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Title: Review of Opioid Pharmacogenetics and Considerations for Pain Management

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Abstract

Opioid analgesics are the standards of care for the treatment of moderate to severe nociceptive pain, particularly in the setting of cancer and surgery. Their analgesic properties mainly emanate from stimulation of the μ receptors, which are encoded by the *OPRM1* gene. Hepatic metabolism represents the major route of elimination, which, for some opioids, namely codeine and tramadol, is necessary for their bioactivation into more potent analgesics. The highly polymorphic nature of the genes coding for phase I and phase II enzymes (pharmacokinetics genes) that are involved in the metabolism and bioactivation of opioids suggests a potential interindividual variation in their disposition and, most likely, response. In fact, such an association has been substantiated in several pharmacokinetic studies described in this review, in which drug exposure and/or metabolism differed significantly based on the presence of polymorphisms in these pharmacokinetics genes. Furthermore, in some studies, the observed variability in drug exposure translated into differences in the incidence of opioid-related adverse effects, particularly nausea, vomiting, constipation, and respiratory depression. Although the influence of polymorphisms in pharmacokinetics genes, as well as pharmacodynamics genes (*OPRM1* and *COMT*) on response to opioids has been a subject of intense research, the results have been somehow conflicting, with some evidence insinuating for a potential role for *OPRM1*. The Clinical Pharmacogenetics Implementation Consortium guidelines provide *CYP2D6*-guided therapeutic recommendations to individualize treatment with tramadol and codeine. However, implementation guidelines for other opioids, which are more commonly used in real-world settings for pain management, are currently lacking. Hence, further studies are warranted to bridge this gap in our knowledge base and ultimately ascertain the role of pharmacogenetic markers as predictors of response to opioid analgesics.

Introduction

Interpatient variability in medication response is a well-known phenomenon. Certain patients respond as expected to certain therapies, whereas others do not respond at all or experience adverse effects. This variation in response is due to clinical and environmental factors such as age, body weight, renal or hepatic function, comorbidities, and concomitant medications. Over the last several decades, genetic polymorphisms have been proven to be one of the main culprits of medication response variability.[1] Pharmacogenetics—the study of the influence of genetic variants on medication response—has been directly implicated in the management of many medical conditions, including pain. Clinical pain management currently involves the use of nonpharmacologic methods and many pharmacologic agents including opioids, nonsteroidal antiinflammatory drugs, antidepressants, and anticonvulsants. Regardless of the available treatment modalities, complete pain relief is still an elusive concept to many patients. It has been observed that 38–74% of patients with cancer experience inadequate pain relief regardless of the management strategy used.[2] In a national survey involving 250 randomly selected postoperative adult patients, 80% expressed inadequate postoperative pain relief.[3] These findings and many others highlight the need for pain management optimization, regardless of patients' comorbidities, to ensure maximum efficacy while preventing and/or minimizing toxicity.

For centuries, opioid analgesics have been used to manage moderate to severe acute and chronic pain. They are generally safe; however, in certain patients they produce adverse effects such as respiratory depression, sedation, nausea, vomiting, constipation, impaired cognition, and sometimes even death.[4-6] Moreover, there are subsets of patients who may not experience the analgesic properties of opioids.[7] Genetic polymorphisms have been labeled as some of the main culprits of opioid response variation. In recent years, several genetic testing companies have developed pain-specific pharmacogenetic panels to help clinicians address this concern. These panels interrogate a number, if not all, of the genes discussed in this review article. To address the clinical utility of these

drug-gene pairs, we conducted a search of the PubMed database for original studies involving human subjects using medical subject heading terms consisting of each opioid's drug name, pharmacogenetics, pharmacogenomics, and polymorphisms, and the terms pharmacokinetics, disposition, response, efficacy, adverse events, side effects, and toxicity. Relevant references from the selected articles as well as resources available on www.pharmgkb.org for each of the opioid medications were reviewed and included where applicable. This review focuses on the pharmacogenetics of opioids and their readiness for adoption into clinical practice.

Overview of Opioids

Metabolic Pathways and Pharmacology

Opioid receptors are present in both the central nervous system (CNS) as well as peripheral tissues throughout the body. Three receptors are largely responsible for the opioid mechanisms of analgesia and adverse effect profiles: μ, κ, and δ receptors.[8] Several subtypes of each receptor exist and are denoted by numbers after the receptor type (e.g., μ_1). μ-Receptor activation leads to supraspinal analgesia and well-known opioid adverse effects (respiratory depression, sedation, euphoria, and decreased gastrointestinal motility). The gene coding for the μ receptors, *OPRM1,* is highly polymorphic, with more than 100 variants identified. One of the most studied alleles is the 118 A>G polymorphism (rs1799971), with a prevalence ranging from 2-48%. κ-Receptor activation leads to spinal analgesia and similar adverse effects (respiratory depression, sedation, and dysphoria). δ-Receptor agonism likely leads to dysphoria and psychomimetic effects. All opioids are μ-receptor agonists and vary in their degree of κ and δ agonism. Some opioids, such as tramadol and methadone, have additional nonopioid receptor–based sites of action.[8]

Drug Metabolism and Disposition

Opioid analgesics are extensively metabolized in the liver. The metabolic pathway of each agent is quite complex and generally entails both phase I and phase II enzymes. Almost all of the phase I enzymes involved in opioid metabolism belong to the cytochrome P450 (CYP) family (mainly CYP2D6, CYP3A4/CYP3A5), whereas the phase II enzymes include the uridine diphosphoglucuronysyltransferases (UGTs). Phase I metabolism results in either active or inactive metabolites, with many active metabolites possessing more potent activity than their parent drug.[9, 10] The complete metabolic pathways of the opioids are described in Figure 1. Given the polymorphic nature of the genes coding for

these enzymes, regardless of whether they are phase I or phase II enzymes, it is reasonable to assume that a significant variation in drug disposition or pharmacokinetics exists among individuals taking these medications for analgesia. This topic has garnered much interest among investigators in light of the improved understanding of human genetics coupled with the advances made in the field of molecular technology. In fact, several studies sought to interrogate the association between polymorphisms in pharmacogenes and interindividual differences in opiate plasma concentration or exposure. Findings from some of these studies will be highlighted in the following sections. However, the critical question is whether the reported variability in drug exposure translates into differences in drug efficacy and incidence of adverse effects. In this review, we describe the effects of various genes on the disposition, efficacy, and toxicity profiles of individual opioids and comment on whether these associations are mature for adoption into clinical practice.

Codeine

Impact of Genetic Polymorphisms on Codeine Disposition

Codeine is a prodrug that undergoes *O*-demethylation into morphine. This process is mediated by CYP2D6 and it accounts for about 10% of the overall elimination pathway of codeine. *CYP2D6* is a highly polymorphic gene that is responsible for the metabolism of approximately 25% of all commonly prescribed medications. To date, approximately 100 *CYP2D6* variants have been identified, which primarily result from single nucleotide polymorphisms (SNPs), nucleotide insertions/deletions (indels), or even whole gene deletion, duplication, or multiplication (copy number variations).[11] As a consequence of these polymorphisms, CYP2D6 enzymatic activity differs among individuals. Those harboring two loss of function variants, as outlined in Table 1, are referred to as CYP2D6 poor metabolizers (PMs). CYP2D6 poor metabolizers produce low plasma concentrations of morphine and most likely do not derive any clinical benefit from codeine. On the opposite end of the CYP2D6 activity spectrum are individuals who carry at least three normal function variants (known as ultrarapid metabolizer [UM] phenotype), who in fact may have supratherapeutic levels of morphine. Several pharmacokinetic studies demonstrated a significant correlation between CYP2D6 activity and morphine exposure. In the study by Kircheiner et al. [12], 26 healthy male volunteers were given a single dose of codeine 30 mg. There was at least a 20-fold increase in morphine's area under the curve (AUC) in individuals with the CYP2D6 normal metabolizer (NM [previously referred to as extensive metabolizer (EM)]) (11 mcg•hr/L) and the UM (16 mcg•hr/L) phenotypes relative to individuals with the PM

phenotype (0.5 mcg•hr/L, p=0.02). Furthermore, the codeine to morphine ratio was about 10 times higher in PMs (198, interquartile range [IQR] 143-599) compared to NMs (19, IQR 9.9-28) and UMs (17, IQR 13-19).

Impact of Genetic Polymorphisms on Response to Codeine

In addition to variation in codeine disposition, polymorphisms in *CYP2D6* [13-15] and *UGT2B7* [16] have been documented to influence codeine's analgesic response. Moreover, in a nested cohort of 98 postcesarean section women prescribed codeine, Baber and colleagues concluded that the *OPRM1* G variant (118 A>G) was significantly associated with the differences in mean dose consumption (p = 0.001).[16] Unlike variants in *ABCB1, COMT*, and *CYP2D6*, patient-specific factors such as age and race-ethnicity were found to be determinants of codeine variability in this study.

