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CYP2D6 phenotypes and opioid metabolism: the path to personalized analgesia

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Abstract

Introduction: Opioids play a fundamental role in chronic pain, especially considering when 1 of 5 Europeans adults, even more in older females, suffer from it. However, half of them do not reach an adequate pain relief. Could pharmacogenomics help to choose the most appropriate analgesic drug?
Areas covered: The objective of the present narrative review was to assess the influence of cytochrome *P450 2D6* (*CYP2D6*) phenotypes on pain relief, analgesic tolerability and potential opioid misuse. Until December 2021, a literature search was conducted through the *MEDLINE, PubMed* database, including papers from the last 10 years. *CYP2D6* plays a major role in metabolism that directly impacts on opioid (tramadol, codeine or oxycodone) concentration with differences between sexes, with a female trend towards poorer pain control. In fact, *CYP2D6* gene variants are the most actionable to be translated into clinical practice according to regulatory drug agencies and international guidelines.
Expert Opinion: *CYP2D6* genotype can influence opioids' pharmacokinetics, effectiveness, side effects, and average opioid dose. This knowledge needs to be incorporated in pain management. Environmental factors, psychological together with genetic factors, under a sex perspective, must be considered when you are selecting the most personalized pain therapy for your patients.

Keywords: chronic pain**,** personalized analgesia, *CYP2D6* phenotypes, opioid metabolism, pharmacogenetics, sex

Article highlights:

- Chronic pain is a silent epidemic situation that occurs in 1 of 5 European adults, and this is even more in older females.
- The goal of a personalized analgesia is to enhance functioning and reduce suffering, while minimizing the risk of analgesics adverse effects. This can depend on medical but also, psychological and genetic conditions.
- Close to 27% of the European population struggles with proper metabolism of *CYP2D6* drugs. Here, pharmacogenomics could play a role in opioid use to assess analgesic effectiveness, tolerability, and mean dose opioid prescription, even more so in females due to hormonal factors.
- Implementing *CYP2D6* to guide pain management, with a sex perspective, is feasible to develop a safer and more effective treatment for chronic pain in adults.

1. Introduction

Nowadays, moderate to severe chronic pain intensity occurs in 1 of 5 European adults. This situation affects seriously their psychological status and the quality of their family, social and working lives [1]. Pain is regarded as chronic when is experienced on most days of the week, for at least 3 months, and the first step is to treat the cause. However, while acute pain can usually be associated to a damage process, finding an identifiable process for chronic non-cancer pain (CNCP) is a challenge. This does not make the pain any less real to the patient that has an enormous interference with his/her daily life activities. Thus, without a clear cause, the most effective approach use to be a combination of medications, therapies and lifestyle changes [2]. However, the subjective characteristic of pain and the need to interpret it by the clinician has hampered its management.

For years, efforts have been made to improve CNCP diagnosis and treatment but, nowadays, only between 2-5% of the cases are currently treated by a pain management specialist [3]. Even less so in older women living in poverty, where the prevalence of chronic pain is higher than in men. Here, at least 1 in 4 females aged 50 years or over report having chronic pain. This finding could be explained by social variables, socioeconomic, marital status, or other health behaviours that should be used to avoid health disparities [4].

It has been a while since professionals recommend a gradual approach to pain management, starting with acetaminophen or nonsteroidal anti-inflammatory drug (NSAID). Here, when pain problem is not solved, it is recommended a weak opioid (e.g., codeine, dihydrocodeine, or tramadol) or ending up with a strong opioid (e.g., fentanyl, morphine, oxycodone) if needed [5,6]. Here, opioids should be chosen wisely only for specific types of pain, as they generate effect tolerability and risk of misuse linked to total dose and/or long-term use [7]. This phenomenon unleashed the current crisis of opioid use disorder (OUD) with a mean incidence of 5% for those prescribed opioids for CNCP [8]. In fact, the use of other concomitant analgesic drugs (e.g., antidepressants, gabapentin or pregabaline) for relieving pain has been promoted based on scientific evidence.

A holistic approach to pain is a need inside the universal healthcare system. Following public pain sensitization campaigns, individualized prescription of opioids began to be used for CNCP outside the context of the palliative medicine [9]. Since then, the levels of opioid use, expressed in defined daily dose (DDD) per million inhabitants per day, has raised (**Figure 1**) and in some cases exceed the recommendations based on clinical evidence [10].

The interface between the medical use of opioids to provide analgesia and the phenomena associated with drug toxicity or abuse continues to challenge the clinical community [11]. Despite the relevant clinical efforts and the translational advances in pain medicine, opioid long-term effectiveness in pain management has not been definitively proven and the appropriateness of the use of opioids remains uncertainty [12-14]. Compared with non-users, long-

term opioid therapy was associated also with bone fracture, cardiovascular problems, sexual dysfunction and a dose-dependent association with other complications [15]. Thus, clinicians and scientists highlight the need for better preventive methods to identify those patients who are potentially more benefited without leading to any adverse events as opioid misuse [16].

In the context of optimizing the risk/benefit balance of prescription opioids, DNA variants could allow practitioners to anticipate how a patient will respond. In fact, more than 300 approved drugs contain pharmacogenomic information in their labeling adding consistency and objectivity to personalize therapy according to patients' gene variants [17,18]. Some of the genes associated with pain management include those for the *opioid μ1 receptor* (OPRM1) and/or *catechol O-methyl transferase* (COMT) enzymes. Here, Ruano and Kost suggested patients with dysfunctional CYP2D6 and OPRM1 should be best managed with non-opioids (high-risk, 14%), o required a close dose monitoring (medium-risk, 48%). The rest (low risk 38%) should be availed to opioid therapy [19]. What´s more, there is moderate evidence linking the *OPRM1* variants and analgesic efficacy or adverse events (AEs). In contrast, there is low evidence of (*COMT*) as a significant regulator of pain sensitivity due to ethnic differences [20-22]. One of the most actionable markers is the *CYP2D6* (a member of the hepatic cytochrome P450 superfamily 2D6) enzyme gene, whose polymorphisms influences the analgesic response to prodrug opioids (codeine, tramadol and oxycodone) [5,6,23,24].

1.1. *CYP2D6* gene and correlation with the metabolizer phenotype

It is well known that polymorphism of the *CYP2D6* gene significantly affects pharmacokinetics of about 50% of the drugs in clinical use, which are CYP2D6 substrates. The consequences of the polymorphism at ordinary drug doses can be either adverse drug reactions or no drug response. Thus, predictive CYP2D6 genotyping could be beneficial for treatment of about 30-40% of CYP2D6 drug substrates, that is, for about 7-10% of all drugs clinically used [25].

The *CYP2D6* gene is located on Chr22q13.1 and, to date, more than 100 major polymorphic alleles of *CYP2D6* are known. The presence of the highly similar closely located pseudogenes carrying detrimental mutations have through, for example, unequal crossover reactions led to the formation of many of the variant CYP2D6 alleles, which most commonly encode defective gene products (see human CYP allele nomenclature committee: http://www.imm.ki.se/cypalleles/cyp2d6.htm).

