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CYP2D6 pharmacogenetics and phenoconversion in personalized medicine

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Abstract

Introduction: CYP2D6 contributes to the metabolism of approximately 20–25% of drugs. However, *CYP2D6* is highly polymorphic and different alleles can lead to impacts ranging from null to dramatic increases through gene duplication. Moreover, there are commonly used drugs that potently inhibit the CYP2D6 enzyme, thus causing "phenoconversion" which has potential to convert the genotypic normal metabolizer into phenotypic poor metabolizer. Despite growing literature on the clinical implications of non-normal *CYP2D6* genotype and phenoconversion on patient-related outcomes, implementation of CYP2D6 pharmacogenetics and phenoconversion to guide prescribing in clinical care is rare. This review focuses on providing the clinical importance of *CYP2D6* pharmacogenetics and phenoconversion in precision medicine and summarizes the challenges and approaches to implement *CYP2D6* pharmacogenetics and phenoconversion into clinical practice.

Areas covered: A literature search was performed using PubMed and clinical studies documenting effects of CYP2D6 genotypes and/or CYP2D6 inhibitor medications on pharmacokinetics, pharmacodynamics or treatment outcomes of CYP2D6-metabolized drugs, and studies on implementation challenges and approaches.

Expert opinion: Considering the extent and impact of genetic polymorphisms of *CYP2D6,* phenoconversion by the comedications, and contribution of CYP2D6 in drug metabolism, *CYP2D6* pharmacogenetics is essential to ensure drug safety and efficacy. Utilization of proper guidelines incorporating both *CYP2D6* pharmacogenetics and phenoconversion in clinical care assists in optimizing drug therapy.

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Declaration of interest

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Keywords

CYP2D6; phenoconversion; enzyme inhibition; pharmacogenetics; opioids; antidepressants; tamoxifen; personalized medicine; precision medicine; drug-drug interaction; drug-drug-gene interaction

1. Introduction

Recent developments in pharmacogenetics research and clinical implementation have advanced pharmacogenetics-based personalized therapy, with the goal of improving drug safety and efficacy[1,2]. The drug metabolizing enzyme, cytochrome P450 2D6 (CYP2D6) is estimated to contribute to the metabolism of approximately 20–25% of drugs. The gene encoding CYP2D6 is also highly polymorphic and given its importance in drug metabolism and genetic variability, *CYP2D6* pharmacogenetics is essential for designing and implementing personalized drug therapy. As a result, pharmacogenetic-based drug therapy guidelines have been developed for at least 50 CYP2D6-metabolized drugs based on the activity of CYP2D6 (Table 1)[3].

Around 100 alleles of *CYP2D6* with different impact on function of the encoded protein have been identified[4]. Variant alleles range from a loss of function and no enzyme activity to gene duplication that can lead to greater activity than normal[5,6]. Based on the activity level of the different alleles, an activity score is given to the *CYP2D6* diplotype. The higher the activity score, the higher the enzyme activity of the CYP2D6. Based on the activity score of CYP2D6, a genotype-based phenotype is assigned. These include poor metabolizer (PM), intermediate metabolizer (IM), normal metabolizer (NM), and ultra-rapid metabolizer (UM) [5,6]. However, CYP2D6 is highly susceptible to inhibition by several commonly used medications, and the expected phenotype based on genotype alone could be erroneous if concomitant use of CYP2D6 inhibitors is not considered while predicting the CYP2D6 phenotype[7,8]. Those inhibitor medications can convert CYP2D6 NMs or UMs to IMs or PMs. This phenomenon is known as phenoconversion, which occurs when the individual's genotype-based prediction of phenotype for drug metabolism does not match with the actual capacity for metabolizing drugs, due to the presence of the CYP2D6-inhibiting comedication[8].

The US Food and Drug Administration (FDA) lists and classifies CYP2D6 inhibitors as strong, moderate, and weak [9]. Strong (e.g., paroxetine, fluoxetine, bupropion) and moderate (e.g., duloxetine, sertraline) inhibitors can decrease the CYP2D6 activity such that genotypically NM individuals are converted phenotypically to PMs and IMs, respectively. Those inhibitor medications are highly prescribed and three of them (fluoxetine, bupropion, and duloxetine) are in the list of top 50 most commonly prescribed drugs in the United States [10]. Moreover, concomitant use of those drugs cannot be overlooked while predicting the phenotype as they are very common among the patients prescribed CYP2D6 metabolized medications [6,11,12]. As personalized medicine is primarily dependent on the prediction of the actual metabolizing ability of the metabolizing enzyme, failure to consider the comedications while predicting the phenotype can be the Achilles' heel of personalized medicine as it relates to CYP2D6 [8]. Considering the importance of phenoconversion,

Clinical Pharmacogenetics Implementation Consortium (CPIC)[13] guidelines suggest incorporating the effects of CYP2D6 inhibitors while calculating the activity score of CYP2D6[7,14–16].

Integration of *CYP2D6* pharmacogenetics and phenoconversion in clinical practice to benefit patients is challenging. *CYP2D6* laboratory testing results often include the genotypes and activity scores without proper interpretation and guidelines for prescribing[17]. In addition, information on phenoconversion and interpretation of phenotypes after considering phenoconversion are challenging yet essential for proper implementation. Current electronic health record (EHR) systems also lack support tools to assist health providers with integrating drug interactions with pharmacogenetics to implement personalized medicine in practice.

This review aims to provide information about the clinical importance of *CYP2D6* pharmacogenetics and phenoconversion in precision medicine for CYP2D6 metabolized drugs. Challenges and approaches to integrating *CYP2D6* pharmacogenetics and phenoconversion into clinical practice are also reviewed.

2. CYP2D6 pharmacogenetics

The CYP2D6 enzyme is encoded by nine exons of the *CYP2D6* gene located on chromosome 22(22q13.1). Being involved in metabolizing 20–25% of all the drugs, CYP2D6 is one of the essential enzymes for metabolism of drugs in humans[18–20]. Furthermore, CYP2D6 is involved not only in metabolizing active drug into its inactive metabolite, including antidepressants (e.g., amitriptyline, nortriptyline, venlafaxine, paroxetine), antipsychotics (e.g., aripiprazole, risperidone), cardiovascular drugs (e.g., metoprolol, carvedilol) but also in metabolizing the inactive drug into its active metabolite including opioid analgesics (e.g., codeine, tramadol, hydrocodone), and the anticancer anti-estrogenic agent (tamoxifen)[21–25]. Therefore, the metabolic activity of CYP2D6 can be associated with adverse drug reactions[7,21] or drug ineffectiveness[26–28]. Table 1 lists the 50 drugs that are metabolized by CYP2D6 either to inactive metabolites or active metabolites and have pharmacogenetics-based drug therapy guidelines. In addition to liver, CYP2D6 is also present in the brain. In the brain, CYP2D6 is involved in local drug biotransformation and metabolism of endogenous substrates[29].

CYP2D6 is extremely polymorphic, and more than 100 alleles have been identified[4]. Variant alleles range from a loss of function and no enzyme activity (PM) to gene duplication/multiplication that can lead to increased activity (UM)[7]. An activity score is given to a specific allele of *CYP2D6*, which correlates with the enzyme function. These allelic activity scores are used to calculate the predicted activity score of the encoded protein[6,30]. Normal functional alleles(e.g. *1, *2, or *35) are considered to have an activity score of 1 whereas reduced functional alleles (e.g. *9, *17, *10 etc.) have an activity score of 0.25 or 0.5 and non-functional alleles (e.g. *3, *4 etc.) have activity score of 0 (Table 2)[5,6]. The diplotype score (sum of the activity scores of the two alleles) is considered the total activity score of CYP2D6 and is used to predict the phenotype of the enzyme. Diplotype scores of 1.25– 2.25 are considered a normal metabolizer (NM), a score

of 0.25–1 as intermediate metabolizer (IM), a score of 0 as PM, and a score more than 2.25 as UM. The frequencies of PM, IM, and UM phenotypes based on genotypes range from 5–10%, 5–11%, and 3–29%, respectively, among various racial/ethnic groups[7,31]. Figure 1 shows the differences in rate and extent of metabolism among different CYP2D6 phenotypes.

