CYP2D6 and pharmacogenomics: where does future research need to focus?

Part 2: clinical aspects

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In a previous commentary [1] we addressed the complexity of the highly polymorphic *CYP2D6* locus. In this second part of the mini-series we address some issues relevant to implementation of *CYP2D6* pharmacogenetics (PGx) into clinical practice and opportunities for future research.

The potential clinical impact of *CYP2D6* variation is illustrated by the inclusion of specific language regarding *CYP2D6* PGx into the product labels for 36 of the 137 drugs or drug combinations listed in the US FDA Table of Pharmacogenomics Biomarkers in Drug Labeling [2]. With few exceptions (e.g., aripiprazole [3]) product labels containing language related to *CYP2D6* PGx rarely contain specific recommendations with respect to how much a drug dose should be increased or decreased for a given genotype or predicted phenotype [4], despite a number of studies describing the magnitude of difference in drug exposure or drug clearance between poor metabolizer and extensive metabolizer phenotypes [5,6], and efforts to consolidate data for guidance purposes [7,8]. Therefore, it is not surprising that sufficient evidence to recommend routine clinical implementation of *a priori* genotyping in support of CYP PGx testing in the psychiatric setting is lacking [9–11]. Rather than bemoan the reluctance of payers, regulators and some clinicians to embrace *CYP2D6* PGx with open (and uncritical) arms, the

primary challenge for future research is to step back and critically assess the knowledge deficits, and design appropriate studies to generate convincing evidence to justify a change in practice; we offer for consideration our thoughts in this regard.

The difficulty in applying the results of genome-wide association studies to individual patients is recognized – even if a genetic variant is significant by genome-wide association study standards, it is difficult to know if an individual carrying the variant of interest will display the phenotype of interest. Likewise, the dose of a medication that, on average, produces a statistically significant decrease in a disease phenotype in a treated population and becomes the approved dose in the product label may not necessarily result in clinical improvement for a specific patient. PGx research seeks to identify the subset of patients that is most likely to respond to a given medication. PGx studies focusing on genes involved in drug disposition primarily involve CYPs [12] as drug clearance is a key determinant of the dose–exposure–response continuum. It is important to bear in mind that the relevant proximal phenotype for CYP allelic variants is the formation of CYP isoform-specific metabolites, and not response to the drug. Disappearance of the substrate as reflected by *in vivo* drug clearance is also a common

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phenotype for allelic variation in *CYP2D6* and other CYP genes. However, we often fail to properly consider some of the nuances associated with ‘clearance’ and ‘exposure’ when attempting to relate genetic variation in CYPs and other genes involved in drug disposition with drug response. The relevant drug exposure is the concentration at the site of action, which is the brain for *CYP2D6* substrates such as atypical antipsychotics, selective serotonin reuptake inhibitors and tricyclic antidepressants, and breast tumor for tamoxifen. By contrast, the pharmacokinetic consequences of *CYP2D6* genetic variation are measured in the plasma. Hence, a considerable part of the disconnect between *CYP2D6* genotype and drug response lies in the myriad factors between drug concentrations in the sampled compartment – blood/plasma – and the concentration at the site of action, not to mention the variability of the drug target itself and downstream effector processes.

Administration of a fixed drug dose to a population varying in size and body composition will result in a range of drug exposures. For drugs highly dependent on *CYP2D6* for their elimination, genotype represents an additional source of interindividual variability, and the magnitude of the effect is a function of the fractional contribution of *CYP2D6* to total clearance; an example is atomoxetine, with a tenfold difference in area under the curve between poor and extensive metabolizers [13]. Viewed from a different perspective, if variability in drug exposure contributes to variability in drug response, is it reasonable to expect that genotype-controlled drug exposure will minimize one source of variability in drug response? Controlling drug exposure could theoretically facilitate the detection of genetic variation in genes more directly involved in drug response. Administration of the same/similar dose of a *CYP2D6* substrate to a population results in a range of drug concentrations/exposures for which *CYP2D6* genotype is a primary source of the observed variability. By analogy, achieving the same or similar drug exposure in a study population has the potential to result in the identification of the major sources of variability in drug response. *CYP2D6* genotype would then become one of several genetic factors contributing to the PGx profile predicting the probability of clinical response. At a minimum, future clinical studies could be designed to determine if genotype-directed dosing to a target exposure reduces the amount of time required to achieve the desired response for those drugs where the usual practice is to titrate to clinical response. This concept has been explored for tamoxifen, a drug dependent upon *CYP2D6* for bioactivation to its active form, endoxifen [14].

