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Pharmacogenetics of Opioid Use Disorder Treatment

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Abstract

Opioid use disorder (OUD) is a significant health problem in the United States and many other countries. A combination of issues, most notably increased prescription of opioid analgesics, has resulted in climbing rates of opioid abuse and overdose over the last decade. This ongoing epidemic has produced a growing population of patients requiring treatment for OUD. Medications such as methadone and buprenorphine have well documented success rates in treating the disorder compared with placebo. However, significant percentages of the population still fail to maintain abstinence or reduce illicit opioid use while using such medications. Genetic variation may play a role in this variability in outcome through pharmacokinetic or pharmacodynamic effects on OUD medications, or by affecting the rate of negative side effects and adverse events. This review focuses on the existing literature on the pharmacogenetics of OUD treatment, with specific focus on medication metabolism, treatment outcomes, and adverse events.

1 Introduction

Opioids are a class of drugs that bind to opioid receptors and are typically used for the relief of pain. They comprise licit drugs including buprenorphine, fentanyl, hydrocodone, and oxycodone, and the illicit drug heroin. The use of opioids has dramatically increased in recent years in the United States, driven primarily by the abuse of prescription opioids [1]. In 2015, it was estimated that 11.5 million Americans misused a prescription opioid and 1.9 million had a prescription opioid use disorder (OUD) [2]. In comparison, 329,000 Americans were current heroin users in 2015 [2]. The abuse liability of prescription opioids is high with some studies reporting misuse behavior in approximately 25% of users [3]. An estimated 80% of new heroin users cite prescription opioid use as their first exposure to opioids [4], and OUD is one of the leading causes of admission into substance abuse treatment programs [5]. The economic burden of the abuse of prescription opioids in the US is substantial with US$78.5 billion lost every year due to crime, unemployment, and healthcare costs, compared with an estimated US$50 billion lost due to heroin use [6, 7].

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Compliance with Ethical Standards

Conflicts of Interest

Drs Crist, Clarke, and Berrettini declare that they have no conflicts of interest.

Prescription opioid abuse is somewhat less notable outside of North America. For example, Europeans were less likely to endorse lifetime nonmedical use of prescription opioids than individuals from the US (7–13% vs 20%) [8]. However, OUD is still a significant issue worldwide; the United Nations Office on Drugs and Crime estimated that opioids were responsible for ~70% of the total global burden attributed to substance use disorders in 2015 [9].

OUD is defined according to the DSM-5 as a pattern of opioid use leading to clinically significant impairment or distress indicated by the presence of two or more symptoms, including withdrawal, tolerance, craving, and loss of control of use in a 12-month period. OUD is typically a chronic relapsing disorder; however, there are a number of pharmacological interventions that can help individuals manage withdrawal symptoms and reduce illicit opioid use. OUD treatment programs frequently replace illicit opioids with longer acting licit opioids that are less euphoric and as such have less abuse potential. Methadone is an oral mu-opioid receptor (MOR) agonist with some affinity for ionotropic glutamate receptors. It is commonly used to treat acute opioid withdrawal and also as part of OUD treatment. Methadone has two enantiomeric forms, (R)-methadone and (S)-methadone, and methadone is a racemic mixture of the two. Activation of the MOR is driven by (R)-methadone, while (S)-methadone has little activity at the receptor. A meta-analysis of methadone efficacy for the treatment of OUD found a significant effect of methadone compared with non-pharmacological approaches [10]. Furthermore, methadone has been shown to decrease mortality [11] and HIV infection rates [12] in those with OUD.

Another commonly used pharmacotherapy for the treatment of OUD is buprenorphine. Buprenorphine is a weak MOR agonist and a partial kappa-opioid receptor antagonist [13]. It is most often administered sub-lingually or as a buccal film, and is also available as a 4:1 combination with the orally inactive opioid receptor antagonist naloxone to prevent injection [14]. Buprenorphine acts to reduce withdrawal symptoms and also to block the effects of other opioids, and has long-lasting effects up to 36 hours. OUD treatment with buprenorphine has been shown to be superior to placebo for OUD [10]; however, comparisons of methadone and sub-lingual buprenorphine suggest that methadone may be superior when administered at the correct dose due to increased retention in treatment [10]. Two extended-release formulations of buprenorphine have also been approved for OUD treatment in the US: Sublocade, a monthly subcutaneous depot injection, and Probuphine, a subdermal implant that lasts 6 months. Extended-release buprenorphine may improve on the treatment retention issues of the daily formulations of the medication.

Naltrexone is another Food and Drug Administration (FDA)-approved treatment option for OUD. This compound is a MOR antagonist, and as such it produces no euphoria and has little abuse potential. Naltrexone promotes abstinence by blocking the effects of opioids and therefore individuals must be opioid free before commencing treatment. Naltrexone is available orally as a tablet and blocks the effects of opioids for 24–36 hours. Meta-analytical studies have found that due to poor adherence the rates of abstinence in oral naltrexone users were not significantly higher than those in users treated with placebo or psychotherapy [15, 16]. For those individuals able to remain in treatment, oral naltrexone has some efficacy seen as a reduction in the number of opioid-positive urine tests [17]. Oral naltrexone therefore

may only be a suitable treatment option for those individuals highly motivated to stop using opioids. Naltrexone is also available as an intra-muscular injection administered monthly that uses an extended-release formula (XR-NTX). This form of naltrexone has been shown to significantly decrease opioid cravings and increase the number of opioid-free days and weeks abstinent in some patients [18, 19].