Here we will discuss the impact of different CYP2D6 genotypes on metabolism and clinical outcomes of the most commonly studied CYP2D6 substrates including CYP2D6 metabolized opioids, antidepressants, antipsychotics, tamoxifen, atomoxetine, ondansetron, tropisetron, and metoprolol.

2.1. CYP2D6 pharmacogenetics and opioids

CYP2D6-metabolized opioids tramadol, codeine, and hydrocodone account for the majority of opioid prescriptions written in the U.S., accounting for more than 50 million opioid prescriptions dispensed in 2020 [32,33]. These opioids are widely used to treat moderate to severe pain[34]. CYP2D6 bioactivates codeine, tramadol, and hydrocodone into active metabolites, and the parent compounds have little to no analgesic activity compared to the active metabolites[7,35,36]. Thus, the active metabolites are entirely or largely responsible for the analgesic effects these specific opioids provide, and therefore the extent of analgesic activity of these opioids largely depends on the activity of CYP2D6[7,36]. Generally, it is expected that PMs and IMs would have reduced generation of the active metabolite and thus reduced pain control whereas UMs would be expected to generate excessive amounts of active metabolites and thus risk of toxicity.

In clinical trials, CYP2D6 PM and IM phenotypes were found to be associated with lower formation of morphine from codeine when compared to NM phenotype[37–42], and thus were associated with poor pain control after codeine administration[43]. In contrast *CYP2D6* gene duplication/multiplication (UMs) causes higher plasma concentrations of morphine[44–46], which can lead to oversedation, respiratory depression, and even death in pediatric population. This is the reason why U.S. Food and Drug Administration (FDA) contraindicated the use of codeine to treat pain and cough in patients under the age of 12 in April, 2017[47].

In the case of tramadol, the effects of different CYP2D6 phenotypes are similar to that of codeine. Lower biotransformation of tramadol to active form O-desmethyl tramadol was observed among the CYP2D6 PMs and IMs when compared to NMs[48–54]. Tramadol's effectiveness in pain control was worse among CYP2D6 PMs compared to NMs or IMs[55–59]. Increased frequency of adverse events, including respiratory depression, were observed in UMs compared to IMs or PMs [54,60,61] and the FDA has also contraindicated use of tramadol in children under 12, as of April, 2017 [47].

CYP2D6 PMs have also been shown to produce a decreased amount of hydromorphone from hydrocodone compared to NMs[62,63], whereas UMs are at increased risk of adverse effects[64]. The data from these three drugs clearly show the importance of considering CYP2D6 pharmacogenetics in the clinical setting while prescribing opioids, where such an approach has the potential to improve efficacy and decrease toxicity, in both cases typically

through selection of a non-CYP2D6 metabolized opioid or non-opioid as alternative therapy[7].

Considering the evidence, CPIC provides recommendations for dosing of codeine, tramadol and hydrocodone based on CYP2D6 genotypes (Table 3).

2.2. CYP2D6 pharmacogenetics and antidepressants

CYP2D6 is involved in metabolizing several antidepressants, including tricyclic antidepressants (e.g., amitriptyline, nortriptyline), selective serotonin reuptake inhibitors (SSRIs) (e.g., paroxetine, fluoxetine), and serotonin and norepinephrine reuptake inhibitors (SNRIs)(e.g., venlafaxine). CYP2D6 metabolizes the many antidepressants to their less or inactive metabolites (and in some cases the parent and metabolite are active, e.g. with amitripline and its metabolism to nortriptyline). Active antidepressant drugs are expected to have higher concentrations in PMs and IMs and thus PMs and IMs are at risk of concentration related adverse effects. Conversely UMs are expected to have low concentrations of active drug, thus increasing the risk of inefficacy.

Multiple studies have shown decreased metabolism of amitriptyline[65–67], and nortriptyline[68] among CYP2D6 PMs and IMs when compared to NMs, leading to higher plasma concentrations of the active drugs. Increased plasma concentrations of were found to be associated with several dose-dependent severe adverse effects including cardiotoxicity among PMs, which required discontinuation of the treatment or dose reduction[66,68]. Conversely, amitriptyline discontinuation was recorded more among CYP2D6 UMs due to decreased response to the drug[69]. CYP2D6 also metabolizes paroxetine and fluoxetine to pharmacologically less active or inactive metabolites[70,71]. The most active alleles had the lowest paroxetine concentrations in plasma[72–74]. As CYP2D6 UMs have very high paroxetine clearance, studies found lower plasma concentration of paroxetine at a steady state in CYP2D6 UMs[75–77] that resulted in decreased response to paroxetine[75]. In contrast, CYP2D6 PMs had significantly higher plasma paroxetine concentrations at a steady state[75,78], contributing to adverse drug effects[79]. For fluvoxamine, lower plasma clearance and longer half-life were observed among CYP2D6 PMs versus NMs[80,81]. Increased exposure to nortriptyline[82–84] and venlafaxine[83,85,86] was also observed among CYP2D6 PMs and IMs. Considering the clinical evidence, CPIC recommends using CYP2D6 pharmacogenetics for prescribing with SSRIs (paroxetine, fluoxetine) and tricyclic antidepressants (e.g., amitriptyline, nortriptyline) (Table 3)[16,21].

2.3. CYP2D6 pharmacogenetics and antipsychotics

Several antipsychotics (e.g., aripiprazole, risperidone) are metabolized to their inactive metabolites by CYP2D6. In CYP2D6 PMs and IMs, due to lower catalytic activity, plasma concentrations of the active drugs are expected to be higher than in NMs, causing concentration-related adverse effects. On the other hand, in UMs, due to higher enzymatic activity, active drug concentration is anticipated to be lower and may result in reduced efficacy. As CYP2D6 is also present in the brain, different phenotypes of CYP2D6 determine drug response not only via drug biotransformation in the liver, but also via drug and endogenous substrate metabolism in the brain[29].

Several studies identified that CYP2D6 PMs and IMs had poor aripiprazole catabolizing capacity when compared to NMs, resulting in increased plasma aripiprazole concentrations among PMs and IMs[87–94]. PMs and IMs also exhibited higher C_{max} and $T_{1/2}$ [88,95],and the mean elimination half-life of aripiprazole was shown to increase from 75 hours to 146 hours among PMs [89,96]. A recent meta-analysis including 12 studies and 1038 patients found that CYP2D6 PMs and IMs had significantly increased exposure to aripiprazole (1.48 ratio of means in PM+IM vs. NM)[83]. Increased concentration of aripiprazole may lead to several adverse drug effects, such as somnolence, headache, insomnia, dizziness, restlessness, palpitations, among others [97].

Among PMs and IMs, risperidone plasma concentration was significantly higher than NMs[89,94,98–103]. In one study, CYP2D6 PMs and IMs also had 1.7-fold increased exposure to risperidone compared to NMs[83]. PMs for CYP2D6 showed a higher risperidone C_{max}, AUC and $T_{1/2}$ and a lower clearance[98,103]. Higher concentrations of risperidone among PMs and IMs may cause several adverse effects, such as somnolence, headache, and dizziness [98,104]. One study on 76 schizophrenic patients reported that CYP2D6 PM phenotype was associated with significant improvement[105] suggesting that the higher drug concentrations led to improved efficacy. Further, previous studies have reported greater side effects and treatment discontinuations in CYP2D6 PMs compared to NMs [106,107]. Plasma concentrations of haloperidol were also found to be significantly higher among PMs and IMs when compared to NMs[83,94,99].

2.4. CYP2D6 pharmacogenetics and tamoxifen

CYP2D6 catalyzes the anticancer antiestrogenic drug tamoxifen to its active form, endoxifen. CYP2D6 phenotypes are found to be associated with variations in plasma concentration of endoxifen [108–112]. CYP2D6 PMs and IMs have no to lower concentration of endoxifen when compared to NMs or UMs[15] and CYP2D6 phenotypes are essential predictors of response to tamoxifen therapy[108]. Several clinical studies reported that recurrence of breast cancer was observed more commonly among CYP2D6 IMs or PMs than among NMs[70,113–116]. Other clinical trial data suggest worse event-free survival among CYP2D6 PMs versus NMs treated with tamoxifen [116–118]. Considering the importance *CYP2D6* genetics, CPIC recommends using *CYP2D6* pharmacogenetics guidelines while prescribing tamoxifen(briefly described in Table 3)[15].

