

# Pharmacogenetics and prediction of adverse events in prescription opioid use disorder patients

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## Abstract

The threats involved in the long-term opioid treatment of chronic non-cancer pain (CNCP) have increased notably. Strategies to identify at-risk patients are important because there is no clear evidence showing which screening or deprescription programmes are appropriate. Our aim was to evaluate the evidence provided by pharmacogenetics applied to predict an analgesic toxicity profile in prescription opioid use disorder (POUD) patients participating in an opioid deprescription programme. Pharmacogenetic markers were analysed in an observational, prospective deprescription programme for POUD patients (n = 88) treated for CNCP. It consisted of monitoring visits (baseline, follow-up and final), opioid rotation or discontinuation and the recording of adverse events and suspected adverse drug reactions (ADRs). Variants in *OPRM1* (A118G), *ABCB1* (C3435T), *COMT* (G472A), *OPRD1* (T921C) and *ARRB2* (C8622T) genes were tested by real-time PCR. Ethics committee approved the study. Wild-type *OPRM1*-AA genotype carriers reported a significantly higher number of adverse events than *OPRM1*-AG/GG (median [p25-75], 7 [5-11] vs 5 [3-9]), particularly gastrointestinal system events (90% vs 63%) such as nausea (33% vs 0%). Suspected ADRs (affecting 17% of the patients) were three times higher in males than in females (30% vs 11%). The deprescription programme was effective and safe, and it achieved a significant progressive reduction in the morphine equivalent daily dose, strong opioids and other analgesics' use, without causing any changes in pain intensity or opiate abstinence syndrome. *OPRM1* gene polymorphisms could identify the risk of gastrointestinal adverse events in POUD patients. Deprescription programmes including pharmacogenetic analysis should be considered during the follow-up of this population.

## KEYWORDS

adverse events, chronic pain, opioid use disorder, pharmacogenetics, prescription opioids

## 1 | INTRODUCTION AND BACKGROUND

The use of analgesic opioids for the treatment of chronic non-cancer pain (CNCP) has increased notably over the

last few decades. Although clinical guidelines for long-term opioid use have been proposed and implemented into clinical routine, CNCP management remains complex, this being mainly due to the opioid safety profile and to misuse.<sup>1,2</sup> Prescription opioid use disorder (POUD) is

reaching epidemic levels in the United States with high levels of misuse (21%-29%) or dependence (8%-12%).<sup>3</sup> Although the non-medical use of opioids is (still) rare in Europe, as are fatal incidents, vigilance is needed.<sup>4</sup> Healthcare providers must be able to identify factors that predispose certain individuals to the misuse of prescribed opioids and/or overdose.<sup>5</sup> A meta-analysis on the misuse of medication in the EU revealed that prescribed opioids were among the main groups concerned; data on mortality directly linked to their consumption in Europe are still, however, unavailable.<sup>6</sup>

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) now includes the term opioid use disorder and has established its diagnostic criteria.<sup>7</sup> Once presented, an individualized opioid tapering or deprescription treatment plan should be applied, together with general recommendations that include monitoring, opioid rotation, discontinuation of therapy and prevention of suspected opioid adverse drug reactions (ADRs) or adverse events (AEs).<sup>8,9</sup> At present, there are only limited guidelines for prescribing opioids and other analgesics for CNCP patients. Given the large economic burden of opioid-related ADRs, the most effective strategy may consist of prevention rather than treatment.<sup>10</sup> This is important because, in addition to POUD, other AEs relating to opioids, such as frequent dry mouth, nausea or constipation, may make their use more difficult for CNCP patients. As a consequence, a substantial proportion of patients (22%) may abandon the treatment.<sup>11</sup> This overall drug profile is often overlooked and oversimplified in clinical trials.<sup>12</sup> Understanding this aspect is even more important when POUD is detected, particularly in the context of CNCP patients who are often prescribed several medications for multiple comorbidities and present significant interindividual variability in drug response.<sup>13</sup>

Drug therapy based on individuals' genetic background may help to reduce adverse outcomes.<sup>14</sup> A recent opioid dependence genome-wide association study of 3058 opioid-exposed European Americans strongly implicated risk pathways, providing insights into novel prevention strategies.<sup>15,16</sup> The pain treatment-related genes that have been studied most thoroughly are the opioid receptors such as the  $\mu$ 1-opioid receptor (*OPRM1*, 118A>G) and the catecholamine degradation (*COMT*, 1947G>A) genes, and evidence suggests that both genes may contribute to the variability in morphine analgesia.<sup>17</sup> *OPRD1*, *ABCB1* and *ARRB2* genes have also been associated with methadone dosage requirements,<sup>18</sup> but little is known about CNCP with any other substance dependence.

