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PERSONALIZED PHARMACOTHERAPY IN PSYCHIATRY

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SUMMARY

The hypothesis of each individual being special and different leading to heterogenity of diseases sets the ground for the concept of personalized medicine. Personalized psychiatry follows the principles of personalized medicine. A constituent part of an individually adapted approach towards the psychiatric patient presents itself thorough personalized psychiatry. The development of pharmacogenomics and pharmacogenetics as well as the nanotechnology based on them ensures implementation of personalized medicine principles in psychiatry to a greater extent than other medical disciplines. In the field of pharmacogenomics, the greatest advance was achieved by the study of genetic variability in drug metabolism. All the predispositions are now present for the implementation of pharmacogenetic tests in routine practice. Pharmacogenetic testing for medications which are metabolised thorough two polymorph cytochromes P 450: CYP2D6 and CYP2C19 is of special significance due to their involvement in most adverse and ultrafast metabolism of psychopharmacs. The potential application of personalized medicine in psychiatry, supported by pharmacogenetics and pharmacogenomics, are: personalized medication choice, personalized dosage, anticipation of possible side-effects individually and personalized follow-up treatment with rehabilitation. The authors conclude how the development of pharmacogenomics and pharmacogenetics as well as the nanotechnology based on them, presents a step forward in creating a personalized therapeutic approach in psychiatry. However, the burden of applying the most appropriate therapeutic agent and medication tapering remains based on clinician decision. Pharmacogenetics can only help by making therapeutic decisions with one less unknown element.

Key words: *personalized – pharmacotherapy – psychiatry – pharmacogenomics - pharmacogenetics*

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INTRODUCTION

The concept of personalized medicine is based upon the hypothesis that each individual is unique therefore diseases are heterogenous regarding specific contributing factors and also a specific drug response. Therefore, the therapeutic approach must be individually adjusted. Personalized medicine offers proper treatment for a real patient at the right time (Ginsburg & Mccarthy 2001). Personalized psychiatry pursues trends in personalized medicine. Although, today personalized psychiatry still represents the goal one has to strive for in a broader sense, it´s principles should be applied now in everyday clinical practice. Due to the possibility of incorporating some elements of personalized medicine, psychiatry took its place as one of the first medical disciplines which could soon manifest the benefits of this new trend in medicine. Personalized psychiatry offers an individual approach in prevention, diagnosis, therapy, follow-up and patient rehabilitation (Gurwitz & Weizman 2004). Personalized pharmacotherapy in psychiatry represents a constituent part of an individually adapted approach to the psychiatric patient. It encompasses the influence of genetic, environmental and personal elements on the pharmacokinetics and pharmacodynamics of medication prescribed to a particular patient (Lesko 2007, Ruano 2004). Though the idea of the individual approach to the psychiatric patient is not a new one, at first glance it seems as if personalized therapy is yet another re-discovery of abandoned postulates of traditional medicine, however this is not the case. The traditional approach to the psychiatric patient in disorder

prevention, diagnosis and defining treatment, is based on family and personal anamnesis, clinical signs and symptoms as well as on available laboratory tests and graphic imaging. All acquired data are compared to mean values and intervals in the general population and based on this comparison, diagnostic evaluation and average therapy with average medication tapering is determined. Mean doses and dose intervals are stipulated for the average psychiatry patient who is rarely found in everyday practice. In reality, the psychiatric patient has a unique genotype and phenotype, one or more comorbidities, specific nutritional habits and specific habits in medication taking which are not always concordant with recommended ones. These personal factors can cause significant deviations in medication pharmacokinetics and pharmacodynamics thereby compromising the treatment process. Still, efforts of traditional psychiatrists are closer to principles of attempt and failure than principles of modern personalized therapy grounded on scientific evidence (Jain 2002). Modern personalized therapy in psychiatry is an emerging therapeutic approach whose full implementation in routine practice can be expected in the near future. This depends on development of pharmacogenomics and pharmacogenetics (Jain 2002, Gurwitz & McLeod 2009) with expansion of new technologies and innovations and their usage in medicine (Schulman et al. 2009).