2.5. CYP2D6 pharmacogenetics and atomoxetine

A selective norepinephrine reuptake inhibitor, atomoxetine is widely used to treat ADHD among children and adults. CYP2D6 is involved in the metabolism of atomoxetine to an inactive metabolite. Decreased metabolism in CYP2D6 PMs causes increased plasma concentration of atomoxetine [119–121], which may cause several moderate to severe adverse drug effects, including an increase in pulse and blood pressure or decrease in body weight [119,120,122]. Higher plasma concentrations of atomoxetine in PMs is also associated with improvement in ADHD among them[119,120,123]. Based on the evidence, CPIC provides guidelines for dosing of atomoxetine based on the genotypes of CYP2D6(Table 3) [14].

2.6. CYP2D6 pharmacogenetics and ondansetron and tropisetron

Ondansetron and tropisetron are selective 5-HT3 receptor antagonists and are metabolized by CYP2D6 to inactive metabolites[124–126]. CYP2D6 PMs had higher plasma concentrations of tropisetron when compared to NMs[127]. CYP2D6 UMs is associated with decreased AUC of ondansetron[128] and tropisetron[129] and thus decreased response to those drugs[127,130] Considering the importance of CYP2D6 genotypes on those drugs, CPIC provides dosing recommendations based on CYP2D6 genotypes (Table 3) [131].

2.7. CYP2D6 pharmacogenetics and metoprolol

Metoprolol, a beta blocker, is widely used to treat hypertension, angina, and heart failure. Metoprolol is also metabolized by CYP2D6[132,133]. Individuals with reduced or CYP2D6 PM phenotype may have plasma metoprolol concentration up to almost five times higher than NMs, which may increase the risk of various side effects[134–137]. However, some studies clinical study reported that neither antihypertensive response rate, blood pressure changes nor adverse event rates significantly differed by activity scores or among different CYP2D6 phenotypes. This is likely the result of the dosing strategy of beta-blockers as doses are selected based on the titration to a heart rate response[138–140].

3. CYP2D6 phenoconversion

Phenoconversion occurs when the individual's genotype-based prediction of phenotype for drug metabolism does not match with the true capacity of metabolizing the drugs caused by some extrinsic nongenetic factors[8]. In other words, CYP2D6 inhibitors can cause the conversion of CYP2D6 genotypic ultra or normal metabolizers (UMs or NMs) into phenotypic intermediate or poor metabolizers (IMs or PMs) and this phenomenon is called phenoconversion. In the context of this review, phenoconversion is the result of drug-drug interactions, whose implications vary by genotype, also known as drug-drug-gene interactions.

The FDA publishes a list of strong, moderate or weak CYP2D6 inhibitors [9], and of them, strong and moderate inhibitors may cause a significant reduction in CYP2D6-mediated metabolism ranging from half (by moderate inhibitors) to null (by strong inhibitors), converting the phenotype from UM or NM to IM or PM[7,141]. Figure 2 shows the phenoconversion in the presence of strong (SI) or moderate (MI) inhibitors and the extent of metabolism of drugs by CYP2D6 phenotypes. Although multiple sources for CYP2D6 inhibitors are available, we contend that the FDA list is the most appropriate for considering clinical implications [17]. This is because FDA categorizes the inhibitors based on strong, moderate, and weak status, defined by the increase in AUC of sensitive index substrates. Specifically, a strong inhibitor increases plasma concentration (i.e. AUC) ≥5-fold, whereas moderate and weak inhibitors increase AUC by ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively [9]. Knowledge of the strength of the inhibitor (moderate or strong) is vital to understanding the degree of phenoconversion, which along with genotype is used in defining the phenotype [142,143]. There is consensus among experts that weak inhibitors are not clinically important to consider because they minimally impact the area under the curve [17]. Table 4 lists the FDA strong and moderate inhibitors that can significantly

inhibit CYP2D6. Consideration of phenoconversion cannot be ignored as concomitant use of the CYP2D6 inhibitors is very common among the patients prescribed CYP2D6 metabolized medications. Specifically, data indicate that up to 20– 70% of the patients who are on CYP2D6 metabolized drugs are at risk of CYP2D6 phenoconversion by concomitant medications[6,11,12].

The impact of CYP2D6 inhibitors in combination with *CYP2D6* genotype has gotten increasing attention in recent years. One study suggested that patients co-administered another CYP2D6-metabolized drug were 9.5 times more likely to have genotype-phenotype discordance[18]. Phenoconversion to IMs or PMs can affect either the metabolism of the active drug to its inactive metabolite or the metabolism of the inactive drug to its active metabolite[144]. In general, whether the patient is a PM or IM due to genetics, CYP2D6 inhibitor or both, the impact on drug metabolism and thus active drug concentration is the same. For example, coadministration of paroxetine (a CYP2D6 inhibitor) with tramadol (an inactive drug metabolized to an active metabolite by CYP2D6) may result in a lack of proper pain control in a CYP2D6 *1/*1 (NM) patient. This is because paroxetine phenoconverts the NM to a PM resulting in decreased formation of morphine (the active metabolite of codeine) that provides the analgesic effect. Similarly, coadministration of bupropion (a CYP2D6 inhibitor) with aripiprazole (an active drug metabolized to an inactive metabolite by CYP2D6) may lead to excessively high aripiprazole concentrations, and potential for discontinuation of the treatment due to adverse drug effects (ADEs).

Considering the importance of phenoconversion, CPIC guidelines for CYP2D6-metabolized drug therapy suggest considering the concomitant use of CYP2D6 inhibitors while calculating the CYP2D6 activity score[7,14–16]. It is recommended that the genotype-based activity score of CYP2D6 is adjusted based on the use of inhibitors, with the specific adjustment for phenoconversion depending on the strength of the inhibitor (moderate or strong)[142,143]. If the individual is taking one of the strong inhibitors concomitantly, then the genotype-based activity score is multiplied by 0, and if the individual is taking moderate inhibitors concomitantly, then the genotype-based activity score is multiplied by 0.5[7]. Details of the activity score of the alleles, calculation of genotype-based score, and adjustment of score based on the use of CYP2D6 inhibitors are summarized in Table 2.

The impact of inhibition by a CYP2D6 inhibitor may differ according to genotype. A CYP2D6 PM by genotype will be unaffected by the concomitant use of an inhibitor since, in PMs, there is no active enzyme to be inhibited [143,145,146]. On the other hand, CYP2D6 UMs, NMs and IMs may have a significant reduction in their metabolic activity by the same inhibitor[8,143,145,146]. Some studies suggest CYP2D6 IMs are likely to be more susceptible to clinically important phenoconversion due to their already compromised activity by the genotype [8,146].

Consideration of CYP2D6 phenoconversion is an integral part of CYP2D6 pharmacogenetics-based personalized therapy. CYP2D6 genetics alone may not result in a better prediction of drug effectiveness or drug safety [8,147–152]. Furthermore, phenoconversion could clarify many of the inconsistent pharmacogenetic findings and might explain the failures of replication of the published results. [143,150,153,154]. Some studies

reported inconsistent findings in pharmacogenetic studies on tamoxifen. [155,156]. Kiyotani et al. [150] reported that this discrepancies in the results may happen due to the concomitant medications the patients received. They observed that recurrence free survival was not associated with CYP2D6 genotypes if breast cancer patients who received other medications in addition to tamoxifen were included in the cohort. Moreover, positive association was found in the subgroup analysis where patients who were only on tamoxifen were included.