Our aim was to evaluate the evidence provided by pharmacogenetics (PGx) applied to predict AEs in POUD patients participating in a scheduled opioid deprescription programme in a real-world ambulatory setting.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

An observational prospective study was conducted over a period of 30 months, from May 2013 to December 2015, on consecutive POUD patients with CNCP, at the Pain Unit of Alicante General Hospital in Spain. The study was approved by the Ethics Committee Board of Alicante Department of Health-General. Once the aim and confidentiality of the study was explained to the patients, informed consent was obtained and questionnaires were completed by the patients.

### 2.2 | Participants and procedures

The patients were assessed during a baseline visit by four physicians (two anaesthesiologists, one clinical pharmacologist and one psychiatrist), one nurse and one occupational therapist trained in pain management. A total of 88 participants who were from the hospital and surrounding areas, and who were attending the Pain Unit, took part in the study. The criteria to be met by those taking part were as follows: patients >18 years old, with CNCP, long-term use of opioids (>6 months) and clinical evolution indicating possible use disorder behaviour. To be included in the study, diagnosis of POUD was performed by a clinical psychiatrist using DSM-5 diagnostic criteria.<sup>7</sup> Patients <18 years old with oncological pain or psychiatric disorders that could interfere with the completion of the study were excluded.

### 2.3 | Deprescription programme

Clinical interviews were performed to evaluate the physical health, the drug use and medical history of the patients. Patients were then enrolled in a deprescription programme,<sup>9</sup> which consisted of opioid rotation together with a tapering procedure. Physicians took account of the clinical conditions of each individual patient when performing this procedure, but the general procedure was as follows: removal of rapid delivery opioids; rotation to opioid patches (buprenorphine or, as an alternative, fentanyl); opioid dose tapering with the addition of tramadol and the progressive reduction in the buprenorphine dose.

The deprescription programme was ideally structured into a baseline visit, follow-up visits (1, 2 weeks, 1 and 3 months) and a final visit at 6 months. Nevertheless, given that the programme covered a complex population, with a mixture of chronic pain and POUD, the number of visits and the length of the periods of deprescription varied from subject to subject.

Patients were monitored in order to prevent opiate abstinence syndrome (OAS) or any other events associated with

the discontinuation procedure (nervousness, insomnia, anxiety, gastrointestinal disorders, etc.), and individualized intervention was undertaken to prevent such events.<sup>9</sup> In addition, for monitoring purposes, patients received weekly phone calls from an occupational therapist.

## 2.4 | Data collected

Information on demographic metrics (age, sex, ethnicity, body-weight and height) and on pharmacological treatment was collected from the hospital records. Validated scales and questionnaires were self-completed with the support of an expert clinician at each visit.

Pain intensity and relief were assessed using the visual analogue scale (VAS).<sup>19</sup> Both consisted of a 100-mm horizontal line ranging from 0 (lowest) to 100 mm (highest), on which the patients indicated the intensity of pain or relief they experienced, respectively.

The OAS was evaluated using the validated Opiate Withdrawal Scale (OWS). This is a questionnaire comprising 32 characteristic signs and symptoms that are common in opioid withdrawal patients.<sup>20</sup> Each item was rated as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe) indicating the degree to which they were experienced by each patient. The result was obtained from the total of 32 items, producing final scores that ranged from 0 to 96 points: the higher the score the greater the severity.

## 2.5 | Drug use and adverse events

The information on the use of pain medication was obtained from the institution's electronic prescribing application. Opioids were recorded and categorized according to the WHO analgesic ladder. This includes buprenorphine, oxycodone, fentanyl, morphine, hydromorphone and tapentadol as strong opioids and tramadol as a weak opioid. Morphine analgesic equivalent daily doses (MEDD) were calculated.<sup>21</sup> Other analgesics and non-steroidal anti-inflammatory drugs were classified as non-opioid analgesics. Neuromodulators including anticonvulsants (pregabalin, gabapentin), antidepressants and anxiolytics (benzodiazepines) were also registered.

An AE was defined as any undesirable event experienced by a patient, regardless of whether this was suspected or not of being attributable to the drug administered. At each visit, subjects were asked whether they had experienced any AEs and their responses were recorded. This was done using a questionnaire comprising a list of the 18 most common events (selected as indicated in the opioid characteristics summary document, with frequencies given as "very common" or "common")<sup>22</sup> and a blank field to enable the patients to add any others. Patients were asked to tick any AEs that had occurred since their

previous medical visit. At the follow-up visits, specific AEs or the use of medication was considered as "present" for the purposes of the analysis, when they were observed in at least 50% of the total follow-up visits performed.

