



# Gender based differences, pharmacogenetics and adverse events in chronic pain management

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## Abstract

Safety data in chronic non-cancer pain (CNCp) with long-term opioid therapy has been poorly studied and can be differently influenced by gender. Furthermore, pharmacogenetics (PGx) could possibly be used to tailor pain medication based on the individual's genetic background. The aim was to assess whether PGx applied to a pharmacovigilance system could help to improve a patient's security profile. A pharmacovigilance data recording system was conducted over 24 months, including genotyping of *OPRM1* variants (opioid receptor, A118G) and *COMT* (enzyme that degrades catecholamines such as norepinephrine, G1947A). Pain intensity (visual analogue scale, VAS), morphine equivalent daily dose (MEDD), adverse events (AEs) and suspected adverse drug reactions (ADRs) were recorded and analysed by gender. The Ethics Committee approved the study and data were analysed with R 3.6.0 software. A total of 748 patients were recruited in the study (67% female, VAS  $62 \pm 29$  mm, MEDD  $119 \pm 114$  mg/day) reporting a median of 6 (3.5–9) AEs/patient. Women presented more nausea, headaches, insomnia, loss of appetite, weight change, depression and dizziness than men. Analysis by genotype demonstrated that PGx influenced the prevalence of vomiting and depression in men, dizziness in women and sexual dysfunction in both. Physicians notified 150 ADRs mostly in females (79%) related to nervous system disorders. PGx applied to a pharmacovigilance recording system provides important information to achieve a better knowledge about AEs in CNCp pharmacological therapy. *OPRM1* and *COMT* polymorphisms were associated with AEs in CNCp patients that differed according to gender.

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## Introduction

Pharmacogenetics (PGx) tries to bring about better understanding of the genetic contribution to inter-individual variability in analgesic response, which is especially required in long-term opioid use [1]. Currently, pharmacological treatments are the first-line therapy for chronic non-cancer pain (CNCp), but there is a highly variable analgesic drug response among patients. Clinical guidelines for the management of CNCp state that opioids may have an important role in its treatment [2, 3].

The efficacy of opioids has been well established [4, 5]; however, the potential benefits of opioids in the management of pain may be limited by adverse side effects such as constipation or sedation, which usually are underdetected [6]. Furthermore, pharmacological differences between women and men might be clinically relevant and most drugs withdrawn from the market presented greater health risks for women [7–9]. In addition, there are ~30% more suspected adverse drug

reactions (ADRs) reported in women than in men. Experimental data point to a different modulation of the endogenous opioid system and sex hormones [10], as factors influencing pain sensitivity in males and females. However gender has rarely been evaluated as a moderator [11]. Gender pain medicine must consider the needs of both genders where specific data on women related to side events are lacking [12].

PGx studies aim to help in the selection and dosing of treatment for a specific patient by improving the patient's adherence and reducing adverse events (AEs); allowing more appropriate assessment of patients and better treatment planning [13, 14]. For opioids, the most studied PGx target genes are genes related to the  $\mu$ -opioid receptor (*OPRM1*) and catechol-O-methyltransferase enzyme (*COMT*). Polymorphisms on these genes have been widely studied and it is suggested that they might contribute to inter-individual differences in pain sensitivity and response to opioids [15].

Our aim was to assess whether PGx applied to a pharmacovigilance system could help to improve patient's security in order to monitor the treatment's security profile and to improve the patient's management by including a gender analysis.

## Material and methods

### Study design

This PGx sub-study (VIGIDOL-gene code) was approved by the Ethics Committee of Alicante General Hospital and carried out in accordance with the Helsinki Declaration principles. PGx informed consent and samples were obtained in the context of a larger observational study (VIGIDOL), conducted over a period of 24 months at the Pain Unit of the Department of Health of Alicante General Hospital, Spain [16].

### Patients

The inclusion criteria were adult  $\geq 18$  years old, with regular opioid prescription (for  $\geq 6$  months), diagnosis of CNCP, and with adequate mental status for properly completing the scales and questionnaires. The exclusion criteria were the patient's decision, no further monitoring or cessation of allocated medication.

The mental status examination includes a medical history report from the patient, and observational data gathered by the physician throughout the clinical visit (i.e. regarding appearance, general behaviour, and speech, mood, thought process, or content).

### Procedure

Patients filled in the forms/questionnaires during their regular visits and clinical data was analysed at the end of the study.

