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Original research paper

Long-term deprescription in chronic pain and opioid use disorder patients: Pharmacogenetic and sex differences

JAVIER MURIEL[1,a]
MÓNICA ESCORIAL[1,2,a]
CÉSAR MARGARIT[1,3]
JORDI BARRACHINA[1,2]
CRISTIAN CARVAJAL[2]
DOMINGO MORALES[4]
ANA M. PEIRÓ[1,2,3,5,*]

[1] *Neuropharmacology applied to Pain (NED) Alicante Institute for Health and Biomedical Research (ISABIAL), c/ Pintor Baeza, 12 03010, Alicante, Spain*

[2] *Institute of Bioengineering, Miguel Hernández University, Avda. de la Universidad s/n, 03202, Elche, Spain*

[3] *Pain Unit, Dr. Balmis General University Hospital, ISABIAL, c/ Pintor Baeza, 12 03010, Alicante, Spain*

[4] *Operations Research Centre, Miguel Hernández University, Avda. de la Universidad s/n, 03202, Elche, Spain*

[5] *Clinical Pharmacology Department Dr. Balmis General University Hospital ISABIAL, c/ Pintor Baeza, 12, 03010 Alicante, Spain*

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ABSTRACT

More than half of patients with opioid use disorder for chronic non-cancer pain (CNCP) reduced their dose through a progressive opioid withdrawal supported by a rotation to buprenorphine and/or tramadol. The aim of this research is to analyse the long-term effectiveness of opioid deprescription taking into account the impact of sex and pharmacogenetics on the inter-individual variability. A cross-sectional study was carried out from October 2019 to June 2020 on CNCP patients who had previously undergone an opioid deprescription (n = 119 patients). Demographic, clinical (pain, relief and adverse events) and therapeutic (analgesic use) outcomes were collected. Effectiveness (< 50 mg per day of morphine equivalent daily dose without any aberrant opioid use behaviour) and safety (number of side-effects) were analysed in relation to sex differences and pharmacogenetic markers impact [*OPRM1* genotype (rs1799971) and CYP2D6 phenotypes]. Long-term opioid deprescription was achieved in 49 % of the patients with an increase in pain relief and a reduction of adverse events. CYP2D6 poor metabolizers showed the lowest long-term opioid doses. Here, women showed a higher degree of opioid deprescription, but increased use of tramadol and neuromodulators, as well as an increased number of adverse events. Long-term deprescription was successful in half of the cases. Understanding sex and gender interaction plus a genetic impact could help to design more individualized strategies for opioid deprescription.

Keywords: chronic pain, drug deprescription, opioid use disorder, long-term monitoring, pharmacogenetics, sex differences

The appropriate use of opioids for chronic non-cancer pain (CNCP) remains uncertain due to the growing global health concern of aberrant drug behaviours observed in 20 % of

*Correspondence; email: apeiro@umh.es
[a] These two authors contributed to this work equally.

patients prescribed opioids (1, 2). Health care providers, including clinical pharmacologists and clinical pharmacists, specialising in pain, must properly screen the risk of developing an opioid use disorder (OUD) and carefully monitor opioid use. All of this incorporates a method to taper opioids when deemed appropriate (3).

Literature has shown that patients with dysfunctional metabolizing enzyme CYP2D6 (cytochrome P450 family 2 subfamily D member 6) (4) or the mutant variant of opioid receptor mu 1 gene (*OPRM1*, A118G, rs1799971) (5, 6) can influence the opioid pharmacological characteristics (7, 8). For codeine and tramadol, the CYP2D6 enzyme is involved in conversion to active metabolites (9) where the CYP2D6 activity can be used to predict analgesic effects. The extreme phenotypes (poor and ultra-rapid metabolizer) have a 5–10 % prevalence in the Caucasian population and have been associated with failure of pain treatment (limited conversion to active metabolites in poor metabolizers) and a higher risk of experiencing adverse events related to painkillers (in ultra-rapid metabolizers) (10). What's more, without being able to confirm that there are sex differences in terms of opioid analgesic effectiveness and tolerability, adverse drug reactions (ADRs) are observed more frequently in women (11). These sex differences can be linked to social (12) or biological (13) factors, but they are still not completely understood (14).

