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Abstract
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Reference

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Screening for genotypic and phenotypic variations in CYP450 activity in patients with therapeutic problems in a psychiatric setting, a retrospective study

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A B S T R A C T

Objectives: This retrospective study aimed to assess to what extent an adverse drug reaction (ADR), an abnormal therapeutic drug monitoring (TDM) or a non-response, was attributable to an abnormal cytochrome P450 activity in a psychiatric setting.

Method: We collected the results of investigations performed in these situations related to psychotropic drugs between January 2005 and November 2014. Activities of different cytochrome P450 were assessed by genotyping and/or phenotyping. Two experienced clinical pharmacologists assessed independently the possible association between the event and the results of the investigations.

Results: One hundred and thirty eight clinical or biological situations had a complete assessment of all major metabolic pathways of the target drug. A majority of clinical or biological situations were observed with antidepressants (n=93, 67.4%), followed by antipsychotics (n=28, 20.3%), benzodiazepines and hypnotics (n=13, 9.4%), and psychostimulants (n=4, 2.9%). Genotype and/or phenotype determination was mainly performed because of ADRs (n=68, 49.3%) or non-response (n=46, 33.3%). Inter-rater reliability of the scoring system between the pharmacologists was excellent (kappa=0.94). The probability of an association between ADR, TDM or non-response and metabolic status was rated as intermediate to high in 34.7% of all cases, with proportions of 30.4% and 36.7%, for non-response and ADR respectively.

Conclusion: When indicated by clinical pharmacologists, ADR, TDM or non-response may be attributable to a variation of the metabolic status with an intermediate to high probability in 34.7% of patients, based on the congruent assessment made by two clinical pharmacologists. Further studies assessing the clinical relevance of prospective explorations and clarifying the appropriate method according to the clinical context are needed.

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1. Introduction

There is substantial unexplained interindividual variability in drug response in the management of psychiatric disorders [1]. This variability can lead to lack of improvement, adverse drug reactions (ADR) as well as variability in time to respond to treatment. Variability may bring a lack of adherence or put the patient at risk to be definitely considered as resistant or intolerant. This will further lead to the choice of another line of treatment, that is not always needed, thus delaying the overall benefit of the therapeutic regimen [2,3]. Predicting variability and using therapeutic individualization could increase the quality of care management [4,5]. Therefore, strategies able to identify the factors of variability and to select the appropriate drug or its adequate dosage represent promising tools in the care of psychiatric disorders.

Many factors may be involved in interindividual variability in drug response, in every step from drug prescription to drug effect (medications errors and lack of compliance to drug-receptor inter-
action and desensitization, for example) [6]. Among them, the variability in drug metabolism, which can result in pronounced differences in steady-state plasma concentrations, may be predicted [7,8]. Hence, research has focused on the promise of individualized treatment in psychiatry. Different studies have supported a link between enzyme/transporter activity and the pharmacokinetic or pharmacodynamic parameters of antidepressant or antipsychotic agents, suggesting genotyped-based dose recommendations [4,5,7,9,10].

Hall-Flavin et al. recently demonstrated that the prospective use of a pharmacometric testing involving cytochrome P450 (CYP450) and an interpretive report was able to improve depression outcome, by allowing the physicians to select the appropriate drug in a small cohort of patients presenting with major depressive disorder. However, assessment of drug metabolism variability, e.g. CYP450 activity, is not a part of the usual care in practice and psychiatrists mainly rely on clinical evaluation or therapeutic drug monitoring (TDM) when available, to start or adapt psychotropic medication.

To date, data are missing about the usefulness of prospective assessment of variability in drug metabolism in psychiatric settings. In the Geneva University Hospitals, clinical pharmacologists of the division of clinical pharmacology and toxicology daily answer to physicians’ questions about adverse drug reactions (ADR), abnormal TDMs, non-response to treatment, or therapeutic management (choice of the drug, dose, route of administration), among other situations. After analysing the clinical situations and in order to clarify pharmacological abnormalities, genetic or phenotypic investigations may be proposed by the clinical pharmacologist, based on his clinical expertise, the clinical context, the nature of the ADR, TDM or non-response and the concomitant medications, potentially limiting the interpretation of the tests.

