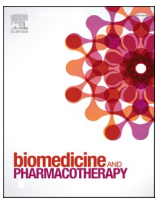
Biomedicine & Pharmacotherapy 176 (2024) 116882

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Use of CYP2D6 substrates and inhibitors during pain management with analgesic opioids: Drug-drug interactions that lead to lack of analgesic effectiveness

J. Muriel [a], M. Escorial [a,b], C. Carratalá [b], C. Margarit [a,c], J. Barrachina [a], A. López [a,b], E. Gallardo [d], MK Kringen [e], A.M. Peiró [a,c,f,*]

[a] Pharmacogenetic Unit, Clinical Pharmacology Department, Alicante Institute for Health and Biomedical Research (ISABIAL), Dr. Balmis General University Hospital, c/ Pintor Baeza, 12, Alicante 03010, Spain
[b] Occupational Observatory, University Miguel Hernández, Avda. de la Universidad s/n, Elche 03202, Spain
[c] Pain Unit, Dr. Balmis General University Hospital, c/ Pintor Baeza, 12, Alicante 03010, Spain
[d] Centro de Investigação em Ciências da Saúde, Universidade da Beira Interior (CICS-UBI), Av. Infante D. Henrique, Covilhã 6201-506, Portugal
[e] Department of Psychopharmacology, Diakonhjemmet Hospital, Forskningsveien 7, Oslo 0373, Norway
[f] Clinical Pharmacology, Toxicology and Chemical Safety Unit, Institute of Bioengineering, Miguel Hernández University, Avda. de la Universidad s/n, Elche 03202, Spain

ARTICLE INFO

Keywords:
Analgesic opioids
Pharmacogenetics
CYP2D6
Drug-drug interactions
Chronic non cancer pain
Substrates/inhibitors

ABSTRACT

Background: Several opioids have pharmacogenetic and drug-drug interactions which may compromise their analgesic effectiveness, but are not routinely implemented into supportive pain management. We hypothesized that CYP2D6 phenotypes and concomitant use of CYP2D6 substrates or inhibitors would correlate with opioid analgesic outcomes.

Materials and Methods: An observational cross-sectional study was conducted with 263 adult chronic non cancer pain (CNCP) patients from a real-world pain unit under long-term CYP2D6-related opioid treatment (tramadol, hydromorphone, tapentadol or oxycodone). Metabolizer phenotype (ultrarapid [UM], normal [NM], intermediate [IM] or poor [PM]) was determined by the *CYP2D6* genotype. The socio-demographic (sex, age, employment status), clinical (pain intensity and relief, neuropathic component, quality of life, disability, anxiety and depression), pharmacological (opioid doses and concomitant pharmacotherapy) and safety (adverse events) variables were recorded.

Results: The whole population (66 % female, 65 (14) years old, 70 % retired and 63 % attended for low back pain) were classified as PM (5 %), IM (32 %), NM (56 %) and UM (6 %). Multiple linear and logistic regressions showed higher pain intensity and neuropathic component at younger ages when using any CYP2D6 substrate ($p = 0.022$) or inhibitor ($p = 0.030$) drug, respectively, with poorer pain relief when CYP2D6 inhibitors ($p=0.030$) were present.

Conclusion: The concomitant use of CYP2D6 substrates or inhibitors during opioid therapy for CNCP may result in lack of analgesic effectiveness. This aspect could be relevant for pharmacological decision making during CNCP management.

1. Introduction

Patients can vastly differ in their individual responses to distinct opioid drug analgesics in terms of poor pain control and adverse drug reactions [1,2]. Although many of these effects are not life-threatening, they can significantly affect the patient's quality of life. A recent prospective study of cytochrome P450 CYP2D6-guided opioid prescribing in patients with chronic non cancer pain (CNCP) demonstrated that this approach resulted in improved patient outcomes and pain control in IM/PM patients, particularly in those treated with codeine, tramadol or hydrocodone [3,4].

As a result of this, the Clinical Pharmacogenetics Implementation

* Corresponding author at: Pharmacogenetic Unit, Clinical Pharmacology Department, Alicante Institute for Health and Biomedical Research (ISABIAL), Dr. Balmis General University Hospital, c/Pintor Baeza, 12, Alicante 03010, Spain.
E-mail address: apeiro@umh.es (A.M. Peiró).

https://doi.org/10.1016/j.biopha.2024.116882
Received 13 February 2024; Received in revised form 15 May 2024; Accepted 3 June 2024
Available online 14 June 2024

Consortium (CPIC) recently published an updated guideline against codeine and tramadol use in CYP2D6 poor (PM) and ultrarapid (UM) metabolizers. Moreover, close monitoring in codeine- and tramadol-treated intermediate (IM) metabolizers (and in IM and PM hydrocodone-treated subjects) is indicated together with switching to an alternative non CYP2D6-metabolized analgesic if inadequate response was observed [3,5]. Notably, codeine and tramadol are metabolized by CYP450 enzymes during phase I reactions, with key metabolites resulted from CYP2D6 enzyme conversion enhancing μ-receptor potency, leading to the predominant analgesic properties of these drugs [1–3,6–9].

