Pharmacovigilance in psychiatry: pharmacogenetic tests and therapeutic drug monitoring are promising tools

Expert Rev. Clin. Pharmacol. 1(2), 183–185 (2008)

Pierre Baumann
Département de Psychiatrie (DP-CHUV), DP-CHUV, Site de Cery, CH-1008 Prilly-Lausanne, Switzerland
Tel.: +41 216 436 434
Fax: +41 216 436 469
pierre.baumann@chuv.ch

"…there is increasing evidence that therapeutic drug monitoring and pharmacogenetic tests are useful tools for optimizing pharmacotherapy."

The diagnosis of the major psychiatric diseases, such as schizophrenia, depression, bipolar disorder and anxiety disorders, is still based on clinical criteria only, since reliable biological diagnostic tests are still not available after approximately half a century of research on the neurochemical dysfunctions of these diseases. Clinical and pharmacological considerations commonly determine the selection of the most appropriate drug treatment. However, there is increasing evidence that therapeutic drug monitoring (TDM) and pharmacogenetic tests are useful tools for optimizing pharmacotherapy.

Patients show high interindividual variability in the pharmacokinetics of drugs and, as a consequence, in clinical response and tolerance to these therapeutic agents. Both on a pharmacodynamic and pharmacokinetic level, it is determined by genetic and environmental factors.

"Both on a pharmacodynamic and pharmacokinetic level, it [clinical response to drugs] is determined by genetic and environmental factors."

From a historical point of view, TDM originated from first studies dealing with the drug plasma concentrations–clinical efficacy (therapeutic response) relationship. Later, when it appeared that, with higher drug concentrations, the risk for serious adverse effects (e.g., anticholinergic effects of tricyclic antidepressants [1]) increased dramatically, the interest for a definition of toxic levels prompted authors to publish case studies. Interestingly, TDM was then widely introduced, but only in a limited number of countries, probably for economic reasons as, for many clinicians (and health politicians?), the cost–benefit ratio is insufficiently in favor of a general use of TDM. Recently, a group of authors (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie [AGNP]-TDM group) published consensus guidelines regarding the use of TDM in psychiatry, but also supporting the combined use of TDM with pharmacogenetic tests [2]. These guidelines define groups of drugs for which TDM was highly recommended and those for which present evidence for the usefulness of TDM is less convincing. Thus, for many psychotropic drugs, there is good evidence for the existence of an optimal plasma concentration range concerning response. For compounds such as clozapine, tricyclic antidepressants and risperidone, an upper threshold plasma concentration has been defined, above which there is an increased risk for serious adverse effects. Exceedingly high drug plasma concentrations may occur in patients suffering from comorbidities (e.g., hepatic and renal diseases), which affect elimination of the drug in patients comedicated with other therapeutic agents, resulting in drug–drug interactions, but also in patients presenting with a genetic deficiency of metabolism.

Of course, drug–drug interactions also occur at a pharmacodynamic level but, until recently, only limited possibilities

EXPERT REVIEWS

 10.1586/17512433.1.2.183 ISSN 1751-2433

existed for biological monitoring of the individual sensitivity of the patients to adverse effects; a pharmacogenetic approach now appears promising. Psychotropic drugs generally act on enzymes (e.g., monoamine oxidase [MAO]), receptors (e.g., dopamine D_2, 5-hydroxytryptamine $[5\text{-HT}]_{2c}$) or transporter proteins of neurotransmitters (e.g., 5-HT transporter [5-HTT]). These mechanisms are considered to be responsible for their therapeutic effect or for the appearance of adverse effects. Genetic polymorphisms have been described for most of these proteins. Their interaction with drugs, and therefore drug response, depends on the structure of the polymorphic forms. Studies concerning the influence of the pharmacodynamic–pharmacogenetic status of the patients on their clinical outcome have yielded promising results [3–5], but the relevance of these findings in daily clinical practice is yet to be demonstrated. Clinicians who submit their psychiatric patients to a pharmacogenetic test for the determination of the pharmacogenetic status of their histamine, dopamine or serotonin receptors in order to select the optimal drug treatment are probably still very rare!