Impact of Genetic Polymorphisms on Codeine Toxicity Profile

There are several published reports documenting the unfortunate impact of genetic polymorphisms on codeine therapy.[4, 6, 17, 18] In a case-control study that sought to determine the characteristics of mothers and infants with and without CNS depression after codeine therapy, high codeine dose, as well as CYP2D6 UM phenotype and *UGT2B7*2/*2* genotypes were found to be risk factors for neonatal toxicity following maternal codeine use.[4] Additionally, there is a single case report of a 29-month-old patient who was found to have the UM phenotype for *CYP2D6* after he developed apnea from codeine therapy.[18] The patient had a scheduled adenotonsillectomy with a history of mild to moderate sleep apnea. On postoperative day 1, it was reported that the patient received four doses of codeine with acetaminophen and an additional dose on the second evening after surgery. Four hours later, the child was found unresponsive and apneic. The child was determined to be a CYP2D6 UM, which is likely a significant contributor to the apneic episode. Moreover, there is another documented case of a 14-year-old female who presented to the emergency department with irritability and drowsiness after taking acetaminophen-codeine for hip pain.[17] The patient was determined to have a *CYP2D6*4/*5* genotype, indicating a PM phenotype, and thereby poor codeine metabolism. In this case, the presenting symptoms were likely due to uncontrolled pain caused by little to no conversion of codeine to morphine.

Clinical Adoption of Codeine Pharmacogenetics

Of all the opioids discussed in this review, codeine-*CYP2D6* is the only example that has a dedicated Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline [19, 20] and, as such, has risen to clinically actionable status as seen in Figure 2. This is chiefly due to the serious nature of the toxicities attributed to genetics, particularly *CYP2D6* polymorphisms among young codeine users. In these guidelines, it is strongly recommended that CYP2D6 UMs and PMs should avoid codeine due to the increased risk of toxicities and lack of analgesic effects, respectively. A CPIC moderate recommendation for CYP2D6 IMs advises to avoid codeine after a failed initial attempt. CYP2D6 NMs can be prescribed codeine at the label-recommended doses. Moreover, the United States Food and Drug Administration (FDA) recently updated its safety warning for codeine and tramadol. This newest safety announcement contraindicates the use of codeine either for pain or cough in those younger than 12 years.[21] They also warn against the use of codeine in obese adolescents (between 12 and 18 years old) or those with obstructive sleep apnea or severe lung disease. Codeine is also not recommended in breastfeeding mothers according to this newest safety notice due to the reasons discussed above in the case reports.

Fentanyl

Impact of Genetic Polymorphisms on Fentanyl Disposition

Fentanyl is metabolized by the polymorphic CYP3A4 and CYP3A5 enzymes (Figure 1), and because of that, it is expected that the metabolism of fentanyl varies among individuals. Indeed, the study by Takashina et al. investigated the impact of polymorphisms in the *CYP3A5* (*CYP3A5*3*) as well as the *ABCB1* (1236 C>T, 2677 G>A/T, and 3435 C>T) genes on fentanyl metabolism.[5] The study recruited 60 adult patients with cancer who received transdermal fentanyl at doses ranging from 25-75 mcg/hour based on their daily consumption of morphine or oxycodone. The median plasma concentration of fentanyl was approximately twice as high in *CYP3A5*3* homozygotes (1.72 [IQR 0.91-2.31] ng/mL) compared to *CYP3A5*1* carriers (*1/*3: 0.84 [IQR 0.76-1.17] ng/mL, and *3/*3: 0.78 [IQR 0.74-0.87] ng/mL, $p<0.05$ for both comparisons). In addition, patients with the *1/*1 and *1/*3 genotypes had at least a 2-fold increase in fentanyl clearance compared with *CYP3A5*3* homozygotes (*1/*1: 67.4 [IQR 47.2-78.2] L/hr, *1/*3: 58.4 [IQR 41.3-75.6] L/hr, and *3/*3: 28 [IQR 20.6-55.1] L/hr, $p<0.03$ for both comparisons).

Impact of Genetic Polymorphisms on Response to Fentanyl

Landau et al. conducted a prospective observational study to discern the role of *OPRM1* (118 A>G) and *COMT* (Val158Met, G>A) polymorphisms with regard to analgesic response to intravenous (IV) fentanyl among 106 female patients in labor pain.[22] The analgesic success rate, defined as numerical verbal pain score ≤ 10/100 15 minutes after administration of IV fentanyl, was not significantly different by *OPRM1* genotypes (20% for AA vs 21% for AG/GG genotypes, p=0.82) or by *COMT* genotypes [10% for Met/Met vs 22% for Val/Met and Val/Val], p=0.24). The authors attributed these negative findings to the small sample size and suggested that larger studies are warranted to uncover the role of these polymorphisms in *COMT* and *OPRM1*. In other studies, investigators have reported the involvement of *OPRM1* in the therapeutic response variability observed with fentanyl [23, 24] and alfentanil [25]. Also, in a study of 60 Japanese patients with cancer treated with transdermal fentanyl, Takashina et al. reported that patients with the *ABCB1* 1236TT allele were less likely to need rescue medication compared to carriers of 1236C allele (odds ratio 0.17, 95% confidence interval 0.03–0.89; p = 0.036).[5] Hence, variants in *OPRM1* and *ABCB1* may be predictors of fentanyl response.

Impact of Genetic Polymorphisms on Fentanyl Toxicity Profile

As described earlier in the Takashina et al. study, when investigating the influence of *ABCB1* and *CYP3A5* polymorphisms on the fentanyl pharmacokinetics and response, no statistically significant findings were reported for fentanyl-related adverse effects and genetic polymorphisms.[5] In *ABCB1* 2677G allele carriers, there was a higher incidence of nausea and vomiting (p=0.16), whereas 3435C carriers had higher rates of constipation (p=0.26). Central adverse effects were reported in more patients with *CYP3A5**3/*3 than those with *1/*1 and *1/*3 (p=0.07). The small sample size of this study is most likely why these outcomes did not reach statistical significance. Further studies are needed to validate this theory.

Clinical Adoption of Fentanyl Pharmacogenetics

Fentanyl pharmacogenetics is currently not ready for clinical adoption due to lack of consistent data, as shown in Figure 2. The most promising evidence seems to be the influence of *OPRM1* polymorphisms on fentanyl response variations; however, these associations have not been consistently replicated. Variants in *CYP3A5* have been observed to play a role in fentanyl disposition, but whether this link with fentanyl's pharmacokinetics translates into differences in response and toxicity is yet to be determined.

Hydrocodone

Impact of Genetic Polymorphisms on Hydrocodone Disposition

Hydrocodone is a semisynthestic opioid that is structurally related to codeine. Hydrocodone undergoes extensive metabolism by CYP2D6 and CYP3A4 to hydromorphone and norhydrocodone, respectively, which are further conjugated by UGTs into water-soluble metabolites that are primarily excreted by the kidneys. The affinity of hydromorphone for the μ receptors is at least 100-fold greater than that of hydrocodone. The study by Stauble et al. sought to assess the impact of polymorphisms in *CYP2D6* on hydrocodone metabolism in female patients who underwent cesarean section.[26] Patients with the CYP2D6 UM phenotype had approximately a 10-fold increase in the plasma concentration of hydromorphone compared to individuals with the CYP2D6 PM phenotype (7.06 vs. 0.66 ng/mL). Patients with the intermediate metabolizer (IM) and NM phenotypes had hydromorphone plasma concentrations between the values reported for UMs and PMs (4.29 and 5.73 ng/ml, respectively).

Impact of Genetic Polymorphisms on Response to Hydrocodone

The influence of polymorphisms in *OPRM1* on pain response was assessed in the study by Boswell et al.[27] Female patients who underwent cesarean section were treated with hydrocodone/acetaminophen (5 mg/325 mg or 7.5 mg/325 mg) every 4 hours as needed for postoperative pain relief after receiving IV or intrathecal morphine for the first 24 hours after surgery. There was a significant association between pain scores and hydrocodone total daily dose, as well as hydromorphone plasma concentration (the active metabolite of hydrocodone), in patients with the AA genotype (118 A>G) for *OPRM1*. However, this relationship did not reach statistical significance in patients carrying either one or two copies of the G variant allele. This finding could most likely be ascribed to the small number of patients with the GG genotype (n=5) enrolled in the study. Furthermore, there was no direct comparison of the differences in hydrocodone daily doses between patients with the AA versus the AG and GG genotypes. Besides *OPRM1*, polymorphisms in *CYP2D6* had a significant impact on the analgesic effects of hydrocodone as demonstrated in the study by Stauble et al (21). High plasma concentrations of hydromorphone as a result of functional CYP2D6 enzymes correlated with pain relief in female patients after cesarean section. Furthermore, hydromorphone concentration was the only significant predictor of pain response to hydrocodone in multiple regression analysis after adjusting for age, body mass index, and duration of treatment (p=0.023).