3.1. CYP2D6 phenoconversion in various clinical studies

Several clinical studies have been conducted to understand the importance of phenoconversion in the clinical setting. These studies mainly focus on the extent of phenoconversion (drug-drug or drug-drug-gene interaction) and impact on pharmacokinetics and clinical outcome of different medications. Here we will discuss several different clinical studies that addressed the clinical relevance of phenoconversion.

While prescribing opioids, consideration of CYP2D6 strong and moderate inhibitors is very important, as 20 – 30% of patients treated for pain are also prescribed a CYP2D6 inhibitor [6,12] which can lead to increased incidences of phenoconversion among opioid users. In studies of acute[157] and chronic pain[158], the percentage classified as PMs went up from 6% to 17% and 5.3% to 19.2%, respectively, when CYP2D6 inhibitors were considered. In one of the first studies on phenoconversion was published in 1991, in a randomized cross-over study, Dayer et al. demonstrated that quinidine, a strong CYP2D6 inhibitor can convert the genotypic NM to a phenotypic PM, and if quinidine was administered with codeine, there was very little to no morphine (active metabolite of codeine) in the genotypic NM[159,160]. Consequently poor response to opioid was observed in genotypic NMs because of their phenoconversion to phenotypic PMs by a CYP2D6 inhibitor [160]. Several other studies compared pain control, and morphine milligram equivalents to manage pain among CYP2D6 inhibitor users vs non-users. Individuals in the CYP2D6 inhibitor user group required significantly more breakthrough morphine milligram equivalents per day compared with patients in CYP2D6 inhibitor non-user group (geometric mean ± SD 18.2 ± 6.3 vs 5.7 ± 6.7 mg morphine milligram equivalents, $p<0.001$)[141]. Another study compared association between pain control vs activity score based on genotype alone (DGI-drug-gene interaction model), and inhibitor and genotype both (DDI + DGI- drug-drug interaction and drug-gene interaction model). In the DDI + DGI model a significant association between activity score and uncontrolled pain was observed whereas in the DGI model no significant association with uncontrolled pain was observed. Among individuals in DDI+DGI model with an activity score of 0.5 or less, approximately 41% complained of uncontrolled pain while only 15.7% of the individuals with an activity score of 1 or greater relayed similar complaints[161]. Furthermore, in a study performed with data from more than 50,000 adults, it was reported that the average expenses for healthcare related services were higher for opioid users with drug-drug interactions (DDI) compared to those without DDIs ($7841 vs. $5625)[162]. Thus, a CYP2D6-guided approach considering both genotype and inhibitor use is recommended by CPIC when prescribing these opioids[7].

When CYP2D6 genotype and phenoconversion are both considered, improved pain control by CYP2D6-metabolized opioids was observed. One study reported that 24% of CYP2D6-

phenotype guided (considering both genotype and phenoconversion) vs. 0% of usual care participants reported greater than 30% reduction in pain score of, which is often considered the clinically significant level of pain improvement. As there were no differences in prescribing between IMs/PMs and NMs, the greater pain control in the CYP2D6-phenotype guided group was due to the intervention. [158]. Another study on postoperative pain management reported that if phenoconversion is considered in addition to CYP2D6 genotypes, fewer morphine milligram equivalents(MME) of opioid provides a similar level of pain control when compared with the usual care arm (200 vs. 230 MME; $p = 0.047$)[157]. The IGNITE network, funded by the NIH, is conducting a large multicenter randomized pragmatic trial to determine the effect of CYP2D6-guided opioid prescribing on chronic pain and post-operative pain control and opioid usage[163].

Phenoconversion was also found to be the limiting factor for predicting clinical outcome of aripiprazole treatment based on the CYP2D6 genotype[106]. A significant percentage of the patients prescribed aripiprazole are also prescribed a CYP2D6 inhibitor. In a study of aripiprazole tolerability in 277 pediatric patients with mood disorders, 72% of the cohort were concomitantly taking a CYP2D6 inhibitor. Consideration of the inhibitors while phenotyping CYP2D6 decreased the NMs from 57% to 27% while increasing the PMs from 6% to 49%[164]. Those phenoconverted IMs and PMs have lower CYP2D6 metabolic activity that caused the accumulation of active aripiprazole in the blood. [106,142]. In one study, among the NM patients who were taking inhibitors concomitantly, aripiprazole concentrations were about 50% higher than the NMs who were not taking the inhibitors [142]. 37% of the patients of a study discontinued treatment for adverse effects where most of them (67%) are phenotypic PMs[164]. The data highlight the importance of considering CYP2D6 inhibitors in patients prescribed CYP2D6 substrates like aripiprazole.

The antiestrogenic clinical activity of tamoxifen is provided by endoxifen that is produced from hydroxylation of N-Desmethyl tamoxifen (primary metabolite of tamoxifen) by CYP2D6[165]. CYP2D6 NMs in the presence of strong or moderate inhibitors can phenoconvert to IMs or PMs and cannot produce adequate active metabolite endoxifen. Endoxifen concentrations can be decreased by 64% (95% CI = 39% to 89%) in women with a NM CYP2D6 genotype after paroxetine coadministration[166]. One study reported that plasma concentrations of endoxifen were significantly lower in CYP2D6 NMs who were taking strong CYP2D6 inhibitors than NMs who were not taking CYP2D6 inhibitors (23.5 nmol/L vs. 84.1 nmol/L, $P < .001$) [165]. For 25%, 50%, and 75% increases in percent overlap days between paroxetine and tamoxifen, hazard ratios for subsequent breast cancer risk were 1.06, 1.13, and 1.20 respectively[167]. Concomitant use of paroxetine resulted in increased risk of death from breast cancer. One study demonstrated that 25%, 50%, and 75% increase in the overlapping time of paroxetine and tamoxifen increased the risk of death from breast cancer to 24%, 54%, and 91% respectively ($P<0.05$ for each comparison) [168]. Therefore, according to the CPIC guidelines, it is strongly recommended not to use any CYP2D6 strong or moderate inhibitors when prescribing tamoxifen among CYP2D6 NMs and UMs[15].

Metabolism of atomoxetine by CYP2D6 is also decreased when coadministered with CYP2D6 inhibitors, which leads to change in pharmacokinetic parameters of

atomoxetine[169–173]. With concomitant paroxetine treatment, AUC_{0-24} of atomoxetine was increased by 2.3-, 1.7-, and 1.3-fold, in CYP2D6*wt/*wt, CYP2D6*wt/*10, and CYP2D6*10/*10 respectively when compared to atomoxetine concentration without paroxetine coadministration[169]. Atomoxetine C_{max} was also increased from 221to 373 ng/mL[172] with concomitant paroxetine. Similar results were also reported for bupropion coadministration where systemic exposure to atomoxetine was increased (5.1-fold) and exposure to its main metabolite was decreased (1.5-fold) when compared to exposure to atomoxetine without bupropion administration[173]. Cardiovascular side effects were observed after atomoxetine and fluoxetine comedication[171,174]. Considering the importance of phenoconversion, CPIC suggests considering CYP2D6 inhibitors when prescribing atomoxetine[14].

4. Implementation in clinical practice

Utilization of *CYP2D6* pharmacogenetics for personalized therapy is uncommon in clinical practice and consideration of the effect of CYP2D6 inhibitors is even more rarely considered. The data summarized herein highlight that CYP2D6 phenotype (as determined by genotype and/or drug interactions) have clinically important implications on the efficacy and/or toxicity of many CYP2D6-metabolized drugs. Thus clinical implementation of *CYP2D6* pharmacogenetics and phenoconversion in clinical practice is a critical component to providing personalized drug therapy.

CPIC currently has pharmacogenetics guidelines for tramadol, codeine, hydrocodone, atomoxetine, tamoxifen, paroxetine, fluoxetine, fluvoxamine, amitriptyline, nortriptyline, ondansetron and tropisetron[7,14–16,21,131]. These guidelines address the effects of CYP2D6 inhibitor on metabolism of those drugs except for ondansetron and tropisetron. Lack of data and/or lack of a recent update might be the reason for not including the phenoconversion in the CPIC guidelines of ondansetron and tropisetron[131]. New CPIC pharmacogenetic guidelines for additional CYP2D6 substrate drugs including antipsychotics(e.g., aripiprazole, brexpiprazole, pimozide etc.), antidepressants (e.g., SNRIs), beta-blockers (e.g., carvedilol, metoprolol etc.) and one update on guidelines for SSRIs are now in progress[175].

