4) are also important in pharmacokinetics of psychotropic drugs (de Leon 2009b). CYP2D6 enzyme is particularly involved in the metabolism of many antidepressants and antipsychotics like haloperidol, thioridazine, perphenazine, chlorpromazine, risperidone, and aripiprazole. CYP2D6 is a highly polymorphic gene, with more than 70 variants resulting in four phenotypes. Special attention should be focused on poor metabolizers or PMs who do not have active enzymes, and ultrapid metabolizers (UMs) with too much active enzyme. CYP2C19, CYP1A2 and CYP3A are all included in metabolic pathways of olanzapine, risperidone, aripiprazole and clozapine (Arranz & Kapur 2007). An average patient among the Caucasions is a CYP2D6 EM (extensive metabolizer), whereas an average patient among East Asians is a CYP2D6 IM (intermediate metabolizer) (de Leon et al. 2008a).

The CYP2D6 polymorphism may clinically result either in the occurrence of adverse drug reactions or in altered drug response. The data on the influence of the CYP2D6 genetic polymorphism on the development of extrapyramidal side effects (EPS) is controversial (Dolžan et al. 2006, Plesničar et al. 2008, de Leon 2009a,). PMs were reported to be prone to the development of more pronounced and more persistent symptoms of tardive dyskinesia or parkinsonism and also to have higher incidence of tardive dyskinesia than patients without CYP2D6 mutations (Ohmori et al. 1998, Kapitany et al. 1998, Brockmoller et al. 2002, Schillevoort et al. 2002). Although Brockmoller et al. showed that the risk for EPS from haloperidol was significantly higher in CYP2D6 PMs; they found that genotyping would prevent side effects in only 5% of the patients receiving haloperidol (Brockmoller et al. 2002). This is the reason why patients who are CYP2D PMs needed lower risperidone doses (for example average dose divided by 2). In a large risperidone study that included 360 patients on risperidone and 252 patients who discontinued the risperidone treatment, CYP2D6 PMs had over 3-times higher risk of significant risperidone adverse effects and 6-times greater risk of discontinuing risperidone in comparison with non PMs (de Leon 2008a). But, across the entire population treated with risperidone in this study, only 16% of risperidone adverse effects and 9% of discontinuation due to adverse effects were explained by the patients being CYP2D6 PMs (de Leon et al. 2008a).

CYP2D6 phenotype and genotype must be taken into consideration in those patients with risk factors for long QT interval; QTc interval was longer in subjects with one active CYP2D6 gene compared with subjects with two active genes (Llerena et al. 2004).

Pharmacodynamic factors influencing adverse effects of antipsychotic drugs

It is still not very well known how exactly antipsychotics work (de Leon 2009b). Pharmacogenetic studies have confirmed the importance of several neurotransmitter systems in antipsychotic efficacy and adverse effects.

Dopaminergic blockade is a common characteristic of most antipsychotics and it is currently still believed that the efficacy of antipsychotic drugs is mainly explained by the blockade of dopaminergic D2 receptors; the same applies to side-effects, such as EPA and hyperprolactinemia. Acute parkinsonism, dystonia and akathisia have been rarely the subjects of pharmacogenetic studies and the results were inconclusive (Foster et al. 2007, Arranz & Kapur 2007).

The density of the D2 receptors is influenced by the genetic polymorphism of the dopamine D2-receptor gene (DRD2), so the effects of antipsychotics that are antagonists of these receptors may be modulated by its polymorphism (Scharfetter 2001). The DRD2 311Ser/Cys variant was associated with clinical symptoms of schizophrenia, with the efficacy of antipsychotic treatment, and probably also with EPS (Lane et al. 2004, Kaiser et al. 2002, Dolžan et al. 2007). The association with the DRD2 -141Ins/Del polymorphism is also inconclusive (Dolžan et al. 2007, de Leon et al. 2008b). A meta-analysis of Zai et al. supported an association between tardive dyskinesia and two DRD2 polymorphisms (C957T and C939T) (Zai et al. 2006).

Second-generation antipsychotics have high affinities for serotonin receptors. It has been hypothesized that the serotonin inhibition of the dopamine function contributes to the development of EPS (Arranz & Kapur 2007). Several studies are showing significant association between the 5-HT2A and 5-HT2C receptor variants and tardive dyskinesia, although some studies could not replicate the findings. The 5-HTTLPR variants were also extensively studied regarding the antipsychotic-induced adverse effects but no association with tardive dyskinesia was found (Dolžan et al. 2008, Guzey et al. 2007, Vásquez-Bourgon et al. 2010). There are some data that Ser9Gly variation of dopamine D3 and glutathione GSTM1 appeared to impose prediction of tardive dyskinesia (de Leon et al. 2005). An additional interaction may occur between DRD3 and CYP1A2 through the combination of glycine-glycine (DRD3) and cytosine-cytosine (CYP1A2) alleles, resulting in the highest risk for tardive dyskinesia (Nnadi et al. 2005).