Impact of Genetic Polymorphisms on Hydrocodone Toxicity Profile

The evidence on the relationship between genetic polymorphisms and hydrocodone adverse effects is quite scant. Madadi et al. reported a case of respiratory depression with hydrocodone that tragically resulted in the death of a 5-year-old child.[28] Nevertheless, the child was also receiving clarithromycin for ear infection, thereby raising the critical question of whether the underlying etiology of her lethal hydrocodone plasma concentration was due to her *CYP2D6* genotype (*2/*41) or the concomitant treatment with clarithromycin, a potent inhibitor of the CYP3A4 pathway involved in hydrocodone metabolism.

Clinical Adoption of Hydrocodone Pharmacogenetics

According to the CPIC guideline for codeine, hydrocodone may not a good alternative to codeine in CYP2D6 UMs and PMs. These CPIC recommendations are mainly based on the fact that hydrocodone is a CYP2D6 substrate and not on particularly robust evidence. Given the lack of evidence, more research is warranted to further elucidate the relationship between genetic polymorphisms in *CYP2D6* or *OPRM1* and response to hydrocodone. In all, the evidence and the CPIC comments surrounding hydrocodone pharmacogenetics places it in the "further research needed" category when considering clinical actionability, as depicted in Figure 2**.**

Methadone

Impact of Genetic Polymorphisms on Methadone Disposition

Methadone exists as a racemic mixture of R- and S-enantiomers, with the former having at least a 10-fold greater affinity for the μ receptors than the latter. The CYP2B6 metabolic pathway represents the major route of methadone elimination or clearance. Similar to other CYP enzymes , the gene coding for CYP2B6 is highly polymorphic, with more than 38 variants identified thus far, which primarily arise from SNPs.[29] The prevalence of each *CYP2B6* allele varies among different populations (Table 1). The *CYP2B6*6* (516 G>T, 785 A>G) is by far the most studied variant given its high prevalence among various racial groups. Several studies (including ex vivo studies) were able to identify *CYP2B6* as a significant genetic determinant of the variability in methadone elimination.[30, 31] Moreover, Kharasch conducted a pharmacokinetic study where 128 healthy volunteers were given simultaneously IV racemic methadone hydrochloride 6 mg (5.4 mg of free base) and labeled oral methadone hydrochloride 11 mg (9.86 mg of

free base).[32] For IV methadone, the *S*-enantiomer clearance (mL/kg/min) was significantly lower in patients with the *CYP2B6*1/*6* (1.2 ± 0.4) and *CYP2B6*6/*6* (0.96 ± 0.33) genotypes compared to those who had the *CYP2B6*1/*1* (1.5 ± 0.3) genotype ($p<0.05$). The *R*-enantiomer clearance did not significantly differ by *CYP2B6* genotype. For oral methadone, the clearances of both the *R*- and the *S*-enantiomers were significantly different in *6 carriers in comparison with *1 homozygotes. In addition to the *CYP2B6*6* variant, the authors investigated the influence of other *CYP2B6* variants on the pharmacokinetic profile of methadone. Contrary to the findings with the *CYP2B6*6* allele, the presence of the *CYP2B6*4* variant resulted in increased methadone clearance, whereas the *CYP2B6*5* allele had no impact on methadone clearance.[32] As represented in Table 2, *ABCB1* and *CYP3A4* have been shown to influence methadone pharmacokinetics as well.[31]

Impact of Genetic Polymorphisms on Methadone Response

There is a significant lack of data relating polymorphisms to clinical response outside of methadone maintenance therapy.

Impact of genetic polymorphisms on Methadone Toxicity Profile

Currently, to our knowledge, there are no data published on the toxicity profile of methadone relative to genetic polymorphisms in patients with pain.

Clinical Adoption of Methadone Pharmacogenetics

Further research is needed in methadone pharmacogenetics particularly to explore the relationship between genetic polymorphisms and analgesic response to methadone, as well as adverse effects. To date, there is insufficient evidence to support the clinical implementation of pharmacogenetic testing for patients with pain treated with methadone (Figure 2).

Morphine

Impact of Genetic Polymorphisms on Morphine Disposition

The principal pathway involved in morphine metabolism is conjugation to morphine-6-glucuronide (M6G, which accounts for 60% of all metabolites) and morphine-3-glucuronide (M3G). These reactions are mediated mainly by the UGT2B7 phase II enzyme in the liver.[33] UGT1A1 plays a minor role in the glucuronidation of morphine to M3G. Polymorphisms in phase II enzymes have also

been studied for association with variability in morphine exposure. Of special interest is the *UGT1A1*28* polymorphism, which results from seven tandem repeats of the dinucleotide TA.[34, 35] Accordingly, the presence of these polymorphisms confers reduced enzymatic activity of UGT1A1 attributable to reduced expression of the enzyme (~8-fold reduction). In the study by Holthe et al., the glucuronidation products to morphine plasma ratios were compared among 70 patients with cancer based on UGT polymorphisms.[33] Findings from this study indicated that the plasma ratios were comparable among patients homozygous for the *UGT1A1*28* variant, carriers of this variant, and those who were homozygous for the wild-type allele (M6G/morphine ratios 7.1 ± 4.1, 7.4 ± 6, and 7.1 ± 3.9, respectively, and M3G/morphine ratios 38 ± 20.8, 40.8 ± 28.5, and 34.4 ± 19.4, respectively). Furthermore, the effects of *UGT2B7* polymorphisms were similar to those observed with the *UGT1A1*28* variant. On the other hand, the study by Darbari et al. demonstrated that polymorphisms in *UGT2B7* could modulate the AUC of morphine and its metabolites.[36] The study included 20 patients with sickle cell disease treated with a single IV dose of morphine 0.1 mg/kg infused over 30 minutes. Blood samples were collected to measure morphine, M3G, and M6G concentrations before, at the end, and at several time points after the infusion. Additionally, *UGT2B7* was genotyped for two SNPs, -840 G>A (rs7438135) and -79 G>A. The authors noted that carriers of the G variant (GA/GG genotypes) for rs7438135 (-840 G>A) had significantly lower M3G/morphine and M6G/morphine AUC ratios compared to patients with the AA genotype (for M6G/morphine: 1.8 ± 0.5 vs. 3.0 ± 1.8, p=0.03; for M3G/morphine: 10.1 ± 2.7 vs. 15.7 ± 9.4, p=0.05).

Impact of Genetic Polymorphisms on Response to Morphine

Results from several studies demonstrated that the presence of the G variant of *OPRM1* (rs1799971) confers reduced analgesic effects on treatment with morphine. In the study by Gong et al, which enrolled 112 patients with cancer treated with opioids for pain relief, the morphine equivalent daily dose needed to achieve adequate analgesia, which the authors defined as the dose needed to reduce the pain score (using a visual analogue scale) to ≤4, was significantly lower among patients with the AA genotype compared with those carrying the G variant (AA: 72.4 ± 64 mg, AG: 97.3 ± 69 mg, and GG: 152.3 ± 83 mg, p=0.005).[37] Polymorphisms in *ABCB1* (3435 C>T) did not contribute to the variability in morphine doses observed among patients. In the same context, Klepstad et al. interrogated the influence of *OPRM1* polymorphisms on morphine daily doses in patients with cancer who reported adequate pain relief using the brief pain inventory (BPI≤4). Of the 207 patients included

in their final analysis, 17 (8%) were heterozygous for the variant G allele (118 A>G), and only four were homozygous (2%) for the G polymorphism.[38] Patients with the GG genotype for *OPRM1* required significantly higher daily doses of morphine to achieve satisfactory pain control in comparison to patients homozygous for the wild-type, A allele (GG: 225 ± 143 mg/day vs. 97 ± 89 mg/day among patients with the AA genotype for *OPRM1*, p=0.006). Even after adjusting for other confounding factors such as age, tumor location, performance status, and time from start of morphine, the effects of *OPRM1* polymorphisms on morphine requirements remained significant and independent of other covariates. Of note, the difference in morphine daily doses did not reach statistical difference between carriers of the G allele and those homozygous for the wild-type, A allele (66 ± 50 mg/day vs. 97 ± 89 mg/day). Reyes-Gibby et al. evaluated the joint effect of polymorphisms in both pharmacodynamics genes, *OPRM1* and *COMT*, on morphine daily dose requirements among patients with cancer.[39] Patients with the A/A and the Met/Met genotypes for *OPRM1* (118 A>G) and *COMT* (Met158Met) required significantly lower morphine doses (87 mg/day, 95% CI 57-116) for pain relief compared to patients with the other *OPRM1* and *COMT* genotypes (147 mg/day, 95% CI 100-180, p<0.012).

Several studies were also conducted primarily in the postoperative setting to discern the effects of *OPRM1* polymorphisms with regard to opioid/morphine consumption for analgesia. In the study by, et al., 138 patients who underwent open abdominal surgery (gastrectomy, colectomy, hepatectomy and pancreaticoduodenectomy) received continuous epidural analgesia with fentanyl or morphine.[24] The distribution of the *OPRM1* genotypes for the 118 A>G SNP was 41 (29.7%) for AA, 70 (50.7%) for AG, and 27 (19.6%) for GG. The 24-hour postoperative opioid dose requirement was significantly higher in patients with the GG genotype compared to patients with the AG and the AA genotype for *OPRM1* (p<0.05). The results of the study by Chou et al, which included 120 patients undergoing total knee arthroplasty, lend further support to the role of *OPRM1* polymorphisms.[40] Patients with the GG genotype (n=11, 11%) consumed significantly larger amounts of parenteral morphine 24 and 48 hours after surgery to achieve adequate pain control compared to patients with the AA and the AG genotypes (p <0.05). The difference in morphine doses between patients with the AG and the AA genotypes was not statistically significant.

