THERAPEUTIC DRUG MONITORING AND PHARMACOGENETICS – IS THIS A WAY TOWARDS CREATIVE PSYCHOPHARMACOTHERAPY?

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SUMMARY

Modern development trends in psychiatry incorporate greater care for patients and above all individualisation of therapeutic approaches. Therapeutic drug monitoring (TDM) for phenotyping and genotyping of drug metabolism are possible determinants of improved treatment efficacy, reduced adverse effects of psychotropic drugs, and enhanced treatment compliance. They render possible individual adjustment of psychopharmacological treatment and thus represent a small, but significant piece in the mosaic of creative psychopharmacotherapy.

Key words: *therapeutic drug monitoring – pharmacogenetics - drug concentration – psychopharmacotherapy - psychotropic drugs*

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Introduction

Approximately 7% of the world living population are suffering from mental disorders and for these disorders around 130 drugs have been available during the last 60 years (WHO 2005, Hiemke & Shams 2013). However, treatment outcome in many patients with mental disorders is inadequate or poor. Patients may be unresponsive or only partially responsive to treatment, they may suffer adverse and even toxic effects of drugs, and psychotropic drugs may interact with other medication. These may all be factors that additionally contribute to negative treatment results, frequent relapses, poorer quality of life, and of course, to higher treatment costs.

Psychopharmacotherapy has transitioned into the era of personalised approach or even creative psycho pharmacotherapy (de Leon 2006). Besides thorough knowledge of psychotropic drugs and their action, it requires of clinicians a personalised approach to their patients and functioning of their bodies, and even forming personal relationships, sharing treatment goals with patients and their relatives, constant monitoring of patients, swift reactions to any psychopathological changes, and orientation towards complete or at least partial remission (Jakovljević 2010, 2013b). Acting physicians should utilise all of their abilities and not become passive. Above all, they should avoid perfunctory skimming of professional articles, or worse, misinterpreting or misunderstanding them.

Is it possible to keep all these goals and principles in the clinician's mind? Yes, it is possible, but some helping aids are needed for the personalized/creative psychopharmacotherapy. Factors that may contribute to significant overall improvement of a mental disorder and to overcoming or reducing unresponsiveness to medication include monitoring of pharmacokinetic variability and optimisation of these variables in individual patients. Speaking of the effective methods, therapeutic drug monitoring (TDM) and genotyping of drug metabolism seem to be in the foreground (de Leon et al. 2006, Hiemke & Shams 2013, Jakovljević 2013a, Loan et al. 2012).

Therapeutic drug monitoring (TDM)

Integration of information about a patient's phenotype and genotype provides a rational basis for drug and dose selection, and for dose regimen for many psychotropic drugs in clinical practice (Eggart et al. 2011). TDM may provide a rational basis for optimal drug therapy and a suitable tool for accurately assessing the drug-related phenotype (Hiemke & Shams 2013). Plasma drug concentrations often help us solve clinical problems and significantly contribute to the personalisation of pharmacotherapy: low, but not non-zero levels might indicate intermittent adherence, suggesting that less demanding dosing schedule might be more useful (Lopez & Kane 2013); however, in patients with confirmed compliance low levels might indicate rapid drug metabolism that requires a more aggressive treatment approach (Hiemke & Shams 2013).

TDM uses the quantification of drug concentrations in blood plasma or serum to titrate the doses in individual patients so that drug concentration associated with the highest probability of response and tolerability, and the lowest risk of toxicity are achieved (Hiemke et al. 2011). In most psychotropic drugs, up to 20 inter-individual variations of plasma levels of each single dose may be observed (Eggart et al. 2011, Hiemke

2008, Hiemke & Shams 2013). Despite significant advances in drug development, interindividual variability of standard doses of psychotropic drugs remains a major problem in clinical practice (Gervasini at al. 2010). A plasma drug concentration can be considered a valid surrogate biomarker of drug concentration in the brain (Lozano et al. 2012).

Beside optimisation of plasma concentration or its adjustment to individual patients, TDM is useful also in monitoring patients' compliance and in preventing relapses and/or rehospitalisation; in patients with schizophrenia, oscillation of clozapine levels may be a predictor of relapses and resulting rehospitalisation due to poor treatment compliance (Gartner et al. 2001, Ulrich et al. 2003). TDM is useful also in the assessment of drug-drug interaction since many patients are taking more than one drug (Lozano et al. 2012).