In addition, a clinical interview was undertaken by a physician in the course of each of the visits during the study to determine whether the AEs reported by the patients suggested that ADRs may have occurred. The ADRs were identified when the patient stated that an AE had appeared after a change in the consumption of opioids (usually a new prescription, a rotation of opioids or a change in the dose prescribed), and the causality (between the AE and the medication) was deemed to be reasonable for medical reasons.

All AEs and suspected ADRs relating to the pharmacological treatment of pain were collected and classified using the terminology of the "System Organ Class" and "Preferred Term" by the Medical Dictionary for Regulatory Activities (MedDRA, version 20.0).<sup>23</sup>

## 2.6 | Genotyping

Participants were genotyped for the following gene polymorphisms: *OPRM1* (A118G, rs1799971), *COMT* (G472A, rs4680), *ABCB1* (C3435T, rs1045642), *OPRD1* (T921C, rs2234918) and *ARRB2* (C8622T, rs1045280).

Approximately 2 mL of saliva was collected in PBS containing tubes. Genomic DNA was isolated by E.N.Z.A. Forensic DNA Kit (Omega bio-tek) in accordance with the manufacturer's instructions. Genotyping was performed by real-time polymerase chain reaction (RT-PCR). Amplifications were carried out in a RT-PCR Rotor-Gene Q (QIAGEN N.V.) using specific TaqMan probes MGB® (Applied Biosystems). Amplification parameters were as follows: pre-PCR section 30 seconds at 60°C, initial 10 minutes denaturation at 95°C, 45 cycles of 15 seconds at 95°C, 60 seconds at 60°C and 30 seconds final extension at 72°C.

## 2.7 | Statistical analysis

Data distribution was analysed using the Shapiro-Wilk's normality test. Quantitative data were presented as mean  $\pm$  standard error (SE), while median (percentile 25-75, p25-p75) was used for non-parametric data and quantitative discrete variables such as AEs. Categorical data were expressed in percentages.

For non-repeated measurements, comparisons for continuous or categorical data between two groups were conducted using independent Student's *t* test and Mann-Whitney *U* test or Fischer's exact test, respectively.

For repeated-measurement quantitative data analysis, a linear regression mixed model with a random effect

associated to the subject was used. In the case of qualitative data, a logistic regression mixed-model with a random effect associated with the subject was used.

For *OPRM1* A118G, *COMT* G472A, *ABCBI* C3435T, *OPRD1* T921C and *ARRB2* C8622T association analysis, Hardy-Weinberg equilibrium, codominant, dominant, recessive and overdominant models were obtained. Multiple linear regression (quantitative data) and logistic regression (qualitative data) were used to evaluate the influence of covariates. Possible interactions between AEs were analysed employing log-linear models in three-way contingency tables. A  $P < 0.05$  was considered statistically significant. All statistical analyses were carried out with the R 3.2.4 software version.

### 3 | RESULTS

#### 3.1 | Descriptive and clinical data

A summary of clinical, safety and drug prescription data of the subjects is provided in Table 1. These data were obtained over the course of the deprescription programme.

A total of 88 CNCP patients under long-term opioid treatment and diagnosed to have POUD diagnosis by using DSM-5 criteria were included in the programme ( $53 \pm 1$  years of age, 64% females, VAS pain intensity  $55 \pm 3$  mm, 100% Caucasian). Five subjects dropped out because of complete loss of follow-up. The baseline visit was performed in 100% of the subjects and the final visit on 89%. The median (p25-p75) number of follow-up visits was 2 (1-4) per patient. The baseline MEDD was  $167 \pm 26$  mg/d, with patients mostly under strong opioids (95%). Weak opioids, non-opioid analgesics, neuromodulators, antidepressants and/or anxiolytics were being prescribed in more than 20% of cases.

The deprescription programme achieved the following significant and progressive reductions which were seen in the baseline, follow-up and final visits of the POUD patients. These reductions were in the MEDD ( $167 \pm 26$ ,  $112 \pm 12$  and  $87 \pm 12$  mg/d, respectively), the use of strong opioids (95%, 88% and 66%) and in the use of other analgesics (28%, 20% and 7%). This was achieved without a significant difference in OWS scores and with pain intensity being maintained at moderate. Prescribed antidepressants were more frequently seen in follow-up and final visits (53%, 63% and 66%). No differences in other clinical variables or in the use of other prescribed drugs (weak opioids, neuromodulators, antidepressants or anxiolytics) were observed between baseline, follow-up and final visits (Figure 1).

#### 3.2 | Adverse events and suspected adverse drug reactions reported

A summary of the AEs reported by patients in real-world ambulatory visits is provided in Figures 2 and 3.