Although the results of these studies provide a plausible explanation for the interindividual variation in opioid dose requirements in relation to *OPRM1* polymorphisms, some studies failed to establish such a causal relationship between these two. As an example, the studies by Coulbault et al. [41] and Klepstad et al. [42] showed no significant association between the 118 A>G polymorphism and

morphine dose requirements. It is important to point out that the studies were most likely underpowered to detect a difference in morphine consumption given the low frequency of the GG genotype for *OPRM1* (118 A>G).

Unlike polymorphisms in *OPRM1*, there is a paucity of evidence linking *COMT* to interindividual variation in opioid dose requirements. Among patients with cancer treated with morphine for pain relief, Rakvag et al. noted that patients harboring the Val/Val (GG) genotype (rs4680, G>A) required significantly higher mean daily doses of morphine for adequate analgesia compared to the other genotypes of *COMT* (Val/Val: 155 ± 160 mg/24 hours, Val/Met: 117 ± 100 mg/24 hours, and Met/Met: 95 ± 99 mg/24 hours, p=0.02).[43] These results were further replicated in another study by Rakvag et al, in which the authors detected significant differences in the daily doses of morphine based on rs4680 (Val158Met) genotypes.[44] The median morphine daily doses for rs4680 (Val158Met) were 90 mg, 80 mg, and 60 mg for the GG (Val/Val), GA (Val/Met) and the AA (Met/Met) genotypes, respectively (p=0.022). Moreover, there was a significant difference in the median morphine daily doses based on the presence of the rs4818 (C>G) SNP in *COMT* (CC: 60 mg/24 hours, CG: 80 mg/24 hours, and GG: 120 mg/24 hours, p=0.042). In addition to these two polymorphisms in *COMT*, other less studied SNPs were interrogated. Nonetheless, none was significantly associated with morphine daily dose requirements. The authors of this study also constructed *COMT* haplotypes for each patient based on his or her genotype information. Interestingly, one of the haplotypes that contained the rs4680 SNP (A>G) was a significant determinant of the variability in morphine daily doses (median morphine dose 60 mg for patients carrying this haplotype vs. 100 mg for those not carrying it, p=0.006).

Impact of Genetic Polymorphisms on Morphine Toxicity Profile

The impact of *ABCB1* genetic polymorphisms on patient outcomes was explored in a study of 273 children undergoing tonsillectomy in which morphine was administered perioperatively.[45] It was determined that the *ABCB1* variant rs9282564 was associated with a prolonged postoperative anesthesia care unit stay due to respiratory depression (p=0.0002). Statistical significance of this association was upheld when the subjects were stratified into race cohorts (white and black). Patients with GG and GA genotypes of rs9282564 experienced greater risks of respiratory depression, and it was determined that one copy of the G allele carried a 5-fold increased odds of prolonged stay due to respiratory depression.

Again, in a case report, two patients who received morphine and experienced adverse effects were genotyped for 20 functional polymorphisms.[46] The first patient received perioperative morphine. Approximately 15 hours postoperatively, the patient had a respiratory rate of 4 breaths per minute and was not responding to painful stimuli. She was determined to have a *CYP2D6**2/*2 genotype, indicating normal *CYP2D6* activity, but a *UGT2B7* C802T TT genotype (rs7439366) may have led to an increase in morphine-6-glucuronide formation. The patient had a *COMT* haplotype TCA (rs4633, rs4818, rs4680) that may have led to an increase in opioid sensitivity. The second case report described a patient who received intraoperative morphine and became unresponsive in the recovery room. The patient was genotyped and found to have mutations in *ABCB1* haplotype TTT (rs1128503, rs2032582, rs1045642) and *COMT* haplotype CCG (rs4633, rs4818, rs4680) that may have led to increased morphine exposure and opioid sensitivity. This patient also had an *OPRM1* polymorphism rs1799971 (G/G), which is associated with increased morphine requirements, so the clinical outcomes of each polymorphism in this case are difficult to ascertain.

Clinical Adoption of Morphine Pharmacogenetics

Despite being the prototype of all opiate analgesics, guidelines supporting pharmacogenetic testing to help guide morphine dose selection are currently lacking; this is partly explained by the controversy in the literature particularly that surrounding the role of *OPRM1,* which, in principle, seems to be a reasonable genetic marker worth pursuing. Nonetheless, the morphine-*OPRM1* association is moderately actionable due to the relative level of evidence currently available for this pair in comparison to all the other genes associated with other opioids and outcomes (Figure 2).

Oxycodone

Impact of Genetic Polymorphisms on Oxycodone Disposition

Oxycodone is semisynthetic opioid that is generally prescribed for management of moderate to severe nociceptive pain. Although it is also structurally related to codeine, oxycodone has analgesic properties by activation of the μ receptors. Whereas CYP3A4/5 is the principal metabolic pathway involved in converting oxycodone to noroxycodone (accounting for more than 50% of the overall metabolic pathway), the CYP2D6 metabolic pathway plays a minor role. However, it is worth noting that the latter pathway (CYP2D6) is responsible for converting oxycodone to a more potent analgesic, oxymorphone.

To our knowledge, the study by Naito et al. is the only study reported in the literature that sought to evaluate the differences in oxycodone, noroxycodone, and oxymorphone plasma concentrations based on polymorphisms in CYP3A5.[47] Sixty-two patients with cancer treated with extended-release oxycodone 5 mg every 12 hours were enrolled in the study; 37 (60%) were homozygous for the *CYP3A5*3* variant or the loss of function allele (i.e., *CYP3A5* nonexpressers). Interestingly, polymorphisms in *CYP3A5* had no significant impact on the mean plasma concentration of oxycodone (121 ng/mL among carriers of *CYP3A5* *3/*3 vs 113 ng/mL among carriers of *CYP3A5**1, p=0.62). Nonetheless, there were significant differences in noroxycodone and oxymorphone concentrations based on polymorphisms in *CYP3A5* and *CYP2D6*, respectively. The median plasma concentration of noroxycodone (the major metabolite of oxycodone) was 54.8 ng/ml (IQR 36-94.6) in patients homozygous for *CYP3A5**3 as opposed to 99.7 ng/ml (IQR 58.6-140) among *CYP3A5*1* carriers (p=0.01). These observed differences in noroxycodone plasma concentrations translated into significant differences in the ratio of noroxycodone to oxycodone (0.63 [IQR 0.15-0.87] ng/mL for *CYP3A5*3/*3* vs 0.92 [IQR 0.56-1.25] ng/mL for *CYP3A5*1/*1* and **1/*3*, p<0.01).

There is a large body of evidence to suggest variation in oxymorphone plasma concentration according to *CYP2D6* polymorphisms. Andreassen et al. conducted a cross-sectional study to evaluate the influence of *CYP2D6* polymorphisms on the pharmacokinetics of oxycodone.[48] The study included 450 patients with cancer who were receiving oxycodone for analgesia, of whom 6%, 92%, and 2% had the PM, NM, and UM phenotypes, respectively. The plasma concentrations of oxymorphone differed significantly between PMs and UMs, as well as between PMs and NMs (p<0.0001). Furthermore, the authors also detected the same trend in the oxymorphone/oxycodone ratio (0.0028 for PMs, 0.0172 for NMs, and 0.0244 for UMs) where the difference was also significant between PMs and UMs, as well as PMs and NMs (p<0.05). The study by Zwisler et al. set out to determine whether CYP2D6 regulates oxycodone exposure among patients undergoing surgery.[49] Following surgery, patients received oxycodone for 24 hours in addition to morphine (for breakthrough pain). In line with the results reported in the previous study,[48] PMs had significantly lower plasma concentrations of oxymorphone, compared with those of EMs. Alternatively, oxycodone plasma concentrations were almost the same among the different CYP2D6 metabolizer phenotypes.

In the study by Naito et al, with 62 patients receiving extended-release oxycodone 5 mg every 12 hours for the management of cancer pain, 16 (26%) had the CYP2D6 IM phenotype.[47] Although the plasma concentrations of oxycodone were comparable (126 ng/mL for CYP2D6 IMs vs 103 ng/mL for

NMs, p=0.3), the authors noted more than a 50% reduction in the plasma concentrations of oxymorphone among patients with the IM phenotype compared to those with the NM phenotype (0.79 ng/mL, IQR 0.34-1.6 vs. 1.69 ng/mL, IQR 0.79-3.39, p=0.02). Additionally, the oxymorphone to oxycodone ratio was significantly lower in patients with the CYP2D6 IM phenotype compared to those with the CYP2D6 NM phenotype (0.0072, IQR 0.004-0.0128 vs. 0.012, IQR 0.007-0.027, p=0.04).

