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# CLINICAL APPLICATION OF THERAPEUTIC DRUG MONITORING AND PHARMACOGENETICS IN PSYCHIATRY, WITH A FOCUS ON BELGIUM

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## SUMMARY

*Response rate to treatment is generally not as high as expected in psychiatric disorders. The lack of clinical improvement under a well-conducted treatment, that complies with guidelines, may be the consequence of genetic abnormalities that impact the metabolizing pathways of the drug. Genetic polymorphism of metabolizing enzymes is frequent in the population and has been proven to have a clinical impact. It may also be the consequence of environmental or organic factors that interact with the pharmacokinetic pathways (absorption, distribution, metabolizing, excretion) of the drug. These intrinsic and extrinsic factors will lead to inter- and intraindividual fluctuations in plasma drug concentrations. Therapeutic drug monitoring permits to measure plasma drug concentrations in order to adapt psychopharmacotherapy individually. In some cases, it can be coupled to pharmacogenetic testings. This review presents recent literature and guidelines on the subject. Eventually, there is a focus made on the French-speaking part of Belgium where neither therapeutic drug monitoring, nor pharmacogenetics testing, are used frequently in clinical practice. Some challenges are to be addressed to implement these techniques in Belgium.*

***Key words:*** *therapeutic drug monitoring – pharmacogenetic - precision medicine - psychopharmacotherapy*

***Abbreviations:*** *AGNP - Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie; TDM - therapeutic drug monitoring*

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## INTRODUCTION

Mental disorders affect a large segment of the global population (Kessler et al. 2009) and represent a significant socio-economic burden (WHO). The impact on patients' quality of life is equally significant. For major depressive episodes, bipolar disorders, and schizophrenia, only one-third of treated patients achieve complete and stable remission of their symptoms (Corponi et al. 2018). In practice in Belgium, we observe a tendency towards polypharmacy to compensate for this lack of clinical response, instead of favouring switches towards monotherapy (Lagreula et al. 2021, 2023). Studies have shown with a high level of evidence that polypharmacy has no advantage over monotherapy in terms of symptom reduction or hospitalization (Galling et al. 2017, Tiihonen et al. 2019, Kasteridis et al. 2019).

Precision medicine, where treatment is tailored to the unique profile of each patient, offers the possibility to bridge the gap between the available pharmacologic knowledge and its proper utilization in health care, by considering pharmacokinetic variability (Hiemke et al. 2018, Biso et al. 2024). To date, two recognized tools meet this need. These are therapeutic drug monitoring (TDM), which is used to measure plasma concentrations of a drug, and pharmacogenetic tests, that account for the genetic polymorphism of hepatic metabolism enzymes, i.e. cytochrome P450 isoenzymes (CYP enzymes).

## SUBJECTS AND METHODS

The aim of this article is to present recent data from the literature concerning therapeutic drug monitoring and pharmacogenetics, and to discuss their implementation in clinical practice, more precisely in the context of Belgium. Literature searches were carried out on Pubmed, Google Scholar, Cairn info with the following key words: “therapeutic drug monitoring” AND “psychiatry”, “pharmacogenetics” AND “psychiatry”, “precision medicine”, “polypharmacy”.

## RESULTS

### Therapeutic Drug Monitoring

#### *Therapeutic Drug Monitoring in psychiatry*

TDM is the measurement and interpretation of a drug’s blood concentrations with a view to optimize pharmacotherapy (Hiemke et al. 2018). It is based on the assumption, confirmed by numerous studies to date, that a drug’s blood concentration correlates with its effect. However, for the same dose of a psychotropic drug, more than 20 interindividual variations in plasma levels can be observed (Berney et al. 2004). Considering a stable drug dose, plasma levels may fluctuate due to pharmacokinetics variabilty (absorption, distribution, metabolism, excretion), which can be influenced by ethnicity, age, comorbidities, comedication, or genetic abnormalities in metabolizing enzymes (Hiemke et al. 2018).

The German-speaking working group on pharmacopsychiatry (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) has defined consensus guidelines on the use of TDM, dose-related reference ranges for plasma concentrations for each psychotropic drug they reviewed, and therapeutic reference ranges, (i.e. plasma concentration references corresponding to pharmacotherapeutic efficacy of psychotropics). Moreover, they included recommendation levels for the use of TDM by molecule based on the strength of scientific evidence.