The treatment of substance use disorders has emphasized the role of specialist physicians and psychiatrists. However, in an effort to expand access to OUD treatment, primary care clinicians, including nurse practitioners and pharmacists, are increasingly engaged in harm reduction and providing office-based opioid agonist treatment (15). A 6-month opioid tapering programme was implemented in our Pain Unit (PU) at Dr. Balmis General University Hospital, Spain, in 2013, on OUD-diagnosed CNCP patients. It was based on a progressive withdrawal of immediate-release opioids and an opioid cessation supported by buprenorphine and/or tramadol rotation along with close monitoring by a pharmacist and clinical pharmacologist (16, 17). This programme presented a favourable response in 64 % of our cases but had a high degree of inter-individual variability. Besides, it was observed a genetic influence since patients' carriers of the 118G allele of the *OPRM1* gene required higher doses of opioids and presented a lower number of adverse events (AEs) (6, 18).

Personalized analgesia plans related to any tapering procedure should minimize symptoms of opioid withdrawal while maximizing non-pharmacologic and non-opioid therapies. Due to our previous results (6, 18), we hypothesized that the deprescribed patients will remain at low opioid doses in the long term, while pharmacogenetic markers and sex could explain the variances observed in the outcomes. In this way, this study represents a novel research direction to further understand the variability in the response to the opioid tapering programme on both sex and pharmacogenetics.

EXPERIMENTAL

Study design

An observational cross-sectional study was performed from October 2019 to June 2020 on CNCP patients with an OUD, who had previously undergone a 6-month opioid tapering programme between 2013 and 2018 (6, 18) at the Pain Unit of a tertiary level hospital (Dr. Balmis General University Hospital, Alicante, Spain).

The study was approved by the Ethics Committee of Dr. Balmis General University Hospital (code PI2019/092). All patients included had previously signed the informed consent form linked to the study. The biological samples were obtained from the Biobank following ethical and legal standard procedures. The study complies with the applicable STROBE guidelines (19).

Participants

All patients included in the present study (n = 119) attended routinely the Pain Unit for pain management. As a consequence of the pain therapy, they developed an OUD and were put through an opioid deprescription programme from 2013–2018. Subjects were selected by the researcher team which consisted of two pharmacists, one clinical pharmacologist, one biologist and one anaesthesiologist. Inclusion criteria were as follows: ≥ 18 years old, chronic non-cancer pain, long-term use of opioids (≥ 6 months) and a diagnosis of opioid use disorder according to DSM-5 criteria (20) by a psychiatrist. Based on the low frequency of patients with an OUD diagnosis in our regular clinical routine, a convenient sample size was proposed.

Opioid deprescription

The tapering programme is extensively described in our previous work (6, 18) and designed according to national and international guidelines (21). In brief, it consisted of six clinical visits (basal visit, 1 week, 2 weeks, 1 month, 3 months, and at 6 months as a final visit) with an opioid rotation to tramadol and/or buprenorphine together with the tapering process, and a 1–2 weekly phone monitoring by a pharmacist expert on pain. The clinical visits were done by a clinical pharmacologist to prevent any withdrawal symptoms (*e.g.*, nervousness, insomnia, anxiety, gastrointestinal). In some cases, withdrawal was mitigated with alpha-2-adrenergic agonist (clonidine) as an adjuvant drug for two weeks including patients' arterial blood pressure monitoring. Methadone use was excluded because it displays large inter-individual variation in bioavailability and elimination half-life, showing a complicated treatment initiation or conversion from another opioid (22).

Long-term outcomes

Long-term deprescription effectiveness was defined by the absence of: (*i*) any opioid regular prescription higher than 50 mg per day of morphine equivalent daily dose (MEDD), (*ii*) any opioid use disorder according to DSM-5 criteria, and (*iii*) any aberrant opioid use behaviour. Analgesic effectiveness and tolerability were regularly evaluated along the deprescription as clinical standard monitoring based on validated scales and full AEs count. All the information was collected from electronic health records data (EHRs), which allows for reviewing medical diagnoses, outcomes and medication use, and was monitored by a pharmacist. In the case of active follow-up in the Pain Unit, it was triangulated with patient interviews.

Variables

Demographic characteristics (such as age and sex), pain history and medication use were collected. Psychological, social and work activities were evaluated with the global assessment of the functioning scale (GAF, score of 0 to 100, where a higher score means better daily and life activity) (23).