Pain intensity was determined using the validated 100-mm visual analogue scale (VAS, 0 "no pain" to 100 "worst possible pain") [17] and a Likert-based scale (descriptors: none, mild, moderate, severe and extreme pain) [18]. Pain relief was determined using a 100-mm VAS (0 "no relief" to 100 "maximum relief") and Likert-based scale (none, mild, moderate, severe and extreme pain relief). Quality of life related to health measures was assessed by the EuroQoL-VAS (0 "worst" to 100 "best health status") [19].

A data recording system designed to report the AEs noticed healthcare use and frequentation was developed at the Hospital Pain Unit [16]. A questionnaire with a list of the most frequent AEs [20] together with a blank field to add any other AE was developed for this. In addition, questions about if patients changed any prescribed drugs, had any visits to the emergency department or hospital admissions, due to pain or other causes, since their last clinical visit were included.

Moreover, suspected ADRs associated with long-term opioid therapy were notified to the Spanish Pharmacovigilance System by the physicians [21]. Medical and pharmacological data were obtained from the electronic hospital system at the clinical visits. Physicians also evaluated the possibility of adjusting the pharmacological pain therapy. Suspected ADRs notified were classified using the terminology of the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0): preferred term and system organ class, which are groupings by aetiology manifestation site (e.g. gastrointestinal disorders) or purpose. MedDRA is an European extensive medical terminology that supports public health monitoring, data analysis, communication (both electronic and traditional) and data management [22, 23].

### Pharmacological pain therapy

Physicians collected: pain type, patients' prescribed therapy understood as opioids and concomitant drugs (antiepileptic, antipsychotic, anxiolytic, antidepressant or muscle relaxant), doses and polypharmacy (defined as  $\geq 5$  drugs prescribed in relation to pain). Total daily dose of opioids was converted to an equivalent daily dose of oral morphine (morphine equivalent daily dose, MEDD), estimated using an equianalgesic dose [24]. The percentages of drug prescriptions at the Pain Unit during the study period were recorded using the Hospital electronic Health Information System.

## SNP genotyping

Four millilitres of saliva samples were collected during clinical visits. DNA was isolated using E.Z.N.A.<sup>®</sup> Tissue.A. Forensic DNA Kit (Omega bio-tek, Norcross, GA, US) following the manufacturer's instructions and quantified with a NanoDrop spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, US). A118G (rs1799971) of *OPRM1* and G472A (rs4633) of *COMT* genes were analysed using real-time PCR. TaqMan<sup>®</sup> technology (Thermo Fisher Scientific, Pleasanton, CA) was used to detect SNP variant alleles using real-time PCR following the manufacturer's instructions. Genotyping was carried out on a Real Time PCR Rotor Gene Q (Qiagen, Hilden, Germany) system. PCR reactions were performed on duplicates and negative controls were included on each PCR reaction.

## Statistical analysis

We include all clinical registers carried out over 24 months to observe the most common safety profile associated to pain drug management. Confidence interval (CI) was calculated (sample size ( $n = 175$ ), total population ( $n = 754$ ) and confidence level 95%) with a percentage of 90%, being 3.9. This means that our estimation is appropriate for arise differences in 86% of the population.

The Shapiro–Wilk normality test was used to select parametric or non-parametric tests for comparisons. Continuous variables are presented by mean  $\pm$  standard deviation or median and interquartile range (IQR), while categorical variables are expressed by absolute counts and/or percentages. *T*-test for independent samples or a Mann–Whitney U test were used to assess differences between the two groups; effect sizes (Cohen's  $d$ ) and 95% CIs were also reported. One-way ANOVA or Kruskal–Wallis test were used to compare three or more groups; effect sizes ( $\eta^2$ ) and 95% CI are given. Frequencies were compared using the Chi-square or Fisher's exact test, with Yate's continuity correction as appropriate and  $\chi^2$  and degrees of freedom (df) or odds ratio (OR) and 95% CI being reported. Hardy–Weinberg equilibrium was determined by comparing the observed genotype frequencies with the expected values using the  $\chi^2$  test with Yates' correction. All statistical analyses were performed with R 3.2.4 software.  $p$  values of  $<0.05$  were considered to indicate statistical significance.

## Results

### Demographic and clinical data

A total of 748 patients with long-term use of opioids for CNCP were included in the study. No cases were excluded

due to mental status. The participant's clinical and demographic data is presented in Table 1.