***TDM: practical aspects***

The goal of TDM is not simply to obtain a blood level, but to be able to analyze the blood level obtained in order to subject it to clinical scrutiny and reach a decision concerning the pharmacological treatment of a given patient. This is a non-linear process, based on the principle of feedback, requiring several stages (Ates et al. 2020). The *sine qua non* condition for a TDM request is that the results obtained will enable the clinician to guide his or her clinical decision (Eap et al. 2021). The indications for therapeutic drug monitoring are as follows:

- TDM is mandatory for lithium for safety reasons because of its narrow therapeutic index (NTI) and its high level of toxicity.
- When initiating treatment or after dose change, TDM is considered obligatory for psychotropic drugs with a high level of recommendation to use TDM (level 1). This concerns tricyclic antidepressants, citalopram, haloperidol, perphenazine, amisulpride, olanzapine, clozapine, as well as most mood stabilizers (lithium, carbamazepine, valproic acid, phenobarbital, phenytoin). Note that most antidepressants and antipsychotics not listed above have a level 2 of recommendation of using TDM, meaning that TDM is still recommended. On the other hand, anxiolytics almost all have a level 4 recommendation (potentially useful) (Hiemke et al. 2018).
- TDM is strongly recommended for all psychotropic drugs in cases of lack of clinical improvement under recommended doses, suspected non-adherence, side effects or drug interactions (Hiemke et al. 2018).
- TDM can also be useful during remission to determine the therapeutic level associated with a response in a given patient. This level can then be used as a reference value in the event of relapse (Unit of Pharmacogenetics and Clinical Psychopharmacology, 2021). At the Centre Hospitalier Universitaire Vaudois (CHUV, Lausanne, Switzerland), it is recommended to perform TDM once a year in case of chronic maintenance treatment. The AGNP guidelines recommend monitoring plasma levels 1x/3-6 months, in case of maintenance therapy, to prevent relapses and hospitalizations.
- When switching from oral to long-acting injectable (LAI) antipsychotics, TDM allows adjusting the dosage of the depot form so that the levels match those obtained during oral treatment. This indication, however, requires further research (Baumann et al. 2006, Schoretsanitis et al. 2021).
- Some patient groups could also benefit from systematic TDM, such as children, adolescents, pregnant or breastfeeding women, elderly persons (> 65 years), patient with differential ethnicity, patient with pharmacokinetically relevant comorbidity (hepatic or renal insufficiency, cardiovascular disease, inflammation state, infection, gastrointestinal resection or bariatric surgery), patients with substance use disorders, individuals with intellectual disabilities, forensic psychiatric patients, or patients with known or suspected pharmacokinetic abnormalities (Hiemke et al. 2018).

It is considered essential to accompany the sample with a request form completed by the clinician (Hiemke et al. 2018). This form should include the patient's demographic data and diagnosis, the date and time of the blood sampling, the reason to undergo TDM, dose and dosing schedule (time of treatment initiation, date of last dose changes, schedule of daily intake), the date and time of the last drug intake regarding the blood sample, any comedications, any comorbidities, whether the patient is a smoker or consumes other substances, and the presence of any favorable clinical effects and/or adverse effects (Eap et al. 2021).

The blood sample must be taken when the plasma concentration is at its lowest (Cmin), and at the drug's steady-state concentration, so that the level measured represents the residual level for which the recommended values have been determined. Cmin is achieved at the end of the longest dosing interval, i.e. just before taking the drug (or before the next injection in the case of a depot), and steady-state is reached under constant doses after 4 to 6 elimination half-lives. If intoxication is suspected, the sample can be taken at any time.

Then, the sample is sent to the laboratory for analysis. The results obtained must be reported within 48 hours after plasma sampling, so that the delay remains clinically relevant for guiding pharmacotherapy (Eap et al. 2021, Hiemke et al. 2018). The laboratory should report the results of plasma level (preferably in ng/ml), the parent-drug/metabolite ratio, and the reference ranges.

Eventually, the results must be correctly interpreted. An expert in psychopharmacology should interpret the results based on the information provided by the clinician in the request form. He/she should determine whether the level corresponds to the dose, if it is within the therapeutic reference range, and provide a pharmacological opinion based on this information (Eap et al. 2021). The psychiatrist takes the final decision.

***Benefits and limitations of TDM in psychiatry***

TDM is a valid tool to optimize efficacy and safety of pharmacotherapy in psychiatry (Schoretsanitis et al. 2018, Baumann et al. 2006). But it is mandatory to respect the procedure. Common errors are poor indication, sampling errors, incorrect laboratory methods,

misinterpretation of results, the absence of available pharmacological expertise (Hiemke et al. 2018, Eap et al. 2021, Ates et al. 2020). Finally, the reference ranges are based on adult individuals. Studies are still needed to estimate the therapeutic window in children, adolescents or the elderly (Hiemke et al. 2018).

#### *Cost-effectiveness*

Traditional trial-and-error prescription can be time-consuming and costly. By integrating TDM into psychiatric practice, clinicians can accelerate treatment optimization, thereby decreasing hospital stays and reducing the risk of relapse and rehospitalization, making TDM cost-effective. More studies on this topic are however still needed (Baumann et al. 2006, Hiemke et al. 2018).