As has been proposed for the last decades and has recently been standardized, *CYP2D6* genotypic information can be translated into a qualitative measure of phenotype . Here, the different allelic variants of the *CYP2D6* gene, primarily the *CYP2D6*2, CYP2D6*4, CYP2D6*5, CYP2D6*10, CYP2D6*17* and *CYP2D6*41* can be classified according to whether they cause abolished, decreased, normal, increased or qualitatively altered the activity of

the CYP2D6 enzyme. Based on the presence of these variants, a CYP2D6 activity score, which correlates with the enzyme function, can be calculated and therefore patients phenotypically classified as ultra-rapid (UM), extensive (EM), intermediate (IM) and poor (PM) metabolizers [26,27]. Here, extreme metabolizers (UM and PM) use to be more likely to experience the adverse events (AEs). Briefly, the UM phenotype is recognized as a cause of therapeutic inefficacy of antidepressant and several cases of life-threatening toxicity with tramadol and codeine. On the other hand, an increased risk of toxicity has been reported in PMs with several psychotropic drugs (as amitriptyline, haloperidol) together with a reduced analgesic effects [28]. In fact, respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being UMs of codeine. Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were UMs of codeine [29]. What´s more, most of these psychotropic drugs have been highly prescribed in females than males as they are twice more likely to be diagnosed of depression or similar mental illnesses [30]. Potential drug (or even food)-drug interactions could be present and contribute to a worst opioid tolerability [31-33]. Furthermore, tramadol prescription guidelines have been released for pediatric population, considering the CYP2D6 functioning [34]. In the same line, international guidelines refers that approximately 8% of the European population are PM of codeine to morphine, with resulting diminished analgesic efficacy. Also genetic polymorphisms, with impact in O-demethylation (via CYP2D6) can lead to alterations in response to tramadol in a similar way to codeine. Thus, The World Health Organization guideline explains that both codeine and tramadol may be less analgesic in PM [35].

An understanding of the metabolic action of CYP2D6 in relation to opioids could provide the basis to illustrate its potential in determining opioid dosage and guiding clinical practice in opioid treatment. That between 77% and 92% of individuals express at least one functional metabolically active allele of CYP2D6, demonstrates high levels of CYP2D6-dependent genome interindividual variability. This is further demonstrated by inter-ethic variability data showing only 50% of CYP2D6 alleles in individuals of Asian ethnicity are metabolically active. Due to adaptive selection, alleles carrying multiple active CYP2D6 genes can be found higher in North East Africa. The subsequent migrations of subjects from North East Africa to the Mediterranean area resulted in the high frequency of increased enzyme function in Southern Europe [36]. In fact, consistent findings focus on pharmacokinetics highlight the significance of CYP2D6 phenotypic variability against the concentration of active tramadol opioid metabolites and methadone, in the blood plasma [37,38]. In **Figure 2** is represented the process of analgesic oral absorption and first pass liver effect [39].

This narrative review tries to summarize clinical knowledge about how *CYP2D6* genotype could impact on pain pharmacological treatment in terms of efficacy or tolerability. The aim pursued will be to incorporate the phenotype profile into patients' Electronic Health records (EHRs) to guide prescriptions of opioid and coadjutant analgesic drug improving their analgesic effects. This

narrative review aims to increase the personalized use of pharmacogenetic evidence, in a real world that needs to incorporate the sexual perspective for pain management. In this way, omics and sex-guided clinical management strategies could be used to improve therapies related to opioid use but also other most used co-adjuvants drugs in pain management.

2. Literature search

A narrative review of the English-language linked literature was conducted. Authors (JM and PB) performed selection, summary and quality assessment of the manuscripts from July to December 2021. They independently monitored each other's processes for accuracy and quality through the MEDLINE, PubMed database. The research queries covered 4 domains using the following terms and Boolean operators: (1) CYP2D6; (2) opioid pharmacological treatment; (3) chronic pain; and (4) analgesic coadjuvant therapy. PubMed filters were used to reduce the scope to those manuscripts published during the last ten years. The following query provides an example of the search strategy performed in the last step [Search: (opioids) AND (chronic pain) AND (CYP2D6); Filters: in the last 10 years]. From the performed queries, the authors obtained 51 and 28 manuscripts each, which met the eligibility requirements. Any original research and/or review article was considered for review. Data extracted included aim, target population, principal findings, and limitations. Here, both authors' results overlapped in 27 manuscripts, where 3 were no longer candidates as they were not written in English. Finally, after further reviews and consensus was reached, 24 articles were full-text reviewed, selected and included.

In addition, the rest of the references included in this paper come from checking the reference lists of the selected articles, which were also reviewed to find additional papers that might not have been retrieved through our original search strategy and irrespective of the year of publication. Evidence linking CYP2D6 phenotype with opioid response is showed at **Tables 1-2** and described thought out this work.

3. Opioid metabolism

The rationale behind the present manuscript is that opioid prescription in Europe is increasing in numbers, and many of the AEs of opioids, as well as their effects, may be related to their liver metabolites. For an insight of the metabolism of opioids, please see **Figure 3.**

Metabolism refers to the process of biotransformation and rupture of opioids so that our body can link to them and finally excrete them. In fact, opioids are typically lipophilic, that enables them to reach their receptors, and they evolve into hydrophilic forms so that we can eliminate then in the urine. Mainly in the liver, opioids are metabolized by enzymes implicated in phase 1 (oxidation or hydrolysis of the drug by CYP enzymes) or phase 2 metabolism that conjugates the drug to hydrophilic substances, such as glucuronic acid,

sulfate, glycine, or glutathione, by the enzyme uridine diphosphate glucuronosyltransferase (UGT) [72].

Moreover, with over a 27% of the European population unable to properly metabolize codeine and related analogs, pharmacogenomics could play an immediate role in the management of opioid therapy if applied. Here, the basal status of metabolism could be influenced by genetic makeup, age, environmental factors, disease stage, ongoing medications and sex interaction. All these factors could alter drug metabolism turning into an opioid or its metabolites excreted from the body too early, not binding to their receptors, or prompting toxic events due to a long stay. In fact, there are some active drugs that don't need to pass through the liver to be active, but there are others whose active metabolites after liver pass and activation may be more powerful than the primary drug [22]. It is also important to mention that, even expressions of brain or renal CYPs and UGTs are minor than in liver, this enzymes are mediating also metabolism of dopamine and serotonin, so some diseases such as epilepsy, Alzheimer's or Parkinson's disease are often associated with the alterations of CYPs and UGTs in brain, which may be involved in processes of these diseases via disturbing metabolism of endogenous substances or resisting drugs [73].