In order to better discuss the benefit of investigating patients’ metabolic status during psychiatric therapeutic management and before engaging in a prospective study, this retrospective study aimed to assess to what extent an ADR, TDM or non-response was attributable to a variant of CYP450 activity when indicated by a clinical pharmacologist.

2. Methods

2.1. Patients and setting

The division of clinical pharmacology of Geneva University Hospitals give pharmacological advice to physicians on individual clinical situations, such as the appropriate drug in case of pregnancy or breastfeeding, in case of weight gain, in case of drug interactions, adverse effects or treatment failure, among others.

Questions come from hospitals physicians as well as from private practices, and this for all medical specialities. Individual propositions are summarized in a report and when considered appropriate by a senior clinical pharmacologist, genetic and/or phenotypic investigations are proposed. If the tests are performed, their results are analysed according to the clinical context and summarized in a second report. We retrospectively collected results of genetic and/or phenotypic investigations performed between January 2005 and November 2014 and selected all data related to psychotropic drugs (N = 250). The study was approved by the local ethics committee (Reference: 14–244). Data were excluded if investigations did not assess all major metabolic pathways of the involved drug, according to the table of cytochrome substrates (http://www.hug-ge.ch/sites/interhug/files/structures/pharmacologie_et_toxicologie_cliniques/documents/substrats_et_inhibiteurs_a5.pdf) [11]. For example, an investigation related to citalopram was only included if CYP2C19 and CYP3A4 activities were studied, CYP1A2 and CYP2D6 for duloxetine, CYP2D6 and CYP3A4 for haloperidol etc. The flowchart of data inclusion is illustrated in Fig. 1: 138 therapeutic situations were analysed, which referred to 89 patients and 34 drugs.

2.2. Evaluation criteria

All clinical pharmacology reports were carefully reviewed and classified into different categories according to clinical events, such as ADR and lack of response to the prescribed drug. Two experienced clinical pharmacologists assessed the possible association between these clinical events and the genetic and phenotypic results independently according to a semi-quantitative scale and their clinical judgment (Appendix A). The semi-quantitative scale was mainly built on scientific databases (e.g. http://www.hugge.ch/sites/interhug/files/structures/pharmacologie_et_toxicologie_cliniques/documents/substrats_et_inhibiteurs_a5; DrugBank, http://www.drugbank.ca/; ‘The Human Cytochrome P450 (CYP) Allele Nomenclature Database’, http://cypalleles.ki.se). For a given drug, each relevant metabolic pathway, whether major or minor, was considered and a global rating was made according to a 3-point scale: 0 = no or low probability of genetic and phenotypic results being linked with a clinical or biological problem; 1 = intermediate probability; 2 = high probability. In case of drugs with active metabolites, the use of the table was completed by the available literature on the respective clinical relevance of the metabolite and the parent compound. In case of disagreement, the opinion of a third expert in clinical pharmacology was sought and retained as the final score. The patient’s treatment at the time of the phenotypic and/or genetic investigation was recorded and taken into account when rating the association between metabolic status and event.

2.3. Metabolic status

Activities of CYP2D6, 2C9 and 2C19 were assessed by genotyping and/or phenotyping, whereas activities of CYP1A2 and 3A4 were only determined by phenotyping.

2.3.1. Genotyping

The following variants of the CYP2D6 gene were genotyped: CYP2D6*3, *4, *5, *6, *35, *41 and duplications, until 2007, when the AmpliChip CYP450 test allowed the simultaneous analysis of 33 CYP2D6 alleles. For the CYP2C9 and CYP2C19 genes, the following variants were genotyped: CYP2C9*2 and *3, CYP2C19*2 and *17 (since 2009).