> "...several small but sound clinical studies suggest that inclusion of therapeutic drug monitoring and pharmacogenetic tests should be part of a pharmacovigilance program."

The pharmacodynamics also depend on the availability (metabolism and pharmacokinetics) of the drug at the target organ. Interestingly, clinical studies on the pharmacodynamic–pharmacogenetics of drugs seldom include investigations into their pharmacokinetics and pharmacokinetic–pharmacogenetics, but promising examples of such studies already exist [4–6], in that these authors examined the genetic variations of pharmacokinetic (cytochrome P-450 [CYP], other metabolic enzymes and P-glycoprotein) and pharmacodynamic (e.g., dopamine receptors and serotonin receptors) parameters and adverse effects.

There is growing and convincing literature on the clinical relevance of genotyping or phenotyping patients for enzymes implicated in the metabolism of psychotropic drugs. Most data concern CYP, particularly the isoforms CYP2D6, CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5/7. Most antidepressants and antipsychotics are basic drugs and therefore frequently substrates of CYP2D6. Genetically determined ultrarapid, extensive, intermediate and poor metabolizers can be defined by genotyping and phenotyping subjects. As a general rule, poor metabolizers have a higher risk of adverse effects, due to an impaired drug metabolism and drug plasma concentrations above the therapeutic range, and ultrarapid metabolizers are at risk for nonresponse due to insufficiently high plasma concentrations at regular doses. Clinically valuable recommendations on the optimal use of pharmacogenetic tests are available and there is some evidence that these tests are clinically useful when combined with TDM [7–9]. It is, however, limited by the fact that well-designed epidemiological studies are rare and the dose recommendations in function of the pharmacogenetic status are generally not supported by sufficient experimental evidence. In a general population, the frequency of patients presenting a particular pharmacogenetic status (poor metabolizers or ultrarapid metabolizers) is generally below 10% [9]. It was estimated that, for pharmacogenetic cohort studies or randomized, controlled pharmacogenetics trials, thousands of patients should be included in order to obtain sufficient power [10]: a rather expensive enterprise!

There is also increasing evidence for the implication of transporter proteins such as P-glycoprotein (multidrug resistance transporter [MDR1]) in the distribution of psychotropic drugs in the organism, and polymorphisms have been described in both humans and animals [11]. An interesting relationship has been reported between the MDR1 pharmacogenetic status and the appearance of postural hypotension in psychiatric patients treated with nortriptyline [12]. This should encourage more research in this field, but the present state of the art suggests that the daily clinical use of genotyping for MDR1 is not yet justified.

Reporting of adverse drug reactions (ADRs) to a governmental organization is now mandatory in most countries. The clinical cases must be carefully described by those who report the ADR, but comprehensive investigations about metabolic and pharmacokinetic causes are generally not requested. It would of course be useful to know whether the ADRs are partly explained by pharmacokinetic and pharmacogenetic factors, and corresponding tests should be carried out.

> "...it seems advisable to improve the treatment of patients with drugs already available and to decrease the risks of adverse effects in tailoring medication to the patient using already available tools..."

Pharmacovigilance programs were initiated in Germany more than 25 years ago by psychiatric university and psychiatric state hospitals on a nongovernmental basis. In the meanwhile, the AMSP program (Arzneimittelsicherheit in der Psychiatrie [drug safety surveillance in psychiatry]) has been introduced in dozens of psychiatric hospitals in Germany, Switzerland and Austria, and its introduction is progressing slowly in some other countries. Data are regularly collected in inpatients regarding the frequency of prescription of particular drugs, either solely or in combination with other psychotropic or somatic drugs. Prospectively, severe adverse effects are collected under the naturalistic conditions of routine clinical treatment and have been fully described. There is a fruitful collaboration between AMSP, governmental organizations implicated in pharmacovigilance and the pharmaceutical industry. There are regular regional and international meetings where the observed cases are discussed, evaluated and reported [13].