3.1. Phase 1 opioid metabolism

Close to 90% of the most clinically used medications metabolism is accounted by seven cytochrome P450 isozymes (3A4, 3A5, 1A2, 2C9, 2C19, 2D6, and 2E1) [74]. Between them, CYP2D6 variations lead to a different clinical response to most analgesic drugs used (e.g. codeine, tramadol and oxycodone) [37]. Moreover, it is implicated in the metabolism of other analgesics adjuvants (e.g. antidepressants, benzodiazepines and anticonvulsants). As well, several drugs that can be substrates, inducers, or inhibitors of the CYP2D6 enzyme and thus, could compete for the enzyme modifying analgesic effects [22]. Here, persons with an CYP2D6 UM phenotype may present higher systemic levels of the active metabolites upon treatment and would need less dose presenting a higher risk of experiencing AEs [75]. In fact, with this phenotype there are life-threatening cases of toxicity described using tramadol and codeine, relating this metabolic profile with difficult endogenous pain modulation and mu-opioid-related toxicity [76]. On the other hand, those with a CYP2D6 PM phenotype may have drug lower levels, so reduced efficacy, and effectiveness of several psychotropics that need to be activated by this metabolic pathway (desipramine, venlafaxine, amitriptyline, haloperidol). If normal or IM phenotype is found, women tend to experience higher rates of AEs compared to men [77]. A brief resume of selected inducers, inhibitors and substrates of CYP2D6 as analgesics, antidepressants/anxiolytics, co-adjuvants drugs frequently used in pain patients can be seen at **Supplemental Table 1.**

Thus, CYP2D6 phenotype could conditioned plasma concentration, toxicity of drug substrates during pharmacotherapy or some cases of drug resistance, with some sex-differences that could be related to neuroanatomical,

hormonal, neuroimmunological, psychological, or cultural aspects and comorbidities that nowadays are not assessed in clinical studies [78]. Regardless the amount of studies that have studied the implication of CYP2D6 polymorphisms on pain sensitivity, pharmacokinetics and pharmacodynamics [76,79], scarce studies consider the role of inhibition or induction effects on CYP2D6 of patients' simultaneous medications, and that must be considered before prescribing [80].

3.2. Phase 2 opioid metabolism

In this part, is important the glucuronidation produced by the enzyme UGT. It improves the hydrophilic character allowing the final excretion of the molecule and ending the process as for oxazepam, lorazepam or some anti-epileptics with mood-stabilizing properties [81]. At least 24 different UGT human genes have been identified and are classified in two families (UGT1 and UGT2) based on sequence homology. The UGT1A subfamily (genes located on chromosome 2) glucuronidates bilirubin, thyroid hormones, and some medications as tricyclic antidepressants and some antipsychotics. The UGT2B subfamily (genes located on chromosome 6) glucuronidates sexual steroids and bile acids. The crucial UGT enzyme involved in the metabolism of opioids is UGT2B7 for morphine, hydromorphone [82] and fentanyl, however, its 2 variants known yet present contradictory and scarce data about their role in opioids metabolism and pain release [22] that uses also CYP3A4 for its metabolism. Research suggests that UGT2B7 functions can be modified by the presence of other drugs that are either substrates or inhibitors of this enzyme [83].

To sum up, the phase I cytochrome P450 (CYP) isoenzymes play a role in opioid metabolism, literature influencing oxidation or hydrolysis processes, and have received substantial attention in the pharmacogenetic. However, the success of the first phase steps is directly related with the ability of the UGT enzyme to transform the drug and allow its excretion. Researchers are beginning to examine the role of the phase II UGT enzymes, even more, for their implications in psychiatry.

4. CYP2D6 impact on specific opioids effectiveness and toxicity

4.1. Tramadol and codeine

Weak opioids are used when a simple analgesic or an NSAID drug is not successful as painkiller. Both are strongly influenced by CYP2D6 phenotypes. This could explain reports of overdosing or under dosing after standard doses in clinical practice. In fact, they would require at least as much monitoring as morphine, despite regulation differences [84,85]. What´s more, the regulatory agencies label includes a warning that breastfeeding is not recommended in mothers with CYP2D6 because their children may be particularly susceptible to codeine-induced central nervous system depression [29,86].

Tramadol, a synthetic weak opioid used both in patients with nociceptive and neuropathic pain. It is metabolized to highly active O-desmethylate by

CYP2D6 and to lowly active N-desmethylate by CYP2B6 and CYP3A4. The correlation of CYP genotype with higher tramadol concentrations is remarkable since its influence on its elimination is also relevant. Here, (+)-O-desmethyltramadol is principally responsible for opioid receptor-mediated analgesia, whereas (+)- and (-)-tramadol contribute to analgesia by inhibiting reuptake of the neurotransmitter serotonin and noradrenaline. It's most common AE include nausea, vomiting, drowsiness, lightheadedness, dizziness, sedation, shortness of breath, constipation, and itching. Serious AEs are usually related to respiratory and cardiac arrest together with rare secondary hemodynamic consequences [87]. Probably in these cases the CYP2D6 genotype could be more relevant through alteration of the tramadol metabolic pathway as can be seen at **Table 1**. Here, several severe cases related with tramadol near-fatal cardiotoxicity [54] and respiratory depression [55] in UMs have been reported. Due to the variable response according to the metabolic phenotype, CYP2D6-guided opioid prescribing on pain control were assessed and the benefits evidenced [40]. What´s more, patients treated with tramadol in emergency departments have a higher risk of opioid use at the one-year follow-up than those treated with other non-opioids analgesics [88]. Another key point is that some simultaneous prescriptions such as terbinafine can alter tramadol effect and increase its side effects [89]. Interestedly, data from the national prescription databases comprising the entire population of Denmark, Norway and Sweden showed that tramadol was generally used more frequently by women receiving higher mean doses than men [90]. This should be taken into account when drug abuse cases are evidenced.

Codeine is an opioid analgesic indicated for the relief of mild to moderate pain and has a 200-fold lower affinity for μ-opioid receptors than morphine thanks to their active metabolites: morphine and morphine-6-glucuronide [91]. Codeine O-demethylation into morphine by CYP2D6 represents a minor pathway in normal metabolizers, accounting for 5-10% of codeine clearance in such individuals but appears to be essential for its opioid activity [92,93]. The percent of codeine converted to morphine can have about a 50% higher in CYP2D6-UMs [94]. As displayed in **Table 1**, there are a couple of papers that have described a PM phenotype major need of codeine dose [42,43], or showed a lower bioavailable levels [47]. Finally, special attention needs to be given to those individuals who have a UM metabolism, as they can experience AEs within regular range doses of opioids prescription [42,58-60]. However, in both analgesics some other papers did not evidence any pharmacology impact related to CYP2D6 phenotypes.

Briefly, codeine and tramadol are opioid analgesics metabolized in the liver to active compounds via CYP2D6 approved for pain management. There is a strong and consistent recommendations proposed in international guidelines to avoid the use of codeine or tramadol in UMs due to potential serious toxicity (as oversedation, respiratory depression, and death) and in PMs because of possibility of diminished analgesia [37]. In 2015, the European drug regulatory agency updated their warnings regarding codeine and tramadol use in the pediatric population, making their use contraindicated in patients under the age of 12 years [95].

