Phenoconversion and Therapeutic Drug Monitoring

Jose de Leon

University of Kentucky, jdeleon@uky.edu

Follow this and additional works at: https://uknowledge.uky.edu/psychiatry_facpub

Part of the Psychiatry and Psychology Commons

Right click to open a feedback form in a new tab to let us know how this document benefits you.

Repository Citation

de Leon, Jose, "Phenoconversion and Therapeutic Drug Monitoring" (2015). Psychiatry Faculty Publications. 33.
https://uknowledge.uky.edu/psychiatry_facpub/33

This Letter to the Editor is brought to you for free and open access by the Psychiatry at UKnowledge. It has been accepted for inclusion in Psychiatry Faculty Publications by an authorized administrator of UKnowledge. For more information, please contact UKnowledge@lsv.uky.edu.
Phenoconversion and Therapeutic Drug Monitoring

Jose de Leon

This is the peer reviewed version of the following article: de Leon, J. (2015) Phenoconversion and therapeutic drug monitoring. British Journal of Clinical Pharmacology, which has been published in final form at http://dx.doi.org/10.1111/bcp.12659. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.
Phenoconversion and therapeutic drug monitoring

Jose de Leon, M.D.\textsuperscript{1,2}

\textsuperscript{1}University of Kentucky Mental Health Research Center, Eastern State Hospital, Lexington, KY, USA
\textsuperscript{2}Psychiatry and Neurosciences Research Group (CTS-549), Institute of Neurosciences, University of Granada, Granada, Spain, and Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apóstol Hospital, University of the Basque Country, Vitoria, Spain.

Keywords: clobazam; clozapine; genotype–phenotype mismatch; personalized medicine; pharmacogenetics; risperidone; therapeutic drug monitoring; venlafaxine.

Address for correspondence: Jose de Leon, M.D., Room 3A15A, Mental Health Research Center, Eastern State Hospital, 1350 Bull Lea Road, Lexington, KY 40511, USA e-mail: jdeleon@uky.edu. Phone (859) 246-8440 Fax (859) 246-8446.

Disclosures of Competing Interests: This letter to the editor was completed without any external funding. No commercial organizations had any role in the writing of this paper for publication. The author has completed the Unified Competing Interest form at http://www.icmje.org/doi_disclosure.pdf (available on request from the corresponding author) and declares: no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years.

Acknowledgment: Lorraine Maw, M.A., at the UK Mental Health Research Center helped with editing.
I would like to congratulate Shah and Smith for their excellent comprehensive review of phenoconversion [1]. They used a narrow definition of personalized medicine restricted to pharmacogenetics as they described phenoconversion as its Achilles’ heel. A more comprehensive view of personalized medicine and its application for prescribing medication, personalized prescription, considers not only genetic factors but environmental and personal factors [2]. Inhibitors, among environmental factors, and inflammation, among personal factors, can cause phenoconversion to a poor metabolizer (PM) phenotype. Personalized prescription can be implemented as personalized drug selection and personalized dosing [2]. Combining pharmacogenetics and therapeutic drug monitoring (TDM) is the best way for implementing personalized dosing [3]. Moreover, with TDM, phenoconversion is no longer a problem but a helpful piece of additional information.

Venlafaxine and risperidone TDM and CYP2D6 genotyping are described as examples. A plasma O-desmethylvenlafaxine/venlafaxine concentration ratio <1 signals the absence of CYP2D6 activity, explained by 1) genetic PM status, or 2) phenoconversion after taking a powerful CYP2D6 inhibitor, or from competitive inhibition after the use of venlafaxine itself [4]. Shah and Smith described them, respectively, as gPM and pPM [1]. Preskorn et al. [4], using this ratio, found that venlafaxine had mild CYP2D6 inhibitory properties and that 21% (159/748) of CYP2D6 extensive metabolizers (EMs) experienced phenoconversion to pPM status. Not unexpectedly, nine subjects with a genotype of CYP2D6 *4/*10 (a null allele and an allele with very low activity) had a median ratio of 1.2, since venlafaxine competitively inhibited the very limited CYP2D6 activity they had.