Therefore, AMSP also has an extraordinary educational value as, in the participating centers, psychiatrists and nurses are sensitized to these problems often neglected in institutions mainly devoted to a psychotherapeutic approach.

Nevertheless, the naturalistic approach bears some disadvantages. In particular, TDM and pharmacogenetic tests are not systematically carried out. As an example, the report *25 years of drug surveillance in psychiatry: the AMSP system* summarizes some of the achievements of the AMSP project, but a pharmacokinetic and pharmacogenetic strategy was hitherto neglected [13]. Additionally, several small but sound clinical studies suggest that inclusion of TDM and pharmacogenetic tests should be part of a pharmacovigilance program [6,14]. In a comprehensive review, an algorithm was recently proposed that describes the application of these techniques in pharmacovigilance [15].

The introduction of novel drugs in psychiatry occurs rarely. Therefore, it seems advisable to improve the treatment of patients with drugs already available and to decrease the risks of adverse effects in tailoring medication to the patient using already available tools, such as TDM and pharmacogenetic tests.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Preskorn SH. Tricyclic antidepressants: the whys and hows of therapeutic drug monitoring. *J. Clin. Psychiatry* 50(Suppl.), 43–46 (1989).

2 Baumann P, Hiemke C, Ulrich S *et al.* The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. *Pharmacopsychiatry* 37, 243–265 (2004).

3 Serretti A, Artioli P, Quartesan R. Pharmacogenetics in the treatment of depression: pharmacodynamic studies. *Pharmacogenet. Genomics* 15, 61–67 (2005).

4 De Leon J, Susce MT, Pan RM, Koch WH, Wedlund PJ. Polymorphic variations in *GSTM1*, *GSTT1*, PgP, *CYP2D6*, *CYP3A5*, and dopamine D2 and D3 receptors and their association with tardive dyskinesia in severe mental illness. *J. Clin. Psychopharmacol.* 25, 448–456 (2005).

5 Murphy GM Jr, Kremer C, Rodrigues HE, Schatzberg AF. Pharmacogenetics of antidepressant medication intolerance. *Am. J. Psychiatry* 160, 1830–1835 (2003).

6 Clark DW, Donnelly E, Coulter DM, Roberts RL, Kennedy MA. Linking pharmacovigilance with pharmacogenetics. *Drug Saf.* 27, 1171–1184 (2004).

7 De Leon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for *CYP450 2D6* and *CYP450 2C19*. *Psychosomatics* 47, 75–85 (2006).

8 Albers LJ, Özdemir V. Pharmacogenomic-guided rational therapeutic drug monitoring: conceptual framework and application platforms for atypical antipsychotics. *Curr. Med. Chem.* 11, 297–312 (2004).

9 Kirchheiner J, Nickchen K, Bauer M *et al.* Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. *Mol. Psychiatry* 9, 442–473 (2004).

10 Kirchheiner J, Fuhr U, Brockmöller J. Pharmacogenetics-based therapeutic recommendations – ready for clinical practice? *Nat. Rev. Drug Discov.* 4, 639–647 (2005).

11 Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. *Clin. Pharmacol. Ther.* 75, 13–33 (2004).

12 Roberts RL, Joyce PR, Mulder RT, Begg EJ, Kennedy MA. A common P-glycoprotein polymorphism is associated with nortriptyline-induced postural hypotension in patients treated for major depression. *Pharmacogenomics J.* 2, 191–196 (2002).

13 Grohmann R, Müller-Oerlinghausen B, Rüther E. 25 years of drug surveilance in psychiatry: the AMSP system. *Pharmacopsychiatry* 37(Suppl. 1), S1–S88 (2004).

14 Rau T, Wohlleben G, Wuttke H *et al.* CYP2D6 genotype: impact on adverse effects and nonresponse during treatment with antidepressants – a pilot study. *Clin. Pharmacol. Ther.* 75, 386–393 (2004).

15 Jaquenoud Sirot E, Van der Velden JW, Rentsch K, Eap CB, Baumann P. Therapeutic drug monitoring and pharmacogenetic tests as tools in pharmacovigilance. *Drug Saf.* 29, 735–768 (2006).