Pain intensity and relief were measured using the visual analogue scale (VAS) (24). This tool consists of a horizontal line ranging from 0 (lowest) to 100 mm (highest intensity or relief). Quality of life was measured with the EuroQol-5D scale where patients can report their perceived health status with a grade ranging from 0 (the worst imaginable health status) to 100 mm (the best imaginable). Patients' reports of AEs were collected using a list of the most frequent opioid analgesic side-effects listed in the summary of product characteristics and with frequency as "very common" and "common" (such as sleepiness, dizziness, nausea, vomiting, constipation, itchiness, sexual dysfunction, loss of libido, weight change, headache, skin redness, dry skin, dry mouth or edema, between others) (25). A blank field was added for any other AEs presented. All these variables were included in a validated questionnaire (26). In addition, patients were asked about depression or anxiety symptoms. When an AE was suspected to be related to pain treatment (ADRs), the pharmacist took over the corresponding notification and classified it according to the medical dictionary for regulatory activities (MedDRA, version 20.0) (27).

Drugs used. – Weak (*e.g.*, tramadol and codeine) and strong (*e.g.*, fentanyl, oxycodone, tapentadol, buprenorphine, morphine and hydromorphone) opioids were registered and converted to oral MEDD (mg per day) using available references (28). The prescription of simple analgesics (*e.g.*, paracetamol, metamizole and NSAIDs), antidepressants (*e.g.*, amitriptyline, fluoxetine, escitalopram and duloxetine), benzodiazepines and neuromodulators (*e.g.*, pregabalin, gabapentin, clonazepam and lacosamide) were also collected. Specifically, we identified all prescriptions that included the ingredients codeine, oxycodone, hydrocodone and tramadol, because their metabolic pathway could be directly affected by CYP2D6 (29).

Genotyping

Genetic information was collected from the opioid deprescription programme study database. Not analysed DNA was used to complete the genotyping. DNA was extracted using E.N.Z.A. forensic DNA kit (Omega Bio-Tek Inc., USA) following the manufacturer's instructions. The *OPRM1* gene variant (rs1799971, 118A>G) was genotyped using the real-time PCR rotor gene Q system (Qiagen, Germany), through the use of specific TaqMan MGB® probes (Applied Biosystems, USA). Amplification parameters were as follows: pre-PCR section 10 minutes at 95 °C, 40 cycles for 15 seconds of denaturation at 92 °C, and 1-minute final extension at 60 °C.

As regards the CYP2D6 genotype, the following SNPs were analysed: **2*, **3*, **4*, **5*, **6*, **10*, **17*, **29*, **35*, **41* and *xN* (30, 31). Genetic analysis was based on the usual PCR methods following the instructions of the Consortium of the Pharmacogenetics and Pharmacogenomics Ibero-American Network for the analysis of samples (32). XL-polymerase chain reaction analysis was used for the identification of duplications and deletions. These amplifications were carried out in a Mastercycler 384 (Eppendorf, Germany).

After the genotype had been obtained, an estimation of the enzyme activity (null, reduced, normal or increased) was carried out based on the activity score (AS) (31). The presence of SNPs *3, *4, *5, *6 has an AS of 0, which means null enzyme activity. Variants *10, *17, *29, *41 are associated with an AS of 0.5 and *1, *2, *35 with an AS of 1, in other words, a reduced and normal enzyme activity, resp. Duplications *1xN, *2xN, *35xN are associated with greater enzyme activity (AS = 2). Metabolic phenotypes were predicted for each patient based on the AS of both alleles: (*i*) AS = 0 for the absence of enzymatic activity (poor

metabolizer, PM), (*ii*) AS = 0.5 to 2 for normal enzymatic activity (extensive metabolizer, EM), and (*iii*) AS ≥ 2 for increased enzymatic activity (ultra-rapid metabolizer, UM) (33).

Statistical analysis

Quantitative parametric data are presented as mean ± standard deviation (SD) while median and (interquartile range, IQR) were used for non-parametric data. Categorical data are expressed as percentages (%). Comparisons for continuous or categorical data between two groups were conducted using an independent *t*-test or chi-square test (or Fisher's exact test), resp. Analysis of non-parametric data was done using the Mann-Whitney U test and Kruskal-Wallis tests for comparison between two and three groups, resp.