Meta-analysis of OUD treatment has found highly variable outcomes across trials, suggesting that there may be pre-existing factors that are important in determining which treatment is best for an individual [10]. Metabolism of methadone and buprenorphine is highly variable between individuals [20, 21]. The use of other medications can also affect methadone pharmacokinetics, potentially by affecting the cytochrome P450 enzymes responsible for metabolizing methadone [20, 22]. Polymorphisms in the genes encoding those enzymes are candidates to alter methadone pharmacokinetics and potentially alter treatment outcomes, since higher doses are strongly associated with increased retention during methadone or buprenorphine treatment [23]. Comorbid psychiatric disorders, stress, alcohol abuse or dependence, and socioeconomic factors have been found to predict relapse in a meta-analysis of patients treated for OUD with methadone, buprenorphine, or naltrexone [24, 25]. Anxiety was specifically associated with continued opioid use during methadone treatment [26], whereas anxiety, alcohol or benzodiazepine use, and hepatitis C status predicted relapse in buprenorphine-treated patients [27, 28]. Genetic variation in patient populations may also contribute to variability in outcomes. This review covers the current knowledge on the pharmacogenetics of OUD treatment, including dose, metabolism, treatment efficacy, side effects, and adverse events.

2 Pharmacogenetics of Opioid Use Disorder Treatment Dose and Metabolism

2.1 ABCB1 and Methadone

The *ABCB1* gene (aka *MDR1*) encodes an efflux pump known as p-glycoprotein. P-glycoprotein transports a wide variety of chemical substrates across the cell membrane in an adenosine triphosphate (ATP)-dependent manner. As evidence suggests that methadone interacts with p-glycoprotein in vitro and in rat models, it was hypothesized that *ABCB1* genetic variation might have effects on methadone dosing or concentration of the drug in the blood [29, 30]. An analysis of a 5 single nucleotide polymorphism (SNP) haplotype block in *ABCB1* found an association with dose in Australian methadone maintenance patients (Table 1) [31]. A subset of the variants in this haplotype block (rs1045642, rs2032582, and rs1128503) were also studied in a population of Israeli methadone-treated patients [32]. The linkage disequilibrium between these variants results in two common haplotypes: CGC and TTT [33]. Patients with two copies of the TTT haplotype were more likely to receive higher doses of methadone (>150 mg/day) [32]. In contrast, patients carrying one copy of each haplotype were more likely to receive lower doses (≤150 mg/day) [32]. A single variant in the haplotype block, rs1045642, predicted dose requirements during methadone maintenance in a Han Chinese population [34]. In two European cohorts, the T/T genotype at rs1045642 alone was also associated with decreased trough plasma levels of methadone (i.e., the lowest

levels before the next dose), further supporting a pharmacokinetic link between this *ABCB1* haplotype block and methadone [35, 36].

However, contradictory results and failed replications have raised doubts about the relevance of *ABCB1* to OUD treatment. Attempts to replicate the original association in independent populations found no significant associations between genotype and dose [37–39]. The association between rs1045642 and methadone plasma concentrations in European patients also failed to replicate in some studies [38, 40]. The plasma concentration of methadone in a treatment program in Taiwan was higher in patients with the T/T genotype at rs2032582, but the effect was the opposite of that predicted based on the previous pharmacogenetic effects on dose observed in Han Chinese [34, 41]. Another study of Han Chinese patients also could not replicate the previous association with dose [42]. Most of these results are based on relatively small sample sizes and therefore the possibility of false positive or false negative findings is increased. To address this problem, a meta-analysis of *ABCB1* effects on methadone was published in 2014 [43]. The analysis found no significant association between rs1045642 genotype and either methadone dose or plasma concentration [43]. Despite the meta-analysis results, research on the role of *ABCB1* in OUD treatment has continued. The G/G genotype at rs2032582 was associated with decreased methadone clearance from the serum in a patient population of mixed ethnicity [44]. An analysis in Malaysian patients also found evidence for an association between the rs1128503-rs2032582-rs1045642 haplotype and dose-adjusted plasma concentrations of methadone, with CGC/TTT heterozygotes having higher concentrations [45]. In total, the observed associations between *ABCB1* polymorphisms are inconsistent and currently of limited clinical relevance.

2.2 Cytochrome P450 Gene Family and Methadone

The cytochrome P450 (CYP450) enzymes are responsible for metabolizing a broad range of chemical compounds. The list of targeted substrates includes many illicit opioids and opioid analgesics. Genetic variation in the genes encoding the CYP450 enzymes has been shown to alter enzyme function [46]. A significant number of functionally relevant haplotypes have been identified in *CYP450* genes, resulting in a range of potential phenotypes whose frequencies vary across ethnic groups [47, 48]. These different haplotypes in *CYP450* genes are referred to as ‘alleles’ and often noted in the format ‘*GENESYMBOL* * #’, where ‘#’ indicates the allele number (e.g. *CYP2B6**6) [48]. The potential metabolism statuses produced by the various alleles for each enzyme are generally termed ‘poor’, ‘intermediate’, ‘extensive’, and ‘ultrarapid’. ‘Slow metabolizer’ may also be used for alleles that are not null but result in severely reduced enzymatic function.

Methadone is metabolized by several members of the CYP450 family but the primary enzyme targeting methadone is thought to be CYP2B6; administration of the CYP2B6 inhibitor ticlopidine alongside methadone resulted in reduced clearance and increased plasma concentration of methadone [49]. CYP2B6 activity was also correlated with methadone metabolism rates in healthy volunteers treated with a single dose [50]. As hypothesized based on the links between CYP2B6 activity and methadone data, two variants identifying the common slow metabolizer allele *CYP2B6**6 were associated with lower

mean methadone doses in a primarily Israeli cohort (Table 2) [51]. Other studies, however, have not found associations between dose and *CYP2B6**6 or *CYP2B6**4 (rs2279343) in either European or Taiwanese patients [39, 52]. In another study of a Taiwanese population, patients carrying *CYP2B6**4 had increased plasma levels of methadone [41]. Although the frequency of *CYP2B6**4 in European (8%), East Asian (15%), and Ashkenazi Jewish populations (14%) are similar (Genome Aggregation Database) [53], other genetic background or environmental differences between these populations could contribute to the observed differences in phenotype.