4.2. Oxycodone

In Europe, the opioid medical use is enhanced, but at a much slower rate with less fatal incidents, than the past two decades medical usage of oxycodone, which increased up to 14-fold in the U.S. and Canada [96]. Although some results indicate an increase of abuse in women, there is as yet no reliable evidence [97].

Oxycodone is a potent semi-synthetic mu-opioid agonist, available orally and frequently used for treatment of acute pain and as long-acting formulation commonly used for treatment of chronic cancer pain [98]. It is metabolized by CYP3A4-N-demethylation to noroxycodone and by CYP2D6-O-demethylation to oxymorphone, a substantially more potent metabolite. In fact, concurrent use of a CYP2D6 inhibitor, but not a CYP3A4/5 inhibitor, altered oxycodone and oxymorphone urine levels [99]. Even though oxymorphone is barely detectable after oxycodone administration and thus its clinical relevance is arguable, several studies have pointed to the role played by the CYP2D6 phenotype. Here, CYP2D6 UM individuals showed an increase of analgesic effects [100] but also experienced more severe AEs reactions compared to EM [101] with a consistent association with a higher oxymophone/oxycodone ratios [64]. As a CYP3A4 and CYP2D6 substrate, in cases where both inhibitors of these enzymes are used simultaneously with oxycodone, dangerous overdosing may occur.

Among other opioids, the hydrocodone, a semi-synthetic opioid, is presented in both extended- and immediate-release formulations and can exhibit 6-fold more analgesic potency than codeine [102]. Although hydrocodone itself has a weak capacity for μ-receptor binding, it is partly metabolized by CYP2D6-O-demethylation to hydromorphone after oral administration, which has much stronger μ-receptor binding affinity [103]. Hydrocodone also undergoes N-demethylation via CYP3A4 to norhydrocodone and other pathways include 6-keto-reduction to dihydrocodeine [103]. Related to hydromorphone, although the CYP2D6 enzyme responsible for metabolism to active hydromorphone, and it would be expected that CYP2D6-PMs suffer a decreased hydromorphone production leading to less analgesia, phenotype has not been demonstrated to affect treatment outcome; however, pharmacologic effects may in some cases be complicated by drug-drug interactions [80].

Most recently commercialized tapentadol is an oral opioid agonist and a norepinephrine reuptake inhibitor, being the first compound to present this mechanism of action in a single molecule and developed to improve analgesic efficiency and therapeutic safety. Tapentadol is approximately two to three times more potent than tramadol while their toxicity profiles are similar [104]. The extended-release formulation seems to guarantee analgesic efficacy similar to oxycodone but with less gastrointestinal AEs [105]. Tapentadol is primarily metabolized in the liver via phase II conjugation, UGT2B7 glucuronidation predominantly, and phase I oxidative reactions via CYP2D6 to hydroxytapentadol (2%) [82]. Furthermore, its metabolites have no pharmacological activity or interact with simultaneous medications [106].

Some pharmacogenetic studies have shown the importance of CYP2D6-mediated conversion of oxycodone to oxymorphone for analgesic efficacy [107]. There is some evidence linking CYP2D6 genotype to variability in opioids metabolized by this cytocrome in oxycodone [62] that should be expanded prior to an clinical recommendation.

5. CYP2D6 impact on adjuvant analgesics

Adjuvant analgesics are drugs with a primary indication other than pain that have analgesic properties. Although not primarily identified as an analgesic in nature, they have been found in clinical practice to have either an independent analgesic effect or additive analgesic properties when used with opioids [108], a visual aid to understand the metabolism of oral adjuvant therapy is illustrated in **Figures 2 and 3.** Despite their therapeutic interest, it should be noted that many patients on long-term opioid treatment, use adjuvant analgesics with potential safety-related drug-drug interactions or interactions that would alter the effectiveness of the opioid [109]. A complete list including selected inducers, inhibitors and substrates drugs of CYP2D6 is provided in **Supplemental Table** 1 [110].

5.1. Antidepressants

Generally, antidepressants metabolized via CYP450 system can significantly inhibit the activity and therefore influence the effect of opioids, leading to convert a genetically normal CYP2D6 metabolizer into a phenotypically PM [111]. Selective serotonin reuptake inhibitors and selective serotonin and norepinephrine reuptake inhibitors CYP2D6 metabolism has been extensively studied [112]. In this group is important to consider that fluoxetine [113] and paroxetine [114] are a CYP2D6 inhibitors that may increase the levels of opioids so it has been suggested that patients taking strong CYP2D6 inhibitors should be treated similarly to CYP2D6 PM [40]. In the same way, potential drug-drug interactions with opioids have been notified [115]. In the case of tricyclic antidepressants, this phenotype has been correlated with greater plasma concentrations and lower dose requirements [116]. Also, a significant correlation was observed between CYP2D6 genotype and the production of the active metabolite of venlafaxine (O-desmethylvenlafaxine), expecting the safety and/or tolerability of venlafaxine may be influenced in patients with extreme CYP2D6 activity [117].

Here, as mentioned above, sex-differentiated findings have been evidenced regarding symptomatology of depression, behavioural indices, endophenotypes, and antidepressant response that make women more likely to be prescribed with this pharmacological group being more being more AEs susceptible.

5.2. Benzodiazepines (BDZs)

Related to BDZs, they can be used especially when pain is accompanied by a strong anxious component or in situations where sleeping disorders are

present. BDZs are metabolized via CYP enzymes mostly by CYP3A-oxidation to active metabolites subsequent conjugation. No implication of CYP2D6 has been evidenced in this group of compounds. However, extensive expansion in warnings about the hazards of drug-drug interactions in co-treatment with opioids have been exposed and can lead to fatal outcomes [118]. In fact, BZDs can alter the pharmacokinetics of opioids [119]. Since some have been defined as CYP3A4 inhibitors [120], that affects other metabolic enzymes and results point that co-administration of BZDs with opioids can potentially increase opioid exposure [121]. This medications as a co-existing treatment need to be closely monitored by providers as the can lead to negative health outcomes, and physicians should increase their awareness to avoid misuse of these medications [122]. What´s more, the economic recession caused by coronavirus disease 2019 (COVID-19) pandemic showed a resurgence of OUDs. A positive trend towards non-prescribed fentanyl was detected in patients consuming other drugs such as 48% for benzodiazepines, or 39% for opiates [123]. In fact, the association between anxiety sensitivity and nonmedical BZDs misuse can be moderated by gender being females more vulnerable in the context or a polysubstance use [124]. This happen in a clinical context were women are more likely than men to be diagnosed with anxiety disorders [125].