The predicted phenotypes were based on enzyme activities of these alleles, as listed in ‘The Human Cytochrome P450 (CYP) Allele Nomenclature Database’ (http://cypalleles.ki.se) or the PharmGKB database (http://www.pharmgkb.org/index.jsp), or in the AmpliChip CYP450 2D6 test. Patients were classified as poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) and ultra-rapid metabolizer (UM) for CYP2C19 and CYP2D6 and as induced, normal or reduced activity for CYP2C9.

2.3.2. Phenotyping

Phenotyping consists in the administration of probe substrates metabolised by specific CYPs and determination of plasma, blood, or urine metabolic ratios. Probe substrates were caffeine for CYP1A2, flurbiprofen for CYP2C9, omeprazole for CYP2C19, dextromethorphan for CYP2D6 and midazolam for CYP3A4. Individual phenotyping corresponded to the administration of the CYP2D6-specific probe, dextromethorphan. Dextromethorphan/dextromethorphan ratio was measured in urinary samples during several years based on cut-off data from previous studies [12,13]. Lately, with the development of dried blood spots...
dosages, this method has been rarely performed. Simultaneous phenotyping corresponded to the concomitant administration of multiple specific probes with caffeine 50 mg, flurbiprofen 10 mg, dextromethorphan 10 mg, midazolam 1 mg, bupropion 20 mg and omeprazole 10 mg. Capillary blood samples 2 h following drug administration allowed measuring the activity of multiple CYP450 enzymes simultaneously, as previously reported [14,15]. Phenotypic classification was based on plasma or urine metabolic ratios according to a validated method developed in the laboratory of clinical pharmacology and toxicology of the University Hospitals of Geneva [14,16,17], CYP1A2, 2C9 and 3A4 enzyme activities were categorized as induced, normal or reduced. Those of CYP2C19 and 2D6 allowed classifying patients as poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) or ultrarapid metabolizer (UM).

2.4. Statistical analysis

Categorical and continuous variables were described using frequency tables (N, %) and median (range), respectively. Comparisons of proportions were performed using Fisher's exact tests. Inter-rater reliability, i.e reliability of the scoring system was assessed with the kappa coefficient. Statistics were computed using SPSS version 22 (IBM Corporation, Armonk, NY). All tests were two-tailed, with significance level at 0.05.

3. Results

3.1. Patients, ADR, TDM or non-response, and involved drugs

As presented in Fig. 1, between January 2005 and November 2014, 695 genotypic or phenotypic explorations were recommended to the patients addressed to the division of clinical pharmacology and toxicology. Among them 260 involved ADR, TDM or non-response to psychotropic drugs. One hundred thirty-eight included then a complete assessment of all major metabolic pathways of the target drug. These assessments were performed in 89 patients (56 women, 33 men), because of one (n = 57) or several (n = 32) ADR, TDM or non-response.

A majority of clinical or biological situations were observed with antidepressants (n = 93, 67.4%), followed by antipsychotics (n = 28, 20.3%), benzodiazepines and hypnotics (n = 13, 9.4%), and psychostimulants (n = 4, 2.9%). Genotype and/or phenotype determination was mainly performed because of an ADR (n = 68, 49.3%) or a non-response (n = 46, 33.3%), followed by abnormal drug concentrations or metabolic ratio (n = 14, 10%).

3.2. Metabolic status

Patients’ CYP450 activity, assessed by phenotyping and/or genotyping, is presented in the Appendix B. Regarding the phenotypic approach, the most frequently investigated enzymes were CYP2D6 (n = 62 patients), followed by CYP1A2 (n = 46), CYP3A4 (n = 45), CYP2C9 (n = 42) and CYP2C19 (n = 40). For the genetic approach, CYP2D6 was the most frequently studied enzyme (n = 50), followed by CYP2C19 (n = 26) and CYP2C9 (n = 17). A large majority of patients were treated with one or more drugs when phenotyping was performed (n = 57 of 63 documented cases, 90.5%). Treatment included CYP2D6 or CYP2C19 inhibitors for 36 (57.1%) and 19 patients (30.2%), respectively.