In the baseline visit, a median of 6 (3-9) AEs/patient was recorded. The most frequent of these were dry mouth (61%), constipation (47%), sleep disruption (47%) and depression (45%). No significant differences between the baseline, follow-up and final visits were identified with regard to the frequency of any AEs (Figure 2). Most frequent AEs classified by system (MedDRA) were gastrointestinal (76%) and psychiatric (76%) disorders (data not shown).

The patients reported a total of 1659 AEs in a total of 359 visits (median of 7 [4-9] EAs/visit). The most frequent AEs classified by system were psychiatric (21%) and gastrointestinal disorders (20%; Figure 3A). Only 17% of the POUD patients presented ADRs during the study. These

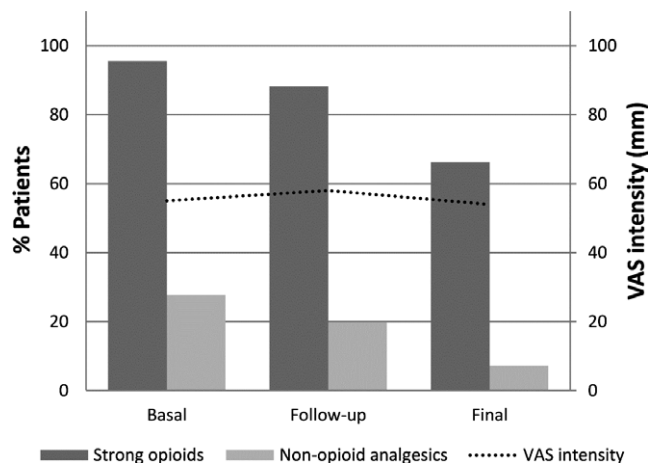
**TABLE 1** Clinical and pharmacological data along the deprescription programme

Visits	Baseline	Follow-up	Final	P-value
VAS pain intensity (mean $\pm$ SE, 0-100 mm)	$55 \pm 3$	$58 \pm 3$	$54 \pm 4$	0.866
Total AEs/patient Median (p25-p75)	6 (3-9)	7 (5-10)	6 (4-9)	0.626
MEDD (mean $\pm$ SE, mg/d)	<b><math>167 \pm 26</math></b>	<b><math>112 \pm 12</math></b>	<b><math>87 \pm 12</math></b>	<b>&lt;0.001*</b>
Strong opioids (%)	<b>95</b>	<b>88</b>	<b>66</b>	<b>&lt;0.001*</b>
Weak opioids (%)	36	49	47	0.264
Analgesics (%)	<b>28</b>	<b>20</b>	<b>7</b>	<b>0.002*</b>
Anticonvulsants (%)	56	54	55	0.476
Antidepressants (%)	56	63	66	<b>0.008*</b>
Anxiolytics (%)	36	36	34	0.200

AEs, adverse events; MEDD, morphine equivalent daily dose; P-value, analysis of baseline, follow-up and final visits obtained from linear regression mixed model (quantitative data) and logistic regression mixed-model (qualitative data); p25-p75, percentile 25 to percentile 75; SE, standard error; VAS, visual analogue scale.

\*P-values <0.050 are shown in bold.





**FIGURE 1** Strong opioids and non-opioid analgesics use and pain intensity along the deprescription programme in prescription opioid use disorder patients. A significant reduction (result obtained by logistic regression mixed-model) in patients using strong opioids or non-opioid analgesics was achieved while maintaining a moderate pain intensity. VAS, visual analogue scale (0-100 mm)

were mainly psychiatric (libido alteration) or related to the reproductive systems (erectile dysfunction; Figure 3B).

### 3.3 | The influence of gender

Comparing males with females, response to the deprescription programme was similar and there were no differences with regard to the frequency of AEs. Males did, however, exhibit a significantly higher frequency of skin-related disorders (79% vs 56%,  $P = 0.049$ ) than females, mostly involving itching (62% vs 24%,  $P = 0.035$ ) in the baseline visit and loss of libido (61% vs 24%,  $P = 0.015$ ) in the final visit. The number of suspected ADRs reported during the study was significantly (three times) higher in males than in females (30% vs 11%,  $P = 0.042$ ).

### 3.4 | Analysis of genotype influence

In the baseline visit, the total number of AEs varies significantly among *OPRM1* genotypes as shown in Figure 4. The total number of AEs was higher in *OPRM1* AA carriers who reported almost two more AEs than AG/GG patients (7 [5-11] vs 5 [3-9],  $P = 0.046$ ). In the overdominant model, *COMT*-AA/GG genotypes showed a significantly higher number of AEs/patient (8 [6-11],  $P = 0.026$ ). Multiple linear regression analysis showed no significant influence of MEDD on these results.