It is important to be aware that certain antidepressants (mainly tricyclic and serotonin selective reuptake inhibitors) act as inhibitors of the CYP2D6 enzyme. If opioids and antidepressants are simultaneously taken, patients need to be considered to be PM, regardless of their current genotype. Furthermore, approximately 40 % of the neuroleptics frequently used in pain management are major substrates of CYP2D6 and are related to anxiolytics, such as benzodiazepines (BZDs), are co-administrated when pain is accompanied by a strong anxious component or in situations where sleeping disorders are present [10]. Here BZDs are metabolized via CYP enzymes, mostly by CYP3A-oxidation to the subsequent conjugation of active metabolites. No implication of CYP2D6 has been evidenced in this group of compounds. However, extensive warnings about the hazards of drug-drug interactions in the concomitant use with opioids have been reported and can lead to fatal outcomes [11,12]. In fact, BZDs can alter the pharmacokinetics of opioids [13]. To our knowledge, no large studies have previously studied the role of the *CYP2D6* genotype on analgesic outcomes in big CNCP populations taking different CYP2D6-dependent opioids and concomitant medication.

Thus we hypothesized that *CYP2D6* phenotypes and concomitant medication would be associated with inadequate analgesia when using standard opioid prescribing patterns for CNCP.

2. Materials and methods

2.1. Design and participants

An observational cross-sectional study was conducted on 263 subjects attending the Pain Unit of the Dr Balmis General University Hospital (Alicante, Spain). Approval by the Ethics Committee Board of the Dr Balmis General University Hospital of Alicante was obtained and all the participants gave and signed an informed consent prior to any activity related with the study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

The participants were prospective and consecutively recruited from 2011 to 2017. The inclusion criteria were: (1) adults aged $\geq$ 18 years; (2) diagnosed with CNCP; (3) CYP2D6 opioids-related therapy (regular prescription for 3 months or longer); (4) with adequate mental status for properly completing scales and questionnaires. The exclusion criteria were loss of follow-ups, patient's decision, requirement of canal stenosis surgery, cessation of allocated medication or chronic cancer pain. The patients with neuropathic pain, caused by damage to the somatosensory system [14] or nociceptive pain, caused by damage to non-neural tissue or *stimuli* that may lead to tissue damage [15], were excluded. Neuropathic pain diagnosis included conditions like trigeminal neuralgia, mononeuritis and multiple sclerosis. Nociceptive pain diagnosis included conditions, such as osteoarthritis, myalgia, myositis, carpal tunnel syndrome and rheumatism. The subjects diagnosed with mixed pain (e.g. migraine, headache, cervicalgia, non-traumatic compartment syndrome) or other conditions that may be pain-related or not (e.g. restless legs syndrome, cerebrovascular disease, paraplegia) were not included in the study.

2.2. Medical records

Subject's age, sex, employment status and reason for medical attention including the type of CNCP (low back, back, cervical and joint pain) were recorded.

Validated scales and questionnaires were completed during each visit. They were all self-administered in the presence of an expert clinician. Pain intensity and relief were determined using the validated 100-mm Visual Analog Scale (VAS, 0 "no pain/relief" to 100 "worst possible pain/maximum relief"). Both variables were also categorized as "none", "mild", "moderate", "severe" and "extremely severe/relieved" using the Likert scale verbally. The PainDETECT questionnaire was used to identify the Neuropathic Component. The final range went from scores of 1–38: scores up to 12 are unlikely to be neuropathic pain (<15 %) and values of > 19 scores are very likely to be neuropathic pain (90 %) [16].

Quality of life related to health measures was assessed by the EQ-VAS (0 "worst" to 100 "best health status"). The Hospital Anxiety and Depression (HAD) Scale was used to assess both anxiety and depression by seven questions. Scores were categorized as normal (scores of 0–7), doubtful (8−11) and cases (11−21) [17]. The Oswestry Disability Index quantified the general disability for low back pain in six statements describing different potential scenarios in patients' lives. Scores were summed and then multiplied by 2 to obtain the index (%, range 0 "no disability" and 100 "maximum disability possible" [0–20 %: minimum functional limitation; 20 % −40 %: moderate; 40 % −60 %: intense; 60 % −80 %: disability, and above 80 %: maximum functional limitation]) [18].

2.3. Pharmacological therapy and drug adverse events (AEs)

Physicians collected patients' prescribed pain therapy including opioids. The total daily dose of opioids was converted into the morphine equivalent daily dose (MEDD), estimated using the equianalgesic dose [19]. Concomitant drugs, commonly prescribed together with opioid therapy as clinical regular routine, such as non-opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), anxiolytics, antidepressants, neuromodulators, antipsychotics, muscular relaxants and local/topical anesthetics were recorded. Of them, CYP2D6 substrates (amitriptyline, citalopram, escitalopram, duloxetine, fluoxetine, haloperidol, lidocaine and venlafaxine) and inhibitors (citalopram, escitalopram, duloxetine, haloperidol and sertraline) were recorded according to current evidence [20]. The Global Pain State Questionnaire was used and included a list of the most frequent AEs selected according to opioids summary product characteristics frequency as "very common" and "common". From this questionnaire, and based on the Likert Pain Intensity and relief (mm), EQ-VAS (mm), the total number of AEs and Emergency Department attendance due to Pain, the Global Pain State (scores of 0–3) was calculated [21].

2.4. DNA collection and genotyping

In line with the cross-sectional design of the study, both the collection of clinical variables and biological samples for pharmacogenetic analysis, were performed at the same inclusion visit. Biological samples were collected in EDTA tubes and DNA was isolated using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden) or E.N.Z.A. Forensic DNA Kit (Omega bio-tek) following the manufacturer's instructions. DNA yield was quantified by a NanoDrop spectrophotometer (Thermo Fisher Scientific, Wilmington, USA) and stored at −20 ºC until used. TaqMan® technology (Thermo Fisher Scientific, Pleasanton, CA, USA) was applied to detect the SNP variant alleles. Genotyping was carried out in a Real-Time PCR Rotor Gene Q (Qiagen, Hilden) system. The PCR reaction was performed in a final volume of 20 μL containing: 100 ng DNA, 10 μL TaqMan® Genotyping 2x Master Mix (Thermo Fisher Scientific, Pleasanton, CA, USA) and 1 μL of specific 20x TaqMan® SNP Genotyping

Assay (Thermo Fisher Scientific, Pleasanton, CA, USA). All the reactions were performed in duplicates and negative controls were included in each PCR reaction. The PCR program was: 95 ºC for 10 min, followed by 40 cycles of 92 ºC for 15 seconds and 60 ºC for 1 min.