The mean age of the patients genotyped was 65 years old, and 67% were females. The majority of patients presented moderate chronic low back pain (VAS  $62 \pm 29$  mm) with mild relief (VAS  $31 \pm 31$  mm) and quality of life (EuroQol-VAS  $41 \pm 23$  mm), with a MEDD of  $119 \pm 114$  mg/day. Most of the patients reported an AE (94%) with a median of 6 AEs per patient (IQR 3.5–9). The most prevalent AEs were dry mouth (65%), constipation (56%), nervousness (53%), drowsiness (44%), insomnia (44%) and depression (42%) (Fig. 1).

Physicians notified 150 ADRs (20% of patients included are called "cases") that were mostly females (79%) with a mean age of  $66 \pm 14$  years old (Table 1). Similarly, to total population, the cases presented moderate pain (VAS  $67 \pm 26$  mm), mild relief (VAS  $30 \pm 28$  mm) and moderate quality of life (EuroQol-VAS  $42 \pm 22$  mm). However, cases presented a higher MEDD ( $139 \pm 144$  mg/day) and a significantly higher polypharmacy (69%,  $p < 0.001$ ; OR = 0.456; 95% CI = 0.3119–0.6675) and number of AEs/patient (median 9 (IQR 6–11),  $p < 0.001$ ;  $d = 0.761$ ; 95% CI =  $-2.899$  to  $-1.371$ ). However, most healthcare resources used for the pain or other causes did not differ from the total population.

AEs and ADRs were classified using the terminology of the MedDRA (Fig. 2). In the total population, AEs most commonly reported by patients belonged to the gastrointestinal system (77%), followed by psychiatric (71%), nervous (70%) and general (67%) systems. In the case population, AEs most commonly reported by patients belonged to the gastrointestinal system (90%), nervous system (86%), psychiatric (83%) and general system (82%). However, ADRs appertained more frequently to the nervous system (24%), followed by psychiatric disorders (17%), gastrointestinal (15%) and skin and general (12%) disorders.

### OPRM1 and COMT genotyping

A total of 172 CNCP (62 cases and 110 controls) patients were genotyped for *OPRM1* and *COMT* polymorphisms. Genotypic and allelic frequencies for *OPRM1* and *COMT* genes are presented in Table 2. *OPRM1* and *COMT* polymorphisms were in Hardy–Weinberg equilibrium ( $p = 0.353$  and  $p = 0.647$ , respectively).

Genotypic and allelic frequencies did not differ between patients with (cases) and without (controls) ADR notification (Supplementary Table 1). Analysis of the influence of the genotype in the presence of specific AEs was performed by Pearson Chi squared or Fisher's exact tests. Significant differences in the total population among *OPRM1* genotypes were observed for insomnia and in *COMT* genotype

**Table 1** Demographic, clinical and pharmacological data

	Total (n = 748)	Cases (n = 150)	Pharmacogenetic study (n = 172)
Gender(% female)	67	<b>79<sup>#</sup></b>	74
Age (years)	65 ± 14	66 ± 14	66 ± 13
Pain intensity (VAS, mm)	62 ± 29	67 ± 26	67 ± 26
Pain relief (VAS, mm)	31 ± 31	30 ± 28	32 ± 31
Likert-pain intensity (%)			
- None	6	3	3
- Mild	6	3	4
- Moderate	24	27	21
- Severe	32	30	38
- Extremely severe	32	37	34
Likert-pain relief (%)			
- None	35	19	18
- Mild	14	24	19
- Moderate	30	36	40
- Severe	11	12	10
- Extremely severe	9	9	12
EuroQoL-VAS (mm)	41 ± 23	42 ± 22	42 ± 23
MEDD (mg/day)	119 ± 114	139 ± 144	119 ± 128
Polypharmacy (%)	50	<b>69<sup>#</sup></b>	61
Adverse events (median, IQR)	6 (3.5–9)	<b>9 (6–11)<sup>#</sup></b>	7 (5–11)
Suspected ADR notified (n)	150	150	62
Due to pain (%):			
- Emergency room visits	20	24	23
- Hospitalization	7	10	6
- Pharmacological modification	26	<b>37<sup>#</sup></b>	24
Due to other causes (%):			
- Emergency room visits	17	18	<b>24<sup>*</sup></b>
- Hospitalization	10	13	14
- Pharmacological modification	13	18	14