Prevalence of nausea (AA = 33%, AG = 0%, GG = 0%,  $P = 0.034$ ) and gastrointestinal AEs (AA = 90%, AG = 67%, GG = 0%  $P = 0.031$ ) varied significantly among *OPRM1* genotypes. Loss of libido (AA = 78%, AG = 18%, GG = 67%,  $P = 0.003$ ) and skin redness

(AA = 22%, AG = 0%, GG = 50%,  $P = 0.003$ ) were found to be less frequent in *COMT*-AG genotype (Figure 5).

In the final visit, the prevalence of vomiting (AA = 67%, AG = 0%, GG = 10%,  $P = 0.003$ ) and sexual dysfunction (AA/GG = 28%, AG = 7%,  $P = 0.040$ ) varied among *COMT* genotypes. Analysis of other polymorphisms showed that *OPRD*-CT genotype was less frequently associated with sexual dysfunction (TT = 46%, CT = 0%, CC = 31%,  $P = 0.001$ ) and reproductive system disorders (TT = 24%, CT = 0%, CC = 45%,  $P = 0.001$ ). In addition, *ARRB2*-TT genotype was found to be less frequently associated with loss of libido (CC = 21%, CT = 79%, TT = 0%,  $P = 0.021$ ), dry skin (CC = 4%, CT = 96%, TT = 0%,  $P = 0.024$ ) and skin system AEs (CC = 60%, CT = 57%, TT = 0%,  $P = 0.027$ ). Logistic regression showed no significant influence of MEDD on these results, except for skin disorders and *ARRB2* genotypes, which were influenced positively by MEDD ( $P = 0.030$ ; Figure S1).

No significant interactions were found between loss of libido with skin redness in the baseline visit and vomiting with sexual dysfunction in the final visit for *COMT* genotypes. Likewise, no interactions were observed between loss of libido with dry skin for *ARRB2* genotypes in the final visit.

After the deprescription programme, *OPRM1*-G mutant allele carriers presented significantly more nausea in the final visit than in the baseline visit ( $P = 0.015$ ). Also, *COMT*-AG genotype presented more skin redness in the final visit ( $P = 0.009$ ) while *COMT*-AA/GG presented less skin redness in the final visit ( $P = 0.007$ ; Figure 2).

## 4 | DISCUSSION

This study suggests that *OPRM1* gene polymorphisms can help us to predict gastrointestinal AEs in POUD patients participating in a scheduled opioid deprescription programme. Variants of key genes in pain, as *OPRM1*, can influence opioid toxicity, with a significantly higher number of AEs in wild-type genotype than allelic variants. This result is important because, while Europe does not face an “opioid epidemic,” addiction to opioids should be considered when using them in CNCP and should therefore be closely monitored.<sup>6</sup> The *OPRM1* gene could therefore help us to evaluate the most frequent opioid AEs: gastrointestinal disorders.

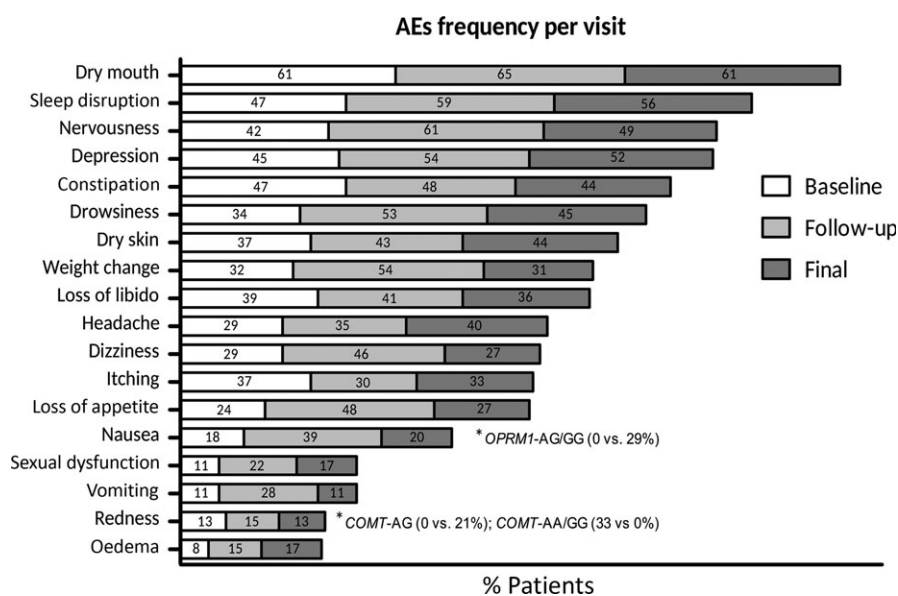
In our study, *OPRM1*-AA genotype showed a significantly higher frequency in gastrointestinal disorders, especially nausea. Interestingly, we had previously found that *OPRM1*-AA patients had lower MEDD requirements for analgesia,<sup>9</sup> suggesting that *OPRM1*-G variant carriers could present a reduced opioid efficacy and a significantly lower

risk of suffering from AEs. Both could be caused by a loss of N-glycosylation site in OPRM1 receptor in *OPRM1-G* carriers.<sup>24</sup> It had previously been suggested that this variant could lead to an increase in MEDD requirements<sup>25</sup> and protection against opioid toxicity at therapeutic levels in *OPRM1-GG* patients.<sup>26</sup>