Excessive body weight gain and the associated metabolic dysfunction are common undesirable effects of antipsychotic drugs, especially of second generation antipsychotics, olanzapine and clozapine being the most prominent. Despite the fact that many antipsychotics have been known to be associated with increased risk of obesity and diabetes, in clinical practice there is little possibility to predict which patients treated with antipsychotics will develop obesity and diabetes, and which will not. This inter-individual variability indicates an extensive genetic-environmental interaction in this field. The risk of these serious adverse events appears to be particularly high among the patients receiving multiple antipsychotic drugs (Nnadi & Malhotra 2007).

Antipsychotics may cause hyperlipidemia either through an indirect mechanism, associated with weight gain, or through direct mechanism by which some antipsychotics (olanzapine, clozapine) may directly cause hyperlipidemia (de Leon et al. 2008c). Some antipsychotics may increase appetite and lead to obesity through the blockade of some neurotransmitter receptors, particularly H1 and 5-HT2C (de Leon et al. 2008c). The results in this field are also not very conclusive. Subjects with the 5-HT2C-759T allele had gained significantly less weight than those without this allele (Templeman et al. 2005). In the study of de Leon et al., the SNPs in the transforming growth factor β1, ACCα and PECAM-1 genes were significantly associated with hypertriglyceridemia in patients on olanzapine, quetiapine or chlorpromazine (de Leon et al. 2008a). The leptin polymorphism 2548A/G was not associated with short-term weight gain but with the long-term one (it developed after 9 months of treatment with antipsychotics) (de Leon 2009a). Ellingrod et al. found a significant relationship between the alleles of leptin and leptin receptor, olanzapine plasma concentration, and body mass index. Subjects with at least one allele at each locus had a 3-fold increase in body mass index and high concentration of olanzapine (Ellingrod et al. 2007). Some antipsychotic drugs may directly increase insulin resistance either by decreasing insulin-sensitive glucose transporters, by elevating serum free fatty acids, by their inability to stimulate the recruitment of glucose transporters from microsomes to the plasma membrane (de Leon et al. 2008b). The exact mechanism is not known.

There are only few pharmacogenetic studies of antipsychotic drug-induced hyperprolactinemia. Polymorphism of the dopamine D2 receptor gene Taq1 has been associated with greater prolactin response to bromperidol in female carriers of the A1 allele of this polymorphism (Mihar et al. 2001). Young replicated this finding in his study, where patients with Taq1 allele, receiving first generation antipsychotics, had 40% higher prolactin levels; prolactin levels in patients in clozapine group were twice as high as in those without A1 allele (Young et al. 2004).

There are a lot of obstacles in studying pharmacodynamic variables of antipsychotics because the genetics of pharmacodynamic targets is much more complicated than the genetics of pharmacokinetic factors.

PERSONALIZED MEDICINE OR PERSONAL PRESCRIPTION IN PSYCHIATRY

Clinicians almost always initiate antipsychotic drugs in schizophrenia “a priori” (Nnadi & Malhotra 2007). However, this may lead to ineffective treatment, to the use of an additional antipsychotic or multiple antipsychotics, to different adverse effects, and result in increased morbidity and mortality. This represents a real concern and calls for accurate scientific methods that could be used to predict a reasonable therapeutic response and also drug-induced side effects. Personalized prescription or “tailoring drugs to a patient’s genetic makeup” would be more than beneficial (de Leon 2009b). In the context of personalized prescription, clinicians need to consider environmental, personal and genetic variables when prescribing any medication.

According to de Leon, personalized prescription in the clinical practice may be described as personalized selection of the drug and as personalized dosing (De Leon 2009b). He proposed that a personalized selection of the drug include exclusion of certain drugs for certain subject (drug and personal contraindication) and that pharmacogenetic testing could be used for identifying individuals with high risk of idiosyncratic adverse effects, for identifying PMs and UMs who are taking pro-drugs, or for determining variations associated with the lack of drug efficacy. The second step should be exclusion of some drugs within one class in some patients due to frequent adverse events or lack of efficacy (eg., exclusion of antipsychotics with high risk of tardive dyskinesia in older females) or exclusion of antipsychotics with high risk of weight gain. The third level of personalized selection of the drug should include choosing the best drug for the average patient (De Leon 2009b).