3.3. Concordance between predicted and measured CYP450 activity

Among the 62 patients who underwent CYP2D6 phenotypic exploration, 28 were also investigated by a genetic approach. In 53.6% of the cases (15/28), concordance was observed between genotype and phenotype.

The details of the discordances for CYP2C19 and CYP2D6, together with the CYP450 inhibitors that may explain the discordances are presented in Table 1. Five patients with an EM genotype showed an IM or PM phenotype, among whom 3 were comedicated with CYP2D6 inhibitors. None of the 4 patients with CYP2D6 UM
profile according to phenotype was detected by genotyping, and none of them was taking a CYP450 inducer.

For CYP2C19, 9 patients were investigated by the two approaches. A genotype/phenotype concordance was observed in 55.6% of the cases. In the 4 cases, discordances were observed. In one case only, the current treatment with omeprazole may have explained a slower metabolism than genetically predicted (Table 1).

Five patients underwent CYP2C9 assessment by phenotypic and genotypic approaches, with 60.0% genotype/phenotype concordance. The two discordant results were not explained by comediations.

Overall, in 7 cases/11, comediations did not explain the discordances between predicted phenotype and measured phenotype.

### 3.4. Link between metabolic status and ADR, TDM or non-response

Inter-rater reliability of the scoring system was excellent (kappa = 0.94), with discrepant results between the two clinical pharmacologists in only 4 of 138 cases. These four cases were related to ADR with venlafaxine (two patients, both PM for CYP2C19), fluoxetine (IM for CYP2D6, induced for CYP3A4) and clomipramine (IM for CYP2D6, induced for CYP1A2 and CYP3A4).

As illustrated in Fig. 2, the probability of a link between ADR, TDM or non-response and metabolic status was rated as intermediate to high in 34.7% of all cases (n = 138). For non-response and ADR, proportions were 30.4% and 36.8%, respectively (Fisher’s exact test, P = 0.55). For concentration or metabolic ratio outside the therapeutic range, the proportion was 38.9%. When considering the low and high concentrations only, the probability of link was rated as intermediate to high in 30.8% (4/13 cases) and 50% (1/2 cases), respectively. Cases related to antidepressants were linked to the genotype or phenotype (intermediate to high probability) in 37.6% of cases, as compared to 25.0% for antipsychotics (Fisher’s exact test, P = 0.26).

Table 2 further documents the link between metabolic status and non-response or ADR for antidepressants and antipsychotics, with examples of each situation. A link was established for 30.8% of cases related to benzodiazepines and hypnotics, and 50.0% for psychostimulants.

### 4. Discussion

This retrospective study shows that, when indicated by clinical pharmacologists, clinical or biological events related to drug intake may be attributable to a variation of the metabolic status with an intermediate to high probability in 34.7% of patients on psychotropic drugs, based on the congruent retrospective assessment made by two clinical pharmacologists.

A decreased or increased CYP450 activity was slightly more frequent when the clinical situation was an ADR (Fig. 2, Table 2), compared with non-response. ADR was easier to identify retrospectively by clinical pharmacologist than non-response, which remained in our retrospective sample an anamnestic subjective criteria, not systematically assessed by the use of standardized validated questionnaires. Moreover, for most antidepressants, there is a lack of formal dose-response curve and a delay of at least 8 weeks is required to observe a positive effect, irrespective of the time needed to reach the pharmacokinetic steady state. This delay was not systematically documented in our study. A third reason may be the fact that management of psychiatric disorders usually rely on multidisciplinary approaches with non pharmacological therapy, making the link between response and drugs weaker than for ADRs. This concordance between CYP450 activity and ADRs is in line with the literature since numerous studies reported an over-representation of PMs among patients with antidepressant adverse events as well as with acute and chronic extrapyramidal ADRs of antipsychotics at conventional doses [2,6,7,18-21].