A risperidone TDM ratio was first used in psychiatry to detect phenoconversion during a risperidone North American randomized clinical trial (RCT) [5]. CYP2D6 EMs had higher plasma 9-hydroxyrisperidone concentrations than risperidone concentrations. If we then calculate a risperidone/9-hydroxyrisperidone ratio for CYP2D6 EMs, the ratio is <1 [6]. An inverted ratio, with higher concentrations of risperidone than 9-hydroxyrisperidone, occurred in CYP2D6 PMs and was expected in 50% of CYP2D6 EMs taking paroxetine or fluoxetine [5]. Unfortunately, the RCT risperidone TDM data
was never published by the company in a peer-review journal but was only presented in a poster. In a review article [7], graphics summarized the TDM data from the RCT by focusing on the mean values of the risperidone/9-hydroxyrisperidone ratio and the total concentration-to-dose ratio (C/D ratio), a measure of risperidone clearance from the body. The total concentration is calculated by adding the risperidone and 9-hydroxyrisperidone plasma concentrations [7].

In a naturalistic study of risperidone pharmacogenetics, 277 patients provided risperidone TDM data [8]. Table 1 shows that an inverted ratio (risperidone/9-hydroxyrisperidone ratio >1) was present in almost every CYP2D6 gPM, 95% (19/20) versus 15% (39/257) for the rest of the patients. Phenoconversion was particularly frequent, 83% (5/6), in the intermediate metabolizers [IMs] taking CYP2D6 inhibitors.

A clobazam TDM ratio may also be used to establish phenoconversion. After reviewing the clobazam literature, we have proposed that a steady-state plasma N-desmethylclobazam/clobazam ratio >25 will identify a CYP2C19 gPM as long as CYP2C19 inhibitors are absent [9]. Interpreting clozapine TDM is more complex, requiring stratification by smoking and gender because they influence CYP1A2 activity. A clozapine concentration/dose ratio of >1.20 in a US female non-smoker is suggestive of poor clozapine metabolism [10].

References


8. de Leon J, Susce MT, Pan RM, Wedlund PJ, Orrego ML, Diaz FJ. A study of genetic (CYP2D6 and ABCB1) and environmental (drug inhibitors and inducers) variables that may influence plasma risperidone levels. Pharmacopsychiatry 2007; 40: 93-102.


Table 1. Frequency of inverted ratios in risperidone TDM study with 277 patients

<table>
<thead>
<tr>
<th>CYP2D6 genotyping</th>
<th>Total sample</th>
<th>On inhibitors</th>
<th>No inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>gPMs</td>
<td>95% (19/20)</td>
<td>63% (27/43)</td>
<td>6% (12/214)</td>
</tr>
<tr>
<td>Non gPMs</td>
<td>15% (39/257)</td>
<td>63% (27/43)</td>
<td>6% (12/214)</td>
</tr>
<tr>
<td>gIMs</td>
<td>43% (13/30)</td>
<td>83% (5/6)</td>
<td>33% (8/24)</td>
</tr>
<tr>
<td>gEMs</td>
<td>12% (26/219)</td>
<td>61% (22/36)</td>
<td>2% (4/183)</td>
</tr>
<tr>
<td>gUMs</td>
<td>0% (0/8)</td>
<td>0% (0/1)</td>
<td>0% (0/7)</td>
</tr>
</tbody>
</table>

1Another factor influencing an inverted ratio was body weight. After excluding the CYP2D6 gPMs, a logistic regression analysis of R/9-OHR >1 was performed. The significant variables were the number of CYP2D6 active alleles (odds ratio OR=0.18, 99% confidence interval, 0.08, 0.43), use of CYP inhibitors (OR=16.7; 6.2, 44.9), and body weight higher than the sample mean (OR=0.27, 0.10, 0.69).

2Bupropion, fluoxetine or paroxetine. Bupropion is a moderate CYP2D6 inhibitor; paroxetine and fluoxetine are potent CYP2D6 inhibitors.

3g refers to genetic. This is the terminology proposed by Shah and Smith [1].

4Any patient who is not a gPM and has an inverted ratio would be a pPM according to the terminology proposed by Shah and Smith [1].

5Phenoconversion is influenced by CYP2D6 genotype. In the 36 gEMs on inhibitors, the frequency of inverted ratios was 61%, but the prevalence varied according to the number of active alleles: 80% (12/15) in those with 1.0 active allele, 71% (5/7) in those with 1.4 active alleles, and 36% (5/14) in those with 2.0 active alleles.