Finally, in a prospective observational study of 121 patients who underwent abdominal surgery or thoracotomy, Samer and colleagues reported significant differences in oxymorphone/oxycodone ratios by CYP2D6 metabolizer phenotype: PMs: 0.1 (95% CI 0.02-0.19), IMs: 0.13 (95% CI 0.11-0.16), NMs: 0.18 (95% CI 0.16-0.2), and UMs: 0.28 (95% CI 0.07-0.49) (p=0.001).[50] Post hoc analysis indicated that a significant difference occurred between PMs and UMs (p=0.009), as well as IMs and UMs (p=0.005).

Impact of Genetic Polymorphisms on Response to Oxycodone

The influence of *OPRM1* polymorphisms on oxycodone dose requirements was evaluated in a study by Cajanus et al. among 993 patients with nonmetastatic breast cancer who elected to undergo mastectomy or breast-conserving surgery.[51] Postsurgical pain was assessed using the numerical rating scale (NRS), and oxycodone 1-3 mg was administered until the patients reported a pain intensity score of less than 4 on this scale. Patients with the GG genotype (118 A>G) required the highest doses of oxycodone (0.16 mg/kg) to achieve an adequate state of analgesia compared to patients with the AG (0.13 mg/kg) and the AA (0.12 mg/kg) genotypes (p<0.0001).

Another study by Zwisler et al. showed that there was no association between *OPRM1* polymorphisms and the analgesic effects of oxycodone.[52] Initially, 268 adult patients received IV oxycodone 5 mg 30 minutes prior to the end of surgery (thyroidectomy, parathyroidectomy, mastectomy, or hysterectomy). This was followed by a 5-mg IV dose administered in the recovery room, which was repeated if the pain score using the NRS remained above 4 following the first postoperative oxycodone dose. According to protocol, all patients received acetaminophen (paracetamol) 1000 mg every 6 hours along with 50 mg diclofenac every 8 hours for postsurgical pain management. Pain response rates based on polymorphisms in *OPRM1* were 83.7% and 83% for the AA and AG/GG genotypes, respectively (p=1). It is important to point out that the administration of around-the-clock doses of acetaminophen and diclofenac raises some concerns as to whether these medications did, in fact, obscure the effect of *OPRM1* polymorphisms on pain response to oxycodone in surgery patients.

Moreover, the study by Naito et al. (described earlier) detected similar findings (i.e., no significant differences in oxycodone doses based on *OPRM1* polymorphisms [118 A>G]).[47] Nonetheless, the prevalence of patients with the GG genotype (118 A>G) for *OPRM1* was not reported in the study since patients carrying at least a single G variant were all grouped together as a single group.

Given the role of CYP2D6 in oxycodone metabolism, Zwisler et al evaluated the impact of this pharmacokinetics gene (*CYP2D6*) on postoperative pain response to oxycodone in 270 adult patients.[49] At the end of the study, the authors detected no significant difference in the 24-hour consumption of oxycodone between NMs (14.7 mg, CI 13.0 - 16.4) and PMs (13.0 mg, CI 8.9 - 17.0, p=0.42)

Impact of Genetic Polymorphisms on Oxycodone Toxicity Profile

In the study by Andreassen et al (described earlier), the higher plasma concentrations of oxymorphone in patients with the *CYP2D6* UM phenotype did not result in higher rates of adverse drug events such as tiredness and nausea. [48]

Clinical Adoption of Oxycodone Pharmacogenetics

Similar to most opioid analgesics, treatment with oxycodone is also based on a trial and error approach. In light of its widespread use for pain management, there is definitely an unmet need for optimizing response to oxycodone. Nonetheless, it is rather challenging to discern whether genetic polymorphisms have any impact on response to oxycodone given the complicated metabolic pathway that the drug undergoes and the fact that the parent drug itself has some intrinsic analgesic effects (unlike tramadol and codeine). Hence, until more evidence becomes available, it is most likely that oxycodone dosing and/or selection will remain empiric for managing pain. Furthermore, the codeine CPIC guideline recommends against the use of oxycodone as an alternative to codeine in CYP2D6 UMs and PMs. Collectively, the body of knowledge surrounding oxycodone and *CYP2D6* suggests that this drug-gene pair's clinical actionability potential is weak at best; hence, further studies are needed (Figure 2).

Tramadol

Impact of Genetic Polymorphisms on Tramadol Disposition

Tramadol is a prodrug, which exists as a racemic mixture of *R*- and *S*-enantiomers. Its analgesic properties reside in its active metabolite, *O*-desmethyltramadol (ODT). Tramadol bioactivation to ODT occurs in the liver via the CYP2D6 enzyme. In the study by Stamer et al., 187 patients who underwent abdominal surgery were genotyped for *CYP2D6* polymorphisms in order to assess the relationship between tramadol disposition and the various CYP2D6 metabolizer phenotypes.[53] Approximately 90 minutes prior to anesthesia termination, patients were given an IV loading dose of tramadol 3 mg/kg. Of the 187 patients, 68 (36%), 18 (10%), and 8 (4%) were NMs, PMs, and UMs, respectively. PMs had the lowest AUC for ODT (0 ng.hr/mL, IQR 0-11.4), which differed significantly from those for IMs (38.6 ng.hr/mL, IQR 15.9-75.3), NMs (66.5 ng.hr/mL , IQR 17.1-118.4), and UMs (149.7, IQR 35.4-235.4) ($p<0.001$). In another study by Pedersen et al., 16 healthy participants (8 NMs and 8 PMs) received a single oral dose of tramadol 150 mg in the first phase of the study.[54] In the second phase, participants were given tramadol 50 mg orally 3 times a day for 48 hours, whereas in the third phase of the study, a single IV dose of tramadol 100 mg was administered to all participants. The authors sought to compare the differences in tramadol pharmacokinetics between the two CYP2D6 metabolizer phenotypes (NMs and PMs). In each of the three phases, the AUC of the active metabolite was at least 6-fold lower in patients with the PM phenotype ($p<0.0001$). Findings from the study by Gan et al. indicated that tramadol clearance varies with CYP2D6 phenotypes.[65] Patients with the IM phenotype had lower tramadol clearance (16 L/hr) compared to those with the UM phenotype (42 L/hr). Subsequently, the half-life of tramadol was approximately 2-fold longer in IMs relative to UMs (3.8 vs 7.2 hrs).

Impact of Genetic Polymorphisms on Response to Tramadol

Tramadol requires bioactivation in the liver in order to exert its analgesic effect. Because this process is mediated primarily by CYP2D6, it is only reasonable to assume that polymorphisms in *CYP2D6* influence response. Indeed, the study by Stamer et al. (described earlier) revealed that tramadol consumption at 48 hours after surgery was significantly higher among patients with the CYP2D6 PM phenotype ($p=0.002$).[53] Additionally, almost 81% of the PMs failed to have an adequate response to tramadol, defined as an NRS pain score < 40 at 48 hours after surgery ($p<0.001$). These data suggest that tramadol may not be an appropriate analgesic for patients with the CYP2D6 PM phenotype.

Impact of Genetic Polymorphisms on Tramadol Toxicity Profile

A single case report exists that describes respiratory depression in a patient with the CYP2D6 UM phenotype receiving tramadol by patient-controlled analgesia device.[55] The patient had baseline renal dysfunction and was undergoing scheduled surgery for renal carcinoma. Respiratory depression was noted 10.5 hours after the procedure and was successfully treated with naloxone. Moreover, the FDA issued a safety announcement for tramadol in April 2017 contraindicating the use of tramadol in individuals younger than 18 years of age following tonsillectomy or adenoidectomy surgeries.[21] The new warning also states that tramadol is contraindicated in children younger than 12 years for pain relief as well as adolescents (between 12 and 18 years of age) who are either obese, have obstructive sleep apnea, or have severe lung disease. Furthermore, the FDA cautions against the use of tramadol in nursing mothers due to the potential risk of serious adverse reactions including respiratory depression and even death. Although the FDA did not recommend *CYP2D6* testing prior to initiating tramadol, their statement suggests variability in tramadol's metabolism, which is mostly likely attributed to *CYP2D6* polymorphisms.

Clinical Adoption of Tramadol Pharmacogenetics

According to the guidelines set forth by the CPIC, opioid analgesics that do not undergo hepatic metabolism via the CYP2D6 pathway are recommended as alternatives to tramadol for patients with the PM and UM phenotypes, and tramadol use in patients with CYP2D6 IM phenotype should be monitored closely for response.[20] Hence, these guidelines support the clinical utility of *CYP2D6* genotyping in routine clinical practice as a tool to identify the subset of patients (i.e., CYP2D6 NMs) who are more likely to benefit from tramadol when used for pain management (Figure 2).