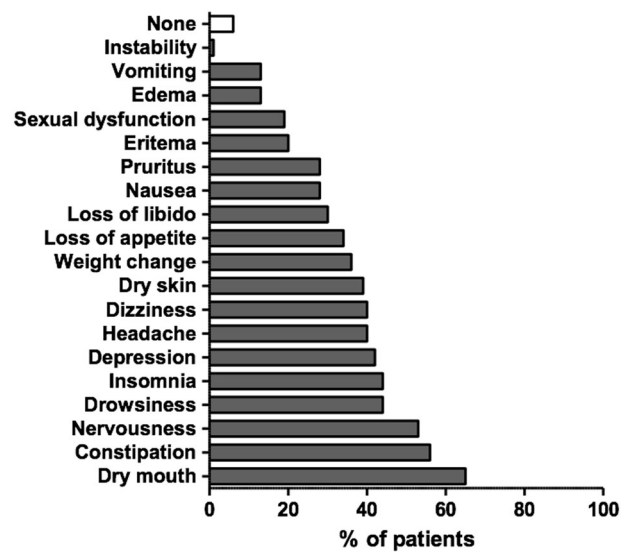
$p < 0.05$  are written in bold

<sup>#</sup> $p < 0.05$  comparison between total population and cases

<sup>\*</sup> $p < 0.05$  comparison between total population and pharmacogenetic study population

for dizziness (Figs. 3 and 4). Insomnia was significantly more prevalent in the presence of G allele in *OPRM1* gene ( $p = 0.043$ ;  $\chi^2 = 6.282$ ;  $df = 2$ ), while dizziness was more frequent in GA individuals of *COMT* gene ( $p = 0.027$ ;  $\chi^2 = 7.209$ ;  $df = 2$ ).

According to genotype, reproductive system related ADRs (cases) were more frequent in *OPRM1*-G allele



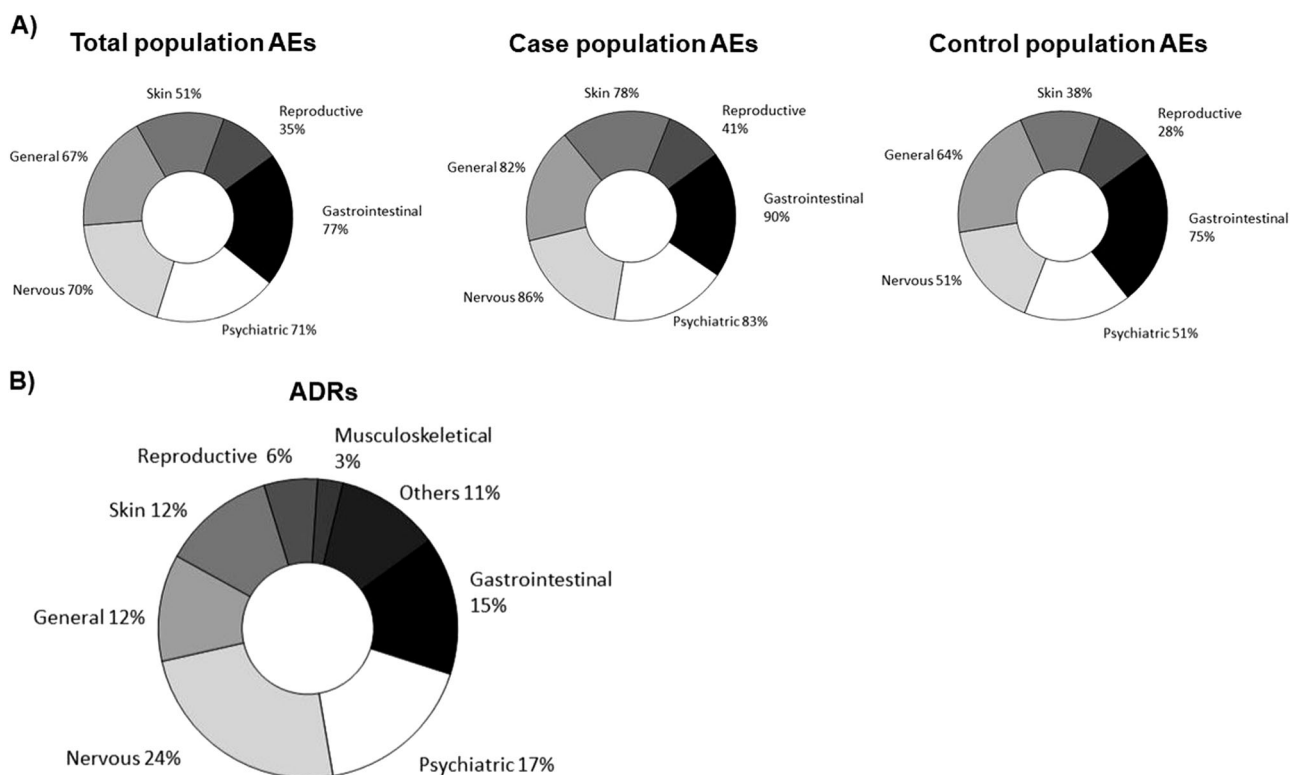
**Fig. 1** Presence of adverse events (AEs) in total population treated for chronic non-cancer pain