Genetic markers of pharmacokinetics can be valuable tools for guiding dosing decisions. More rapid metabolizers may require higher doses, while poor metabolizers require less medication. There is evidence, however, that the effect of *CYP2B6* genotype on methadone plasma concentrations is driven primarily by metabolism of (S)-methadone, the enantiomer of the drug with minimal efficacy at the MOR. This correlation between CYP2B6 metabolism status and (S)-methadone plasma levels has been found in several independent studies, while effects on (R)-methadone concentrations were smaller or not significant at all [35, 36, 44, 54]. Similar results have also been observed in patient populations from Taiwan [55]. A resequencing study that analyzed Swiss patients with extremely low or high (S)-methadone plasma concentrations implicated the *4, *6, *9 (rs3745274), and *11 alleles in reduced CYP2B6 function, while the *5 allele was linked to increased enzyme activity [56]. Postmortem plasma levels of methadone are also higher in individuals carrying the *4, *6, and *9 alleles [57]. In total, these data suggest that *CYP2B6* genotype may not be a relevant pharmacogenetic marker for the opioid receptor agonism of methadone.

Like *ABCB1*, many of these *CYP2B6* studies feature relatively small cohorts, which may explain inconsistencies in some of the results. A meta-analysis found that methadone-treated patients who were homozygous for the *CYP2B6**6 allele did have significantly higher plasma concentrations of methadone [43]. However, no consistent effect on dose was observed [43]. The preference of CYP2B6 for (S)-methadone may explain the apparent inconsistencies between effects of CYP2B6 metabolism status on dose and plasma concentrations of methadone. The small effect of the enzyme on (R)-methadone means that CYP2B6 metabolism status is not causing a significant change in the amount of functional methadone.

CYP2D6, CYP2C19, and CYP3A4 may contribute to overall metabolism of methadone, although the specific contribution of each enzyme is not entirely clear [35, 49, 58–62]. Crettol et al. found that higher CYP3A4 activity, as determined by phenotyping, and CYP2D6 ultrarapid metabolism status were associated with lower trough methadone plasma levels [35]. In this population, CYP3A4 and CYP2D6 metabolized both (R)- and (S)-methadone equally, rather than showing the stereoselectivity observed in CYP2B6 [35]. A significant difference in methadone dose was also observed between CYP2D6 poor and ultrarapid metabolizers in another European cohort [63]. Unfortunately, multiple other studies have not found an effect of *CYP2D6* genotype on dose [39, 51] or plasma concentrations in methadone maintenance patients [64, 65].

CYP2C19 and CYP3A4 results have also been equivocal. The *CYP3A4**22 allele (rs35599367) was associated with increased (R)-methadone clearance [36] but no effects of *CYP3A4* genotype on methadone dose were observed in other studies [51, 52]. *CYP3A4**22 is rare in almost all populations and does not explain most of the variability in CYP3A4 activity between individuals, which may explain the lack of consistent results. The *CYP2C19**2 and *3 alleles, both resulting in reduced enzyme activity, were also associated with increased methadone plasma concentration : dose ratios in Europeans [64] but no association for the gene was found by a Taiwanese group [41]. In contrast, CYP2C19 status predicted methadone dose in Taiwanese [52] but not European patients [39]. Reduced function alleles for other enzymes in the CYP450 family, specifically CYP3A5 and CYP2C9, were associated with increased methadone plasma concentration : dose ratios in one study, despite little evidence those enzymes are involved in metabolizing the medication [64]. These data suggest that the metabolism of methadone in vivo may involve enzymes outside the canonical list.

2.3 Additional Genes and Methadone

Less information on methadone dose, clearance, and plasma concentration is available on the effect of genetic variation outside the *ABCB1* and *CYP450* genes. Candidate gene studies have identified some potentially relevant variants. In a German population, the A/A genotype at rs2070995 in *KCNJ6*, encoding a voltage-gated potassium channel, was associated with increased methadone dose (Table 3) [66]. Two variants in the dopamine receptor D2 gene (*DRD2*) were associated with lower dose in Han Chinese methadone-treated patients, as well as several haplotypes in the *DRD2-ANKK1* locus [34]. *ANKK1*, as well as other polymorphisms in *BDNF and NTRK2*, were also associated with dose in Israeli patients after permutation testing [67]. These genes encode ankyrin repeat and kinase domain containing 1, brain-derived neutrophic factor, and neurotrophic receptor tyrosine kinase 2, respectively. A more recent study in Han Chinese found an association between dose and an *OPRD1* polymorphism, but not SNPs in the beta-arrestin 2 (*ARRB2*) or dopamine receptor D1 (*DRD1*) genes [42]. A French study titled METHADOSE also failed to find associations between dose and common functional variants in *DRD2*, *COMT*, and *OPRM1* [39]. *COMT* encodes catechol-o-methyl transferase, an enzyme that degrades catecholamines including dopamine and norepinephrine. A subsequent analysis in an Australian cohort found an interactive effect on methadone dose and plasma concentration of an *ABCB1* haplotype and *OPRM1* variant rs1799971 (aka A118G) [68]. Another study found an allele of the gene encoding CYP450 reductase to be associated with (R)-methadone concentrations specifically [36]. CYP450 reductase transfers electrons to many CYP450 family members and is required for enzymatic function. These findings suggest that the pharmacogenetics of OUD treatment dosing are likely complex and that polymorphisms with mixed findings thus far may still be relevant to methadone treatment depending on other genetic variation in the patient.