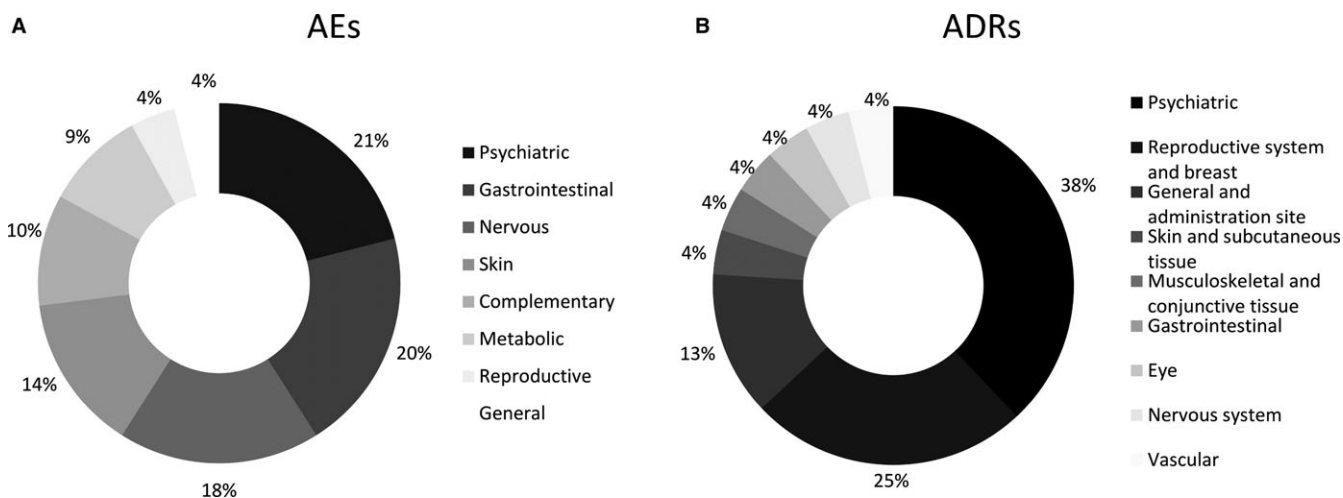
Previous studies suggested that OPRM1 high-expression variants appear to cause a high risk of nausea/vomiting in tramadol treatment.<sup>27</sup> Also, a meta-analysis of 23 studies (n = 5902) indicated that the *OPRM1* A118G variant was the one with the greater influence on pain management in post-operative patients. It has been shown that *OPRM1-G* mutant allele carriers consumed more opioids for analgesia and presented less nausea and vomiting during the first 24 hours.<sup>28</sup> This is similar to our findings.

Together with the opioid toxicity profile, one of the most frequent opioid AEs is constipation. A broad range of peptides with opioid-like effects has been identified in the central nervous system (loss of balance, drowsiness)<sup>29</sup> and peripheral tissues, including the gut (nausea, vomiting). These peptides exert their effects through the opioid receptors with agonism in the gastrointestinal system and can result in nausea, vomiting or constipation as a result of the interruption of both excitatory and inhibitory neural inputs in the musculature tract as well as inhibition of ion and fluid transport.<sup>30</sup>

Related to this effect, catechol-O-methyltransferase (COMT) degrades catecholamines and thus modulates adrenergic, noradrenergic and dopaminergic neuronal transmission. The gene 472A mutant allele variant results in a



**FIGURE 2** Frequency of adverse events (AEs) along the deprescription programme at baseline, follow-up and final visits. Each bar is subdivided by % of patients presenting with the corresponding AE at baseline, follow-up and final visits. Results were obtained by logistic regression mixed-model for repeated data including basal vs final visit for *OPRM1* and *COMT* genotypes. (\*)Significant differences ( $P$ -value <0.05) between baseline and final visit by genotype



**FIGURE 3** Frequency of each affected system with respect to the total affected systems (100%) according to the total number of adverse events (AEs = 905, A) and suspected adverse drug reactions (ADRs = 24, B) registered from the subjects along all the visits of the study