### Pharmacogenetics

#### *Pharmacogenetics in psychiatry*

Almost all psychotropics (90%) are metabolized by cytochrome P450 (CYP) isoforms: CYP1A2, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 (Eap et al. 2021). Pharmacogenetics allows to identify genetic variants that are determinant for CYP enzymes' activity (Stingl et al. 2013).

#### *Benefits and limitations of pharmacogenetics*

By identifying specific genetic variants, clinicians can predict drug responses and select the drugs that are most likely to be effective and safe for each patient. This measurement takes no account of environmental factors and is therefore valid for life, which is interesting. It only needs to be carried out once in an individual's lifetime, and independently of drug intake. To guide pharmacotherapy, CYP pharmacogenetic tests are more useful at the start of treatment (Eap et al. 2021), and gene-panel testing could be the most clinically useful, while being cost-effective (Swen at al. 2023, Del Casale et al. 2023). There is increasing evidence of the interest in pharmacogenetics in psychiatry, but the subject remains controversial due to a need of further research in this field (Van Shaik et al. 2020, Eap et al. 2021, Saadullah et al. 2024, Bousman et al. 2021).

#### *Combination of TDM with pharmacogenetics*

To date, pharmacogenetic tests are mainly recommended in combination with TDM when there is a hypothesis of genetic polymorphism of the drug-metabolism enzymes (Hiemke et al. 2018, Berney et al. 2004). This will be suspected when the blood level does not correspond to the dose, with an increased or decreesed parent drug/metabolite ratio (Hiemke et al. 2018).

## DISCUSSION

Research made it clear that TDM should be integrated into clinical routine. However, in Belgium, TDM is only routinely used for lithium, for which plasma monitoring is mandatory. The gap between theory and practice can be explained by a number of factors. Firstly, there is a lack of knowledge on the subject, both among qualified psychiatrists and hospital teams, as in the training of psychiatrists, where the subject of TDM to guide treatment is absent. Secondly, TDM is not yet optimized for field application: there is no request form available, expert advice in psychopharmacology is lacking, and laboratory results are generally available beyond the maximum 48-hour timeframe.

What are the avenues and challenges posed by this situation? By educating psychiatrists in training (Baumann et al. 2017) and raising awareness among those already graduated about TDM, its use could quickly become part of good practices. It is also important to train nursing teams in TDM methodology to ensure blood samples are taken correctly (respecting Cmin and steady-state). In this regard, Schoretsanitis et al. have written a practical summary of the 2017 AGNP guidelines with a focus on the clinical application of TDM, which can serve as a support for psychiatrists (Schoretsanitis et al. 2018). A valid request form needs to be set up for interpreting results. Again, the AGNP presents a template in its article which could serve as inspiration.

Laboratories must use correct and validated methods. The main challenge for laboratories relates to the time needed to obtain results. If the psychiatrist must wait several days each time to get the results, the treatment plan is significantly extended (thus hospitalization), and TDM loses its value. Another issue, is the severe lack of experts in clinical pharmacology in Belgium. Based on Sjoqvist's minireview, Belgium ranges within the European countries with the poorest amount of clinical pharmacologist (Sjoqvist 2014). In the end, implementing TDM in clinical practice requires close collaboration between clinicians, laboratories, pharmacologists and academic partners (Ates et al. 2020, Eap et al. 2021). It is essential to understand that TDM is an interdisciplinary tool (Hiemke et al. 2018). Financial resources are therefore required, but as the cost-benefit ratio of TDM has been proven to be favorable, these investments seem relevant. Ultimately, it's a budgetary decision, and therefore a political one, whether to allocate the resources. Concerning pharmacogenetic testing, to date, it is recommended in adjunction to TDM. Before considering the practical implementation of pharmacogenetic testings, it appears necessary to overcome the challenges posed by TDM in Belgium so that TDM could become a recognized and used technique to enhance psychopharmacotherapy.

## CONCLUSION

TDM offers the prospect of improving psychopharmacotherapy, speeding up recovery for many patients, and reducing healthcare costs. The level of evidence is sufficiently high for well-established indications, and the cost- benefit ratio is favorable. Pharmacogenetic testing look promising but should still be used in complement to TDM.

In Belgium, therefore, it is advisable for TDM to become part of good practices, as recommended by the AGNP. To achieve this, clinicians, laboratories, and (psycho)pharmacologists need to be trained and made aware of the need to apply TDM correctly throughout its process. It should be remembered that this is above all a multidisciplinary and dynamic tool, based on the principle of feedback. Given these challenges, and knowing that TDM is often a prerequisite for pharmacogenetic testing, it seems premature to implement pharmacogenetic testing in Belgium before TDM.

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