Implementation of Opioid Pharmacogenetics in Clinical Practice

Pain management is critical in clinical practice because uncontrolled pain can delay healing, decrease appetite, introduce and augment stress, disturb sleep, and may even lead to anxiety and depression. As such, effective pain treatment regimens are necessary to improve quality of life. As documented in studies described throughout this review, opioids, although widely used, do not produce optimal analgesia for all patients. Nevertheless, personalization of opioid selection and dosing is not widely practiced. This is likely a reflection of the relative paucity of data regarding clinical outcomes and opioid pharmacogenetics. Currently, CPIC guidelines are available for codeine and *CYP2D6*.[20] Tramadol is not an appropriate alternative to codeine in CYP2D6 UMs and PMs or IMs who have failed codeine

therapy due to tramadol's reliance on CYP2D6 for bioactivation. Opioids not metabolized by CYP2D6, such as morphine, hydromorphone, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, and other nonopioid analgesics should be considered instead. Due to the pharmacologic similarities of codeine and tramadol (both exert their analgesic properties from their CYP2D6 metabolites), and the consistency of the supporting evidence, the *CYP2D6*-guided therapeutic recommendations for codeine can be extrapolated to tramadol in practice.

With the exception of codeine and tramadol, the current body of literature does not strongly support clinical adoption of pharmacogenetics for other opioids. As such, clinicians should closely evaluate clinical pharmacogenetics panel test results, particularly those providing guidance for genetically guided pain management. As reviewed in this article, supportive evidence is lacking for majority of these drug-gene associations.

To the best of our knowledge, only a handful of institutions in the United States have actually adopted *CYP2D6* genotyping to guide codeine/tramadol usage. Such establishments include, but are not limited to, The Mount Sinai Hospital, St. Jude Children's Research Hospital, University of Florida, Sanford Health, Indiana University, and Moffitt Cancer Center. Challenges comprising limited pharmacogenetics knowledge base of practicing clinicians, complexity of *CYP2D6* genotyping, lack of reimbursement for genetic testing, lack of supportive institutional infrastructure, lack of randomized controlled trials demonstrating benefit of *CYP2D6*-guided prescribing, and availability of other analgesics that are not affected by pharmacogenetics have all contributed greatly to the slow adoption of personalized pain management.

Summary and Future Directions

The goal of pharmacogenetics as a clinical tool in opioid therapy is to optimize pain relief and prevent adverse effects. When pharmacogenetics is coupled with clinical factors such as age, weight, renal and hepatic function, concomitant medications, personalized pain management can be actualized. However, to date, the evidence is not compelling enough for widespread clinical adoption of opioid pharmacogenetics.

In the cases of codeine and tramadol, there are many case reports that have revealed consistent and persuasive evidence of the significant impact of *CYP2D6* polymorphisms on serious adverse effects including respiratory depression and death. This association caught the attention of the FDA in August 2012 when they issued a safety announcement to health care professionals. In February 2013, they

issued their strongest warning—a boxed warning—which made codeine contraindicated in post-adenoidectomy/tonsillectomy pain management of children.[56] Additionally, the codeine-*CYP2D6* example is the only opioid-gene instance with a CPIC guideline.

With the exception of codeine and tramadol, morphine-*OPRM1*, oxycodone-*CYP2D6*, and hydrocodone-*CYP2D6* may be the closest cases to clinical implementation, in descending order, due to their supporting evidence and recommendations from expert peer-reviewed CPIC guidelines. Hydrocodone is one of the least-studied opioids in pharmacogenetics, and further studies are warranted with this agent. On the other hand, methadone has been well studied, although with varying genetic targets and for nonpain indications. Fentanyl is in the same space as methadone, as more studies are needed to clearly elucidate the influence of genetics on its response. The "clinical adoption" sections throughout this article highlight the gaps in the literature for each of these examples and state what is needed to translate each opioid-gene pair into clinical practice. Moreover, studies that investigate the combined effects of multiple genes on opioid disposition, response, and adverse events are critically needed. These studies will provide heightened insight into these genetic associations and will enhance the use of pharmacogenetics as a therapy personalization tool in medicine.

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Table 1. Commonly Studied Variant Alleles of Pharmacokinetics and Pharmacodynamics Genes and Their Prevalence Across Different Populations[a]

Gene	Variants	Prevalence of Variants (%)			Functional Status
		Caucasians	African-Americans	Asians	
CYP3A4	*22: rs35599367 (intron 6 C>T)				Reduced function
CYP3A5	*3: rs776746 (6986 T>C)	92.1	31.6	74.2	Loss of function
	*6: rs10264272 (14690 C>T)	0	11.1	0	Loss of function
	*7: rs41303343 (27131 - 27132 insertion A)	0	12	0	Loss of function
CYP2B6	*4: rs2279343 (18053 A>G)	4	0	5 - 12	Enhanced function
	*5: rs3211371 (25505 C>T)	9 - 12	1 - 4	1 - 4	Reduced function
	*6: rs3745274 (15631 G>T), rs2279343 (18053 A>G)	14 - 27	33 - 50	20 - 21	Reduced function
	*18: rs28399499 (21011 T>C)	0	4 - 8	0	Reduced function
	*22: rs34223104 (-82 T>C)	2.4	0 - 2.5	0 - 2.5	Enhanced function
CYP2D6	*2: rs16947 (2850 C>T), rs1135840 (4180 G>C)	37	14	12.8 - 32	Normal function
	*3: rs35742686 (2549 deletion A)	1.3	1.3	0	Loss of function

	*4: rs1065858 (100 C>T), rs3892097 (1846 G>A), rs1135840 (4180 G>C)	18.5	6.2	0.4 - 6.5	Loss of function
	*5: gene deletion	2.6	6.14	2.5 - 5.6	Loss of function
	*6: rs5030655 (1707 deletion T)	1	0.2	0	Loss of function
	*10: rs1065852 (100 C>T), rs1135840 (4180 G>C)	3.1	4.1	19.7 - 42.3	Reduced function
	*17: rs28371706 (1023 C>T), rs16947 (2850 C>T), rs1135840 (4180 G>C)	0.3	18.2	0.4	Reduced function
	*41: rs16947 (2850 C>T), rs28371725 (2988 G>A), rs1135840 (4180 G>C)	8.5	9.4	2 - 10.5	Reduced function
ABCB1	rs2032582 (2677 G>T)	2	0	5	Reduced function
	rs1128503 (1236 C>T)	42	14	59	Reduced function
	rs2032582 (2677 T>A)	41	2	59	Reduced function
	rs1045642 (3435 C>T)	52	15	57	Reduced function
	rs9282564 (61 A>G)	8	0	2	Reduced function
UGT1A1	*6: rs4148323 (c. 211 G>A)	1	0	2	Normal function (wild-type)
	*28: rs35350960 (c. -53-52 $[TA]_6$ > $[TA]_7$)	31.6	39.1	14.8 - 41.4	Reduced function
	*36: rs8175347 (c. -53 - 52 $[TA]_6$ > $[TA]_5$)	0	6.6	0	Enhanced function
	*37: rs815347 (c. -53 - 52$[TA]_6$> $[TA]_8$)	0.1	3.6	0	Reduced function
UGT2B7	*2: rs7439366 (c. 802 C>T)	49	23	40	Reduced function
	rs7438135 (-840 A>G)	49	23	40	Reduced function
OPRM1	rs1799971 (A>G)	15 - 30	1 - 3	40 - 50	Impaired reception function
COMT	rs4680 (1947 G>A, Val158Met)	50	28	44	Reduced function
	rs4818 (C>G)	40	17	31	Reduced function

[a] The frequencies for this table were referenced from the 1000 Gneomes Database Ensembl which is available via: http://grch37.ensembl.org/Homo_sapiens/Info/Index

Other information can be found here: http://www.cypalleles.ki.se/

Table 2. Compilation of Relevant Studies on Opioids and Their Associated Genes of Interest

Opioids	Has Significant Genetic Influence on Drug Disposition		Has Significant Genetic Influence on Response (Efficacy)		Has Significant Genetic Influence on Adverse Drug Effects (Toxicity)		Readiness for Clinical Adoption
	Yes	No	Yes	No	Yes	No	
Codeine				*ABCB1*[16]			CPIC guidelines are currently available to guide CYP2D6-driven codeine therapy. In this guideline, codeine use is not recommended in CYP2D6 UMs and PMs due to potential risk of toxicity and lack of analgesic benefit, respectively. Also, CYP2D6 IMs who are prescribed codeine should be
				COMT[16]			
	CYP2D6[57]		*CYP2D6*[7, 13-15]	*CYP2D6*[16]	*CYP2D6*[4, 6, 13, 15, 17, 18]		
			OPRM1[16]				
			UGT2B7[16]		*UGT2B7*[4]		

							monitored for response and switched to a different analgesic in the absence of analgesic benefit.
Fentanyl			*ABCB1*[5]			*ABCB1*[5]	Not ready for clinical adoption due to lack of consistent data. Most associations are with *OPRM1* and *CYP3A5* polymorphisms.
				COMT[22]			
	CYP3A5[5]					*CYP3A5*[5]	
	OPMR1[25]		*OPRM1*[23-25]	*OPRM1*[22]			
Hydrocodone							Not ready for clinical adoption due to lack of compelling evidence to support its utility. However, it should be noted that hydrocodone is not an alternative to codeine in CYP2D6 PMs and UMs.
	CYP2D6[26]		*CYP2D6*[26]	*CYP2D6*[7]			
			OPRM1[27]				
Methadone	*ABCB1*[31]						Not ready for clinical adoption; further research is needed.
	CYP2B6[30-32]						
	CYP3A4[31]						
Morphine			*ABCB1*[58]		*ABCB1*[41, 45]		Moderately