Observed gene frequencies were compared with those expected using the chi-square (χ^2) goodness-of-fit test and the Hardy-Weinberg proportion. In cases of significant genetic associations, co-dominant, dominant, recessive and over-dominant models were calculated. For the *OPRM1* genotype, the G-carriers were grouped as they presented a low allelic frequency. Linear multiple regressions were performed to analyse the impact of multiple variables when significant associations between *OPRM1* genotypes or CYP2D6 phenotypes and MEDD were detected. p-value ≤ 0.050 was considered statistically significant. In multiple testing, the Bonferroni correction was adjusted. All statistical analyses were carried out using the system for statistical computation R (Version 3.2.0).

RESULTS AND DISCUSSION

Participants

From 119 potential patients (54 ± 13 years, 67 % women), after a median of 4 (2–4) years of follow-up, a total of 111 patients were finally included (8 *exitus*) in the present study. At

Fig. 1. Flow chart of the opioid deprescription and long-term follow-up (CI – informed consent, EHRs – electronic health records data, EQ – EuroQol-5D, GAF – global assessment of functioning, AEs – adverse events, ADRs – adverse drug reactions).

this point, 71 % (n = 79/111) were still attending PU. The rest were: 33 % discharged, 12 % repeat offenders, 33 % follow-up losses and 22 % had their pain followed up in another clinical unit (Fig. 1).

Demographic, clinical and therapeutic outcomes

Sex, age, clinical data and medications used by the participants are shown in Table I. Recent research indicates that socio-economic inequities and environmental factors, as well as access to substances of abuse or barriers to treatment, influence the risk of substance use disorders (34). In our study, patients were mostly middle-aged women, who routinely come to PU visits and are under a multidrug analgesic treatment.

Long-term effectiveness of deprescription showed a positive response in 49 % of patients (n = 54/111) as they neither presented opioid use disorder nor aberrant opioid use behaviour and were under an opioid regular prescription of fewer than 50 mg per day (mean ± SD, 10 ± 17 mg per day). A significant reduction of opioid use from the 6-month opioid deprescription of 23 % (89 *vs.* 66 %, resp., $p < 0.001$) was observed, including a 10 % decrease in immediate-release opioid consumption (13 *vs.* 3 %, $p = 0.017$). All this was accompanied by significantly higher long-term pain relief in VAS (40 ± 29 *vs.* 51 ± 25 mm, $p = 0.013$) together with a 24 % increase in simple analgesics use (11 *vs.* 35 %, $p < 0.001$), 34 % of neuromodulators (33 *vs.* 67 %, $p < 0.001$) and 33 % of antidepressants (22 *vs.* 55 %, $p < 0.001$).

Related to long-term opioid use, MEDD was reduced in women [120 (49–203) mg per day in basal to 53 (0–144) mg per day at long-term] more than in men [126 (47–212) mg per day in basal to 80 (0–256) mg per day at long-term]. In this way, although men tended to maintain an unusually high MEDD, worse tolerability was observed in women. This is probably due to the higher use of other painkillers such as tramadol and neuromodulators that could have increased the probability of drug-to-drug interactions or the summation of side-effects (35), or due to a different pattern of tolerability between sexes that needs to be studied (11).

In this context, amongst the group of patients with the highest MEDD (> 90 mg per day), women were on lower doses compared with men [160 (123–248) mg per day *vs.* 241 (161–451) mg per day, resp., $p = 0.043$]. What's more, women showed a 15 % lower long-acting transdermal fentanyl use (13 *vs.* 29 %, $p = 0.009$) and 9 % of lower use of immediate-release opioids (0 *vs.* 9 %, $p = 0.003$), but 14–19 % higher use of tramadol (17 *vs.* 3 %, $p = 0.002$) and neuromodulators (70 *vs.* 51 %, $p = 0.009$), resp., related to men (Table I and Fig. 2). This should be further explored in order to design specific strategies in the opioid tapering procedure, or for addressing OUD risk models (36, 37).

Therapeutic safety pattern

An 8 % reduction of ADRs (11 *vs.* 3 %, $p = 0.049$) was observed despite the increased number of long-term AEs [6 (2–8) *vs.* 9 (6–11), $p < 0.001$] (Table II). Different reviews have shown a significantly increased risk ratio with opioids compared to placebo for constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus and vomiting (38). Nevertheless, the scarce data on AEs in clinical studies, especially in OUD-diagnosed CNCP patients, represents a serious limitation to compare our tolerability pattern.