For those with archival CYP2D6 results, metabolizer phenotypes were assigned using genotypes and copy number results. Our primary analysis was based on this CYP2D6 genotype-predicted phenotype. Each allele was given an activity score and the metabolizer phenotype was assigned according to the cumulative value. Scores of 0, 0.5 and 1 were assigned for each no activity, decreased activity and normal activity allele, respectively. The phenotype was assigned based on the sum of the scores (0, PM; 0.5, IM; 1–2, NM; > 2, UM) using the phenotype classification schema that was in force during the study period [22,23]. However, we acknowledge that an updated system has been recently adopted that would potentially increase the number of patients classified as IMs by a very small fraction [3,24].

2.5. Statistics

The Shapiro-Wilk normality test was performed to choose parametric or non-parametric tests for comparisons. Quantitative data are presented as means (standard deviation, SD), the discrete variables as medians (interquartile range) and the categorical variables are expressed by absolute frequencies (percentages). Data were compared among the CYP2D6 phenotypes (PM, EM, IM, UM). A one-Way ANOVA or a Kruskal-Wallis test was performed for the quantitative data and Pearson's Chi-squared test was used for the categorical variables. Multiple testing was adjusted by the Bonferroni correction method. Multiple linear and logistic regressions were calculated for the quantitative and qualitative dependent variables, respectively. In all cases, the included independent variables were sex, age, the *OPRM1* genotype, the CYP2D6 phenotype, and the use of any CYP2D6 inhibitors and substrates. The best fitting model obtained is presented for every significant result. The final model selection for the categorical dependent variable regressions was obtained according to a small Akaike information criterion (AIC). Analyses were carried out with the GraphPad Prism®, version 5.02, and R version 3.2.4 software packages. $P < 0.05$ was considered to be statistically significant.

3. Results

This study recruited 411 adult patients with CNCP on strong opioids who chronically attended our pain unit. After excluding those not using CYP2D6-related opioids (n=75, 18 %) or with an unavailable or unresolved *CYP2D6* genotype (n=73, 18 %), 263 subjects were included in these analyses, as shown in the flow chart (Fig. 1).

This study described and analyzed 263 CNCP patients using long-term CYP2D6-related opioids (66 % female, 65 (14) years old). Our population was mainly retired (70 %) and attended our pain unit for low back pain (63 %). Subjects showed moderate chronic VAS pain intensity (59 (28) mm) and low relief (37 (29) mm) with an unlikely neuropathic component (83 (67) PainDetect scores). Moderate quality of life (VAS 45 (21) mm), moderate-severe disability (75 %) and likely anxiety (18 %) or depression (26 %) were reported. The total GPS score was 1.6 (0.6), while 46 % fell within the cut-off ranges.

All the participants were classified according to their estimated *CYP2D6* metabolic phenotype: 14 (5 %) were PM; 85 (32 %) were IM; 148 (56 %) were NM; 16 (6 %) were UM. Table 1 displays the most relevant socio-demographic and clinical status data of our study population. The additional variables are presented in the Supplementary material (Table S1). Here, no socio-demographic or clinical differences between CYP2D6 phenotypes were observed.

3.1. Pharmacological use

The total population's pharmacological data, which were classified by the CYP2D6 metabolic phenotypes, appear in Table S2.

Oxycodone (45 %), tramadol (27 %) and fentanyl (16 %) were the most frequently used opioids in our cohort, with a MEDD of 90 (84) mg/day. Regarding concomitant medication, neuromodulators, anxiolytics and antidepressants were prescribed in 64 %, 45 % and 40 % of our subjects, respectively. 34 % of our patients used at least one CYP2D6