			COMT[39, 43, 59]				actionable. The evidence supporting the influence of *OPRM1* polymorphisms on morphine therapy suggests that this opioid-gene pair may be considered for clinical adoption. .
			OPRM1[24, 37-40, 58-62]	*OPRM1*[41]			
		UGT1A1[33]					
	UGT2B7[36]	*UGT2B7*[33]					
Oxycodone				*ABCB1*[52]			Not ready for clinical adoption due to lack of consistently replicated evidence to support its utility. However, it should be noted that oxycodone is not an alternative to codeine in CYP2D6 PMs and UMs.
	CYP2D6[47-50, 63]		*CYP2D6*[7, 63, 64]	*CYP2D6*[48, 49]		*CYP2D6*[48]	
	CYP3A5[47, 50]		*CYP3A5*[47]				
			OPRM1[51]	*OPRM1*[47, 52]			
Tramadol	*CYP2D6*[53, 54, 65]		*CYP2D6*[7, 53]		*CYP2D6*[55, 65]		The CPIC guidelines for codeine comments on the relationship between CYP2D6 and tramadol and even postulates that tramadol is not a viable alternative to codeine in CYP2D6 UMs, PMs, and those IMs who have failed initial codeine therapy. As such, CYP2D6 genotyping can be used to guide tramadol therapy.
			OPRM1[66]				

CPIC = Clinical Pharmacogenetics Implementation Consortium; UM = ultrarapid metabolizer; PM = poor metabolizer; IM = intermediate metabolizer.

Figure 1. Metabolic pathways of opioid analgesics in the liver. CYP = cytochrome P450; UGT = uridine diphosphoglucuronysyltransferase.

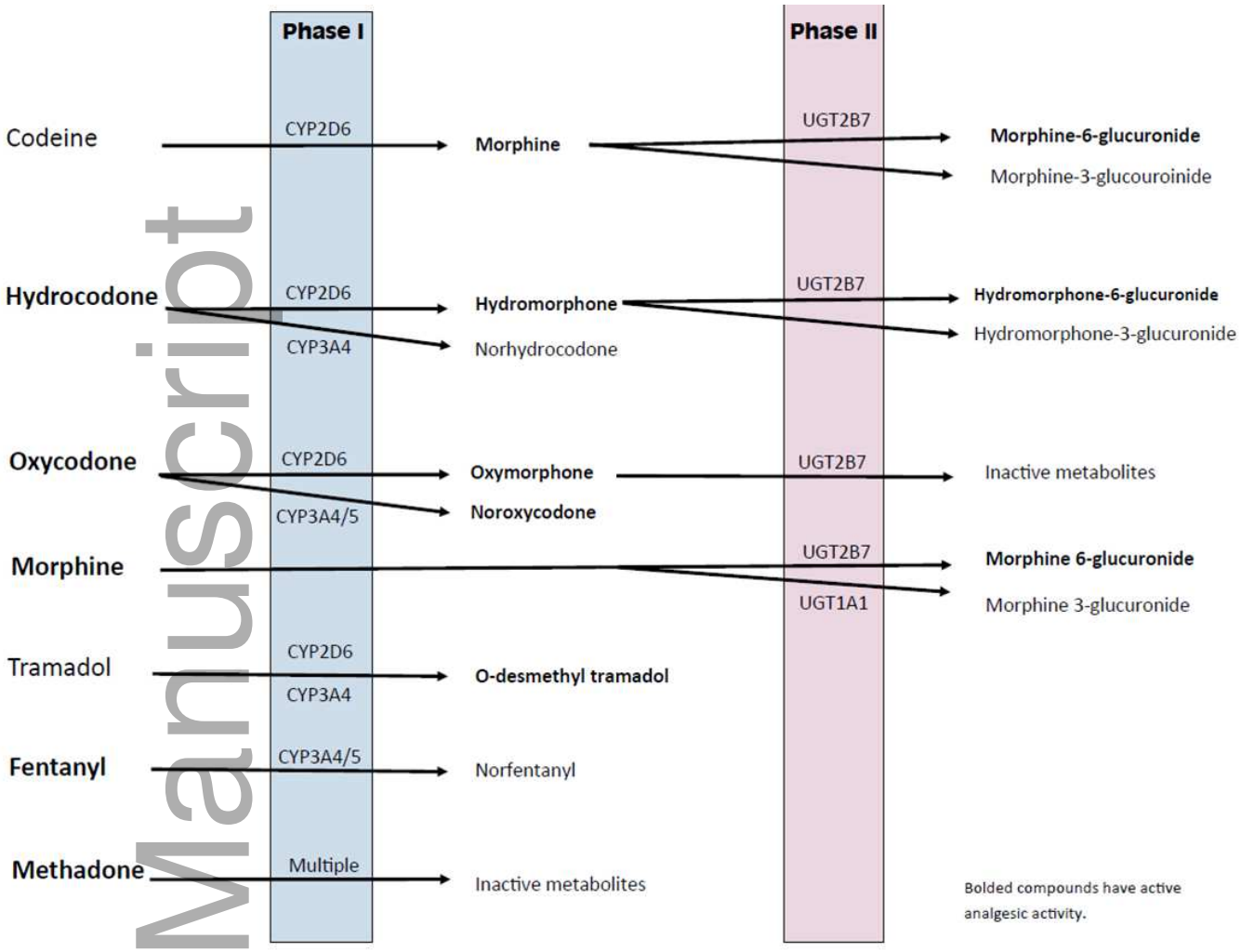


Figure 2. Degree of readiness of opioids for clinical adoption based on evidence for specific opioid-gene pairs. Actionable = Clinical Pharmacogenetics Implementation Consortium guidelines are currently available to guide therapy individualization; moderately actionable = sufficient evidence exists to suggest clinical adoption, yet there are no expert peer-reviewed guidelines; further research needed = current evidence is weak at best, and there is no comment from expert peer-reviewed guidelines.