5.3. Anticonvulsants

The prescription of anticonvulsants, as gabepentine or pregabaline, for neuropathic pain management has increased in recent years [126]. Both drugs share a similar mechanism of action, inhibiting calcium influx and subsequent release of excitatory neurotransmitters and neither drug is metabolized by nor inhibits hepatic enzymes and no pharmacological effects associated with CYP2D6 variants are expected [127]. But, carbamazepine, phenytoin, phenobarbital and primidone are CYP and UGT inductors, so a drastically reduction of opioid levels is expected [128].

It is important to be aware that certain mainly antidepressants (mainly tricyclic and serotonin selective reuptake inhibitors) act as inhibitors of CYP2D6 enzyme. If taking opioids and antidepressants simultaneously, patients need to be considered as PM regardless their current genotype. Otherwise, nor benzodiazepines or anticonvulsants are metabolized by CYP2D6. However, when co-prescribed with opioids, they may increase or reduce the opioid levels, respectively. More attention should be paid to these drug combinations as some side effects could be avoided.

6. CYP2D6 phenotypes in the actual opioid crisis scenario

The aberrant prescription of opioids caused an opioid epidemic in North America starting from mid-1990s with a gazillions of deaths by overdose [129]. This health treat moved to Europe involving mainly northern and eastern countries and finally also the Mediterranean area (see **Figure 1**) [130].

6.1. CYP2D6 and opioid abuse in the Coronavirus disease 2019 (COVID-19) era

The public health emergency due to the COVID-19 pandemic caused social isolation, and a trend that favors new buprenorphine inductees and a leveraging technology to improve pain care [131]. Here, some pharmacogenetic markers could help to achieve a safer personalized analgesia. Current evidence suggests this variability can be attributed to genetic factors and could be used in the context of predicting opioid harmful effects or addictive potential [132]. Differentiating patients who are susceptible to present an AE from those who are not, has been absent in standard practice mainly ruled by statistics-based medication prescribing [133]. Creating evidence-based prescribing guidelines and long-term opioids use AEs, encouraging safe opioid disposal is critical to ensure a safety use and to understand individuals' vulnerabilities [67,134]. Here, the absolute event rate for any AE with opioids in trials using a placebo as comparison was 78%, with an absolute event rate of 7.5% for any serious AE. However, scarce data are nowadays available related to opioid abuse or dependence even less considering genetic markers [135].

6.2. CYP2D6 and opioid abuse with sex differences

Still, the remarkable female predominance in pain prevalence merits further attention. Nearly two thirds of pain patients are adult women [136] where literature data strongly suggest that men and women could differ in their analgesic drug responses [137]. The complex interdependence between biological sex (hormones, chromosomes, genes) and gender (social needs that stem from family stimuli, education, and society) could determine the functional capacity of the individual, influencing their behavior and health states [138]. These effects could be amplified in severe AEs as OUD, where psychological factors (stress, depression, anxiety, responses to pain related to avoidance, coping) can have a greater impact on disability and quality of life, than on pain, per se [139]. It is not currently known how sex and even less, with a gender interaction can potentially associate differences in tolerability or OUD vulnerability along clinical-care processes. This gap of knowledge could be inducing a different functional prognosis, in terms of quality of life, between males and females promoting health disparities [140]. What's more, without being able to confirm that there are sex-differences in terms of opioid response, there are a wide range of genetic and hormonal factors that may influence analgesic outcomes. CYP gene expression and enzymatic activity can be potentially modified by sex due to estradiol homeostasis [141].

The current opioid epidemic crisis in the US that may pose a threat to other regions worldwide, have entered into a new phase with the addition of the COVID-19 global pandemic, requiring new approaches and therapeutic strategies, including pharmacogenetic markers that could anticipate the risk of opioid misuse. Also, we have an opportunity to change the guidance of general pain prescriptions moving towards a system that puts the person at the center, taking into account potential sex-differences. Then, incorporating a sex plus gender perspective will improve how real world clinical practice is performed.

7. CYP2D6 phenotypes implementation in clinical practice

Help providers with clinical decision support tools integrated in EHRs can shape patients care [142-146]. In fact, multiple evidence supports the use of PharmaGKB or CPIC guidelines [147]. According to EHRs' features and site preferences the above-mentioned website approach may differ across organizations. What is essential is to consider clinical workflow to locate pharmacogenetic results, and clinical interpretation indexed in the EHR in an appropriate space inside patient portal. To help using patients' phenotype during clinical practice, the lab genotype results need to be provided with a clinical interpretation [147,148]. Considering time constrictions during clinical visits, information should be displayed as a problem list entry or in a patient summary section, so they can be available to all providers to facilitate using them when prescribing [147-149]. To facilitate this process, guidelines should providing gene-specific information with widely used nomenclature systems [146,147]. Given CYP2D6 can suffer from copy number variation, copy number should be disclaimed, if tested. In Europe, a recent guideline with a selection of variants that are recommended to be tested has been released [150], containing two subsets that may aid clinicians when designing an assay.

Apart from that, other factors cause possible uncertainty in CYP2D6 genotyping test results and phenotype identifications as follows: 1) Consider in the test results the pharmacological treatment, especially if taking CYP2D6 inhibitors when reporting the phenotype; 2) Rare or unknown variants may not account when estimating the phenotype CYP2D6; 3) Some alleles are susceptible of having suballeles, with other variants which may be also playing a role; 4) Genes implicated in duplication and other major rearrangements [151] are not specifically tested for, the phenotype prediction, so results can be inaccurate and CYP2D6 activity over/under-estimated; 5) Some Single Nucleotide Polymorphisms (SNPs) exist on multiple alleles [151]; 6) Regarding ancestry, allele frequencies may vary considerably among individuals, for example, among Asian descendants CYP2D6*10 is common in Asian populations, and CYP2D6*17 when a Sub-Saharan African ancestry; 7) Some genes are susceptible to be carried in arrangements in some alleles; and 8) Finally, when considering the phenotyping approaches, not only genetic, but also environmental factors when describing individual metabolic profiles in clinical settings [152].

In this context, there are other limitations such as the time that the patient has to spent in the Hospital to perform all procedures, the extra cost that this adds to the system, all the messages and info buttons that need to be added to the HER to add the generated knowledge (e.g., drug (opioids)-drug(antidepressants) interactions). Finally, all the information generated in a specialized Pain Unit would be difficult to transfer towards other services such as primary care, given that these providers are already over whelmed with all the different aspects of care they have to provide.

Considering the previous listed items into the updates of the software used in EHRs may impact in the future patient care, turning into a personalized care and avoiding side effects. Future algorithms to interpret CYP2D6 function from sequencing data that consider structural variants, and machine learning

knowledge to evaluate the impact of novel variants, are being created. Finally, in consideration of ethical and inclusive representation in global science, we recommend further precision medicine biomarker research and funding in support of neglected or understudied populations worldwide [153].

In this section, we have provided the different hot topics, genetic, clinical and technical that may interfere in the actual pharmacogenetic implementation in clinical routine. If services address this, they may overcome the potential problems and be able to offer this service.