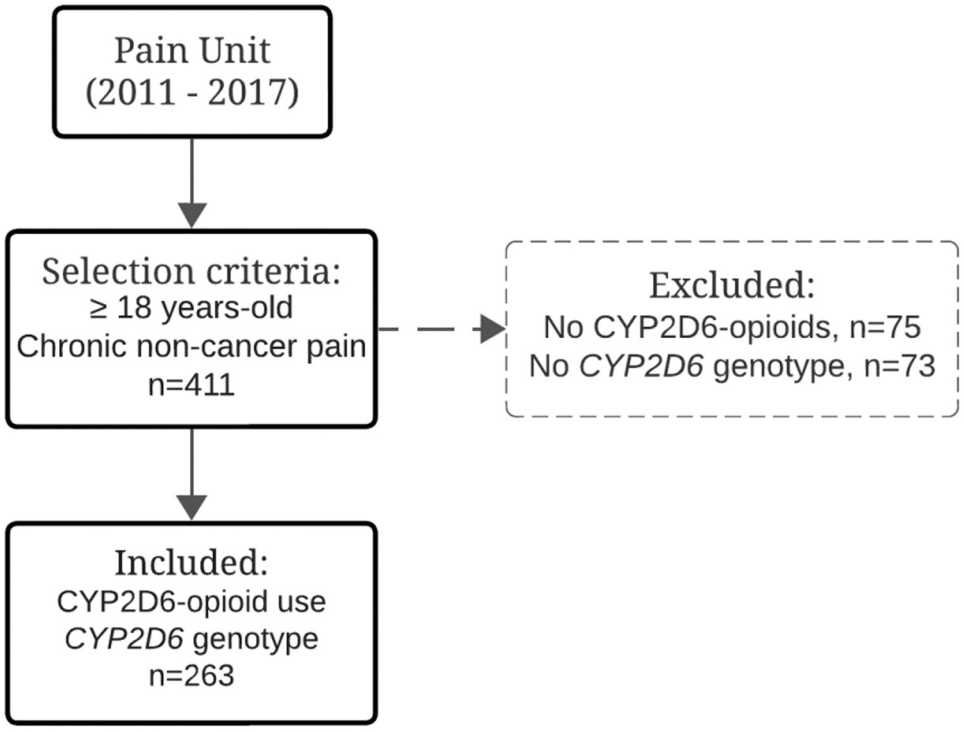


Fig. 1. Flow chart showing the number of available subjects, the selection criteria and the final sample size.

Table 1
Socio-demographic and clinical variables (total and compared by the CYP2D6 phenotype).

N (%)	TOTAL	PM	IM	NM	UM	*p*-value
Sex (female)	174 (66)	10 (71)	53 (62)	103 (70)	8 (50)	0.338
Age (years), mean (SD)	65 (14)	63 (14)	66 (14)	66 (14)	64 (14)	0.811
Pain etiology						0.820
- Low back pain	162 (63)	11 (79)	50 (60)	93 (64)	8 (50)	
- Joint pain	17 (7)	0 (0)	6 (7)	9 (6)	2 (13)	
- Cervical pain	9 (4)	0 (0)	4 (5)	4 (3)	1 (6)	
- Dorsalgia	13 (5)	0 (0)	3 (4)	8 (5)	2 (13)	
- Others / Non-specific	58 (22)	3 (21)	20 (24)	32 (22)	3 (19)	
Pain intensity (VAS, 0–100 mm), mean (SD)	59 (28)	58 (27)	66 (26)	54 (17)	58 (27)	0.656
Pain Relief (VAS, 0–100 mm), mean (SD)	37 (29)	41 (30)	33 (39)	53 (24)	40 (30)	0.615
Neuropathic component (PD, scores of 0–38)						0.684
- Unlikely	83 (67)	5 (83)	28 (72)	46 (63)	4 (67)	
- Unclear	25 (20)	0 (0)	6 (15)	17 (23)	2 (33)	
- Likely	16 (13)	1 (17)	5 (13)	10 (14)	0 (0)	
Quality of life (VAS, 0–100 mm), mean (SD)	45 (21)	46 (25)	50 (14)	50 (18)	46 (23)	0.829
Disability (Oswestry Disability Index)						0.409
- Minimal	10 (8)	0 (0)	1 (2)	9 (13)	0 (0)	
- Moderate	46 (37)	3 (50)	18 (44)	24 (33)	1 (17)	
- Severe	47 (38)	3 (50)	14 (34)	28 (39)	2 (33)	
- Crippled	20 (16)	0 (0)	7 (17)	10 (14)	3 (50)	
- Bedbound or exaggerating	2 (2)	0 (0)	1 (2)	2 (3)	0 (0)	
Anxiety (Hospital Anxiety Scale)						0.431
- Unlikely	79 (63)	6 (86)	23 (56)	48 (68)	2 (33)	
- Unclear	24 (19)	1 (14)	10 (24)	11 (15)	2 (33)	
- Likely	22 (18)	0 (0)	8 (20)	12 (17)	2 (33)	
Depression (Hospital Depression Scale)						0.203
- Unlikely	70 (56)	6 (86)	18 (44)	44 (62)	2 (33)	
- Unclear	23 (18)	1 (14)	9 (23)	12 (17)	1 (17)	
- Likely	32 (26)	0 (0)	14 (34)	15 (21)	3 (50)	
Global Pain State (GPS, scores of 0–3), mean (SD)	1.6 (0.6)	1.9 (0.7)	1.7 (0.8)	1.8 (0.8)	1.8 (0.8)	0.484

PM: Poor metabolizer; IM: Intermediate metabolizer; NM: Normal metabolizer; UM: Ultrarapid metabolizer; VAS: Visual Analog Scale; PD: PainDetect Questionnaire; GPS: Global Pain State Questionnaire. Pearson's Chi-squared test for the categorical data; ANOVA for the quantitative data.

substrate and 24 % used at least one CYP2D6 inhibitor, with duloxetine being the most commonly used drug in both cases (16 %). For antidepressants (other than duloxetine and amitriptyline), differences were observed by metabolic phenotype (p=0.041), although this effect was lost when the Bonferroni correction was used. No other differences between the *CYP2D6* phenotypes and pharmacological use were observed.

3.2. Safety profile

The description of the safety variables description and their comparison between the CYP2D6 metabolic phenotypes is shown in Table S3.A median of 4 (5) AEs per patient is herein reported. Constipation (52 %), dry mouth (49 %), somnolence (39 %) and nervousness (33 %) were the most prevalent. Grouped by affected system, nervous system events were the most frequent with a median of 1.5 (3) per patient. No differences between the *CYP2D6* phenotypes and AEs frequency were present. Finally, 21 % of the patients attended the emergency room due to pain during the study, 5 % required hospitalization and 39 % changed pain medication, but no differences were noted when compared by the CYP2D6 phenotype.

3.3. Drug-drug and drug-gene interactions

Linear and logistic regressions were performed to analyze the influence of CYP2D6, *OPRM1*, age, sex and use of CYP2D6 substrates or inhibitors on the clinical variables (Table 2).