Genome-wide association studies (GWAS) have also been used to identify relevant polymorphisms that would be overlooked using a candidate gene approach. A variant >300kb upstream of *OPRM1* was associated with methadone dose in African-Americans [69]. The variant also predicted post-operative analgesic requirements in African-American

children, suggesting it may be broadly applicable to opioid pharmacodynamics in patients of this ethnicity [69]. A GWAS in Han Chinese patients found additional associations between (S)-methadone plasma levels and haplotypes in the spondin-1 (*SPON1*) and germ cell-specific gene 1-like (*GSG1L*) genes [70]. Both of the encoded proteins have been linked to neural phenotypes; spondin-1 is an adhesion molecule that promotes proper axon development in vitro [71] and GSG1L regulates AMPA receptor-mediated neurotransmission [72]. However, it is not clear how these established functions might be related to methadone metabolism. An intergenic SNP (rs17180299) was also associated with the plasma concentration of (R)-methadone in this Han Chinese cohort [70]. For both the GWAS and candidate gene findings, lack of replication is currently a concern. The significant associations have also come from a variety of ethnic groups and it is currently unclear how broadly applicable those results are. A number of the identified genes would also be predicted to affect the pharmacodynamics of methadone rather than the pharmacokinetics, which makes any potential mechanisms more complicated than directly altering metabolism of the medication. These indirect pharmacodynamic effects may have complex interactions with CYP450 metabolism status, comorbid substance use, local dosing policies, and other factors that are not elucidated by the current literature.

2.4 Buprenorphine and Naltrexone

No polymorphisms associated with buprenorphine or naltrexone dose or serum concentration have been identified. This lack of information most likely reflects limited sample sizes rather than a lack of genetic contribution to those phenotypes. For example, buprenorphine is known to be metabolized by CYP450 enzymes [73–75]. Polymorphisms associated with altered metabolism status in those enzymes are strong candidates for effects on buprenorphine dose or serum concentration. Genetic variants that predict continued opioid use during buprenorphine or naltrexone treatment may also be relevant to dose and metabolism. These pharmacogenetic analyses have simply not been performed yet.

3. Pharmacogenetics of Opioid Use Disorder Treatment Response

3.1 Pharmacogenetics of Methadone Response

OUD is a complex issue and treatment outcomes can be analyzed in a number of different ways. The percentage of urine drug screens positive for opioids, other than the one prescribed in treatment, can be used as a quantitative measurement of efficacy. A 24-week randomized trial of methadone and buprenorphine for the treatment of OUD, known as START (Starting Treatment with Agonist Replacement Therapy), collected weekly urinalysis data on participants. In this population, African-American methadone-treated patients carrying the T allele at rs678849 in *OPRD1* were significantly more likely to test positive for opioids compared with patients with the C/C genotype (Table 4) [76]. No effect was observed in individuals of European descent. However, methadone efficacy in European-Americans in that study was associated with a polymorphism in the *OPRM1* 3’ untranslated region (rs10485058) [77]. A single urine drug screen following treatment has also been used as a measurement of efficacy. Using this metric, plasma levels of cadherin 2 were associated with methadone efficacy [78]. Those plasma levels were found to be associated with two SNPs in *CDH2*, the gene encoding cadherin 2 [78]. The CDH2 protein

is a cell adhesion molecule that regulates function of excitatory synapses [79]. The observed connection between *CDH2* genotype and methadone efficacy may therefore be related to learning and memory differences.

Patients can also be analyzed using binary 'responder/non-responder' metrics, where a successful response is defined by the percentage of opioid-positive urine drug screens alone or in combination with other factors. One Spanish study applied a candidate gene approach to their responder analysis, looking at variants previously associated with OUD risk [80]. Responders were defined as having no opioid-positive urines in the last four drug screens, while non-responders had two or more positive urines in that period. An interaction between variants in the myocardin (*MYOCD*; rs1714984) and glutamate metabotropic receptor 6 (*GRM6;* rs953741) genes predicted an increased risk of a patient being a non-responder [81]. A second study found a functional non-synonymous polymorphism in *ALDH5A1*, encoding aldehyde dehydrogenase 5 family member A1, to also be associated using the same definitions for response and non-response [82]. SNPs in *GRM8*, *CRY1*, *OPRM1*, and *NR4A2* showed no association [81].

A Swiss group found no effect of *CYP2D6* genotype on successful treatment, despite linking metabolism status for the enzyme to methadone plasma levels [63]. Subsequent studies in another Swiss methadone cohort found associations between response and polymorphisms in *DRD2* (rs1800497 aka Taq1A) and *ARRB2* (rs3786047, rs1045280 and rs2036657) but not in *DRD1* (rs4532), *OPRM1* (rs1799971), or *OPRD1* (rs2234918) [83, 84]. In these analyses, responders were patients with one or fewer opioid-positive urines in the last 3 months and non-responders were patients with regular opioid and/or cocaine use in that 3-month period. While another study also found an association between this *DRD2* variant and methadone response, no significant associations were found in two other populations [85–87]. Similar issues have arisen for the *BDNF* gene. The non-synonymous SNP rs6265 showed no association in a Canadian cohort [86] but a haplotype in the gene predicted outcome in a Spanish methadone population using the response and non-responses definition outlined in the previous Spanish study described above [88]. The mixed results in the studies of *BDNF* and *DRD2* may potentially be explained by methodological differences; the studies varied in both the specific SNPs analyzed and the definitions of success.

Measurements beyond opioid use have also been studied as predictors of current or future effectiveness of methadone. Haplotypes in *OPRK1* and 12 variants in *UGT2B7* were associated with withdrawal symptoms in a group of 366 Taiwanese methadone-treated patients [89, 90]. Europeans with the A/A genotype at the *KCNJ6* variant rs2070995 also showed reduced prevalence of withdrawal symptoms, although the sample size in that genotypic group was very small [66]. Patients experiencing withdrawal symptoms may be more likely to relapse to illicit opioid use, making these markers potential predictors of treatment outcome. Patient satisfaction with treatment is another potential predictor of treatment retention and relapse risk. CYP2D6 ultrarapid metabolizers were less satisfied with methadone maintenance when compared with poor or extensive metabolizers [91], while no significant associations with satisfaction were found in a panel of variants from *OPRM1*, *OPRD1*, and *OPRK1* [92].