In personalized dosing the knowledge of pharmacodynamic and pharmacokinetic dosing properties should be applied. Understanding of pharmacokinetics poses little or no problems as long as it is linear (like in most antipsychotics); however, understanding of drugs with non-linear pharmacokinetics is challenging. When the doctors are using drugs with a very narrow therapeutic window they are very careful, but a wider therapeutic window offers more maneuvering space. Personalized dosing of drugs with wide a therapeutic window is not so relevant and is also not very well developed. In the case of a narrow therapeutic window all three factors should be considered: the patient may be a PM, he/she may be concomitantly taking a potent CYP2D6 inhibitor, and has poor renal clearance (De Leon 2009a,

De Leon 2009b). A patient being a PM or behaving as a PM may result in unforeseeable adverse effects; with antipsychotics it is mostly EPS, hypotension, and sedation (e.g. with risperidone) (De Leon 2009b).

Bearing in mind all this in real practice is very difficult because of economic limitations and because of the complexity of developing methods for balancing safety and efficacy.

PHARMACOGENETIC TESTING IN CLINICAL PSYCHIATRIC PRACTICE

The ultimate goal of pharmacogenetic research is the clinical application of genetic information for optimizing treatment for each patient. A pharmacogenetic test should be a decision-support tool, providing useful information, with several advantages over available predictor tests (eg, blood levels of the drug). The information obtained remains valid during a lifetime and does not require any substance intake.

At the present, in psychiatry there are five pharmacogenomic tests that are currently available on the market or are ready to be introduced (Arranz & Kapur 2007, De Leon 2009a, de Leon et al. 2009c). However, three of the five tests have not published complete details concerning the genes used in them (de Leon et al. 2009a, de Leon 2009c).

AmpliChip CYP 450 Test employs microarray technology for cytochrome P450 (CYP) 2D6 and CYP 2C19 genotyping (de Leon et al. 2009c). Genomic DNA is extracted from a whole-blood sample to identify 27 alleles in CYP2D6 that are associated with four CYP2D6 phenotypes, and to identify three alleles in CYP2C19 that are associated with two CYP2C19 phenotypes (de Leon et al. 2009c). The genotypes are then translated with software algorithms into a predicted phenotype, which is indicative of the CYP2D6 and CYP2C19 enzymatic activity. This is the first FDA-approved pharmacogenetic test. The Luminex Tag-It Mutation Detection Kit is not as sophisticated and has less functions, but it is a good system for detecting PMs for both CYP2D6 and CYP2C19 (de Leon et al. 2009 c).

These tests are applicable everywhere in medicine where substrates for these two enzymes are used. Nevertheless, the utilization of AmpliChip in clinical practice is still limited which could be attributed mostly to lack of knowledge, problems with interpreting data, high costs, and – last but not least – lack of enthusiasm of the pharmaceutical industry (de Leon 2009c). Psychiatrists can employ CYP2D6 and CYP2C19 genotyping for personalized prescription. Genotyping may have some implications in dosing recommendations, for example CYP2D6 PMs should be treated with 50% of the TCAs, phenothiazines and risperidone dose, and they should be treated with lower doses of haloperidol. In UMs haloperidol should be avoided (de Leon et al 2009c).

One company offers a genetic test for the determination of high (1,5%) or low (0,5%) risk of drug-induced agranulocytosis (Arranz & Kapur 2007). The test can make a valuable prediction in the treatment with clozapine, but does not obviate the need for regular monitoring and has not a significant impact on routine practice.

A new system, called PhyzioType System uses an ensemble of DNA markers from several genes to predict an individual's risk of developing some adverse drug reactions (de Leon et al. 2009c). The clinical applicability of this array is still under investigation.

A recent study describes an array containing probes to identify genetic variants for the risk of hyperlipidemia (De Leon et al. 2008c).

Arranz et al. tried to combine genetic information on the prediction of response to clozapine. The prediction level in British Caucasian patients on long-term treatment was 76%, but the results were not replicated in German cohort (Arranz et al. 2000, Schumacher et al. 2000).

It is too early to predict the value of blood expression or biomarkers in the diagnosis of psychiatric disorders (eg, schizophrenia, post-traumatic stress disorder). New strategies for identifying novel factors related to treatment include study of the genome-wide sequence variants, transcriptomics and proteomics, and epigenetics (non-genetic inherited factors).

CONCLUSIONS

Pharmacogenetics progresses in psychiatry very fast, almost as fast as in oncology. The future of personalized prescription in psychiatry lies with well-trained psychiatrists and with better pharmacokinetic and pharmacodynamic genetic testing. In clinical practice it could lead to a more personalized treatment. The knowledge about pharmacogenetic testing, the environmental and the personal factors that influence the efficacy and safety of prescribed drugs will undoubtedly take psychiatry much further. In 10 years time a personalized prescription may be reality.

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