To benefit patients based on the recommendations in CYP2D6 pharmacogenetics guidelines, *CYP2D6* pharmacogenetic testing can be ordered if not already available in the EHR [7,14–16,21,131]. As pharmacogenetics results are lifelong results it is not required to be retested again, unless additional clinically important alleles are discovered[176]. The test results often include the *CYP2D6* genotypes (e.g., CYP2D6 *1/*4) and activity score (AS) of CYP2D6 (e.g., AS 1, intermediate metabolize) or both. To get the actual clinical phenotype of the patient, CYP2D6 genotypic phenotype and concomitant inhibitor medication should both be taken into consideration. Based on the type of inhibitor, activity score should be modified and the clinical phenotype can be determined. Details of the activity score of specific alleles, calculation of the activity score for genotype alone and adjustment for CYP2D6 inhibitors and interpretation of clinical phenotype have been described in Table 2. CYP2D6 can regain its normal activity after 5–7 days of discontinuation of CYP2D6

inhibitors[177]. So, concomitant medications need to be considered routinely since the phenotype based on inhibitor presence or absence can change over time.

As no tool is currently available in the EHR to assist in consideration of CYP2D6 phenotype based on both genotype and drug interactions, adjustment of the activity score needs to be done manually for patients. To make this process easier and to implement phenoconversion in practice, a CYP2D6 phenoconversion calculator tool was developed (https://precisionmedicine.ufhealth.org/phenoconversion-calculator/) [17]. This calculator needs genotype information (e.g., CYP2D6 *1/ *4), number of alleles present, and comedication information to provide the predicted clinical CYP2D6 phenotype of the individual. Using the clinical phenotype and pharmacogenetics guidelines provided by CPIC, clinicians can provide the best available personalized therapy to the patients. While this is a valuable tool to assist clinicians, widespread adoption of personalized CYP2D6 treatments will require and approach that is automated within the EHR.

There are several challenges to incorporate CYP2D6 pharmacogenetics and phenoconversion into clinical practice, which have been highlighted by several groups who have undertaken such a clinical implementation [178–181]. Of those, one of the most important challenges is out-of-pocket cost of pharmacogenetic testing. Presenting the reimbursement data to patients and prior authorizations to cover the pharmacogenetic tests costs can help to overcome the barrier[179]. As data emerge on the clinical impact of using CYP2D6 phenotype to guide drug therapy, it is anticipated that more payers will provide coverage for the pharmacogenetic testing. Another barrier to proper implementation is lack of use of clinical decision support tools to provide proper guidance and knowledge on genotype-based actions[180]. The use of clinical decision support tools can help integrate pharmacogenetics into clinical practice, but incorporation of phenoconversion along with genotype is more difficult and there are not EHR-based tools available yet to support this. In the clinical setting, an updated list of current medications is essential to determine whether phenoconversion is present for individuals who are also taking a CYP2D6-relevant drug. So routine update of the medication list in the medical record is a prerequisite. Moreover, phenoconversion should be continually evaluated at least before every prescription as concurrent medication may change. Manual calculation of the activity score adjusted for phenoconversion can also be challenging though utilization of the phenoconversion calculator tool can ease this process for healthcare providers [17]. Most of the resources commonly used by prescribers (e.g., Drug.com, RxList, or other drug interaction checkers) include limited information about CYP2D6 genetics, drug interactions and guidelines for incorporating *CYP2D6* pharmacogenetics and phenoconversion in clinical practice [144]. Proper clinical integration and training can help to disseminate the importance of *CYP2D6* pharmacogenetics and phenoconversion among clinicians.

5. Conclusion

Considering the extent and impact of genetic variability of *CYP2D6,* vulnerability of CYP2D6 after co-administration of inhibitor drugs, and significance of CYP2D6 in drug metabolism, *CYP2D6* pharmacogenetics is highly important for designing and implementing personalized drug therapy to ensure drug safety and efficacy. Proper genetic

testing and interpretation of the results, and adjustment of the phenotype considering the concomitant CYP2D6 inhibitors is essential for *CYP2D6* pharmacogenetics-based personalized therapy. Approaches to overcome the challenges including appropriate use of clinical decision support tools, integration of CYP2D6 phenoconversion into clinical care, reimbursement of pharmacogenetic testing costs, and a local clinical expert to assist other clinicians can help achieve proper implementation of CYP2D6 pharmacogenetics and phenoconversion in the clinical setting to improve drug therapy outcomes in patients.

6. Expert opinion

CYP2D6 is involved in metabolizing 20–25% of all the drugs available on the market. This enzyme can either metabolize the active drug to inactive metabolite(s), facilitating the excretion of the drug, or metabolize the inactive prodrug to the active drug, assisting in exerting the proper pharmacological activity of the drug. Reduced or absent (IM or PM) CYP2D6 can lead to increased plasma concentrations for the active drug for a longer time, increasing risk of adverse drug effects and non-adherence. Conversely, decreased conversion of prodrugs to active drugs in those with impaired CYP2D6 activity is likely to impair efficacy. Conversely, gene duplication/multiplication or an increase in the activity of CYP2D6 (UM) may inactivate an active drug very quickly, leading to reduced efficacy whereas in the case of a prodrug, the excessive conversion to an active metabolite may cause serious adverse drug effects. While the UM phenotype can only be accomplished through genetic variation, the PM and IM phenotypes may occur based on genotype, drug interactions or the combination. The large number of drugs metabolized by CYP2D6, the frequency of genetic variation in CYP2D6 that leads to a non-normal phenotype, and the common clinical use of CYP2D6 inhibitors, which can alter the CYP2D6 phenotype makes attention to CYP2D6 phenotype essential in the quest to optimize therapy through personalized approaches.

Recent developments within pharmacogenetics and various guidelines from CPIC have promoted personalized therapy, ensuring drug safety and efficacy, especially for the medications metabolized by CYP2D6 (including tramadol, codeine, hydrocodone, atomoxetine, tamoxifen, paroxetine, fluoxetine, fluvoxamine, amitriptyline, nortriptyline, ondansetron and tropisetron). Although genotype-guided therapy for CYP2D6 metabolized drugs has gained popularity in the last decade, use of *CYP2D6* pharmacogenetics while prescribing in clinical practice is not yet standard of care. And in the absence of genetic data, even the consideration of phenoconversion while prescribing is extremely limited. The impact of CYP2D6 inhibitors on the efficacy and safety of CYP2D6-metabolized drugs and percentages of concomitant use of the CYP2D6 inhibitors can easily explain the need to implement phenoconversion along with *CYP2D6* pharmacogenetics to lead to optimal therapeutic outcomes. And in the absence of genetic data, clinicians should still consider the impact of a concomitant CYP2D6 inhibitor on the therapeutic outcomes. Concomitant use of CYP2D6 inhibitors can make the genotypic NM act like a PM, although the individual doesn’t carry any non-functional allele. Moreover, data indicate that approximately 20– 70% of patients on CYP2D6 metabolized medications are at risk of CYP2D6 phenoconversion by concomitant medications. Thus, consideration of CYP2D6 genotype alone is insufficient in the quest for personalizing therapy with CYP2D6 substrates. This approach can only be

optimal if CYP2D6 genotype and drug interactions are considered together in assigning a CYP2D6 phenotype.