Here, pain intensity was influenced inversely by age and directly by

Table 2
Linear and logistic regressions showing the best fitting model obtained and the significant influence of age and use of CYP2D6 inhibitors/substrates on pain intensity, relief and neuropathic component.

Linear regression	Formula	*p*-value
Pain Intensity (VAS, 0–100 mm)	~ (-) Age + (+) Substrate	0.067
Pain Intensity (Likert)	~ (-) Age + (+) Substrate	**0.022***
Neuropathic component (PD, scores of 0–38)	~ (-) Age + (+) Inhibitor	**0.03***
Pain Relief (VAS, 0–100 mm)	~ (-) Inhibitor	0.168
Pain Relief (Likert)	~ (-) Inhibitor	**0.044***
Quality of life (VAS, 0–100 mm)	~ (+) Age + (+) Substrate + (-) Inhibitor	0.414
Adverse Events	~ (+) Female + (+) Substrate	0.074
Logistic regression		**AIC**
Disability (Oswestry Index)	~ (+UM) *CYP2D6* + (+) Inhibitor	632.05
Depression (HAD category)	~ (-PM) *CYP2D6* + (+) Inhibitor	457.74
Anxiety (HAD category)	~ (-PM) *CYP2D6* + (+) Age + (-) Inhibitor	459.44
Antidepressants use	~ (+) Female + (+) Inhibitor + (+) Substrate	18.79

VAS: Visual Analog Scale; HAD: Hospital Depression Scale; PD: PainDetect Questionnaire. (+) and (-) represents positive and negative correlation with the independent variable, respectively.

the use of any CYP2D6 substrate according to the following regression equation: Pain intensity (Likert) = 2.973 + (-0.013 x age + 0.233 x substrate use (coded as 1)), p = 0.022. Likewise, neuropathic component was higher at younger ages and in those using any CYP2D6 inhibitor according to the following regression equation: Neuropathic pain (PainDetect) = (-0.13 x age + 4.06 x inhibitor use), p = 0.03 (Fig. 2 A). Consequently, pain relief level was influenced inversely by the use of any CYP2D6 inhibitor according to the following regression equation: Pain relief (Likert) = 1.754 + (-0.413 x inhibitor use (coded as 1)), p = 0.044 (Fig. 2B). An insignificant trend was observed in relation to the direct influence of being female and the use of any CYP2D6 substrate on the total number of AEs. The interaction of the CYP2D6 phenotype and the *OPRM1* gene variants was analyzed for the same clinical variables and showed no associations.

4. Discussion

Our data showed that the use of CYP2D6 inhibitors and/or substrate drugs compromises pain control (including the neuropathic pain component), and insufficient analgesia is experienced when used with common CYP2D6-related opioids. Here, their combination with the extreme (UM/PMs) phenotypes could influence the disability and depression cases, which suggests a different pain management experience among the CYP2D6 phenotypes. What is more, a sex-related differences tendency was found, which revealed higher CYP2D6 substrates (especially antidepressants) use and total AEs in women. A standard opioid prescribing pattern may be inappropriate or potentially harmful for those patients with CYP2D6 inhibitor/substrate use, and also in the UM/PM phenotypes. Prospective studies will be necessary to confirm these important findings for pharmacological approaches as part of CNCP care.

Pain response is influenced by a range of complex factors, including genetics, age and concomitant medication [25]. The main goal of this study was to perform CYP2D6 pharmacogenetic characterization and to investigate the association with pain scores due to the presence of CYP2D6 substrates and inhibitors. The analysis of the metabolic profile identified 5 % PM and 6 % UM, which agree with previous estimations in European Caucasian populations [26].

Personalized analgesia heralds a new pharmacological approach to pain management. Almost 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 the mean dose opioid prescription, and even more so in females due to hormonal factors. In the present study, females were more prone to suffer AEs and antidepressant drug prescription. Comedication should be reviewed by both physicians and clinical pharmacologists, and potent CYP2D6 inhibitors ought to be switched to weaker alternatives [27].

Incorporating CYP2D6 genotype results into electronic health records could help to guide safer opioid use. Baseline screening with regular monitoring of analgesic side effects using validated scales is strongly recommended before starting any medication regime in pain management [28]. This includes the routine assessment of analgesia tolerability, as well as the need for pharmacological interventions that take into account possible common drug-drug interactions. Appropriate management of treatment-emergent side effects is also crucial to facilitate compliance and to achieve the best possible clinical outcomes. Thus a multidisciplinary approach is essential to provide tailored preventive measures for these CNCP patients. Furthermore, clinicians should be aware that potential abusive behaviors are frequent and persistent during prolonged opioid use because patients attempt to resolve them on their own in many cases [10].

Pragmatic clinical trial data are required in this field to better know the impact on diverse populations, therapeutic interventions and clinical care environments on genotype-guided drug therapy for chronic pain. In fact, a pragmatic proof-of-concept trial has tested the effects of CYP2D6-guided opioid prescribing on pain control [4] with CYP2D6-guided (n=235) or usual care (n=135) arms by means of a cluster design. The IMs/PMs initially prescribed tramadol/codeine (n=45) displayed more improvement in the CYP2D6-guided *versus* the usual care arm, as CPIC guides have suggested [3]. However, the factors that affect the unbound fraction of drugs (i.e., hyperglycemia or co-administration of drugs highly bound to plasma proteins) should be monitored because this parameter dominates the elimination of tramadol enantiomers [29] and, thus, clinical analgesic response variability.