3.2 Pharmacogenetics of Buprenorphine Response

In the START trial, a genotype at rs678849 in *OPRD1* was also associated with buprenorphine efficacy in African-Americans (Table 4) [76]. However, the effect was the opposite of that observed in methadone-treated patients; individuals with the C/C genotype produced significantly more opioid-positive urines than T-allele carriers. An additional study using the START cohort focused on sex differences in European-Americans. Variants in *OPRD1* (rs581111 and rs529520) were associated with continued opioid use during buprenorphine treatment in women but not men [93]. The associations between buprenorphine efficacy and *OPRD1* variants are somewhat surprising since buprenorphine is primarily thought to act as a partial MOR agonist and a kappa-opioid receptor (KOR) antagonist. However, buprenorphine has some affinity for the DOR, although it does not appear to activate downstream signaling through the receptor [13]. It is possible that at therapeutic doses buprenorphine could act as a DOR antagonist and disrupt signaling through the receptor, which is known to be involved in OUD and opioid tolerance [94, 95]. In addition to *OPRD1* variants, a 2014 analysis of 107 Italians diagnosed with heroin dependence found the variable number of tandem repeats (VNTR) polymorphism in the 3′ untranslated region of *SLC6A3*, which encodes the dopamine transporter, to be associated with buprenorphine efficacy when patients were separated into ‘responder’ and ‘non-responder’ categories [96]. No effect of the *OPRK1* variant rs1051660 was observed in this patient population, nor was an effect of the *DRD2* rs1800497 polymorphism in an Australian cohort [85].

3.3 Pharmacogenetics of Naltrexone Response

Pharmacogenetic effects in naltrexone treatment for OUD have not been published to date. This is likely a reflection of a lack of genetic data on the small number of available cohorts.

4 Pharmacogenetics of Adverse Events During Opioid Use Disorder Treatment

Pharmacogenetics is not solely focused on treatment efficacy and dose requirements. The field also encompasses side effects that are affected by an individual patient’s genetic background. Understanding the pharmacogenetics of adverse events can identify patients who are at risk of severe complications or who would be less likely to sustain treatment due to the negative effects of a medication. The pharmacogenetics of adverse events during buprenorphine or naltrexone treatment have not been explored. In contrast, methadone has been studied in this context. Methadone-treated patients have increased mortality rates compared with the general population [97, 98]. Polymorphisms in some *CYP450* genes are likely candidates to affect risk of methadone-related death, since they encode enzymes responsible for metabolizing methadone and therefore regulate serum levels of the medication. Supporting this hypothesis, the minor alleles of variants in *CYP3A4* (*CYP3A4**1B; rs2740574) and *CYP2B6* (*CYP2B6**9 and rs8192719) were found to be enriched in a population of European-Americans who died of methadone overdose (Table 5) [99, 100]. *CYP3A4**1B and *CYP2B6**9 are known to alter the metabolism status of their respective enzymes. Of the two, however, only rs3745274 has been associated with

methadone dose or plasma concentration in patients of European descent. Individuals carrying the minor allele of the variant were found to have increased (S)-methadone plasma concentrations [56]. Other studies have also found CYP2B6 slow metabolizer status to be associated with increased methadone plasma concentrations in victims of methadone-related death [101].

Another potentially related side effect of methadone use is a lengthening of the heart rate-corrected QT (QTc) interval, which is a measurement of the electrical cycle regulating contraction of the heart ventricles [102]. This effect is not observed in buprenorphine-treated opioid-dependent patients [102, 103]. However, some lengthening of QTc interval was observed in healthy controls treated with buprenorphine, particularly at doses above standard therapeutic levels, suggesting that the medication does have some effect on this phenotype [104]. Prolonged QTc interval increases the risk of arrhythmia, cardiac arrest, and death, which may partially explain the increased fatality rate among methadone-treated patients. Importantly, buprenorphine has not been associated with increased risk of arrhythmia. Clinicians have noted that the effect of methadone on QTc interval varies widely in the patient population, suggesting that there are other factors relevant to this potentially deadly side effect [105]. Methadone plasma levels show a correlation with QTc interval and (S)-methadone concentration was found to have a larger effect on the phenotype than (R)-methadone concentrations [36]. Given the enantiomer-specific effects of some polymorphisms, genetic variation in the population may therefore explain some of the variable risk of prolonged QTc interval. The associations between *CYP2B6* genotype and methadone-related fatalities may be explained by this specific side effect, since CYP2B6 slow metabolizers had increased QTc intervals compared with extensive metabolizers [106].

Additional data further suggest that variants that affect methadone metabolism may alter susceptibility to cardiac phenotypes. A polymorphism in *CYP2C19* that results in a nonfunctional enzyme (rs4244285; *CYP2C19**2) was associated with higher plasma levels of ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP), a metabolite of methadone, in a population from the US [107]. EDDP levels were associated with QTc interval in this population, suggesting a possible link from *CYP2C19* genotype to cardiac issues [107]. In a Taiwanese cohort, CYP2C19 metabolism status was also associated with the change in QTc interval in methadone-treated patients who tested positive for opioids during treatment entry; however, in this study extensive metabolizers had a larger change in QTc during treatment [108]. The discrepancy between these results may be the result of ethnicity-specific effects, different methodologies in treatment or experimentation, or the relatively small sample size in the American study. Notably, EDDP was previously found to not block the channel encoded by the *HERG* gene, which is often used to test medication effects on cardiac repolarization [109]. Genes encoding ion channels involved in polarizing or repolarizing the heart may also contain polymorphisms that increase risk. Methadone-treated patients carrying a variant (rs1805123) in the cardiac potassium channel gene *KCNH2* had longer QTc intervals on average [110]. A similar but much smaller effect was observed in healthy subjects, suggesting a potential interaction between medication and genotype [111].