7.1. Limitations

Some of the most common limitations detected in the reviewed studies included the absence of CYP2D6 concomitant treatments in the analysis. A large number of drugs are CYP2D6 substrates and can potentially alter (increase or decrease) opioid levels. Limited controlled and randomized clinical trials have been performed; however observational studies results are in consonance with them. The difficulty in assigning and standardizing the metabolic phenotypes may be a limitation, both technically as some laboratories may have complications for genotypes with copy-number variation given the inability to determine which allele was duplicated. New SNPs and their corresponding activity scores have been changing during the recent years, so slightly discrepancies between studies in a relative small period of time should be expected.

8. Conclusion

Personalized analgesia heralds a new pharmacological approach to pain management. Recent literature proves individual genetic differences due to CYP2D6 phenotypes that partially explain variable and unpredictable responses to opioid and coadjutant drugs. Since, discoveries continue in the genetics of pain and analgesia, pharmacotherapy will rely more on an individualized, and targeted approach. Thus, CYP2D6 genotyping seems to play a decisive role in future approach to pain prescription. If we wish to continue proposing new therapeutic recommendations, evidence and new approaches on potential drug interactions, sex-differences or their use in pandemic contexts must be generated.

Following the knowledge generated in this work, physicians should routinely monitor analgesic tolerability along pain management, considering sex/gender biases in pain experience. These aspects are essential, given the scarce scientific evidence of long-term opioid real world use, in the context of CNCP.

9. Expert opinion

Chronic pain is a frequent condition, affecting an estimated 20 % of people in Europe, with a high interindividual in analgesic response. Here, opioid analgesics are the standards of care for the treatment of moderate to severe

pain. However, long-use remains controversial even more in CNCP due side-effects and potential misuse. In this context, pharmacogenetics could analyze the way in which the presence of variations in the DNA sequence could be responsible for portions of the population reaching different levels of pain relief (phenotype) due to gene interference in the drug mechanism of action and/or its concentration at the place of action. In this case, hepatic metabolism is the main route of excretion for some opioids, namely codeine and tramadol, and compulsory for their transformation into more potent analgesic metabolites. When considering the drug response, the highly polymorphic nature of CYP2D6 coding genes need to be considered for a deep inside of opioids' metabolism and activation, and for evaluating interindividual variation and response to treatment. In fact, some international guidelines provide CYP2D6-guided therapeutic recommendations to individualize treatment with tramadol and codeine. What´s more, other concomitant analgesics are metabolized to some extent by CYP2D6 and could interfere with opioid (e.g., codeine, hydrocodone, tramadol, oxycodone) clinical effect and safety. However, implementation guidelines for pain management are currently lacking.

Incorporating CYP2D6 genotype results in EHRs could help to guide a safer opioid use. A baseline screening with a regular monitoring of analgesic side-effects, using validated scales, is strongly recommended prior to starting any medication regimen in pain management. This includes routinely the screening of patient's perceptions regarding analgesia tolerability, and the need for further intervention taking into account the common potential drug-drug interactions. Here, a multidisciplinary approach is essential to offer preventive measures adapted to these chronic pain patients. Managing treatment-emergent side effects adequately is also crucial to facilitate compliance and achieve the best possible outcomes. Furthermore, clinicians should be aware that, during long-term opioid use, potential misuse behaviors are common and persistent because in many cases patients try to resolve them by themselves.

Chronic pain in patients with opioid dependence or addiction may lead to a complex condition where pain is presented in multiple locations, and other events such as psychosocial medical and psychiatric disorders can appear. All of these conditions interacting with each other in a clinical setting where multiple co-morbidities are common. It is thus paramount to improve the information provided and research about potential pharmacogenetic biomarkers that could help to understand these vulnerabilities. What´s more, there is much evidence to suggest that sex and gender interaction is an important factor in the modulation of pain. Men and women could differ in the response to opioids for pain relief, but these differences could also be significantly influenced by other factors like age and comorbid mental disorders or other psychosocial processes (e.g. pain coping, early-life exposure to stress), in addition to stereotypical gender roles that may contribute to differences in pain expression, analgesic use (e.g. tramadol, codeine, antidepressants or BZDs) and misuse. This sex differences in pain and analgesia may have important implications for the development of analgesic and personalized strategies.

Pragmatic clinical trial data are required in this field to better know the impact in diverse populations, therapeutic interventions and clinical care environments on genotype-guided drug therapy for chronic pain.

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***This work highlights that impact of new abuse deterrent formulations should be assessed with a special focus on data concerning female subjects.**

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****Gene variants in the cytochrome P450 enzymes genes (CYP2D6) influence metabolism of codeine, tramadol, hydrocodone, oxycodone, and tricyclic antidepressants. Blood concentrations of some NSAIDs depend on CYP2C9 and/or CYP2C8 activity.**

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Legends for figures and tables

Figure 1. World defined daily dose (DDD) use of opioids. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

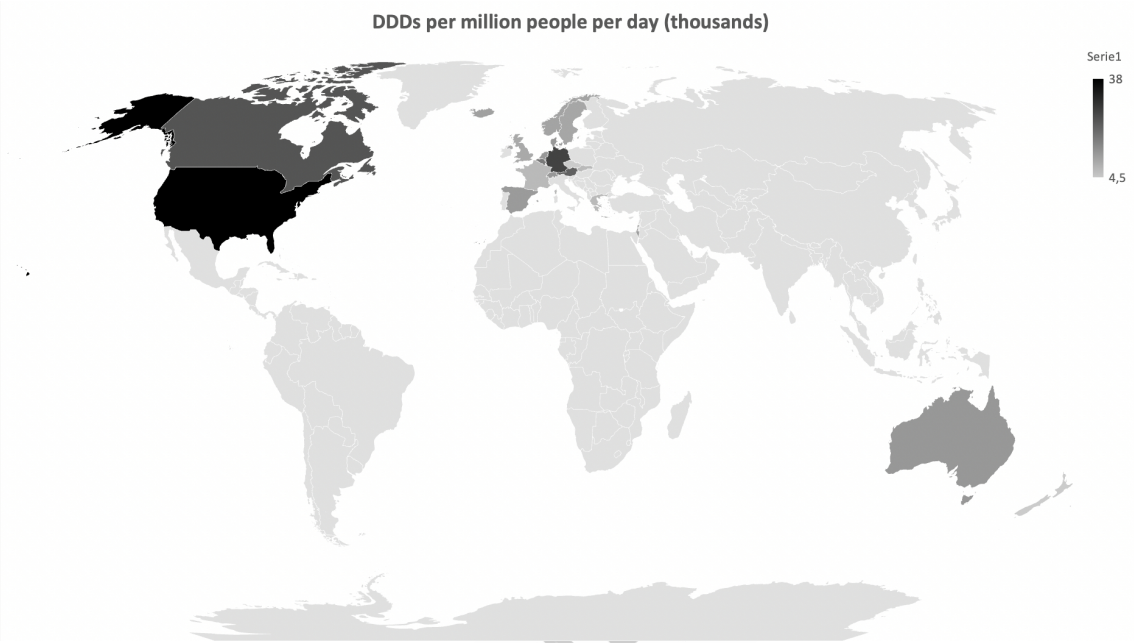

Figure 2. CYP2D6 role in opioid and co-analgesic clearance metabolism. Steps for the oral absorption of opioids and coadjutant analgesic by the portal blood system for phase 1 and phase 2 liver metabolism.