PHARMACOGENOMICS AND PHARMACOGENETICS IN PERSONALIZED PHARMACOTHERAPY IN PSYCHIATRY

Announcements of a revolution in psychiatric nosology and personalized therapy came from the plenitude of information offered through pharmacogenomics and pharmacogenetics after the completion of the Human Genome Project in the year 2000. Pharmacogenomics is a new concept trying to interpret hereditary grounds of monogenetic and multigenetic disorders by identifying genes responsible for their genesis and those regulating the function of aimed meta therapeutic agents (receptors, transporters etc). Pharmacogenetics is a narrower concept referring to analysis of the genetic variability responsible for pharmacokinetics and individual drug response. Pharmacogenomics offered no clear connection between genes and mental disorders therefore there is no specific and sufficiently sensitive gene marker applicable for undoubted identification of a single psychiatric disorder. Even so, the use of pharmacogenomics and pharmacogenetics could lead to immense results in the treatment of mental disorders (Broich & Möller 2008, Gurwitz 2003). Today we speak about genes indicating an increased risk of the occurrence of mental disorders, usually multigeneticaly conditioned, and their potential contribution for innovative discoveries of new medications appropriate for personalized therapy (Bondy & Zill 2004). Pharmacogenomic limitations on anticipation and identification of individuals with mental disorder came from fact that, besides multigenetic hereditary predisposition (risk genes), environmental elements have a significant influence beyond gene control. The greatest achieved of pharmacogenetic advancement is in researching the genetic variability of drug metabolism. Drug metabolism is generally divided into two phases. Phase one reactions involve oxidation, reduction and drug hydrolysis. Phase two reactions include metabolite conjugation produced in phase one in order to eliminate medication from the organism. Phase one reactions are largely mediated by CYP enzimes from the Cytochrome P450 group which are, largely, found in the endoplasmatic reticullum of hepatocytes and other drug metabolising cells (such as enterocytes in the bowel wall). CYP1A2, CYP3A4, CYP2D6, CYP2C9, CYP2C19 are mostly involved in the metabolism of psychopharmaceuticals (Ozdemir 2002). Pharmacogenetics of two polymorph CYP´s: CYP2D6 and CYP2C19 is of special significance due to their responsibility for poor and ultrafast metabolism of psychopharmacs. CYP2D6 is responsible for the metabolism of some antipsychotics (risperidone, clozapine, olanzapine, aripriprazole) and some antidepressants. The CYP2C19 is linked with the metabolism of some antidepressants and some benzodiazepines. The genetics of pharmacodynamics is far more complicated than the genetics of pharmacokinetics (De Leon 2009). Perspectives for routine usage, for now, only have pharmacokinetic genetic tests for detecting poor and ultrafast metabolizers. Well-known among them is the AmpliChip CYP450 test for analysis of the CYP2D6 and CYP2C19 genes. The test detects the patients genotype and based on DNA

polymorphism analysis predicts the patient's phenotype respectively categorizing into poor, moderate, extensive or ultrafast drug metabolizers for medications having CYP2D6 or CYP2C19 metabolism. Theoretically, this could be of great help in a personalized therapeutic approach for the clinician, especially in drug tapering because of the fast test results which can be immediately applied to therapy with proper medication in adequate dose (Gurwitz & McLeod 2009, De Leon 2006, "Roche" 2009, Stahl 2008).