The practice of titrating dose (adjusting drug exposure) to achieve the desired clinical response implies that a relationship exists between drug exposure and drug response. Although therapeutic drug monitoring is not routinely employed for many *CYP2D6* substrates, therapeutic reference ranges have been compiled by a German working group (AGNP) [15] for many drugs used in psychiatry. Furthermore, these and more recently published data have been utilized for genotype-stratified dosing recommendations for several classes of drugs, including *CYP2D6* substrates, that are used to treat neuropsychiatric disorders [8]. Future research could be directed toward validating the proposed dose adjustments for the major genotype classes to achieve the ‘population’ target reference range, or establish new genotype-stratified dosing guidelines. Furthermore, pharmacometric modeling has been explored as a means to develop exposure-matching dosing guidelines for pimozide [16], and holds promise for further refinement of dose individualization through the inclusion of additional patient-specific variables in addition to *CYP2D6* genotype.

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As the AGNP expert panel cautions, however, the proposed therapeutic reference ranges represent population-based ranges and may not be applicable to all patients. On the other hand, patients who fail to respond despite having achieved a specified target drug exposure in blood/plasma may represent a subpopulation with altered transporter function affecting drug concentration at the site of action (brain, breast and tumor), or a disease subtype that is unmasked by the drug, with drug response serving as a molecular probe for disease stratification. Although it is unlikely to be the sole solution to individualizing drug therapy for CNS-active medications, it seems reasonable to expect that exploiting *CYP2D6* genotype to achieve a target plasma drug exposure should result in less variability in drug concentration at the site of action than administering a fixed dose in the absence of genotype-based adjustments.

CYP2D6 is one of the more highly expressed CYPs in the brain and is expressed in an anatomically sequestered manner that implies a role in the regulation of endogenous compounds that modulate brain function [17].

Neuroimaging studies are also consistent with a functional role for CYP2D6 in the brain. For example, resting blood perfusion has been reported to be associated with *CYP2D6* genotype [18], and it has been suggested that sustained performance in attentional tasks and vigilance may be a functional consequence of variability in brain CYP2D6 expression [19]. Thus, an intriguing area of future CYP2D6 research is the potential to exploit the potential, but as yet uncharacterized, role of CYP2D6 in mediating endogenous functions that may be relevant for disease pathogenesis and drug response; pharmacometabolomic investigations analogous to recent reports involving CYP2C19/citalopram and escitalopram [20], and CYP3A4/sertraline [21] drug pairs offer one strategy to pursue.

Optimizing the use of most medications in clinical practice is hampered by the absence of reliable biomarkers to predict which patient will respond to what medication at what dose, and CYP2D6 substrates used to treat psychiatric disorders, pain, cardiovascular disease and cancer are no exceptions. The lack of concordance among studies investigating *CYP2D6* genotype as a determinant of response to tamoxifen is a particularly good example of the difficulty in translating genetic variation affecting drug biotransformation phenotype to clinical response as several additional factors may obscure the *CYP2D6* genotype–tamoxifen response relationship, including tumor heterogeneity in the breast cancer population, a complex tamoxifen metabolism/bioactivation pathway that includes several phase 1 and phase 2 pathways, genotyping procedure(s), concurrent treatment with CYP2D6 inhibitors and adherence to the prescribed treatment regimen, among others [22]. The inherent

challenges of such retrospective PGx biomarker studies have been clearly articulated by Province *et al.* [22], and yet waiting for definitive, incontrovertible ‘proof’ of value seems to be an inordinately high bar to achieve.

We propose that the focus of future CYP2D6 research should shift from a debate about whether preemptive genotyping for a given gene–drug pair is cost effective and warranting reimbursement by third-party payers to an emphasis on providing more concrete guidance on genotype-guided dosing adjustments. The rationale for this position is that the *CYP2D6* genotype needs to be determined once (given that the test was reliable and of high quality) and the information likely will be applicable to other medications the patient may receive in the future. Furthermore, an increasing number of individuals will have knowledge of their *CYP2D6* and other genotypes from direct-to-consumer genetic companies, and the cost of acquiring genotype data, *per se*, will become less important; what will become important will be access to high-quality data with which to provide the best possible treatment options to patients and their providers. Generating these data is the challenge for the future.

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