The TDM methodology is over 40 years old; however, it reflourished with AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) consensus guidelines on the indications for TDM in 2004 and with their update in 2011 (Hiemke et al. 2011). In these guidelines the attention is drawn primarily to »therapeutic reference ranges« (formerly therapeutic windows with lower and upper concentration limits) and to the »dose-related reference range«. The latter is a new category and it is calculated as a concentration range within the expected ranges according to pharmacokinetic studies in human blood specimens from subjects under medication with a given dose of the drug (Hiemke et al. 2011). It contains 68% of all the drug concentrations determined under normal conditions in the blood of a »normal« patient or subject (no comorbidity, no co medications or genetic abnormalities). »Reference ranges« are suitable for laboratory use and for further determination of psychopharmacological treatment. (Hiemke et al. 2011). »Laboratory alert levels« indicate drug concentrations above the recommended reference range that causes laboratory to feedback immediately to the prescribing clinician and should lead to dose reduction when the patient exhibits signs of intolerance or toxicity (Grundmann et al. 2013). When a psychotropic drug has metabolites it is reasonable to measure their plasma levels as well. The analysis of these values additionally contributes to determining the metabolic status of a patient and to the assessment of treatment compliance.

Practically all psychopharmacological drugs are used in a series of repeated doses in order to reach a steady-state concentration within therapeutic reference range. Steady-state concentrations are achieved approximately after 4 times the elimination half-life; this means after one week of continued dosing of nearly all psychiatric drugs (Hiemke et al. 2011). This is also the time for the first measurement of plasma drug levels in order to determine orientation values (Hiemke et al. 2011).

For performing TDM suitable analytical methods that yield quick results (within 48 hours) are imperative.

A single measurement of a plasma drug level is usually insufficient; for determining poor compliance, non-adherence, reduced bioavailability, or rapid elimination often several measurements are necessary (Heimke et al. 2011, Heimke & Shams 2013). In case of adverse effects, the blood sample should be obtained immediately regardless of the treatment phase and steady-state. AGNP guidelines also recommend regular monitoring of drug concentration under maintenance therapy, at least every 3-6 months, to prevent relapses or rehospitalisation. In order for the results to be interpreted correctly, often an interdisciplinary co-operation is warranted (clinicians, laboratory scientists, ect.).

AGNP guidelines list the following indications for measuring plasma concentrations of psychotropic drugs (Hiemke et al. 2011):

- dose optimization after initial prescription or after dose change;
- suspected complete or partial non-adherence to control if the patient has taken his/her medication;
- drugs, for which TDM is mandatory for safety reasons (e.g. lithium);
- lack of clinical improvement under recommended dose;
- clinical improvement associated with adverse effects under recommended dose;
- combination treatment with a drug known for its interaction potential or suspected drug interaction;
- TDM in pharmacovigilance programme;
- prevention of relapses under maintenance drug therapy;
- recurrence under adequate doses;
- genetic peculiarity concerning drug metabolism;
- pregnant or breastfeeding patient;
- children, adolescents, elderly patients (>65 years) and those with intellectual disabilities;
- patients with pharmacokinetically relevant co-morbidities, hepatic or renal insufficiency);
- forensic patients;
- problems occurring after switching from original to generic preparations.

AGNP guidelines classified the scientific strength of the recommendations for TDM of drugs into four groups: strongly recommended, recommended, useful and potentially useful (Hiemke et al. 2011):

- TDM is strongly recommended for tricyclic antidepressants and venlafaxine because of well established concentration-effect relationship. For SSRIs TDM might be useful in some cases, mostly as a predictor of therapeutic response (citalopram, escitalopram, fluoxetine) (Grundmann et al. 2013). TDM for duloxetine can be useful for treatment optimization (Waldschmitt et al. 2009).
- TDM is strongly recommended for classical antipsychotics haloperidol, perphenazine and fluphenazine, and for some second generation antipsychotics like clozapine, olanzapine, risperidone and ami-

sulpride. However, in the case of second-generation antipsychotics like clozapine, olanzapine, risperidone, and amisulpride, several questions regarding the usefulness of TDM have been raised. In a review article, Lopez and Kane reveal a relative paucity of data relating plasma concentrations of atypical antipsychotics and clinical response in acutely psychotic patients (Lopez & Kane 2013). They found evidence that the use of TDM is reasonable with clozapine, but less so with olanzapine, risperidone, quetiapine, and aripiprazole. They found that psychiatrists more often use plasma concentrations for determining patients' treatment compliance and for the assessment of clinical toxicity.