Methadone has a number of other less severe side effects that may nonetheless affect patient retention. These include dry mouth, insomnia, changes in libido, fatigue, and changes in

appetite. Since methadone is an MOR agonist, the medication also has the common side effect of constipation. In a population of Taiwanese methadone-treated patients, 12 *OPRM1* variants were associated with insomnia after multiple testing correction [112]. Four of these variants (rs1074287, rs510769, rs495491, and rs589046) were also associated with changes in libido [112]. No significant associations with methadone-related fatigue were observed. An *OPRD1* variant previously associated with OUD (rs2236855) [95] predicted libido problems in Iranian methadone-treated patients [113]. Two *OPRK1* polymorphisms were associated with libido (rs997917) or insomnia (rs6985606) in the same cohort [114].

5 Conclusion

Progress on the pharmacogenetics of OUD treatment has been slow and the amount of research in the field is remarkably limited given the current OUD epidemic. Treatment efficacy is a complex phenotype that is affected by genetic variation, comorbid substance use and psychiatric disorders, environmental factors, and other variables that may operate independently and through interactions with one another. This complexity highlights the importance of deep phenotyping in OUD treatment data sets so that these factors can be integrated into statistical models to the extent possible. Another significant issue is the lack of large data sets that have outcome or dosage data matched with DNA samples. The cohorts that actually meet these requirements are generally small and this has resulted in many underpowered candidate gene studies with few readily available replication populations. A number of the studies discussed in this review have also been treated as exploratory and as such did not correct *p*-values for multiple testing, further increasing the possibility of false positives and emphasizing the need for replication of any findings. Small samples sizes and a lack of independent replication means that none of the pharmacogenetic effects described here are currently clinically actionable. This is reflected in the lack of any pharmacogenetic tests for OUD treatments that have been approved by the FDA. A concerted effort needs to be made in the field of OUD pharmacogenetics to significantly increase the number of appropriate samples going forward, both through the collection of new study populations and the merger of existing cohorts for meta-analysis. Focus must also shift to buprenorphine and extended-release naltrexone, as these medications are rapidly expanding at the expense of methadone treatment and will be increasingly relevant to OUD treatment in the future.

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Key Points

Opioid use disorder treatments are not effective in all patients.

Genetic variants associated with treatment response or medication metabolism have been identified, but few have been reproduced.

The most reproducible result is an association between the *CYP2B6**6 allele and (S)-methadone plasma concentrations.

Table 1

ABCB1 genetic variants associated with methadone metabolism

Ethnicity	Measurement	Alleles/ variants	MAF (minor allele)[a]	Finding	Reference
European-Australian (*n* = 60)	Dose	rs9282564	8% (G)	AGCGC haplotype homozygotes required higher doses. AGCTT haplotype carriers required higher doses	[31]
		rs2229109	3% (A)		
		rs1128503	42% (T)		
		rs2032582	41% (T)		
		rs1045642	48% (C)		
Israeli (*n* = 98)	Dose	rs1128503	42% (T)	TTT haplotype homozygotes required higher doses. CGC/TTT heterozygotes required lower doses	[32]
		rs2032582	41% (T)		
		rs1045642	48% (C)		
Han Chinese (*n* = 321)	Dose	rs1045642	38% (T)	T allele carriers required higher doses	[34]
European (*n* = 245)	Plasma concentration	rs1045642	48% (C)	T/T genotype decreased (R,S)-methadone	[35]
Taiwanese (*n* = 178)	Plasma concentration	rs2032582	41% (T)	T/T genotype increased (R,S)-methadone	[41]
Mixed, American (*n* = 206)	Plasma concentration	rs2032582		G/G genotype increased (R,S)-methadone	[44]
Malaysian (*n* = 148)	Plasma concentration	rs1128503	42% (C)[b]	CGC/TTT heterozygotes had higher (R,S)-methadone	[45]
		rs2032582	37% (T)[b]		
		rs1045642	36% (T)[b]		
European (*n* = 244)	Plasma concentration	rs1045642	48% (C)	T/T genotype decreased (S)-methadone	[36]
European-Australian (*n* = 119)	Dose	rs9282564	8% (G)	AGCTT haplotype with A/A genotype decreased dose	[68]
		rs2229109	3% (A)		
		rs1128503	42% (T)		
		rs2032582	41% (T)		
		rs1045642	48% (C)		

[a]Estimates from 1000 Genomes Project

[b]Frequency from study population

MAF Predicted minor allele frequency in study ethnicity

Table 2

Cytochrome P450 genetic variants associated with methadone metabolism

Ethnicity	Measurement	Gene	Alleles/ variants	MAF (minor allele)[a]	Finding	Reference
Han Chinese (n = 321)	Dose	*CYP2B6*	*9	16% (T)	*9 allele carriers required higher doses	[34]
European (n = 245)	Plasma concentration	*CYP2B6*	*6	23% (–)[b]	*6/*6 genotype increased (S)-methadone	[35]
		CYP2D6	*1/*xN	5% (–)[b]	Ultrarapid metabolism status decreased (R,S)-methadone	
Taiwanese (n = 178)	Plasma concentration	*CYP2B6*	*4	25% (G)[b]	*4/*4 genotype increased (R,S)-methadone	[41]
Mixed, American (n = 206)	Plasma concentration	*CYP2B6*	*9		*9 allele increased (S)-methadone	[44]
Israeli (n = 74)	Dose	*CYP2B6*	*6	24% (–)[b]	*6/*6 genotype required higher doses	[51]
European (n = 209)	Plasma concentration	*CYP2B6*	*6	24% (–)[b]	*6/*6 genotype increased (S)-methadone	[54]
European (n = 244)	Plasma concentration	*CYP2B6*	*6	23% (–)[b]	*6/*6 genotype increased (R,S)-methadone	[36]
		CYP3A4	*22	5% (A)	*22 allele increased (R)-methadone	
Taiwanese (n = 366)	Plasma concentration	*CYP2B6*	rs10403955	16% (G)	Minor alleles decreased (S)-methadone	[55]
			rs2279345	31% (T)		
			rs707265	33% (A)		
			*9	16% (T)		
European (n = 276)	Plasma concentration	*CYP2B6*	*4	19% (G)[b]	Minor alleles overrepresented in high (S)-methadone group	[56]
			*6	17% (–)[b]		
			*9	17% (T)[b]		
			rs2279344	37% (G)		
			rs8192719	24% (T)		
Mixed, American (n = 40)	Postmortem plasma concentration	*CYP2B6*	*4	45% (G)[b]	Minor alleles increased (R,S)-methadone	[57]
			*6	20% (–)[b]		
			*9	20% (T)[b]		
European (n = 256)	Plasma concentration	*CYP2D6*	*1/*xN	4% (–)[b]	Ultrarapid metabolism status decreased (R)- and (S)-methadone compared with poor metabolism status	[63]
			*3	1% (–)[b]		
			*4	24% (–)[b]		
			*6	<1% (–)[b]		