carriers ( $p = 0.021$ ;  $\chi^2 = 7.765$ ;  $df = 2$ ) (Fig. 3). Similarly, psychiatric ADRs were more prevalent in *COMT*-A allele patients ( $p = 0.026$ ;  $OR = 0.083$ ;  $95\% \text{ CI} = 0.005\text{--}1.494$ ), while *COMT*-AA individuals presented skin ADRs more frequently than *COMT*-G allele carriers ( $p = 0.001$ ;  $\chi^2 = 13.21$ ;  $df = 2$ ) (Fig. 4).

### Gender and genotype analyses

Analysis by gender showed that nausea ( $p = 0.002$ ;  $OR = 2.016$ ;  $95\% \text{ CI} = 1.388\text{--}2.928$ ), headache ( $p = 0.009$ ;  $OR = 1,540$ ;  $95\% \text{ CI} = 1.111\text{--}2.135$ ), insomnia ( $p = 0.016$ ;  $OR = 1,487$ ;  $95\% \text{ CI} = 1.080\text{--}2.047$ ), lack of appetite ( $p = 0.007$ ;  $OR = 1,597$ ;  $95\% \text{ CI} = 1.135\text{--}2.247$ ), weight change ( $p = 0.000$ ;  $OR = 1,853$ ;  $95\% \text{ CI} = 1.317\text{--}2.606$ ), depression ( $p = 0.000$ ;  $OR = 1,905$ ;  $95\% \text{ CI} = 1.374\text{--}2.642$ ) and dizziness ( $p = 0.000$ ;  $OR = 1,859$ ;  $95\% \text{ CI} = 1.334\text{--}2.590$ ) were more prevalent in women.

When analysing by genotype, the *OPRM1* genotype had a greater influence in men with the presence of vomiting ( $p = 0.001$ ;  $\chi^2 = 15$ ;  $df = 2$ ), sexual disorders ( $p = 0.006$ ;  $\chi^2 = 10.3$ ;  $df = 2$ ) and depression ( $p = 0.032$ ;  $\chi^2 = 6.92$ ;  $df = 2$ ); while in women, this was for dry skin ( $p = 0.037$ ;  $\chi^2 = 6.57$ ;  $df = 2$ ) and drowsiness ( $p = 0.027$ ;  $\chi^2 = 7.26$ ;  $df = 2$ ) (Fig. 3). On the other hand, *COMT* genotype influence prevalence of skin redness ( $p = 0.047$ ;  $\chi^2 = 6.14$ ;  $df = 2$ ) in men and loss of libido ( $p = 0.040$ ;  $\chi^2 = 6.46$ ;  $df = 2$ ) in women (Fig. 4). Men carriers of *OPRM1*-G allele were more susceptible to have vomiting ( $p = 0.000$ ;  $OR = 22.9$ ;  $95\% \text{ CI} = 2.30\text{--}228$ ) and sexual disorders ( $p = 0.003$ ;  $OR = 14.9$ ;  $95\% \text{ CI} = 1.72\text{--}130$ ). Females with *OPRM1*-G allele presented more drowsiness and less skin dryness. *COMT*-GG genotype was



**Fig. 2** Distribution of adverse events (AEs) (a) in total, case (with adverse drug reactions (ADRs)) and control populations (without ADRs); and (b) distribution of case ADRs population, classified by MedRA terminology

**Table 2** Genotypic and allelic distribution of *OPRM1* A118G and G472A *COMT* polymorphisms ( $n = 172$ )

Gene	Genotype frequency (%)	Allele frequency (%)	Caucasian population (%)
<b><i>OPRM1</i> A118G</b>			
- A/A	65	A 80	85
- A/G	30	G 20	15
- G/G	5	HWE 0.353	
<b><i>COMT</i> G472A</b>			
- G/G	24	G 51	53
- G/A	52	A 49	47
- A/A	23	HWE 0.647	