There are many challenges to implementing use of CYP2D6 phenotype to guide prescribing. These include proper interpretation of genotype-based phenotype from CYP2D6 alleles or activity score, adjustment of phenotype considering the concomitant administration of CYP2D6 inhibitor medications, routinely checking concomitant medications for phenotype adjustment, reimbursement of genetic testing costs, proper training of the clinicians among other challenges. For widespread utilization of personalized approaches for drugs metabolized by CYP2D6, proper integration of *CYP2D6* pharmacogenetics and phenoconversion in the EHR is necessary. While much progress has been made in recent years in optimizing the reporting of *CYP2D6* genotype in a meaningful way in the EHR, we are aware of no EHR system that does this along with incorporating the drug interaction effectively to provide the clinician with a predicted phenotype. Laboratory *CYP2D6* genotyping reports with appropriate interpretations of the CYP2D6 phenotype and quick access to evaluate the risks of phenoconversion could ease the path to personalized medicine in clinical care. In addition to integrating those support tools, increasing awareness among prescribers of the clinical implications of CYP2D6 inhibitors and their ability to create phenoconversion is also critical to optimal use of drug therapy.

In summary, the utilization of proper guidelines incorporating both *CYP2D6* pharmacogenetics and phenoconversion in clinical care is essential to ensure the most benefits of personalized medicine.

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Article highlights:

- CYP2D6 is estimated to contribute to the metabolism of approximately 20–25% of drugs. CYP2D6 is involved not only in metabolizing active drugs into its inactive metabolites (e.g., paroxetine, aripiprazole) but also in metabolizing inactive drugs into its active metabolite including (e.g., codeine, tamoxifen). Therefore, the metabolic activity of CYP2D6 is associated with adverse drug reactions or drug ineffectiveness.
- The gene encoding CYP2D6 is highly polymorphic and around 100 alleles of *CYP2D6* with different impact on function of the encoded protein have been identified. An activity score is given to a specific allele of *CYP2D6* and summing the activity scores of the two (or more) alleles leads to the diplotype activity score. Using the diplotype score, genotypic phenotype of CYP2D6 is estimated, with resulting phenotypes including poor metabolizer (PM), intermediate metabolizer (IM), normal metabolizer (NM), ultra-rapid metabolizer (UM).
- Strong (e.g., paroxetine, bupropion) and moderate (e.g., duloxetine, sertraline) inhibitors can also decrease the CYP2D6 activity, phenoconverting the genotypic NMs or UMs into phenotypic PMs or IMs. So, concomitant use of those drugs cannot be overlooked while predicting the CYP2D6 phenotype. Moreover, data indicate that up to 20– 70% of the patients who are on CYP2D6 metabolized drugs are at risk of CYP2D6 phenoconversion by concomitant medications.
- It is important to adjust the activity score of CYP2D6 based on use of CYP2D6 inhibitors. If the individual is taking one of the strong or moderate inhibitors concomitantly, then the genotype-based activity score should be multiplied by 0 or 0.5 respectively. Then the actual clinical phenotype can be estimated based on the adjusted activity score.
- Pharmacogenetic-based drug therapy guidelines have been developed for at least 50 CYP2D6-metabolized drugs based on the activity of CYP2D6. Considering the importance of phenoconversion, Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines suggest incorporating the effects of CYP2D6 inhibitors while calculating the activity score of CYP2D6 for CYP2D6 metabolized opioids, tricyclic antidepressants, tamoxifen and atomoxetine.
- There are many challenges to implementing use of CYP2D6 pharmacogenetics and phenoconversion to guide prescribing. These include proper interpretation of genotype-based phenotype from CYP2D6 alleles or activity score, adjustment of phenotype considering the concomitant administration of CYP2D6 inhibitor medications, routinely checking of concomitant medications for phenotype adjustment, reimbursement of genetic testing costs, proper training of the clinicians etc.

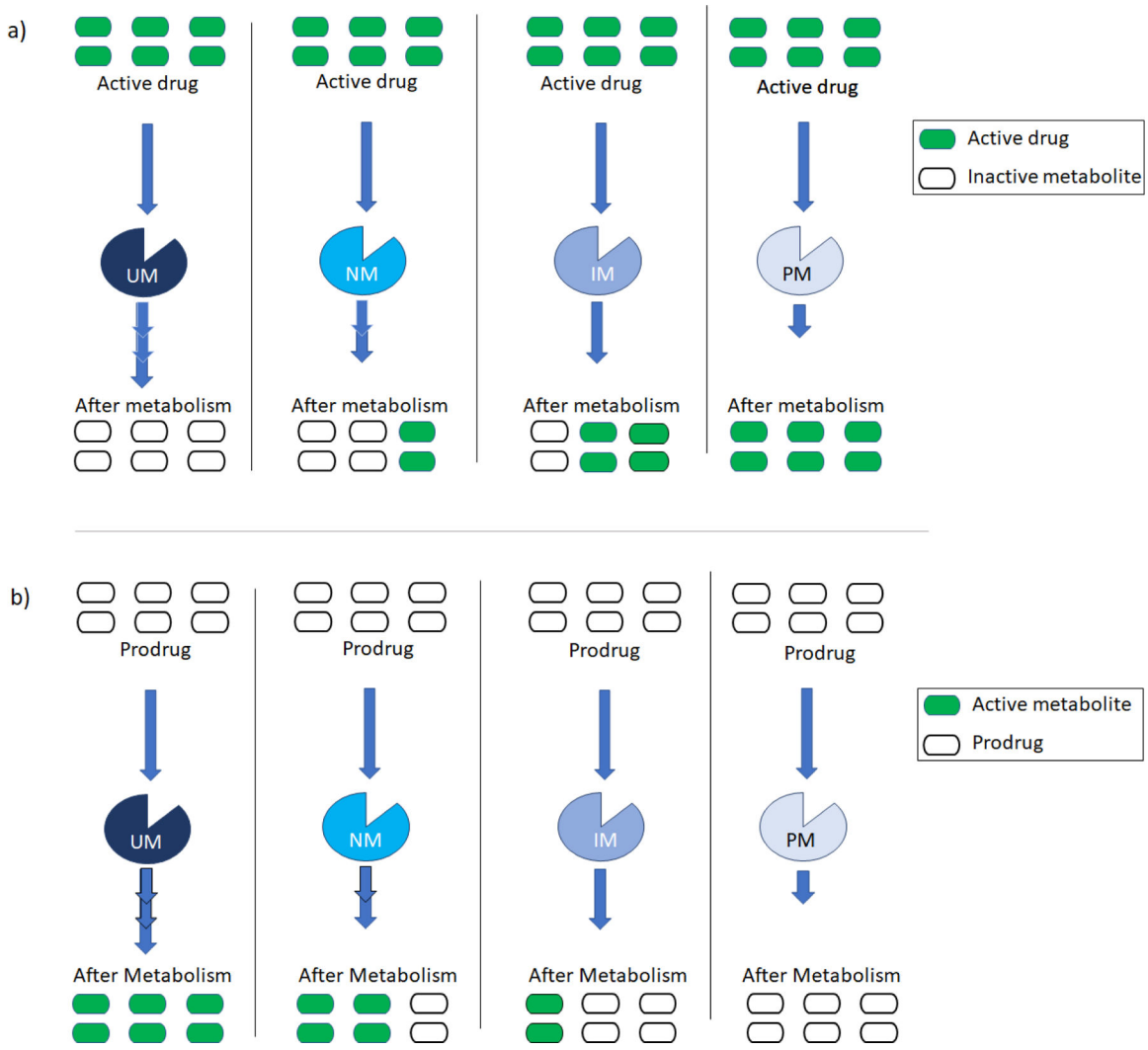

Figure 1. Representative differences in rate and extent of metabolism among different CYP2D6 phenotypes

Figure 1a shows metabolism of active drug (green bars) to inactive metabolite (open bars) and Figure 1b shows the metabolism of a prodrug (inactive) (open bars) to active metabolite (green bars) in absence of CYP2D6 inhibitors. NM can metabolize the drugs in an expected standard rate (represented by two (>>) arrows) and extent (4 out of 6 units in a given time) to provide the pharmacological activity. UM, being more active and rapid, can metabolize the drugs at a higher rate (represented by three (>>>) arrows) and extent than NM (6 out of six units in a given time). IM is slower (represented by one (>) arrow) and can metabolize less(2 out of 6 units in each given time) than NM. PM has no metabolic activity and cannot metabolize a drug.

UM- ultrarapid metabolizer; NM- normal metabolizer; IM- intermediate metabolizer; PM- poor metabolizer.