Related to the neuropathic component, several neuropathic pain medications have the potential for drug-drug interactions. Examples include duloxetine, paroxetine and methadone (CYP2D6 inhibitors) and oxycodone HCL, hydrocodone (CYP2D6 substrates) vs. metoprolol and bisoprolol (CYP2D6 substrates) [30]. Of the 2436654, Veterans Health Administration Opioids were commonly coprescribed with antidepressants that interact with CYP2D6 (28 %). An estimated 21.6 % (n=526905) of these patients were at high risk of an undesirable response to their opioid medication based on predicted phenotypes and drug-drug interactions. Despite the high coprescription rate of opioids and interacting drugs, CYP2D6 testing was infrequent in the sample

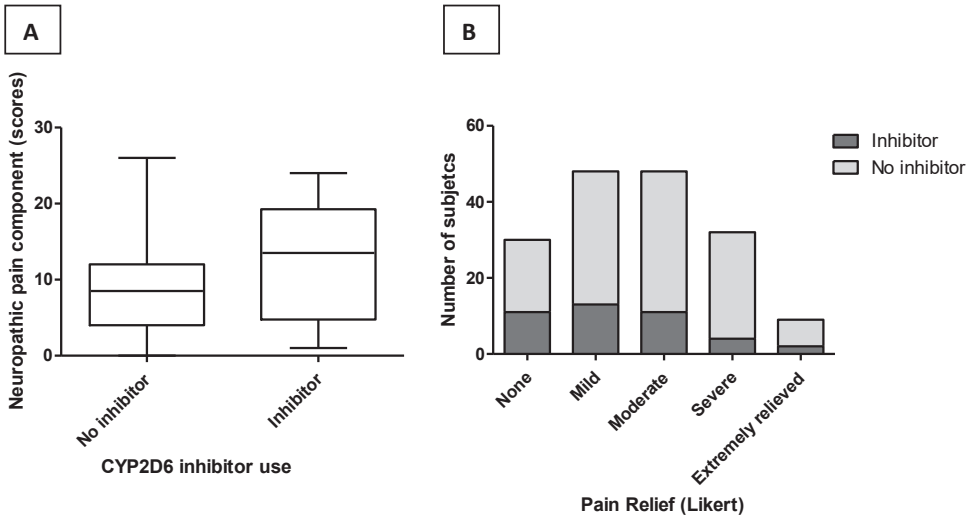


Fig. 2. (A) Subjects with CYP2D6 inhibitors use showing a higher neuropathic component on their pain based on the PainDetect scores; (B) Subjects with CYP2D6 inhibitors use showing lower pain relief based on a Likert scale.

(0.02 %), and a chart review has suggested that the test results were used to optimize antidepressant treatments rather than pain medications. [31]. Inhibitors can also decrease CYP2D6 activity by phenoconverting genotypic NMs or UMs into phenotypic PMs or IMs. Therefore, the concomitant use of opioids and CYP2D6 inhibitors or substrates should be considered when estimating the CYP2D6 phenotype [32]. What is more, higher costs associated with CYP2D6 opioid use under drug-drug interaction conditions could suggest inadequate CYP2D6 opioid prescribing practices. Efforts to improve chronic opioid use in adults should reduce interacting drug combinations, especially with patients on CYP2D6 activated opioids [33].

Another observed aspect was that PMs showed a high use of antidepressants (50 %) in our study, without presenting higher depression or anxiety levels. Although the effect was lost after applying Bonferroni correction, patients with reduced CYP2D6 metabolism could be expected to have inefficient analgesia when on opioid analgesics, and they could require antidepressants as an adjuvant for pain relief to a greater extent [34].

The revealing results from the clinical practice of our center should be interpreted taking into account a number of limitations. Firstly, the duration of use of opioid analgesics and concomitant medications could not be accurately collected and was not analysed. Here, potential mismatches between the patients' real intake and prescribed doses and duration of the treatment could exist. However, we did ensure that all patients participating in the study used opioids chronically ($\geq$ 3 continuous months) as part of their CNCP management, favoring the homogeneity of the sample. The impact of the duration of medication on the clinical and safety outcomes should be explored in future analyses. Secondly, the variables collected and analyzed were focused on pharmacological response, so other variables specific to our tertiary care setting, such as comorbidities and nonpharmacological interventions, were not considered. Their potential confounding effects should be explored in new investigations. In relation to the etiology and type of pain, an effort was made to homogenize the sample by including only patients with chronic ($\geq$ 6 months of evolution), musculoskeletal, non-cancer pain. Finally, the cross-sectional nature of the study precludes drawing conclusions on the causality of the associations detected. Therefore, prospective studies are needed to validate these findings and to establish the clinical utility of taking into account CYP2D6 phenotype and drug-drug interactions when prescribing opioids.

5. Conclusions

Our findings suggest that CYP2D6 inhibitors use could compromise pain control management, and even more so at younger ages. Along the same line, the extreme UM/PM CYP2D6 phenotypes could affect disability and mental depression. To a greater extent, female sex could contribute to a different safety pattern due to the CYP2D6 drug substrate together with higher psychotropic use, which needs to be analyzed from a gender perspective. These results support the prospective consideration of preemptive CYP2D6 genotyping to assist in personalized opioid prescribing for CNCP patients in real-world pain unit settings.

Funding

This work was supported by The Health Research Fund from the Spanish Ministry of Science and Innovation (TRA-056, 2010) and the Carlos III Health Institute (ISCIII, Madrid, Spain) with a grant to Independent Clinical Research Projects of Strategic Action in Health 2017–2020 (AES, ICI20/00146) Alicante Health and Biomedical Research Institute (ISABIAL) Area 1 fundings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2024.116882.