HWE Hardy–Weinberg equilibrium

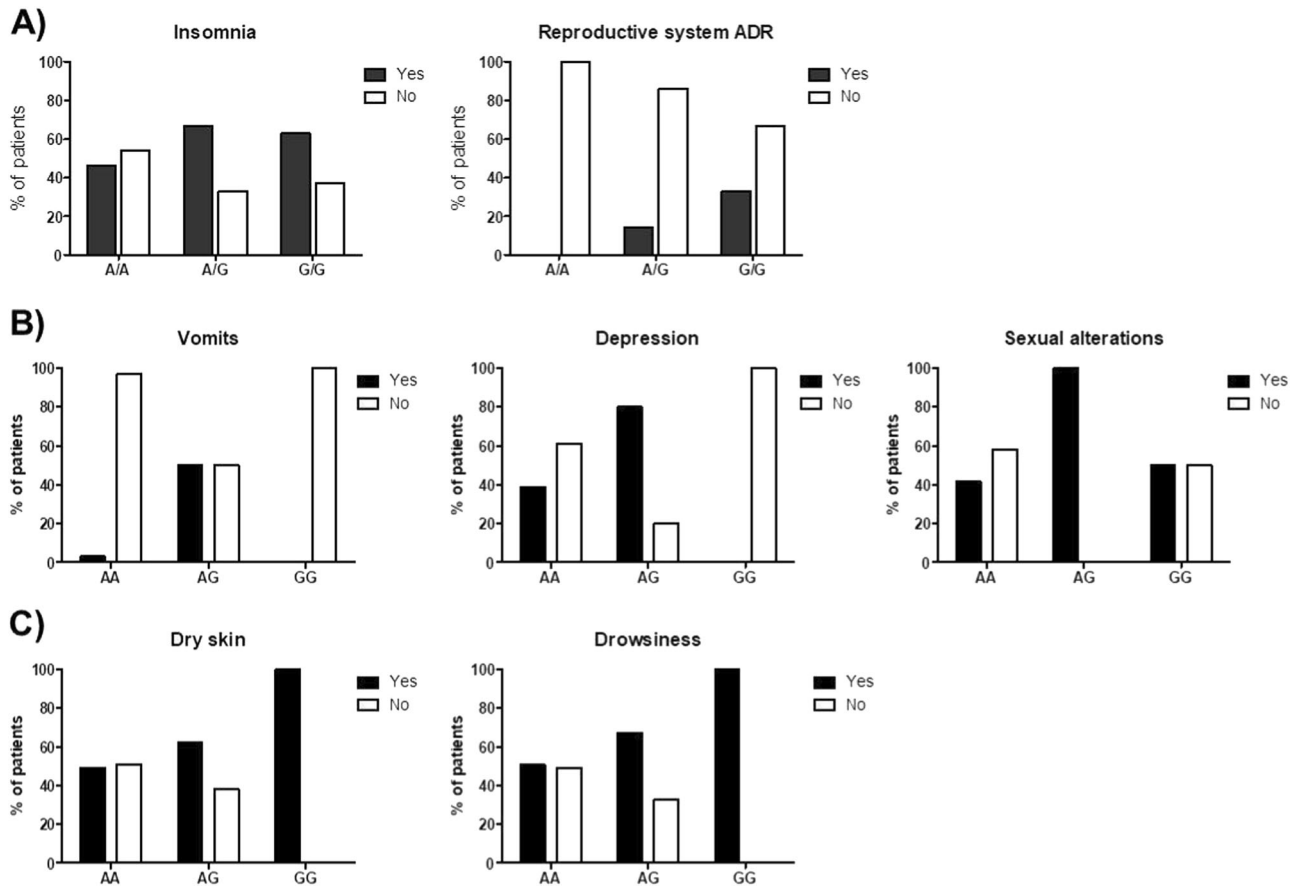
associated in females with a loss of libido ( $p = 0,029$ ; OR = 3,434; 95% CI = 1.210–9.749).

## Discussion

Differences according to gender exist and are evident in clinic. In our study, we observed a higher prevalence of

women with CNCP, visiting pain physicians and presenting ADRs (79%). Our results also suggest that gene polymorphisms applied to a pharmacovigilance system could help to improve patient's security profile and opioid's safety. By gender, genotype of *OPRM1* and *COMT* influenced AEs for vomiting and depression in men, dizziness in women and sexual dysfunction in both.