Table I. Description and analysis of demographic, clinical and therapeutic variables by visit (basal, 6-month and long-term) and sex

Clinical and therapeutic data	Basal			6-month			Long-term		
	Total (n = 119)	Women (n = 80)	Men (n = 39)	Total (n = 102)	Women (n = 69)	Men (n = 33)	Total (n = 111)	Women (n = 76)	Men (n = 35)
Sex (%, females)	67			68			68		
Age (years, mean ± SD)	54 ± 13	54 ± 13	53 ± 12	54 ± 12	53 ± 11	55 ± 11	58 ± 12	58 ± 13	57± 11
Pain intensity (mm, mean ± SD)	58 ± 27	59 ± 27	57 ± 27	56 ± 29	55 ± 27	59 ± 33	64 ± 31	63 ± 33	64 ± 32
Pain relief (mm, mean ± SD)	35 ± 29	35 ± 30	33 ± 29	40 ± 29	39 ± 29	41 ± 31	**51 ± 25**[c]	**52 ± 25**[c]	**50 ± 25**[c]
Quality of life (mm, mean ± SD)	45 ± 24	43 ± 24	49 ± 25	44 ± 22	48 ± 20	36 ± 24	42 ± 23	43 ± 22	41 ± 25
GAF (score)	71 ± 15	71 ± 14	71 ± 16	69 ± 16	70 ± 17	68 ± 15	67 ± 10	67 ± 9	70 ± 14
Effectiveness in deprescription (%)	–	–	–	74	77	66	49	50	6
Simple analgesics (%)	18	18	18	11	7	18	35[d]	38[d]	29
MEDD (mg per day) [median (IQR)]	120 (50–203)	120 (49–203)	126 (47–212)	80 (35–157)	80 (26–124)	110 (40–160)	60 (0–160)[d]	53 (0–144)[d]	80 (0–256)
Opioid prescription (%)	98	99	97	89	87	94	66[d]	66[d]	63[d]
Fentanyl (%)	32	29	38	12	13	12	18[c]	13[c]	29[d,e]
Oxycodone (%)	20	18	15	5	6	6	5[d]	[7c],e	0[d]
Tapentadol (%)	20	22	15	6	3	12	7[c]	7[d]	9
Buprenorphine (%)	17	21	18	29	28	33	18	17	20[c]
Morphine (%)	4	5	0	6	7	3	2	3	0[c]
Hydromorphone (%)	1	1	0	2	3	0	2	3	0
Tramadol (%)	6	3	12	29	28	36	14[d]	17[d,e]	3[d]
Immediate-release opioid (%)	8	8	9	13	13	12	3[d]	0[c]	9[e]
Neuromodulators (%)	23	22	26	33	33	33	67[d]	70[d,e]	51[d]
Antidepressants (%)	12	11	14	22	19	27	55[d]	57[d]	51[d]
Benzodiazepines (%)	23	27	14	35	40	27	40[d]	38[c]	43[d]

[a] GAF – global assessment of functioning (0–100 scores); MEDD – morphine equivalent daily dose.
[b] In the long-term, the total sample size for the clinical outcomes was n = 89: women n = 56 and men n = 21.
Statistically significant difference: [c] $p < 0.050$ and [d] $p < 0.001$ comparing basal, 6-month and long-term visits (shown in bold); [e] $p < 0.050$ comparing women *vs.* men (in the long-term are shown in grey).