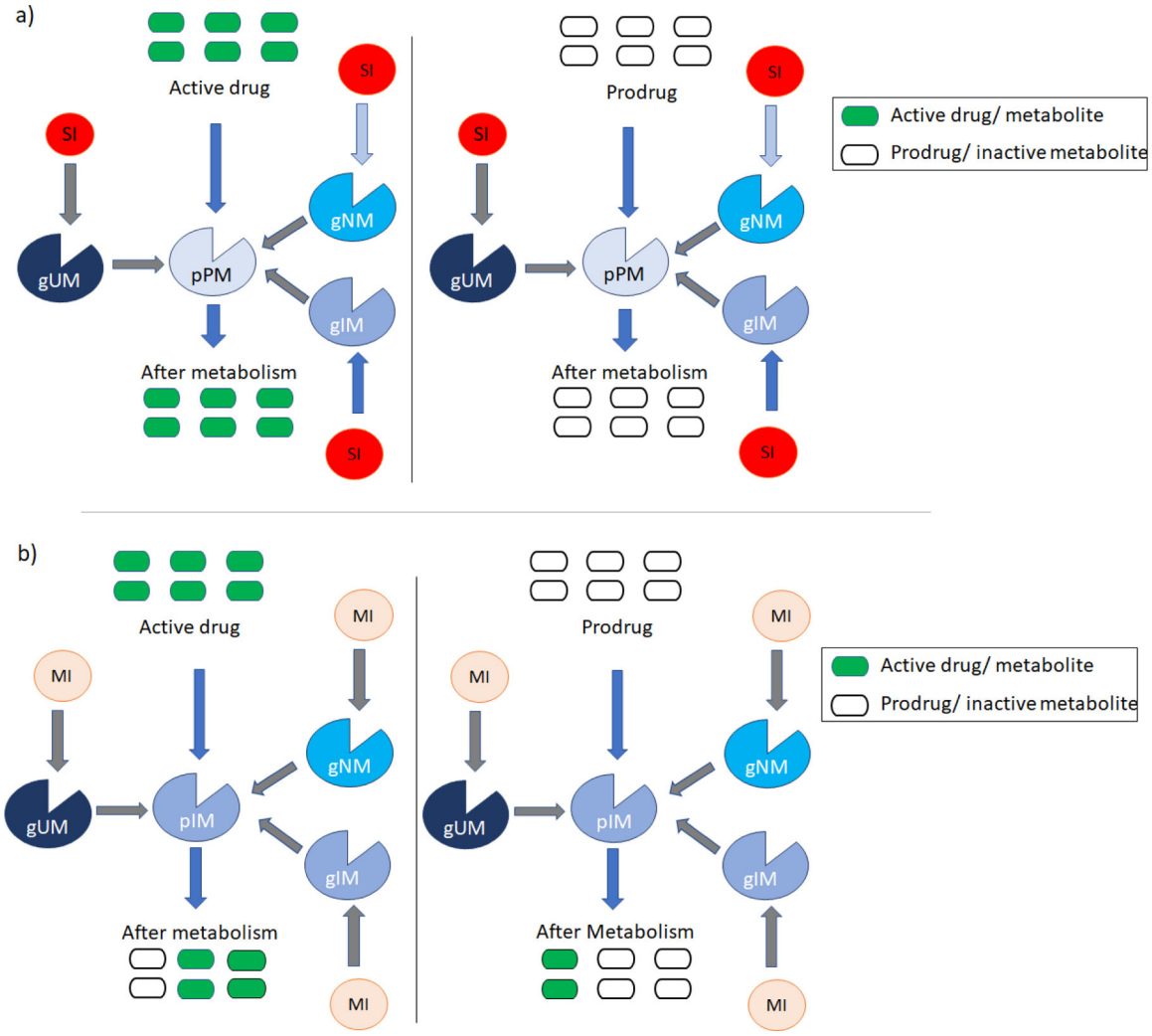

Figure 2. Phenoconversion of CYP2D6 in presence of strong (SI) or moderate (MI) inhibitors and metabolism of drugs by CYP2D6 phenotypes

Figure 2a shows the phenoconversion in presence of SI and metabolism of active drug (green bars) to inactive metabolite (open bars) and prodrug (open bars) to active metabolite (green bars) in phenoconverted CYP2D6 phenotypic PMs(pPM). SI can decrease the activity of the CYP2D6 enzymes to null and phenoconvert the gUM, gNM or gIM to pPM. Thus, the pPM cannot metabolize the drug.

Figure 2b shows the phenoconversion in presence of MI and metabolism of active drug (green bars) to inactive metabolite (open bars) and prodrug (open bars) to active metabolite (green bars) in phenoconverted CYP2D6 phenotypic IMs(pIM). MI can decrease the activity of the CYP2D6 enzymes to nearly half and can phenoconvert the gUM, gNM or gIM to pIM. Thus, the pIM metabolizes the drug very slowly and to a lower extent (2 out of 6 units).

Note: For gUMs, in presence of three or more normal functioning alleles MI can phenoconvert them to NM or UM (not shown in the figure).

SI- strong inhibitors; MI- moderate inhibitor; gUM- genotypic ultrarapid metabolizer; gNM- genotypic normal metabolizer; gIM- genotypic intermediate metabolize; pPM- phenotypic PM; pIM- phenotypic IM; PM- poor metabolizer; IM- intermediate metabolizer.

Table 1.

Drugs metabolized by CYP2D6 to their inactive or active metabolites

Type of metabolism	Drug class	Drug names
Active drugs metabolized to less active or inactive drug by CYP2D6 [#]	Antidepressants	amitriptyline
		citalopram
		clomipramine
		desipramine
		doxepin
		duloxetine
		escitalopram
		fluoxetine
		fluvoxamine
		imipramine
		mirtazapine
		nortriptyline
		paroxetine
		sertraline
		trimipramine
		venlafaxine
	Antiphychotics	aripiprazole
		brexpiprazole
		clozapine
		flupenthixol
		fluphenazine
		haloperidol
		olanzapine
		pimozide
		quetiapine
		risperidone
		zuclopenthixol
	Beta blocker	atenolol
		bisoprolol
		carvedilol
		metoprolol
	Antiarrhythmic	amiodarone
		disopyramide
		flecainide
		propafenone
		quinidine
		sotalol

Type of metabolism	Drug class	Drug names
	Opioid	methadone
		oxycodone
	ADHD treatment	atomoxetine
		methylphenidate
	Gaucher's disease treatment	eliglustat
	Antiemetic	odansetron
		tropisetron
	Antihypertensive	clonidine
Inactive drugs metabolized to active drug by CYP2D6	**Opioids**	codeine
		tramadol
		hydrocodone
	Antiestrogens	tamoxifen
	Anticancer	gefitinib

[#]Some metabolites might be similarly active as the active parent drug.

Table 2.

CYP2D6 activity scores (AS) and phenotype adjustment for CYP2D6 inhibitors

Alleles and assigned score	Alleles		Activity score
	Functional allele	*1, *2 or*35	1
	Reduced functional allele	*9, *17, *29 or*41	0.5
		*10	0.25
	Nonfunctional allele	*3 through*8, *11 or*15	0
AS considering only genotype: Genotype-based Activity Score=Sum of the scores of the alleles			
AS considering both genotype and CYP2D6 inhibitor: CYP2D6 activity score= Inhibitor factor (IF) x genotype-based AS; IF= 0, 0.5 and 1 for strong, moderate and no CYP2D6 inhibitor			
Phenotype based on genotype and inhibitors	**Phenotype**		**CYP2D6 activity score**
	Ultra-rapid metabolizers (UM)		>2.25
	Normal Metabolizers (NM)		1.25–2.250
	Intermediate metabolizers (IM)		0.25–1
	Poor Metabolizers (PM)		0

Table 3.