POTENTIAL APPLICATIONS OF PERSONALIZED MEDICINE IN PERSONALIZED PSYCHIATRIC PHARMACOTHERAPY

The causes of psychiatric disorders are multifactorial. Despite the same diagnosis, biological, psychological and social factors in the occurrence of a disorder can considerably fluctuate among patients. Actually, there is no strict line between certain diagnostic categories because of their vague boundary, so they are often described in a dimensional concept or a diagnostic continuum concept. This concept is closer to the neurobiological one, which relates the etiology of mental disorders in the interaction of multifactorial genetic predisposition, epigenetic factors, and biological and psychological stressors and their consequences. These factors, as well as neuroendocrine abnormalities and neurotransmitter disfunctions, recurrently result in manifestations of certain clusters of symptoms or syndromes within a specific disorder spectrum (schizophrenic, bipolar, anxious etc.). The diagnostic inability of pharmacogenomics to clearly identify the different types of mental disorder raises the question of the existence of diagnostic categories and hence nosological entities. Regarding this is is the fact that psychopharmacological efficacy is not limited to a specific diagnostic category but is dimensionally spread across a part of the diagnostic continuum. Therefore, pharmacogenomics and pharmacogenetics should be reasonably accepted as a welcome tool which can precisely estimate the genetic contribution to mental disorder with precise choice of and monitoring of pharmacotherapy. Individual vulnerability and resistance to the development of mental disorder belongs to the premorbid characteristics of individual. At first glance, this could be the subject of genetic evaluation, life experiences and stress, and in some cases, more than the disorder itself, these factors can bear more significance for the occurrence or absence of the disorder than the genetic code. This is why pharmacogenomics has only a limited predictive value which can be enhanced by associating with a constellation of other elements during the assessment procedure for a mental disorder. Personalized therapy in psychiatry overcomes the frames of pharmacogenetics and pharmacodynamics and can never rely solely on their results, no matter how impressive they may be. Since psychiatry without psychopathology is not possible, the phenomenological concept of mental disorders will still be accepted. In the forecoming time of personalized medicine, psychiatrists will be forced to abandon the nosologic disease concept and turn to a dimensional model embracing the new pharmacogeneticaly assisted treatment options for their patients. Pharmacogenetics is not the key of personalized medicine but a new scientific field with a plenitude of new tools to help the psychiatrist in the personalized patient treatment approach (Műller-Spahn 2008).

Personalized medication choice

Personalized medication choice is the process of finding the best drug for a specific patient. First step in this process is the discontinuation of medications contraindicated for patient by their biological characteristics. In medication selection, the clinician can not rely only on pharmacogenetic results. For example, discontinuation of drugs with teratogenic potential in pregnant women is based on knowing the teratogenic potential of psychopharmaceuticals. On the other hand, pharmacogentic tests can be of great use in order to aviod idiosynchratic reactions of a particular patient to a specific medication. The second step is narrower drug choice, choosing the most suitable ones for the patient, in relation to the characteristics of the mental disorder, age, sex, body weight, possible comorbid states, compliance and other psychosocial features. The medication price in various environments has a distinctive influence on the therapeutic agent choice and this will always be kept in mind by one or more interested parties (doctor, patient, insurance company). The third phase of personalized choice is the most complicated one. It evaluates the risk and damage ratio and the efficacy and safety ratio considering

all available information on the characteristics of the specific medication and features of the particular patient finally resulting in the best possible medication for the illness. (De Leon 2009) Personalized medication choice is especially important in young patients undergoing pharmacotherapy for the first time due to ethical reasons, efficacy and tolerability. Special ethical doubts arise with the idea of preventive usage of psychopharmaceuticals in adolescents with prodromes and genetically clear indicators for the high risk development of a psychotic disorder. In this particular area great help is expected from personalized psychiatry assisted by pharmacogenomics and pharmacogenetics (Filaković 2007, Foster 2009, Kadenhead 2002).

Personalized medication tapering

After the performance of the procedure of personalized medication choice, there follows the procedure of personalized tapering. The necessary daily dose of medication, prescribed for the first time to a patient, is unknown and is limited by the dose average and the dose interval recommended by the manufacturer after testing the medication on a selected patient population with very limited associated therapy. It can easily occur that the recommended average dosage causes a too low or too high available drug concentration in blood of a specific patient. For adequate dose assessment, pharmacogenetic tests can be of great aid in identifying the patient as a poor, moderate or ultrafast drug metabolizer thorough the CYP 450 enzyme system. That is especially important if the medication follows the principles of linear pharmacokinetics, as is the case of most psychopharmaceuticals. For example, if drugs are autoinhibitors (fluoxetine, paroxetine, fluvoxamne) or autoinductors (carbamazepine, lamotrigine) in the pharmacokinetic sense and do not follow the linear kinetics, their pharmacokinetics changes in time leading to necessary evaluation of drug concentration in the blood throughout the entire course of treatment. Finally, in medication tapering, pharmacodynamic factors should not be omitted. For example, the serotonine transporter would not be equally sensitive in depression and in one of the anxious disorders so the optimal therapeutic dose will be different. Also, the D2 receptors are not equally sensitive in young and old shizophrenic patients. Finally, precise determination of the required dosage aided by pharmacogenetic tests has sense only for medications with a narrow therapeutic window such as some antidepressants and first generation antipsychotics. For second generation antipsychotics pharmacogenetic assisted dosing is needless because of their efficacy and wide range tolerability (De Leon 2009).