In our study, the relevance of pharmacological investigations in cases of non-response was higher in patients receiving antidepressants than in patients receiving antipsychotics. This is in accordance with numerous studies showing the better outcome of depression among patients with CYP2C19 and CYP2D6 PM activity [22-24]. Only few studies on the influence of metabolism variability on antipsychotic efficacy have been conducted, and are either negative or inadequately powered [2,7,18-20,25]. The small sample size of this retrospective study does not allow drawing conclusion about the link between metabolism variability and antipsychotic non-response. But the question is worth to be further explored, since in our sample of patients on antipsychotic medication, pharmacological explorations were mainly proposed for treatment failure. Overall, an abnormal metabolic status was associated with an ADR, TDM or non-response with an intermediate to high probability in 28.2% of cases of antidepressant or antipsychotic non-response and 37.9% of antidepressant or antipsychotic adverse events. This is important to consider in situations with therapeutic challenges such as resistant depression and chronic psychiatric diseases, as all improvement in care would benefit the patient.

In this study, metabolic activity was largely assessed by a phenotypic approach. This method was often chosen because of its good efficiency and because our laboratory has specialised in a fast, safe and effective method of assessment. We have previously shown the utility of the Dried Blood Spot sampling technique for assessment of the activities of several CYP450 isozymes using a low-dose phenotyping cocktail and limited blood samples [14]. This method
allows a simultaneous and direct measurement of CYP450 status, contrary to the genetic method [14]. Genetic combinatorial approach to CYP2C9, CYP2C19 and CYP2D19 allele scoring was developed to facilitate the translation from pharmacogenomics to personalized medicine and this is particularly valuable in psychiatry where many drugs are metabolised or bioactivated by multiple CYP450 isoenzymes. Besides the high prevalence of patients (52%) with multiple gene alteration yielding altered drug metabolism supports a major interest of the combinatorial approach [26]. However, other isoenzymes known to play a role in the metabolism of psychotropic agents, for instance CYP1A2 and CYP3A4, have been excluded from genetic combinatorial approach so far, due to insufficient evidences to characterize their relevance to psychotropic drug metabolism. Moreover, CYP2D6 genotype analysis remains a challenging task due to the large number of allelic variants and the presence of structural and copy number variation [27]. Several testing platforms exist but some rare variants or population-specific allelic variants may be missed [27,28]. One further barrier for the implementation of CYP450 genetic testing into clinical practice is the complexity of gene locus and genotype interpretation. Although no doubt exists that genetic variations contribute to the variability of several CYP, genotyping to predict drug levels is a blunt instrument because of greater additional variability than those explained by genetics.

Genotype and phenotype can be discordant due to co-
medications [13]. This is illustrated in this study, in the case of patients with slower measured CYP2D6 activity than those expected from genotyping. More than a half of these patients received drugs known to inhibit CYP2D6 at the time of phenotyping. Moreover, the genetic approach was unable to detect 4 CYP2D6 UM, suggesting that phenotyping is of particular interest to explore psychiatric patients with ADR, TDM or non-response.

**Table 2**

<table>
<thead>
<tr>
<th>Link with genotype or phenotype</th>
<th>Adverse events</th>
<th>Non-response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>probability</strong></td>
<td><strong>frequency</strong></td>
<td><strong>%</strong></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants (N=49)</td>
<td>intermediate</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>13</td>
</tr>
<tr>
<td>Antipsychotics (N=9)</td>
<td>intermediate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>1</td>
</tr>
<tr>
<td>Non-response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants (N=25)</td>
<td>intermediate</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>3</td>
</tr>
<tr>
<td>Antipsychotics (N=14)</td>
<td>intermediate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>1</td>
</tr>
</tbody>
</table>

* Rating scale is provided in the Appendix.
Genotyping also failed to predict some IMs who had not received inhibitors, in accordance with a previous study [13].