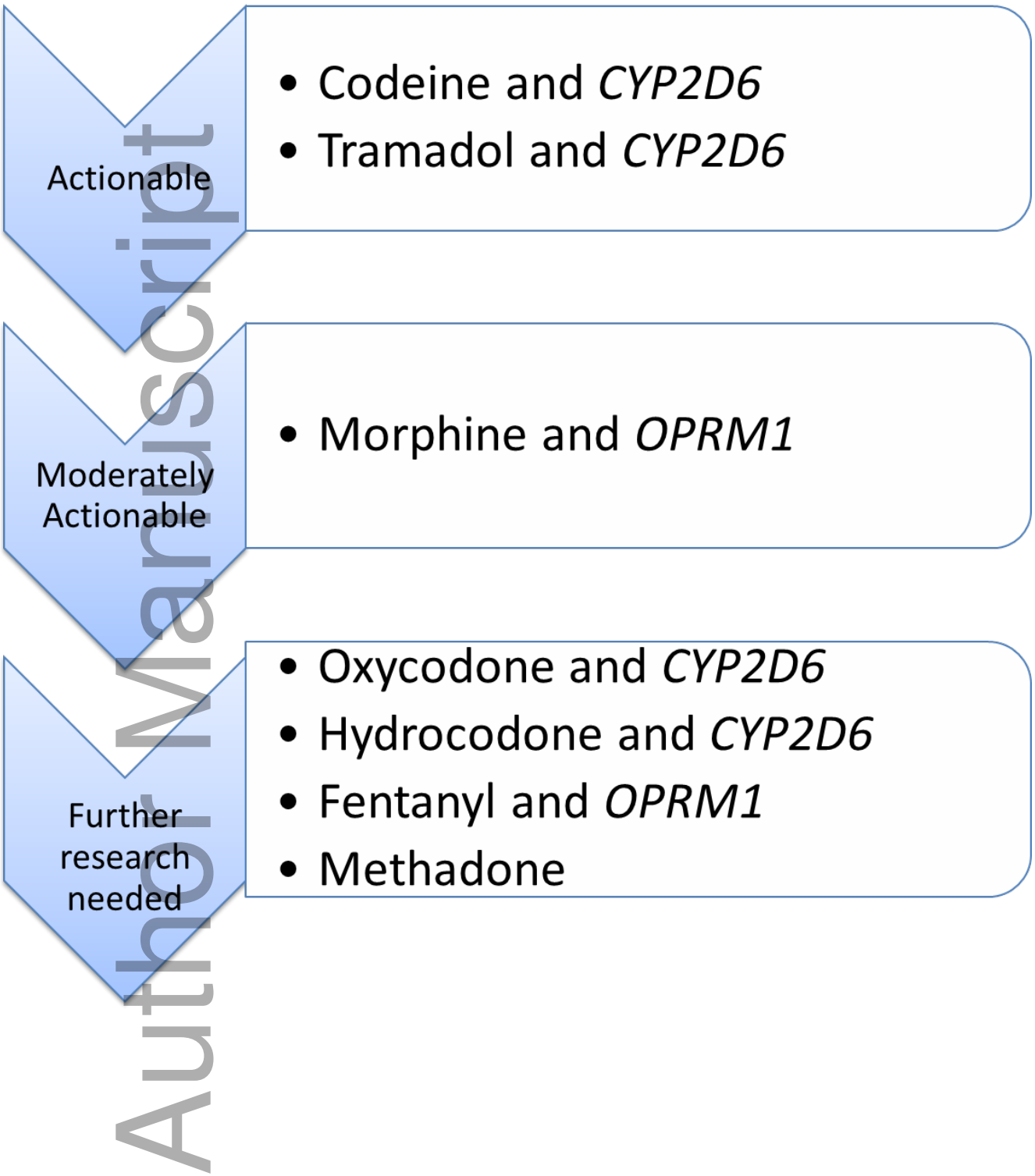


Figure 1: Metabolic pathways of opioid analgesics in the liver

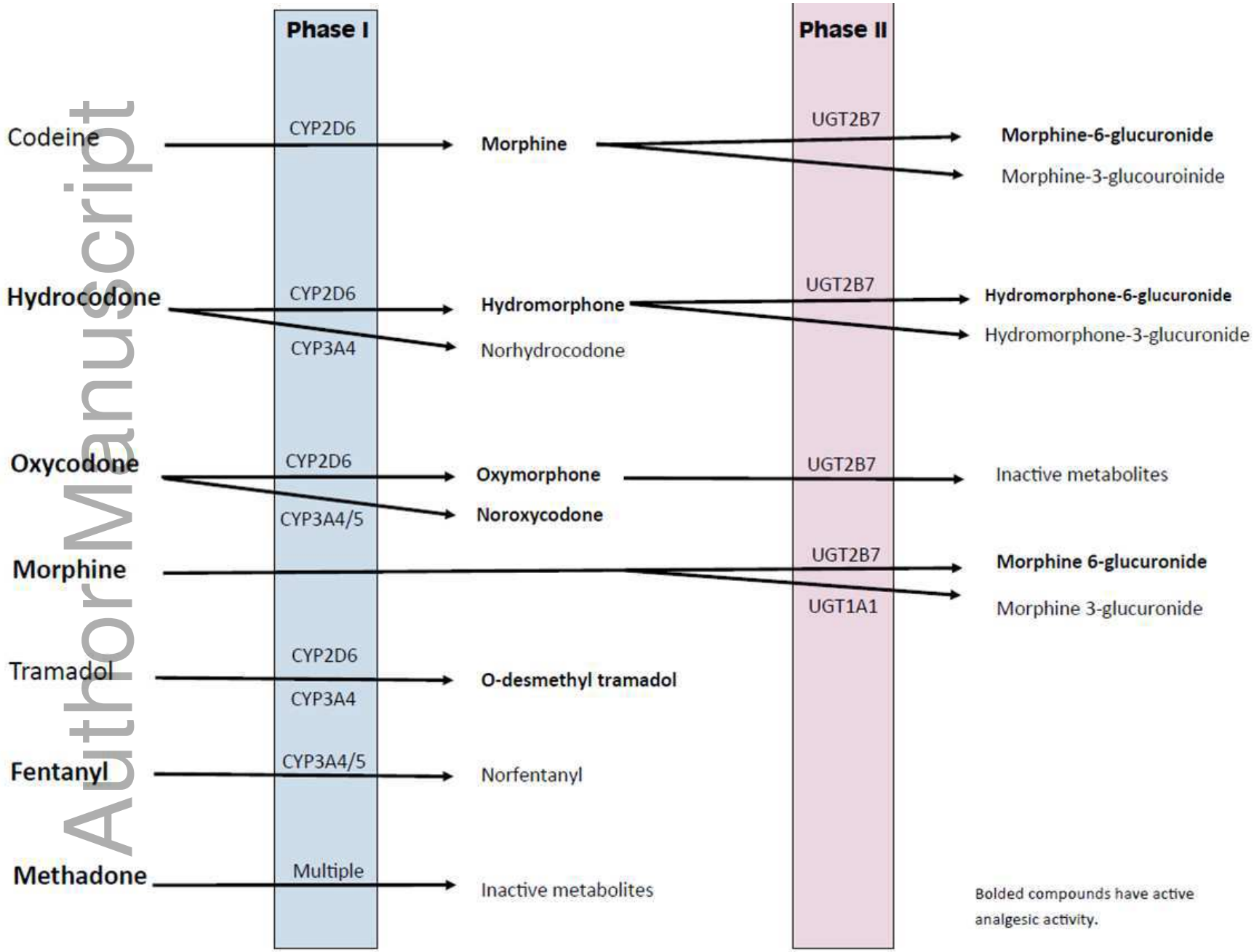
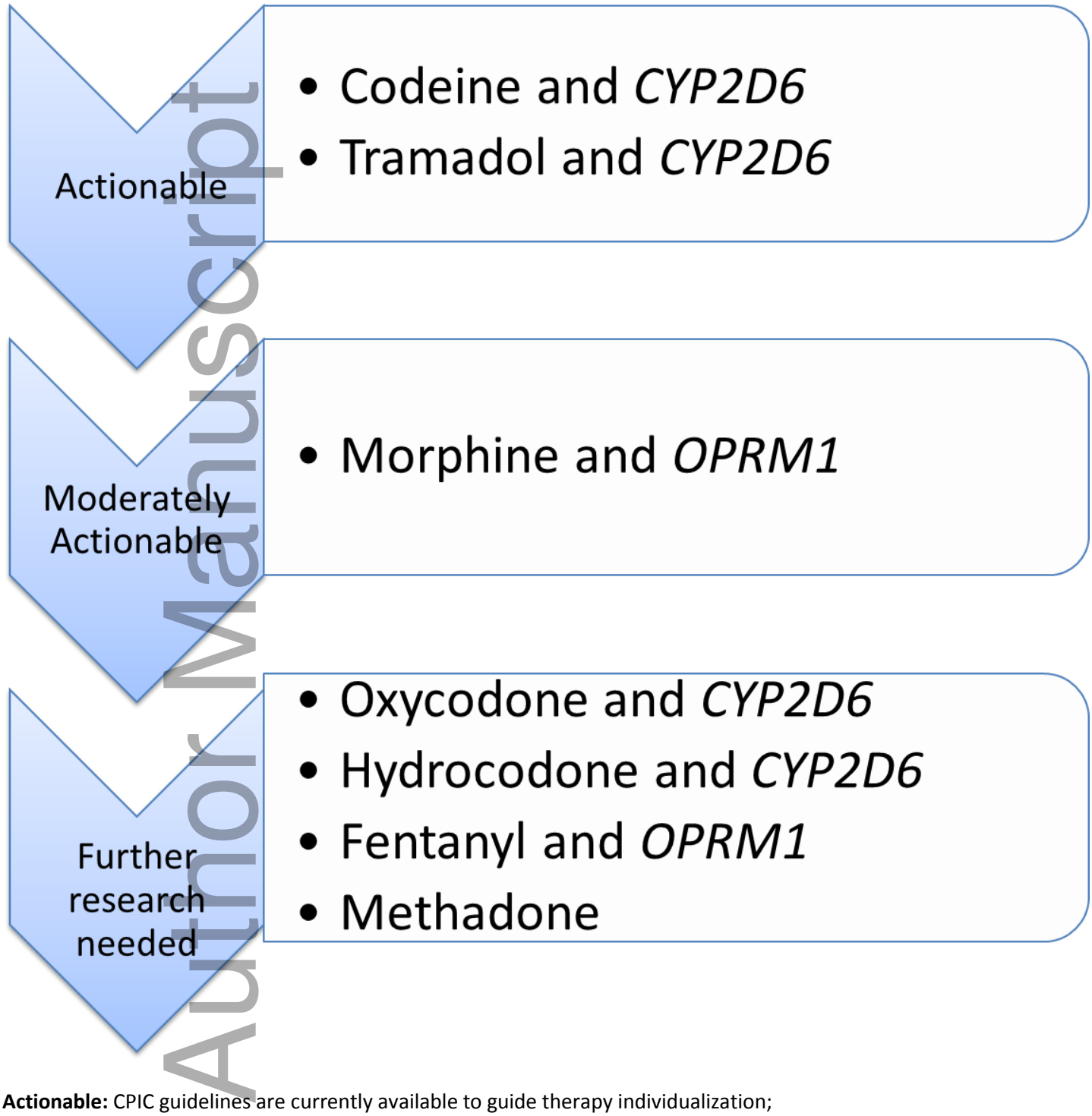


Figure 2: Readiness of Opioids for Clinical Adoption



Actionable: CPIC guidelines are currently available to guide therapy individualization;

Moderately Actionable: Sufficient evidence exists to suggest clinical adoption yet there are no expert peer-reviewed guidelines.

Further research needed: current evidence is weak at best and there is no comment from expert peer-reviewed guidelines.