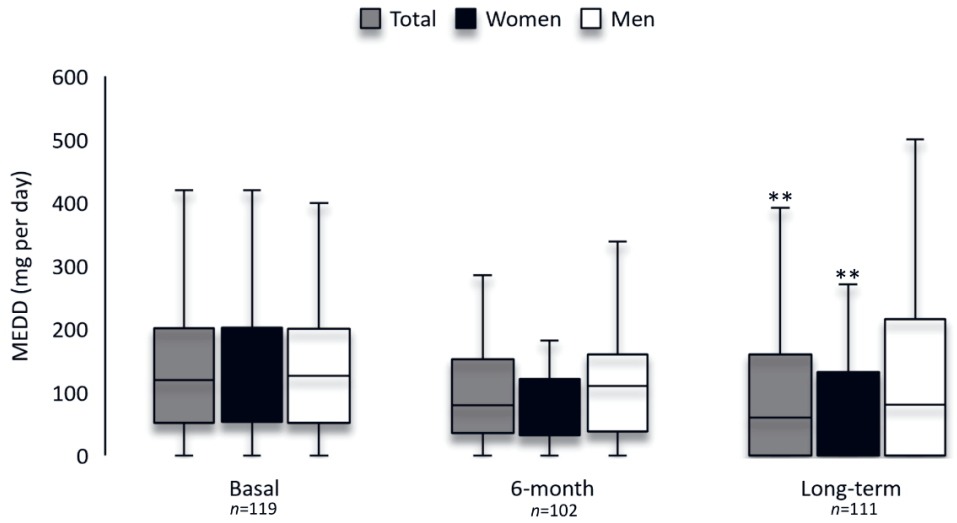

Fig. 2. Morphine equivalent daily dose [MEDD, mg per day), bars median (IQR)] per visit (basal, 6 months, long-term) and sex (all patients in grey, women in black, men in white colour). Statistically significant difference: $^{**}p < 0.001$ comparing basal, 6-month and long-term visits.

In the long term, a 36 % higher incidence of dry skin (43 *vs.* 79 %, $p < 0.001$), 25 % of weight change (31 *vs.* 56 %, $p < 0.001$), 24 % of sexual dysfunction (11 *vs.* 35 %, $p < 0.001$), 22 % of dry mouth (62 *vs.* 84 %, $p < 0.001$), 21 % of dizziness (25 *vs.* 46 %, $p = 0.003$), 19 % of sleepiness (39 *vs.* 58 %, $p = 0.011$), 17 % of constipation (44 *vs.* 61 %, $p = 0.023$) and 15 % of nervousness (41 *vs.* 56 %, $p = 0.047$) were reported.

Sex differences were evidenced in 40 % of the AEs recorded (Table II and Fig. S1). Here, cognitive and digestive AEs were more prevalent amongst women, whilst in men, those of a sexual nature prevailed (39, 40). Specifically, in women, 36 % more cases of nausea (women *vs.* men, 40 *vs.* 14 %, $p < 0.001$), 20 % of sleepiness (63 *vs.* 43 %, $p = 0.007$), 17 % of dry mouth (88 *vs.* 71 %, $p = 0.005$), 15 % of constipation (65 *vs.* 50 %, $p = 0.045$) and 14 % of vomiting (21 *vs.* 7 %, $p = 0.007$) occurred than in men. In contrast, men showed significantly higher sexual dysfunction for 29 % (28 *vs.* 57 %, $p < 0.001$) and loss of libido for 24 % (33 *vs.* 57 %, $p = 0.001$). This falls in line with our previous results (11), where more AEs occurred in women, specifically cognitive and digestive ones.

In addition, men showed a significant reduction of ADRs (24 *vs.* 3%, $p < 0.001$). This highlights the importance of incorporating long-term monitoring measures with a gender perspective (41, 42). This is scarcely analysed due to biological or cultural influence (43), however, it could potentially guide clinicians in optimal drug choices (44).

Pharmacogenetics impact

OPRM1 *A118-G gene variant*. – The frequencies found were: 66 % ($n = 61$) wild-type (*OPRM1*-AA) and 34 % ($n = 31$) G carriers (*OPRM1*-AG/GG), being in line with the previous literature data (45). Related to the pharmacogenetics impact, the *OPRM1* A118-G allele was

Table II. Safety variables description and analysis by visit (basal, 6-month and long-term) and sex