For all these reasons, phenotypic approach of drug metabolism may be a potent help in personalized medicine even though its limits and strengths merit further prospective studies. When requested and interpreted by a clinical pharmacologist, a careful analysis of the medical context allows the choice of the appropriate method (genetic or phenotypic approach) and interpretation of their results. As a consequence, co-medications should not refrain the exploration of the metabolic status. In accordance with this, the high inter-rater reliability between the pharmacologists was excellent.

This study presents several limitations due to its retrospective setting. First of all, plasma drug concentration was available in few cases, thus, limiting the interpretation of the relationship between drug metabolism enzymes activity and the clinical situation. Next, some discordance between genotype and phenotype was not elucidated. Despite adequate inter-rater reliability, the table used to score the probability of an association between clinical events and genetic and phenotypic results has not been validated before. In particular, it might provide an oversimplified picture for drugs with active parent compound and metabolite. Accordingly, its use should be supplemented with literature data and experience in clinical pharmacology. The number of studied patients for each drug remained small, but in each case, the main metabolic pathways were systematically studied. Then, feedback that would improve the probability of the association was missing. Finally, we cannot exclude that exploring drug metabolism variability would be only useful in refractory patients, since not all psychiatric patients are given specialised pharmacological advice.

In conclusion, we documented, for the first time, the part of ADR, TDM or non-response related to drugs that may be attributable to a modified CYP450 activity in a real life setting. As a link was found in a third of the cases, TDM coupled with exploration of metabolism pathways would certainly be relevant in this challenging psychiatric population. The phenotypic approach may represent a fast, safe and effective method to simultaneously determine the activity of several CYPs, giving the opportunity to be clinically applicable for therapy and taking into account the frequent polymedication of a real life setting. Since metabolic ratio have not been formally validated in the presence of on-going drug treatment and since compliance could never been ruled out, TDM, when available, as well as phenotypic and genotypic determination of CYP450 activity should be integrated in a multidisciplinary approach involving clinical pharmacologists and psychiatrists. Nevertheless these techniques would certainly have a place to retrospectively assess causes of resistance or of unbearable adverse effects and to tailor therapy.

Further studies evaluating the benefit of these investigations, according to the drugs, the adverse drug reactions and the degree of non-response using validated questionnaires, would help to define the most relevant clinical situations for phenotypic and genotypic investigations, and to draw conclusions about the prospective and/or retrospective clinical utility of CYP-typing in a psychiatric setting.

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None.

Conflicts of interest
The authors report no financial or other relationship relevant to the subject of this article.

Appendix A. : Rating scale for the link between type of demand and predicted phenotype based on diplotype and/or actual phenotype

<table>
<thead>
<tr>
<th>Type of demand</th>
<th>Probability of link according to phenotype for major (minor) metabolic pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UM</td>
</tr>
<tr>
<td>Non-response to parent compound (or low concentration)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Non-response to active metabolite (or low concentration)</td>
<td>0</td>
</tr>
<tr>
<td>Adverse reaction to parent compound (or high concentration)</td>
<td>0</td>
</tr>
<tr>
<td>Adverse reaction to active metabolite (or high concentration)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

For a given drug, consider each relevant metabolic pathway, whether major or minor. Rate each pathway according to the table above, with 0 = no or low probability of link with clinical problem; 1 = intermediate probability; 2 = high probability. The total score is obtained by adding the scores for all relevant pathways (if sum ≥ 2, consider a total score of 2). In case of drugs with active metabolites, the use of the table was completed by the available literature on the respective clinical relevance of the metabolite and the parent compound.

Appendix B. : Predicted phenotype based on diplotype and actual phenotype (N = 89 patients)
### References