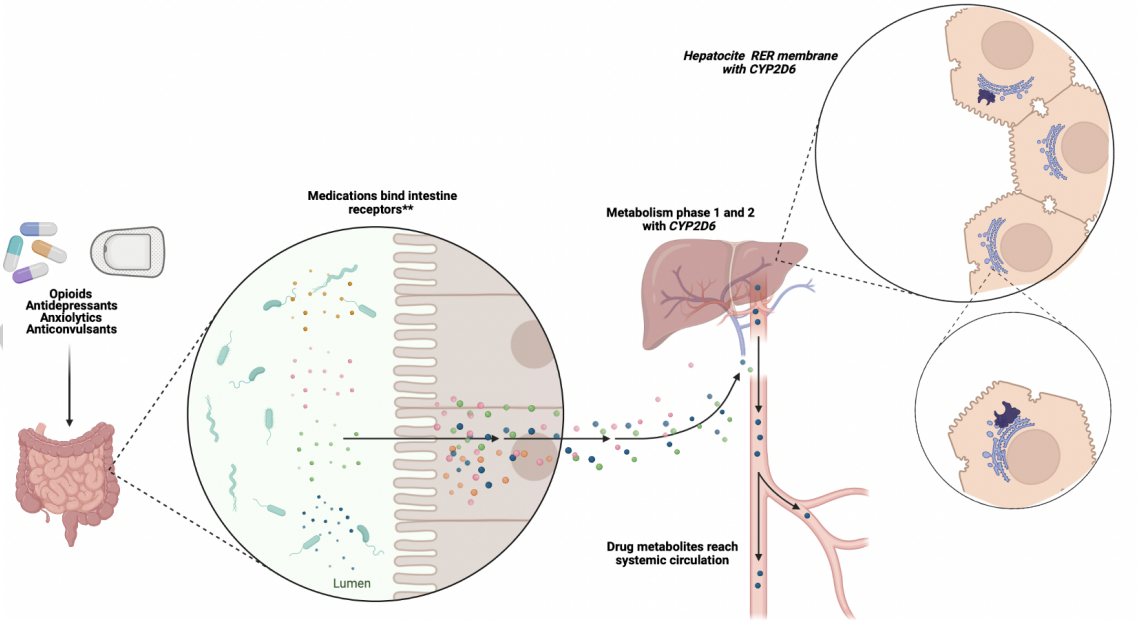

Figure 3. Description of the relationship that the different opioids and coadjutant analgesic drugs have with CYP2D6 enzyme.

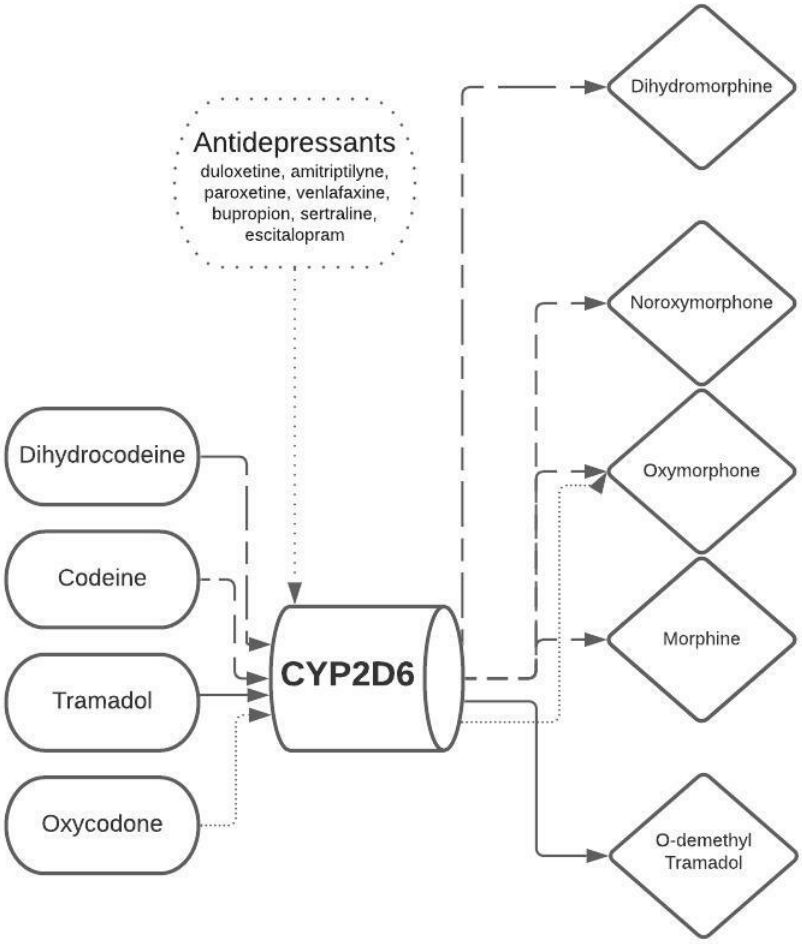

Table 1: *Influence of CYP2D6 phenotype* on tramadol and codeine pharmacology outcomes, related with dose, metabolism or side effects related to treatment.

Table 2: *Influence of CYP2D6 phenotype* on oxycodone and other opioids pharmacology outcomes, related with dose, metabolism or side effects related to treatment.

Supplemental Table 1: Selected substrates, inhibitors, and inducers of CYP2D6, classified according to the mechanism of action as analgesics, antidepressants/anxiolytics, other medications commonly used in patients with pain and other drugs.

Table 1: *Influence of CYP2D6 phenotype* on tramadol and codeine pharmacology outcomes, related with dose, metabolism or side effects related to treatment.