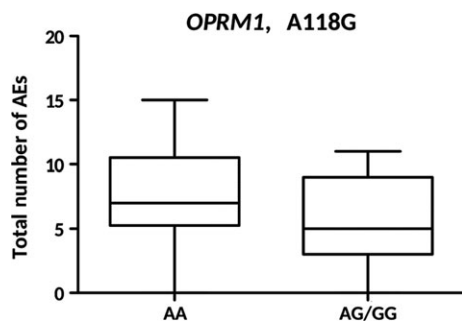
protein with lower associated activity and lower morphine requirements.<sup>31</sup> We found that the frequency of loss of libido and skin redness was lower in *COMT*-AG genotype.<sup>22</sup> In relation to AEs, some evidence exists relating to *COMT* genotype and the appearance of pruritus (1947-GG genotype: 2.9 times more,  $P < 0.05$ )<sup>22</sup> and with acute intoxication in patients with opioid addiction (472-AA genotype).<sup>32</sup> These results were not replicated in our study, although we observed in the baseline visit that skin redness was more frequent in *COMT*-GG patients.

Our results have shown differences in the baseline visit only. This was considered to be the best time to assess AEs because withdrawal symptoms were not present at that time. Once deprescription and the opioid dose reduction had been carried out, no differences were observed among *OPRM1* genotypes. Validation studies would be necessary to assess *OPRM1* as a biomarker in opioid safety.

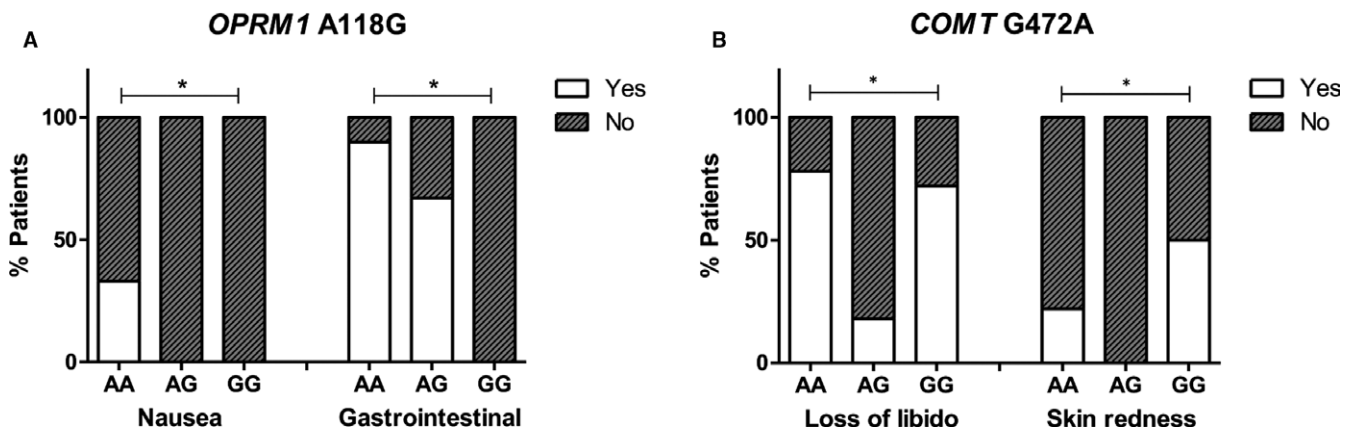
As far as gender differences are concerned, it had previously been shown that women present greater morphine-induced respiratory depression,<sup>33,34</sup> increased negative

feelings as well as more severe nausea and vomiting.<sup>35,36</sup> Our study revealed that the two genders had similar frequencies of the total number of AEs. Nevertheless, skin itching and reproductive AEs were more frequent in males and the number of suspected ADRs was three times higher in males than females. This was rather surprising because, in the general population, women present a 50%-70% higher risk of suspected ADRs than men, and 60% of AE patients admitted at the hospital are females.<sup>37,38</sup> Although the underlying reasons are not clear because women are only included in 38% of human research studies, hormonal factors, differences in pharmacokinetics and pharmacodynamics may play a significant role.<sup>39</sup> This discrepancy might be explained too much emphasis placed on sexual dysfunction because of a parallel open study of long-term opioid patients in our unit at that time,<sup>40,41</sup> as 67% of males suspected ADRs in our study are loss of libido or erectile dysfunction.