A multitude of polymorphisms in candidate genes related to different pain neurotransmission pathways have been described. Most relevant are those located in the gene that encodes for the opioid receptor *OPRM1*, whose variants can give rise to a receptor three times more active and to a request of higher doses of morphine, or in the *COMT* gene, which can decrease its enzymatic activity three to four times. However, PGx studies are often contradictory, slowing the uptake of their information into clinical routine. This is likely due in large extent to a lack of robust evidence demonstrating clinical utility and to its polygenic response modulated by other exogenous or epigenetics factors. The largest genetic association study in pain was the European Pharmacogenetic Opioid Study (EPOS,  $n = 2.294$ ), on cancer pain under opioid treatment, which included 112 SNPs in 25 genes, with A118G (rs1799971, *OPRM1* gene) [25] being the most analysed. This variant increases its affinity for endogenous opioids, with a decrease in pain perception and lower cortical response to the painful stimulus.



**Fig. 3** Influence of *OPRM1* genotype in the presence of adverse events (AEs) and adverse drug reactions (ADRs). **a** Total population: insomnia AE (left) and reproductive system ADRs (right). **b** Male

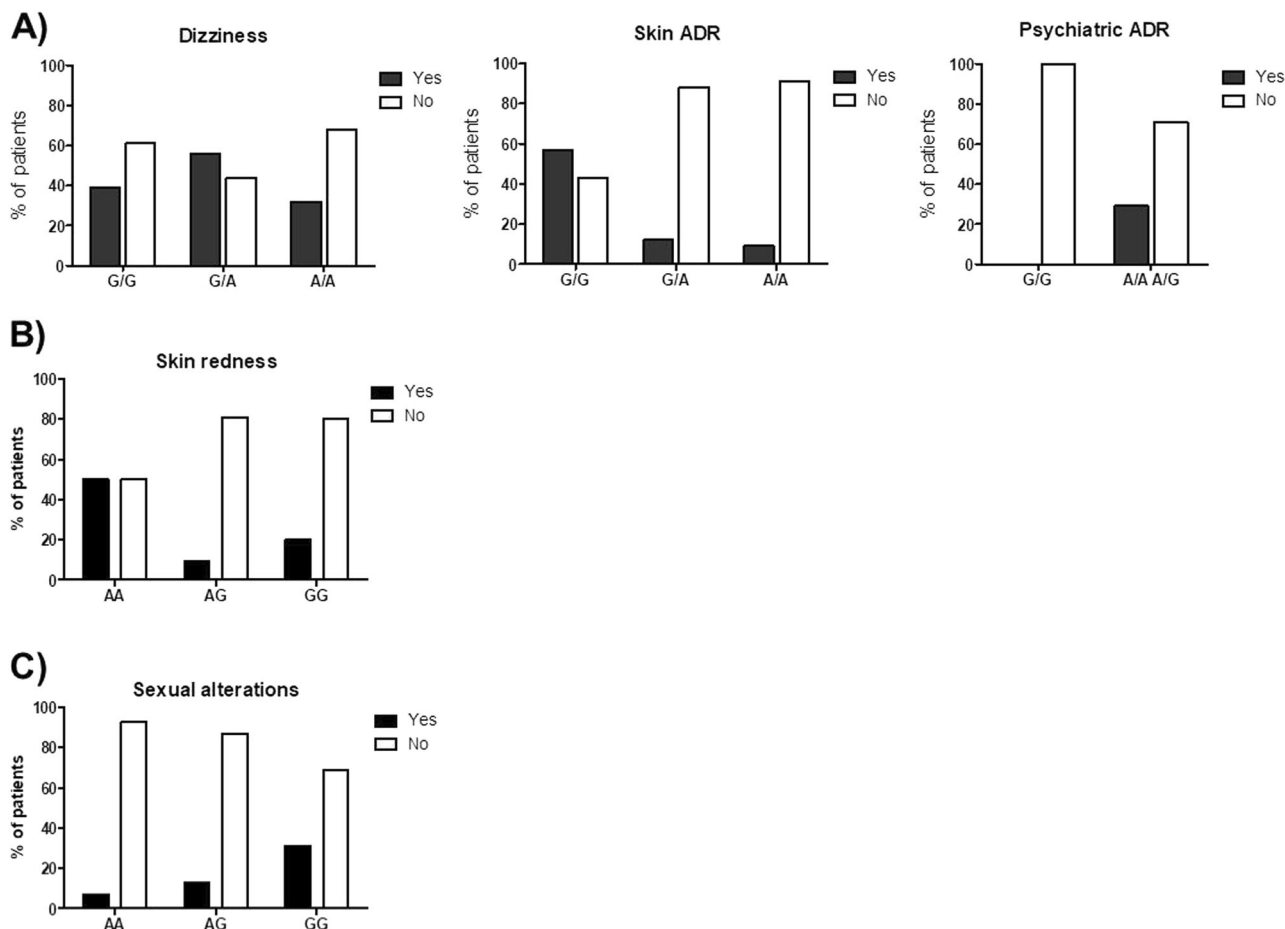
population: vomiting, depression and sexual disorders AEs. **c** Female population: dry skin and drowsiness AEs