	Outcomes	Major findings	References
TRAMADOL	Dose Adjustment		
	Dose adjustment	CYP2D6 UM and PM guided prescribing improves analgesia, 24% of CYP2D6-dose guided Vs. 0% non-guided reported ≥30% (clinically meaningful) reduction in the pain measurement.	Smith, *et al.* 2019 [40]
	Major doses	The consumption of tramadol in CYP2D6*10/*10 group was significantly higher than that in CYP2D6*1/*1 or CYP2D6*1/*10 ($P < 0.05$).	Dong, *et al.* 2015 [41]
	Major doses	CYP2D6 PM decreased analgesia from codeine	VanderVaart, *et al.* 2011 [42] Shaw, *et al.* 2012 [43]
	Equal doses	No difference of codeine dose requirements	Baber, *et al.* 2015 [44]
	Metabolism		
	Equal metabolism	No statistical difference of tramadol concentrations between phenotypes	Bastami, *et al.* 2014 [45] Tanaka, *et al.* 2018 [46]
	Decreased metabolism	Cmax and AUC of morphine decreases as the number of *CYP2D6*10* alleles increases. Compared with the *1/*1 group, the AUC (0-∞) for morphine in the *1/*10 and *10/*10 groups decreased by ratios (95 % CI) of 0.93 (0.26-1.59) and 0.494 (0.135-0.853) respectively.	Wu, *et al.* 2014 [47]
	Decreased metabolism	CYP2D6 UM and PM phenotypes are associated with a reduction of the O-desmethylation process compared to EM	Bastami, *et al.* 2014 [45] Lane, *et al.* 2014 [48] Haage, *et al.* 2018 [49] Tanaka, *et al.* 2018 [46]
	Decreased metabolism	Decreased rations of O-desmethyltramadol/tramadol ratio and N, O-desmethyltramadol/N-desmethyltramadol in *CYP2D6*5/*5* and **10/*10.*	Yu, *et al.* 2018 [50] Yu, *et al.* 2018 [51]
	Decreased metabolism	*CYP2D6*4* or **10* have a decreased excretion of O-desmethyltramadol.	Arafa, *et al.* 2018 [52]
	Decreased and Increased	The plasma concentration of O-desmethyltramadol and its ratio to tramadol were lower in the CYP2D6	Tanaka, *et al.* 2018 [46]

	metabolism	IM + PM group than in NM group (P = 0.002 and P = 0.023). The plasma concentration of N-desmethyltramadol and its ratio to tramadol were higher in the CYP2D6 IM + PM group than in the NM group (P = 0.001 and P = 0.001).	
	Increased metabolism	CYP2D6 UM and PM phenotypes are associated with an increase of the N-desmethylation process compared to EM	Haage, *et al.* 2018 [49] Tanaka, *et al.* 2018 [46]
	Increased metabolism	N-desmethyltramadol/O-desmethyltramadol concentration ratios are increased in PM genotype.	Fonseca, *et al.* 2016 [53]
	Increased metabolism	*CYP2D6*10/*10* is associated with increased formation of N-desmethyltramadol from tramadol ($p<0.05$).	Yu, *et al.* 2018 [50]
	Side effects		
	Increased side-effects	CYP2D6 PM increased frequency of tramadol-induced AEs	Elkalioubie, *et al.* 2011 [54] Orliaguet, *et al.* 2015 [55]
	Increased side-effects	In carriers of *9/*9, *5/*5, *5/*4, and *10/*10, also in 4 allele polymorphisms (*4/*1 [38.4%] and *4/*4 [42.8%]).	Batiskayi et al., 2020 [23]
	Decreased side-effects	*CYP2D6*4* or **10* alleles are associated with decreased severity of tramadol-induced hepatotoxicity $p<0.05$.	Arafa, *et al.* 2018 [52]
CODEINE	Equal metabolism	CYP2D6 UM and EM no significant difference in plasma concentration of morphine and related metabolites	Frost, *et al.* 2016 [56]
	Side effects		
	Increased side-effects	Higher risk of codeine-induced AEs increased, associated with the presence of ≥1 full function CYP2D6 alleles (P < 0.001), and sex (P = 0.027).	Prows, *et al.* 2014 [57]
	Increased side-effects	CYP2D6 UM increased opioid related AEs with standard dose of codeine	VanderVaart, *et al.* 2011 [42] Kelly, *et al.* 2012 [58] Friedrichsdorf, *et al.* 2013 [59] Sistonen, *et al.* 2012 [60]
	Increased side-effects	In carriers of *9/*9, *5/*5, *5/*4, and *10/*10, also in 4 allele polymorphisms (*4/*1 [38.4%] and *4/*4 [42.8%]).	Batiskayi et al., 2020 [23]
	Equal side-effects	Equal risk of codeine-induced sedation	Prows, *et al.* 2014 [57]
	Equal side-effects	No significant difference in codeine-related AEs	Radfrod, *et al*. 2019 [61]

Abbreviations: PM - Poor metabolizer, IM - Intermediate metabolizer, NM - Normal metabolizer, EM - Extensive metabolizer, UM - Ultrarapid metabolizer, Cmax - Maximum (or peak) serum concentration achieved by the drug, AUC - Area under the curve, AEs - Adverse events.

Table 2: *Influence of CYP2D6 phenotype* on oxycodone and other opioids pharmacology outcomes, related with dose, metabolism or side effects related to treatment.

	Outcomes	Major findings	References
OXYCODONE	Dase		
	Dose adjustment	CYP2D6 UM and PM guided prescribing improves analgesia	Linares et al. 2014 [62]
	Equal doses	CYP2D6 PM and EM no statistical differences of oxycodone doses	Naito, et al. 2011 [63]
	Metabolism		
	Reduced metabolism	*CYP2D6* PM genotypes are associated with decreased exposure to oxymorphone and noroxymorphone	Stamer, et al. 2013 [64] Andreassen, et al. 2012 [65] Balyan, et al. 2017 [66] Stamer, et al. 2013 [64] Andreassen, et al. 2012 [65]
	Equal metabolism	No statistical differences of oxycodone concentrations	Naito, et al. 2011 [63] Andreassen, et al. 2012 [65] Balyan, et al. 2017 [66]
	Side effects		
	Equal side-effects	No statistical differences of opioid-induced AEs	Andreassen, et al. 2012 [65]
	Major efficacy and side effects	CYP2D6*6 and *9 carriers had a reduced (*9) or absent (*6) cytochrome activity, and therapeutic failure, and CYP2D6 UM showed an increased risk of side effects. Plus, CYP2D6 *1/*11, *4/*6 and *41/* 2N showed higher efficacy and side effects when chronic opioid treatment.	Dagostino et al., 2018 [67]
	Equal side-effects	CYP2D6 PM and EM no statistical differences of incidence of AEs	Andreassen, et al. 2012 [65] Slanar, et al. 2012 [68]
OTHER	Doses		
	Major doses	*CYP2D6 *10/*10* genotype associated with increased fentanyl consumption and reduced analgesia	Wu, et al. 2015 [69]
	Equal doses	*CYP2D6 *1/*10* genotype is not associated with fentanyl consumption or analgesic effect	Wu, et al. 2015 [69]
		Metabolism	

	Reduced metabolism	*CYP2D6* PM the mean plasma hydromorphone concentration was 8-fold lower when compared to that of UM.	Stauble, et al. 2014 [70]
	Side effects		
	Equal side-effects	No statistical differences of severity of neonatal abstinence syndrome between the number of functional *CYP2D6* alleles	Mactier, et al. 2017 [71]

Abbreviations: PM - Poor metabolizer, EM - Extensive metabolizer, UM - Ultrarapid metabolizer, AEs - Adverse events.