Ethnicity	Measurement	Gene	Alleles/ variants	MAF (minor allele)[a]	Finding	Reference
European (n = 155)	Plasma concentration	*CYP2B6*	*6	24% (--)[b]	*6/*6 genotype increased (R,S)-methadone	[64]
		CYP2C9	*2	12% (T)	*2 and *3 alleles increased (R,S)-methadone	
			*3	7% (C)		
		CYP2C19	*2	15% (A)	*2 and *3 alleles increased (R,S)-methadone	
			*3	<1% (A)		
		CYP3A5	*3	6% (T)	*3 increased (R,S)-methadone	
Taiwanese (n = 366)	Dose	*CYP2C19*	*2	33% (A)	Poor metabolism status decreased doses	[52]
			*3	4% (A)		
Taiwanese (n = 360)	Plasma concentration	*CYP2B6*	8 haplotypes		Haplotypes associated with (S)-methadone levels	[70]

[a] Estimates from 1000 Genomes Project

[b] Frequency from study population

MAF Predicted minor allele frequency in study ethnicity

Table 3

Other genetic variants associated with methadone metabolism

Ethnicity	Measurement	Gene	Alleles/ variants	MAF (minor allele)[a]	Finding	Referenc
Han Chinese (*n* = 321)	Dose	*DRD2*	rs1799978	20% (C)	Minor allele carriers required lower doses	[34]
			rs6275	48% (G)		
Israeli (*n* = 227)	Dose	*ANKK1*	rs7118900	18% (A)	A allele carriers required lower doses	[67]
		BDNF	rs10835210	44% (A)	C/C homozygotes required higher doses	
			rs1491850	43% (C)	C/C homozygotes required lower doses	
		NTRK2	rs2289658	4% (C)	C allele carriers required higher doses	
			rs4358872	45% (T)	Minor allele homozygotes	
			rs1948308	44% (G)	required lower doses	
			rs2378676	44% (A)		
European (*n* = 244)	Plasma concentration	*POR*	*28	30% (T)	*28/*28 genotype decreased (R)-methadone	[36]
European (*n* = 85)	Dose	*KCNJ6*	rs2070995	20% (T)	A/A genotype required higher doses	[66]
Han Chinese (*n* = 257)	Dose	*OPRD1*	rs529520	16% (T)	G/T heterozygotes required higher doses	[42]
European-Australian (*n* = 119)	Plasma concentration	*OPRM1*	rs1799971 (A118G)	16% (G)	G allele with *ABCB1* AGTTT haplotype decreased (R)-methadone	[68]
African-American (*n* = 383)	Dose	*OPRM1*	rs73568641	10% (C)	C allele increased dose	[69]
Taiwanese (*n* = 360)	Plasma concentration	*Intergenic*	rs17180299	3% (G)	G allele increased (R)-methadone	[70]
		SPON1 GSG1L	7 haplotypes		Haplotypes associated with (S)-methadone levels	

[a]Estimates from 1000 Genomes Project

MAF Predicted minor allele frequency in study ethnicity

Table 4

Genetic variants associated with opioid use disorder treatment response

Drug	Ethnicity	Measurement	Gene	Variant/ allele	MAF (minor allele)[a]	Finding	Reference
Methadone	African-American (*n* = 36)	Urine drug screens for opioids	*OPRD1*	rs678849	26% (T)	T allele increased risk for positive tests	[76]
Methadone	European-American (*n* = 283)	Urine drug screens for opioids	*OPRM1*	rs10485058	15% (G)	G allele increased risk for positive tests	[77]
Methadone	Taiwanese (*n* = 360)	Urine drug screen for morphine	*CDH2*	rs8094439	21% (A)	A/A associated with increased CDH2 plasma levels	[78]
				rs17446819	21% (C)	C/C associated with increased CDH2 plasma levels	
						Increased plasma level correlated with increased risk of positive test	
Methadone	European (*n* = 169)	Responder = no opioid-positive urines in last 4 tests.	*MYOCD*	rs1714984	23% (A)	Carrying the A allele at rs1714984 and the A/G	[81]
		Non-responder = 2 or more tests positive in last 4	*GRM6*	rs953741	34% (G)	genotype at rs953741 increased risk of being non-responder	
Methadone	European (*n* = 169)	Responder = no opioid-positive urines in last 4 tests. Non-responder = 2 or more tests positive in last 4	*ALDH5A1*	rs2760118	32% (T)	T allele increased risk of being non-responder	[82]
Methadone	European (*n* = 238)	Responder = 1 or fewer positive weekly urine drug screens in last 3 months. Non-responder = regular opioid and/or cocaine use in last 3 months	*DRD2*	rs6277	46% (C)	C/C genotype increased risk of being non-responder	[84]
Methadone	European-Australian (*n* = 95)	Successful outcome = continued use of methadone with reduced heroin use or planned completion of methadone treatment without heroin use. Poor outcome = dropping out of treatment or using heroin at least weekly	*DRD2*	rs1800497	19% (T)	T allele associated with increased risk of poor outcome	[87]
Methadone	European (*n* = 238)	Responder = 1 or fewer positive weekly urine drug screens in last 3 months and absence of withdrawal symptoms. Non-responder = regular opioid and/or cocaine use in last 3 months	*ARRB2*	rs3786047	32% (A)	Minor allele homozygotes for all variants increased risk of being non-responder	[83]
				rs1045280	31% (C)		
				rs2036657	32% (G)		
Methadone	European (*n* = 91)	Responder = no opioid-positive urines in last 4 tests. Non-responder = 2 or more tests positive in last 4	*BDNF*	rs7127507	30% (C)	CCGCCG haplotype increased risk of being a non-responder	[88]
				rs1967554	–		
				rs11030118	–		
				rs988748	24% (C)		
				rs2030324	48% (G)		