References

[1] H.S. Smith, Opioid metabolism, Mayo Clin. Proc. 84 (7) (2009) 613–624, https://doi.org/10.1016/s0025-6196(11)60750-7.
[2] D.M. Smith, K.W. Weitzel, L.H. Cavallari, A.R. Elsey, S.O. Schmidt, Clinical application of pharmacogenetics in pain management, Per Med 15 (2) (2018) 117–126, https://doi.org/10.2217/pme-2017-0032.
[3] K.R. Crews, A.A. Monte, R. Huddart, K.E. Caudle, E.D. Kharasch, A. Gaedigk, H. M. Dunnenberger, J.S. Leeder, J.T. Callaghan, C.F. Samer, T.E. Klein, C.E. Haidar, S.L. Van Driest, G. Ruano, K. Sangkuhl, L.H. Cavallari, D.J. Müller, C.A. Prows, M. Nagy, A.A. Somogyi, T.C. Skaar, Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy, Clin. Pharm. Ther. 110 (4) (2021) 888–896, https://doi.org/10.1002/cpt.2149.
[4] D.M. Smith, K.W. Weitzel, A.R. Elsey, T. Langaee, Y. Gong, D.T. Wake, B.Q. Duong, M. Hagen, C.A. Harle, E. Mercado, Y. Nagoshi, K. Newsom, A. Wright, E. I. Rosenberg, P. Starostik, M.J. Clare-Salzler, S.O. Schmidt, R.B. Fillingim, J. A. Johnson, L.H. Cavallari, CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial, Genet Med 21 (8) (2019) 1842–1850, https://doi.org/10.1038/s41436-018-0431-8.
[5] Y. Zhu, G.S. Lopes, S.J. Bielinski, B.J. Borah, N.B. Larson, A.M. Moyer, J.E. Olson, L. Wang, R. Weinshilboum, J.L. St Sauver, Impact of Pharmacogenomic Information on Values of Care and Quality of Life Associated with Codeine and Tramadol-Related Adverse Drug Events, Mayo Clin. Proc. Innov. Qual. Outcomes 5 (1) (2021) 35–45, https://doi.org/10.1016/j.mayocpiqo.2020.08.009.
[6] B.R. Overholser, D.R. Foster, Opioid pharmacokinetic drug-drug interactions, Am. J. Manag Care 17 (Suppl 11) (2011) S276–S287.
[7] L. Gong, U.M. Stamer, M.V. Tzvetkov, R.B. Altman, T.E. Klein, PharmGKB summary: tramadol pathway, Pharm. Genom. 24 (7) (2014) 374–380, https://doi.org/10.1097/fpc.0000000000000057.
[8] A.Z. DePriest, B.L. Puet, A.C. Holt, A. Roberts, E.J. Cone, Metabolism and Disposition of Prescription Opioids: A Review, Forensic Sci. Rev. 27 (2) (2015) 115–145.
[9] Y. Gasche, Y. Daali, M. Fathi, A. Chiappe, S. Cottini, P. Dayer, J. Desmeules, Codeine intoxication associated with ultrarapid CYP2D6 metabolism, N. Engl. J. Med 351 (27) (2004) 2827–2831, https://doi.org/10.1056/NEJMoa041888.
[10] P. Ballester, J. Muriel, A.M. Peiró, CYP2D6 phenotypes and opioid metabolism: the path to personalized analgesia, Expert Opin. Drug Metab. Toxicol. 18 (4) (2022) 261–275, https://doi.org/10.1080/17425255.2022.2085552.
[11] P. Karaca-Mandic, E. Meara, N.E. Morden, The growing problem of co-treatment with opioids and benzodiazepines, Bmj 356 (2017) j1224, https://doi.org/10.1136/bmj.j1224.
[12] J. Lee, H.D. Yoo, J.W. Bae, S. Lee, K.H. Shin, Population pharmacokinetic analysis of tramadol and O-desmethyltramadol with genetic polymorphism of CYP2D6, Drug Des. Devel Ther. 13 (2019) 1751–1761, https://doi.org/10.2147/dddt.s199574.
[13] B. Ji, S. Liu, Y. Xue, X. He, V.H. Man, X.Q. Xie, J. Wang, Prediction of Drug-Drug Interactions Between Opioids and Overdosed Benzodiazepines Using Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation, Drugs R. D. 19 (3) (2019) 297–305, https://doi.org/10.1007/s40268-019-00282-3.
[14] R.D. Treede, T.S. Jensen, J.N. Campbell, G. Cruccu, J.O. Dostrovsky, J.W. Griffin, P. Hansson, R. Hughes, T. Nurmikko, J. Serra, Neuropathic pain: redefinition and a grading system for clinical and research purposes, Neurology 70 (18) (2008) 1630–1635, https://doi.org/10.1212/01.wnl.0000282763.29778.59.
[15] B. Nicholson, Differential diagnosis: nociceptive and neuropathic pain, Am. J. Manag Care 12 (9 Suppl) (2006) S256–S262.
[16] R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle, painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain, Curr. Med Res Opin. 22 (10) (2006) 1911–1920, https://doi.org/10.1185/030079906×132488.
[17] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr. Scand. 67 (6) (1983) 361–370, https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.
[18] J.C. Fairbank, P.B. Pynsent, The Oswestry Disability Index, discussion 2952, Spine (Philos. Pa 1976) 25 (22) (2000) 2940–2952, https://doi.org/10.1097/00007632-200011150-00017.
[19] J. Pergolizzi, R.H. Böger, K. Budd, A. Dahan, S. Erdine, G. Hans, H.G. Kress, R. Langford, R. Likar, R.B. Raffa, P. Sacerdote, Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine,