- TDM is strongly recommended for lithium, valproate and carbamazepine and some other older anticonvulsants.
- TDM is rarely used in clinical practice for anti-dementives and also for anxiolytics and hypnotics (because of their rapid effect).
- TDM is indicated for patients treated with methadone or R-methadone, but is not established for antiparkinsonian drugs.

The "strongly recommended" category is based on well established and evaluated therapeutic reference ranges or on pharmacokinetic clinical studies.

TDM and genotyping of drug metabolism

The combined use of TDM as a phenotyping approach and genotyping of drug metabolic capacity is the most sophisticated way to individualize the dosage of several psychotropic drugs (Sjoqvist & Eliasson 2007). The majority of psychotropic drugs are metabolized by cytochrome P450 izoenzymes, particularly with CYP2D6, CYP2C19, CYP1A2, and CYP3A4; most antidepressants and antipsychotics are metabolized with the CYP2D6 enzyme. The dosage of about 50% of these drugs is greatly dependent on the CYP2D6 genotype (Kirchheiner et al. 2004). CYP2D6 genotypes are important factors in patients taking tricyclic antidepressants, venlafaxine, first generation antipsychotics, and risperidone (de Leon et al. 2006, Kirchheiner et al. 2004). Future studies will determine whether CYP2D6 genotyping is beneficial for patients taking aripiprazole, atomoxetine, and duloxetine (de Leon et al. 2006). CYP2C19 isoenzyme is also involved in the metabolism of different psychotropic drugs. Genotyping of CYP2C19 can be useful in patients treated with citalopram, escitalopram and sertraline (de Leon et al. 2006, Noehr-Jensen et al. 2009).

In poor metabolizers (lack of functional alleles), unexpected adverse effects and toxicity may occur due to elevated plasma levels of the drug, while with ultra rapid metabolizers (with amplifications of functional alleles) plasma concentrations of substrates for CYP2D6 will be probably low, resulting in the absence of therapeutic response.

Cytochromal genotyping methods are becoming more available and clinical guidelines for their use have already been established (de Leon et al. 2006). Although functional significance of many genotypes is yet unknown, the data gathered with pharmacogenetic testing are "trait markers" and as such remain unchanged throughout life.

The most important indications for the combined use of TDM and genotyping are (Hiemke et al. 2011):

- The patient is treated with a substrate for metabolism which shows a wide interindividual variability.
- A drug with small therapeutic index: risk of toxicity in the case of genetically impaired metabolism or risk of non-response and inability to reach therapeutic drug concentration.
- The patient has unusual plasma concentration of the drug or its metabolites and genetic factors are suspected to be responsible.
- The patient suffers from chronic illness which requires life-long treatment.

The data on plasma concentrations of drugs and their metabolites, i. e. the knowledge of the patient's phenotype and genotype, enables optimization and individualization of psychopharmacological treatment. This is especially important in the elderly with co-morbidity who are taking several drugs resulting in significantly increased risk of pharmacokinetic and pharmacodynamic interactions (Hiemke et al. 2011).

Studies on cost-effectiveness of TDM and pharmacogenetic testing in clinical practice are very scarce. Cost-effectiveness for the use of newer antidepressants in the elderly has been proven since the implementation of TDM reduced direct costs by 10 % (Lundmark et al. 2000). There are even less data on cost-effectiveness for second generation antipsychotics (Hiemke 2008); however, in order for TDM and genetic biomarking to be accepted in clinical practice, those particular data will have to be obtained.

It is believed that in the future pharmacogenetic testing will have to show more than just a significant correlation with the treatment outcome – it will have to ensure significant predictive values and anticipate necessary drug alternatives and dosage alterations (Gervasini et al. 2010).

Conclusions

With the aim of treatment optimization, certain phenotypic genetic biomarkers undoubtedly play an important role in the recognition of treatment-responsive and unresponsive patients, and they reduce the risk of drug toxicity by enabling individual dosage adjustment. TDM and pharmacogenetic testing both may improve acute and long-term treatment, prediction of therapeutic response, possible correlations with treatment outcome, and monitoring of treatment compliance and can represent a prominent step towards creative

psychopharmacotherapy. However, despite ample evidence to the efficacy of these individualized procedures, they are still met with insurmountable financial and educational obstacles.

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