Drug	Ethnicity	Measurement	Gene	Variant/ allele	MAF (minor allele)[a]	Finding	Reference
				rs11030119	28% (A)		
Methadone	Taiwanese (*n* = 366)	Clinical Opioid Withdrawal Scale	*UGT2B7*	rs6600879	31% (C)	Major allele homozygotes associated with increased withdrawal symptoms	[90]
				rs6600880	31% (T)		
				rs4554144	31% (C)		
				rs11940316	31% (T)		
				rs7438135	31% (G)		
				rs7662029	31% (A)		
				rs7668258	31% (T)		
				rs7439366	31% (T)		
				rs4292394	31% (C)		
				rs6600893	31% (T)		
Methadone	Taiwanese (*n* = 366)	Clinical Opioid Withdrawal Scale	*OPRK1*	rs7832417	7% (T)	TTCT haplotype increased bone or joint ache symptoms	[89]
				rs16918853	7% (T)		
				rs702764	7% (C)		
				rs7817710	7% (T)		
				rs10958350	11% (A)	Haplotypes associated with gooseflesh, yawning, and restlessness	
				rs7016778	11% (T)		
				rs12675595	12% (A)		
Methadone	European (*n* = 85)	Withdrawal symptoms by clinical assessment	*KCNJ6*	rs2070995	20% (T)	A/A genotype reduced withdrawal symptoms	[66]
Methadone	European (*n* = 205)	Verona Service Satisfaction Scale	*CYP2D6*	*1 × 2	1% (–)[b]	Ultrarapid metabolism status decreased satisfaction	[91]
				*2 × 2	2% (–)[b]		
Buprenorphine /naloxone	African-American (*n* = 41)	Urine drug screens for opioids	*OPRD1*	rs678849	26% (T)	T allele decreased risk for positive tests	[76]
Buprenorphine /naloxone	European-American (female; *n* = 81)	Urine drug screens for opioids	*OPRD1*	rs581111	28% (A)	A allele increased risk for positive tests	[93]
				rs529520	45% (A)	A/A genotype increased risk for positive tests	
Buprenorphine	European (*n* = 107)	Non-responder = any of the following: drop out in first 12 weeks, ≥33% urine drug screens positive for opioids or cocaine, behavioral problems resulting in	*SLC6A3*	3’ UTR VNTR	–	11-repeat allele decreased risk of being a non-responder	[96]

[a]Estimates from 1000 Genomes Project

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[b] Frequency from study population

MAF predicted minor allele frequency in study ethnicity, *UTR* untranslated region, *VNTR* variable number tandem repeat

Table 5

Genetic variants associated with methadone treatment adverse events

Ethnicity	Measurement	Gene	Variant/ allele	MAF (minor allele)[a]	Finding	Reference
European-American (n = 136)	Overdose fatality	*CYP3A4*	*1B	2% (C)	*1B allele enriched in overdose cases	[99]
European-American (n = 125)	Overdose fatality	*CYP2B6*	*9	28% (T)	*9 enriched in overdose cases	[100]
			rs8192719	29% (T)	T allele enriched in overdose cases	
European (n = 40)	Plasma concentration in fatalities	*CYP2B6*	*6	38% (–)[b,c]	*6 allele increased (R,S)-methadone	[101]
European (n = 179)	QTc	*CYP2B6*	*6	22% (–)[b]	*6/*6 genotype increased QTc	[106]
European-American (n = 25)	QTc	*CYP2C19*	*2	13% (A)	*2 allele increased plasma concentration of EDDP, which increased QTc	[107]
Taiwanese (n = 366)	QTc	*CYP2C19*	*2 *3	33% (A) 4% (A)	Poor metabolism status increased QTc change in patients who continued using illicit opioids	[108]
European (n = 82)	QTc	*KCNH2*	rs1805123	25% (G)	C allele decreased QTc	[110]
Taiwanese (n = 366)	Reduced libido Insomnia	*OPRM1*	rs1074287	18% (G)	Minor alleles for all variants associated with changes in libido	[112]
			rs6912029	12% (T)		
			rs12209447	12% (T)		
			rs510769	17% (T)	Minor homozygous genotypes for all variants associated with insomnia	
			rs3798676	12% (T)		
			rs7748401	12% (G)		
			rs495491	17% (G)		
			rs10457090	12% (G)		
			rs589046	17% (T)		
			rs3778152	12% (G)		
			rs563649	12% (T)		
			rs2075572	23% (G)		
Iranian (n = 202)	Reduced libido	*OPRD1*	rs2236855	17% (A)	T allele associated with reduced libido	[113]
Iranian (n = 202)	Reduced libido Insomnia	*OPRK1*	rs997917	30% (T)	C allele associated with reduced libido	[114]
			rs6985606	27% (T)	C allele associated with insomnia	

[a] Estimates from 1000 Genomes Project

[b] Frequency from study population

[c] Frequency of *CYP2B6*6* carriers

EDDP 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, *MAF* predicted minor allele frequency in study ethnicity, *QTc* heart-rate-corrected QT interval