Our findings should be interpreted in the light of some limitations. We have limited understanding of how different genetic markers interact with one another to protect against or exacerbate AEs, particularly in the context of complex and diverse subjects as CNCP POUD patients. With more cases, we might be in a better position to evaluate the predictive value of this panel of candidate genes and to determine whether they might be useful in the prevention of AEs. Functional studies may help to cast light on how these genetic variants may modulate treatment and response to opioid medications. In our study, the prevalence of AEs was based on self-reports made by the patients, without the physician applying a diagnostic test that is often used in other studies. As can be observed, some of the most common opioid-related AEs can be the same or overlap with those produced by the OAS. To minimize the effect of withdrawal period, the analyses of AEs were focused in the baseline visit as withdrawal symptoms had not yet appeared.



**FIGURE 4** Difference in the total number of adverse events (AEs) according to *OPRM1* genotype at baseline visit. *OPRM1*-AA genotype showed a significantly higher total number of AEs (Student's *t* test and multiple linear regression were used)



**FIGURE 5** Difference in the frequency of nausea and gastrointestinal events among *OPRM1* genotypes (A), and in loss of libido and skin redness among *COMT* genotypes (B) in the baseline visit. The prevalence of nausea and gastrointestinal AEs was significantly higher in *OPRM1*-AA genotype at baseline visit. Loss of libido and skin redness were found to be less frequent in *COMT*-AG genotypes at baseline visit. Chi-squared or Fisher's exact tests and logistic regression were used. \*Significant differences ( $P$ -value  $< 0.05$ ) between percentage of patients presenting AEs by genotypes

There were no differences in the number of AEs encountered in the baseline, follow-up and final visits. This surprised us at first because we expected to have fewer AEs with lower opioid doses or avoiding opioid use disorder. It may well be related to the complexity of our population, the persistence of pain and other comorbidities. Furthermore, we observed in the follow-up and final visits that the use of antidepressants increased. Antidepressants and the one that was most frequently prescribed during the study (duloxetine) can lead to AEs that are similar to those caused by opioids, such as weight change and dry mouth. This could (in part) account for the fact that the frequency of AEs did not decrease during the opioid deprescription programme.

Overall, this could mean that patients have reduced their MEDD without changes in pain intensity, abstinence syndrome or their safety profile at short term. In the long run, we do not know whether there would be an improvement in tolerability as the data provided only covered a period of 6 months. In future studies, we will include an extra follow-up period of 6 months after the conclusion of deprescription programme so that we can examine the long-term safety profile. It also should be noted that pain sufferers attending our Pain Unit are complex patients who often exhibit higher levels of psychosocial dysfunction, cognitive difficulties and comorbidities. They usually require polypharmacy, including neuromodulators. It is not therefore possible to associate these AEs exclusively with opioids. This may explain why the total number of AEs did not vary during the course of the study. Nevertheless, the list of AEs given to patients included the most common AEs in opioid therapy. In addition, the main deprescription was performed for opioid drugs, while concomitant use did not decrease significantly. Furthermore, some clinical conditions, such as cognitive difficulties, are more frequent in patients experiencing higher pain intensity levels (VAS ranging between 64 and 71 mm) in patients.<sup>42</sup> Untreated pain itself may therefore pose a greater risk to cognitive dysfunction and cannot always be associated with analgesic prescription AEs, particularly in POUD patients who do not have any other addiction, this being a population which is not usually included in research.

Despite these limitations, our view is that this observational study, which was carried out in a “real-world” Pain Unit may provide useful information.

## 5 | CONCLUSION

The use of opioids to alleviate pain is complicated by the risk of AEs as POUD. PGx may possibly be used to tailor pain medication based on an individual's genetic background, especially in the case of patients who are at risk of

severe AEs. Based on the present data, *OPRM1* genotype seems promising for application in clinical practice for predicting the analgesic toxicity profile in POUD patients, especially in relation to gastrointestinal disorders in a scheduled opioid deprescription programme at ambulatory setting. Future studies should focus on the under-reporting of suspected ADRs in females.

## CONFLICT OF INTEREST

All authors declare no competing interests.

## AUTHOR CONTRIBUTIONS

Olga Alda, Biologist, PhD, Pain Research coordinator, ISABIAL, Alicante, Spain: study design and ethical approval. Raquel Ajo, Pharmacist, PhD, Pain Research coordinator, ISABIAL, Alicante, Spain: prescreening and screening, clinical support training patients to complete questionnaires. Raquel Martín, Pain Nurse assistance, Pain Unit, General Hospital, Alicante, Spain: clinical support training patients to complete questionnaires. Carlos García-Navas, Pharmacist, UMH, Elche, Alicante, Spain: database design. Ana Londoño, MD, PhD, Psychiatry and Clinical Pharmacology, Clinical Pharmacology Unit, General Hospital, Alicante, Spain: patients' psychiatry evaluation and clinical visits support. María-del-Mar Inda, Biologist and Biochemist, PhD, Pain Research coordinator, ISABIAL, Alicante, Spain: paper review.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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