Subjects homozygous for A118-GG allele required lower doses of morphine and lower number of analgesic rescues [25]. However, a significant association between genetic profile, opioid dose and analgesia could not be demonstrated and findings did not support the use of pharmacogenetic analyses for the assessed variants gene to guide opioid treatment. We have previously found that *OPRM1* A118G-AA CNCP patients with iatrogenic opioid dependence had lower MEDD requirements [26], suggesting an increased opioid efficacy and a significantly higher risk to suffer AEs. This *OPRM1* genotype can be probably associated to a higher resistance to both, analgesia and AE frequency [27]. Research also indicates that *COMT* and *OPRM1* variants synergistically interact, affecting analgesia and both genes have additional functional variants that may further shape analgesic effects [28, 29].

The involvement of catecholamines in pain modulation is known from both clinical and experimental studies. *COMT* is a key modulator of dopaminergic and adrenergic neurotransmission, and, as a consequence, in the reward signalling response to opioids. Overall, meta-analysis showed that *COMT* Val/Met carriers consumed

less opioid for analgesia within the first 24 h after surgery (standardized mean difference = 0.14, 95% CI = 0.03–0.25,  $p = 0.01$ ) [30]. G472A allelic variant supposes a lower capacity to metabolize monoamine neurotransmitters and, therefore, higher levels of dopamine, and a lower pain threshold that implies an increase in pain sensitivity 1.5. In addition, this low activity increases the availability of opioid receptors, increasing analgesia and AEs [31]. However, other studies with oncological patients found differences in the presence of AEs related to dizziness, confusion and hallucinations [32, 33] or gastrointestinal (nausea and vomiting) [34]. Our results indicated that *COMT*-AA mutant genotype presented less dizziness but more psychiatric and skin ADRs. It remains unclear, however, whether long-term opioid therapy can induce a large number of AEs [35–37], which could lead to a loss of adherence to treatment and its consequent abandonment [38, 39].

With regards to gender differences, some evidence indicates that gender can influence AEs prevalence in opioid prescription. In experimental settings, women showed a greater morphine-induced respiratory depression



**Fig. 4** Influence of *COMT* genotype in the presence of adverse events (AEs) and adverse drug reactions (ADRs). **a** Total population: dizziness

AE (right); and skin (middle) and psychiatric (right) ADRs. **b** Male population: skin redness AE. **c** Female population: sexual disorders AE

[40, 41], increased negative feelings as well as enhanced nausea and vomiting [42, 43]. In the general population, women presented a 50–70% greater risk of suspected ADRs although the underlying reasons are not clear because women are only included in 38% of in human research studies, hormonal factors, differences in pharmacokinetics and pharmacodynamics, may have a relevant role [44]. Women comprise the majority of the elderly pain population, and, of course, more diseases occur and more drugs are prescribed in the elderly. It is, therefore, obvious that science is interested in knowing how women react to drugs.

Our findings should be interpreted in light of some limitations. Patients attending tertiary care pain clinics could differ from patients in primary care, as they are presented with higher levels of psychosocial dysfunction, cognitive difficulties and comorbidities and a variable drug treatment. These variables could be confounding factors. Furthermore, prevalence of AEs was based on self-assessments of the patients without the physician applying a validated diagnostic test as is often used in other studies.

Thus, these symptoms cannot be always or exclusively associated to an AE to opioid treatment [45]. In addition, opioid interaction with other drugs could be responsible for the AEs/ADRs observed or even more, concomitant drugs could be the responsible for these side effects making a more detailed analysis necessary. Furthermore, the number of patients genotyped to study some of the polymorphisms that have low frequencies for variant allele is low. Being a retrospective, non-interventional study we only could obtain a sample from a reduced number of subjects. Despite all these limitations, we considered that observational studies developed in “real world” Pain Units, like this one, can generate useful information and should be taken in consideration.

In conclusion, PGx could possibly be used to tailor pain medication based on an individual’s genetic background especially in patients at-risk of severe AEs. Based on this data, *OPRM1* and *COMT* genotyping seems promising to be applied in clinical practice in order to monitor analgesic security profile and to improve patient’s management including a gender analysis.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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