Personalized prediction of side-effects

While first generation antipsychotics are often associated with frequent occurence of extrapyramidal syndrome and tardive dyskinesias, some second generation antipsychotics show increase in body weight, diabetes and hyperlipidemias with consequentially elevated cardiovascular risk. Some antidepressants show frequent cardiovascular side-effects. Each one of these side-effects is partly multigenetically determined. Identification of specific genes responsible for side-effects would largely contribute to personalized choice of therapeutically efficacious, safe and tolerable psychopharmacs for a specific patient. Around 5% of the Caucasian population is CYP2D6 poor metabolizers leading to possible increased drug concentration and alternative metabolic pathway activation causing unwanted side-effects. Foreseeing of unwanted side-effects is not possible only through genetic testing. Results of genetic testing should be just one constituent part of a predictive algorithm involving all other information about the patient and planned therapy (Lerer 2008, Stahl 2008).

Personalized follow-up treatment and rehabilitation

Follow-up treatment and rehabilitation, are an inseparable element in the overall treatment of psychiatric patients, and should also be individually adapted. Patients with good premorbid functioning, who attain good recovery and return to their families and workplace, will require follow-up psychopharmacotherapy. This should be individually adjusted to optimise tolerability, providing good remission and ensuring the fulfilment of the patient's personal, family, social and work goals. The rehabilitation program should also be individually adjusted for the particular patient. Each individual rehabilitation plan, in different ratios, must contain: cognitive-behavioural, family, occupational, creative and work therapy with reference to social skill training. This plan should be composed of a psychoeducational

program explaining the disease nature, the stressors which cause worsening, procedures alleviating illness and the importance of regular medication taking. Pharmacotherapy and psychosocial rehabilitation are inseparable.

Without the positive effect of pharmacotherapy it is not possible to conduct successful rehabilitation and vice versa. Psychopharmacotherapy will not help a patient to understand the importance of regular medication taking but it will enhance cognitive abilities and create a space for psychoeducational motivation enough to achieve long-term compliance (Kopelowicz & Liberman 2003, Liberman 2006, Vizirianakis 2002).

WHAT CAN WE EXPECT OF PERSONALIZED PHARMACOTHERAPY IN PSYCHIATRY

Immense interindividual variability in the efficacy of psychopharmaceuticals has been perceived long ago, but efforts to solve this problem were, until recently, condemned solely to a trial and error method (Sjöquist 1999, Geoffrey et al. 2001, De Leon 2009). The advantage in pharmacogenomics and pharmacogenetics has given new hope for clinicians, promising more assured diagnosis and providing patients with the proper medication at the right time. Such an attitude created the impression how the goal is within reach. However, is it truly so? While for some authors complete implementation of personalized medicine and personalized psychiatry, as a result of progress in genetics, is a question of the day (Ginsburg & Mccarthy 2001, Gurwitz 2004, Gurwitz 2003, Bondy B & Zill 2004, Ozdemir 2002) others discreetly notice the necessity for verification in practice and further education of clinicians in the rational usage of new understandings and technologies within routine practice (Broich K & Möller 2008, De Leon 2009, De Leon 2006). Everyone agrees how new genetic nanotechnologies facilitate genotypisation and within a few hours help the clinician in making a therapeutic decision very same day. Particularly promising is the genotypisation of poor and ultrafast metabolizers.

Ignoring the relatively high price of pharmacogenetic tests as a limitation in routine practice, still remains open question: is pharmacogenetic information simply enough for personalised dosage in clinical practice? Genotypisation could predict metabolism intensity of one medication in ideal conditions. These conditions do not exist in real clinical practice. Hence, genetic tests cannot substitute clinical evaluation based on much broader information. Metabolism of one medication considerably depends on other concurrent medications which can inhbite or stimulate it`s metabolism. Inhibiting or stimulating agents do not always have to be pharmacologic ones but could include drugs of addiction (smoking, alcohol) or food (orange juice) thereby significantly affecting the real metabolism of one drug. The burden of decision making about the most appropriate therapeutic agent and dosage still lies with the clinician using pharmacogenetics as a help in the elimination of one less unknown element in this process.

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