CPIC dosing recommendations for different drugs based on CYP2D6 phenotype

Drug class	Medications	CYP2D6 phenotypes	Implications	Recommendations	Classification of recommendation	Reference
Tricyclic antidepressants	Amitriptyline and nortriptyline	UM	Increased metabolism to less active compounds increasing the probability to lack of efficacy.	Avoid use of amitriptyline and nortriptyline. Consider alternative drug not metabolized by CYP2D6.	Strong	Hicks et. al., 2017 [16]
		NM	Expected metabolism to less active compounds	Initiate therapy with recommended starting dose.	Strong	
		IM	Reduced metabolism to less active compounds increasing risk of adverse effects	Consider a 25% reduction of recommended starting dose	Moderate	
		PM	Greatly reduced metabolism to less active compounds increasing risk of adverse effects	Avoid use of amitriptyline and nortriptyline. Consider alternative drug not metabolized by CYP2D6.	Strong	
	Clomipramine, desipramine, doxepin, imipramine, and trimipramine	UM	Increased metabolism to less active compounds increasing the probability for lack of efficacy.	Avoid use of the drugs. Consider alternative drug not metabolized by CYP2D6.	Optional	
		NM	Expected metabolism to less active compounds	Initiate therapy with recommended starting dose.	Strong	
		IM	Reduced metabolism to less active compounds increasing risk of adverse effects	Consider a 25% reduction of recommended starting dose.	Optional	
		PM	Greatly reduced metabolism to less active compounds increasing risk of adverse effects	Avoid use of the drugs. Consider alternative drug not metabolized by CYP2D6.	Optional	
Selective serotonin reuptake inhibitors	Paroxetine	UM	Increased metabolism to less active compounds increasing the probability for lack of efficacy.	Avoid paroxetine. Consider alternative drug not predominantly metabolized by CYP2D6	Strong	Hicks et. al., 2015 [21]
		NM	Expected metabolism to less active compounds	Initiate therapy with recommended starting dose.	Strong	
		IM	Reduced metabolism to less active compounds increasing risk of adverse effects	Initiate therapy with recommended starting dose.	Moderate	
		PM	Greatly reduced metabolism to less active compounds increasing risk of adverse effects	Avoid paroxetine. Consider alternative drug not predominantly metabolized by CYP2D6	Optional	

Drug class	Medications	CYP2D6 phenotypes	Implications	Recommendations	Classification of recommendation	Reference
	Fluvoxamine	UM	No data available for CYP2D6 ultrarapid metabolizers	No recommendation due to lack of evidence	Optional	
		NM	Expected metabolism to less active compounds	Initiate therapy with recommended starting dose.	Strong	
		IM	Reduced metabolism to less active compounds increasing risk of adverse effects	Initiate therapy with recommended starting dose.	Moderate	
		PM	Greatly reduced metabolism to less active compounds increasing risk of adverse effects	Consider a 25–50% reduction of recommended starting dose and titrate to response. Or, Consider alternative drug not predominantly metabolized by CYP2D6	Optional	
Antiemetic	Ondansetron and tropisetron	UM	Increased metabolism to less active compounds increasing the probability to lack of efficacy.	Avoid use of the drugs. Consider alternative drug not metabolized by CYP2D6.	Moderate	Bell et. al., 2017 [131]
		NM	Expected metabolism to less active compounds	Initiate therapy with recommended starting dose.	Strong	
		IM	Very limited data available	Initiate therapy with recommended starting dose.	No recommendation	
		PM	Very limited data available	Initiate therapy with recommended starting dose.	No recommendation	
ADHD treatment	Atomoxetine	UM	Very limited data available	Initiate with a dose of 0.5mg/kg/day in children or 40 mg/day in adults and increase to 1.2mg/kg/day in children or 80 mg/ day in adults after 3 days. If no clinical response, consider titration to reach 400 ng/mL peak plasma concentration. Details here.	Moderate	Brown et. al., 2019 [14]
		NM	Expected metabolism to less active compounds	Initiate with a dose of 0.5mg/kg/day in children or 40 mg/day in adults and increase to 1.2mg/kg/day in children or 80 mg/ day in adults after 3 days. If no clinical response consider titration to reach 400 ng/mL peak plasma concentration. Details here. If unacceptable side effects are present at any time, consider a reduction in dose. Details here.	Moderate	
		IM	Reduced metabolism to less	Initiate with a dose of 0.5mg/kg/day in	Moderate	

Drug class	Medications	CYP2D6 phenotypes	Implications	Recommendations	Classification of recommendation	Reference
			active compounds increasing risk of discontinuation	children or 40 mg/day in adults. If no clinical response, consider titration to reach 400 ng/mL peak plasma concentration. Details here. If unacceptable side effects are present at any time, consider a reduction in dose. Details here.		
		PM	Greatly reduced metabolism to less active compounds increasing risk of adverse effects but may result in greater improvement of ADHD.	Initiate with a dose of 0.5mg/kg/day in children or 40 mg/day in adults. If no clinical response, consider titration to reach 400 ng/mL peak plasma concentration. Details here. If unacceptable side effects are present at any time, consider a reduction in dose. Details here.	Moderate	
Opioids	Codeine	UM	Increase formation of morphine leading to higher risk of toxicity	Avoid use of codeine. Consider use of non-tramadol opioid or other analgesics	Strong	Crews et. al., 2021 [7]
		NM	Expected metabolism to morphine	Initiate therapy with recommended starting dose.	Strong	
		IM	Reduced formation of morphine	Initiate therapy with recommended starting dose. If no response consider use of non-tramadol opioid or other analgesics	Moderate	
		PM	Greatly reduced formation of morphine leading to diminished analgesia	Avoid use of codeine. Consider use of non-tramadol opioid or other analgesics	Strong	
	Tramadol	UM	Increase formation of o-desmethyltramadol leading to higher risk of toxicity	Avoid use of tramadol. Consider use of non-codeine opioid or other analgesics	Strong	
		NM	Expected metabolism to o-desmethyltramadol	Initiate therapy with recommended starting dose.	Strong	
		IM	Reduced formation of o-desmethyltramadol	Initiate therapy with recommended starting dose. If no response consider use of non-codeine opioid or other analgesics	Optional	
		PM	Greatly reduced formation of o-desmethyltramadol leading to diminished analgesia	Avoid use of tramadol. Consider use of non-codeine opioid or other analgesics	Strong	
	Hydrocodone	UM	Very limited data available	No recommendation due to lack of evidence	No recommendation	

Drug class	Medications	CYP2D6 phenotypes	Implications	Recommendations	Classification of recommendation	Reference
		NM	Expected metabolism to hydromorphone	Initiate therapy with recommended starting dose.	Strong	
		IM	Very limited data available	Initiate therapy with recommended starting dose. If no response consider use of non-codeine or non-tramadol opioid or other analgesics	Optional	
		PM	Reduced formation of hydromorphone, but there is insufficient evidence to determine if these effects on pharmacokinetics translate into decreased analgesia or side effects	Initiate therapy with recommended starting dose. If no response consider use of non-codeine or non-tramadol opioid or other analgesics	Optional	
Antiestrogens	Tamoxifen	UM	Expected metabolism to endoxifen	Avoid moderate and strong inhibitors. Initiate therapy with recommended starting dose.	Strong	Goetz et. al., 2018 [15]
		NM	Expected metabolism to endoxifen	Avoid moderate and strong inhibitors. Initiate therapy with recommended starting dose.	Strong	
		IM	Reduced formation of endoxifen. May increase the risk of breast cancer recurrence, event-free and recurrence-free survival	Avoid moderate and strong inhibitors. Consider hormonal therapy such as an aromatase inhibitor with/without ovarian function suppression. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day). Details here.	Moderate	
		PM	Reduced formation of endoxifen. May increase the risk of breast cancer recurrence, event-free and recurrence-free survival	Recommend alternative hormonal therapy such as an aromatase inhibitor with/without ovarian function suppression. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day). Details here.	Strong	

Table 4.

Strong and moderate CYP2D6 inhibitors according to US FDA[9]

Type of inhibitors	CYP2D6 inhibitors
Strong inhibitors	bupropion, fluoxetine, paroxetine, terbinafine, quinidine
Moderate inhibitors	abiraterone, cinacalcet, mirabegron, duloxetine, lorcaserin, rolapitant