oxycodone), Pain. Pr. 8 (4) (2008) 287–313, https://doi.org/10.1111/j.1533-2500.2008.00204.x.
[20] T. Flockhart DA, D, McDonald, C., Desta, Z., The Flockhart Cytochrome P450 Drug-Drug Interaction Table, 2021. https://drug-interactions.medicine.iu.edu. 2023).
[21] J. Barrachina, J. Muriel, C. Margarit, B. Planelles, P. Ballester, M. Richart-Martínez, E. Cutillas, T. Zandonai, D. Morales, A.M. Peiró, Global Pain State Questionnaire: Reliability, Validity, and Gender Gap, Arch. Intern. Med. Res. 4 (2021) 091–113, https://doi.org/10.26502/aimr.0061.
[22] A. Gaedigk, S.D. Simon, R.E. Pearce, L.D. Bradford, M.J. Kennedy, J.S. Leeder, The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype, Clin. Pharm. Ther. 83 (2) (2008) 234–242, https://doi.org/10.1038/sj.clpt.6100406.
[23] K.R. Crews, A. Gaedigk, H.M. Dunnenberger, T.E. Klein, D.D. Shen, J.T. Callaghan, E.D. Kharasch, T.C. Skaar, Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype, Clin. Pharm. Ther. 91 (2) (2012) 321–326, https://doi.org/10.1038/clpt.2011.287.
[24] K.E. Caudle, K. Sangkuhl, M. Whirl-Carrillo, J.J. Swen, C.E. Haidar, T.E. Klein, R. S. Gammal, M.V. Relling, S.A. Scott, D.L. Hertz, H.J. Guchelaar, A. Gaedigk, Standardizing CYP2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group, Clin. Transl. Sci. 13 (1) (2020) 116–124, https://doi.org/10.1111/cts.12692.
[25] L. Kaufner, S. Heimann, D. Zander, K. Weizsäcker, I. Correns, M. Sander, C. Spies, M. Schuster, A. Feldheiser, A. Henkelmann, K.D. Wernecke, C. V.O.N.H, Neuraxial anesthesia for pain control after cesarean section: a prospective randomized trial comparing three different neuraxial techniques in clinical practice, Minerva Anestesiol. 82 (5) (2016) 514–524.
[26] I. Cascorbi, Pharmacogenetics of cytochrome p4502D6: genetic background and clinical implication, Eur. J. Clin. Invest 33 (Suppl 2) (2003) 17–22, https://doi.org/10.1046/j.1365-2362.33.s2.3.x.
[27] L. Binkhorst, R.H. Mathijssen, M.P. van Herk-Sukel, M. Bannink, A. Jager, E. A. Wiemer, T. van Gelder, Unjustified prescribing of CYP2D6 inhibiting SSRIs in women treated with tamoxifen, Breast Cancer Res Treat. 139 (3) (2013) 923–929, https://doi.org/10.1007/s10549-013-2585-z.
[28] R.A. Bonakdar, Integrative Pain Management, Med Clin. North Am. 101 (5) (2017) 987–1004, https://doi.org/10.1016/j.mcna.2017.04.012.
[29] N.V. de Moraes, G.R. Lauretti, E.B. Coelho, A.L. Godoy, D.V. Neves, V.L. Lanchote, Impact of fraction unbound, CYP3A, and CYP2D6 in vivo activities, and other potential covariates to the clearance of tramadol enantiomers in patients with neuropathic pain, Fundam. Clin. Pharm. 30 (2) (2016) 153–161, https://doi.org/10.1111/fcp.12168.
[30] M. Matic, M. Nijenhuis, B. Soree, N.J. de Boer-Veger, A.M. Buunk, E.J.F. Houwink, H. Mulder, G. Rongen, J.V. Weide, B. Wilffert, J.J. Swen, H.J. Guchelaar, V.H. M. Deneer, R.H.N. van Schaik, Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6 and opioids (codeine, tramadol and oxycodone), Eur. J. Hum. Genet 30 (10) (2022) 1105–1113, https://doi.org/10.1038/s41431-021-00920-y.
[31] C. Chanfreau-Coffinier, S. Tuteja, L.E. Hull, S. MacDonald, O. Efimova, J. Bates, D. Voora, D.W. Oslin, S.L. DuVall, J.A. Lynch, Drug-drug-gene interaction risk among opioid users in the U.S. Department of Veterans Affairs, Pain 163 (12) (2022) 2390–2397, https://doi.org/10.1097/j.pain.0000000000002637.
[32] N.A. Nahid, J.A. Johnson, CYP2D6 pharmacogenetics and phenoconversion in personalized medicine, Expert Opin. Drug Metab. Toxicol. 18 (11) (2022) 769–785, https://doi.org/10.1080/17425255.2022.2160317.
[33] V. Michaud, R. Bikmetov, M.K. Smith, P. Dow, L.I. Darakjian, M. Deodhar, B. Cicali, K.T. Bain, J. Turgeon, Use of Drug Claims Data and a Medication Risk Score to Assess the Impact of CYP2D6 Drug Interactions among Opioid Users on Healthcare Costs, J. Pers. Med 11 (11) (2021), https://doi.org/10.3390/jpm11111174.
[34] V. Solhaug, E. Molden, Individual variability in clinical effect and tolerability of opioid analgesics - Importance of drug interactions and pharmacogenetics, Scand. J. Pain. 17 (2017) 193–200, https://doi.org/10.1016/j.sjpain.2017.09.009.