Safety data	Basal			6-month			Long-term		
	Total (n = 62)	Women (n = 44)	Men (n = 18)	Total (n = 61)	Women (n = 43)	Men (n = 18)	Total (n = 57)	Women (n = 43)	Men (n = 14)
Adverse events [median (IQR)]	6 (3–8)	6 (3–8)	5 (2–7)	6 (2–8)	5 (2–7)	7 (4–9)	**9 (6–11)[b]**	**9 (6–11)[b]**	8 (4–12)
Sleepiness (%)	31	34	22	39	35	50	58[b]	63[b,c]	43[b]
Dizziness (%)	37	43	22	25	19	39	46[a]	49[b]	36[a]
Nausea (%)	24	23	28	21	19	28	33	40[a,d]	14[a]
Vomiting (%)	10	7	17	8	5	17	18	21[b,c]	7
Constipation (%)	45	45	44	44	37	61	61[a]	65[b,c]	50
Itching (%)	32	25	50	30	28	33	37	35	43[a]
Sexual dysfunction (%)	8	5	17	11	2	33	35[b]	28[b]	57[b,d]
Loss of libido (%)	29	23	44	28	19	50	39	33	57[c]
Weight change (%)	29	34	17	31	33	28	56[b]	56[b]	57[b]
Headache (%)	34	39	22	41	42	39	44	44	43[a]
Skin redness (%)	10	7	17	15	19	6	23[a]	21[a]	29[b]
Dry skin (%)	34	36	28	43	40	50	79[b]	81[b]	71[b]
Dry mouth (%)	60	66	44	62	63	61	84[b]	88[b,c]	71[b]
Edema (%)	11	16	0	13	16	6	21	23	14[b]
Depression (%)	35	39	28	41	40	44	49	51	43[a]
Sleep disturbance (%)	53	52	56	52	51	56	56	58	50
Nervousness (%)	47	52	33	41	37	50	56	60[a]	50[a]
Loss of apetite (%)	27	32	17	25	21	33	33	33	36[a]
Exitus (%)	0	-	-	2	1	3	6	4	8
Adverse drug reactions (%)	0	0	0	11	8	24	3[a]	3	3[b]

Statistically significant difference: [a] $p < 0.050$ and [b] $p < 0.001$ comparing basal, 6-month and long-term visits (shown in bold); [c] $p < 0.050$ and [d] $p < 0.001$ comparing women *vs.* men in the long-term visit (shown in grey).

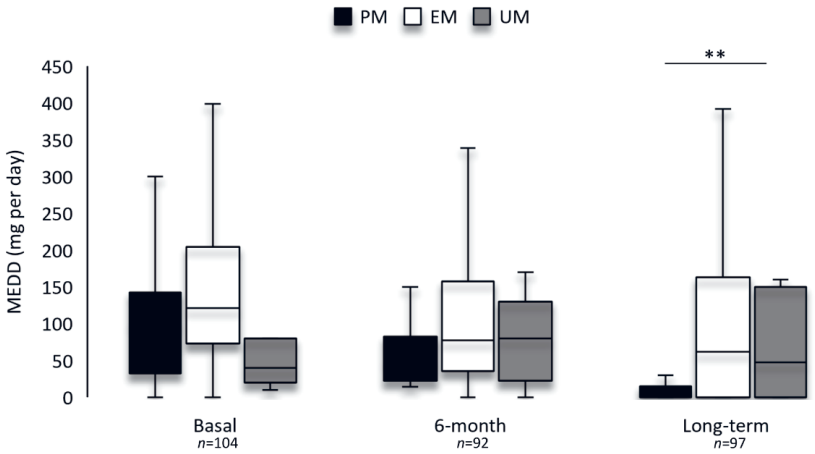

Fig. 3. Morphine equivalent daily dose [MEDD, bars median (IQR)] per visit and CYP2D6 phenotypes. Statistically significant difference: $^{**}p < 0.001$ comparing CYP2D6 phenotype.

associated with a 21 % higher use of tramadol (AA: 7 % *vs*. G carriers: 28 %; $p = 0.014$) (Table SI), which may contribute to a possible vulnerability to greater addiction-related behaviours (5, 45, 46). Here, women were reported for a 47 % greater prevalence of weight change (AA: 35 % *vs*. G carriers: 82 %, $p = 0.012$) (Table SII). No other long-term safety outcomes evidenced any significant changes related to the *OPRM1* genotype (Table SIII).

CYP2D6. – The frequencies of metabolic phenotypes were: 83 % ($n = 87$) EMs, 10 % ($n = 10$) UMs and 7 % ($n = 7$) PMs, being in line with the previous literature (33). In this way, CYP2D6 poor and ultra-rapid metabolizers are expected to hardly obtain any pain relief (since drugs are not efficiently converted to more active metabolites) or to experience higher toxicity, resp. (47). Thus, clinical guidelines recommend genotype testing prior prescription of tramadol or codeine, with weak evidence for oxycodone (9).

A linear multiple regression (variables: sex, age, CYP2D6 phenotypes, pain intensity and quality of life) was performed to confirm that PM phenotypes had the lowest long-term MEDD (PM: 27 ± 59 mg per day *vs*. EM-UM: 117 ± 140 mg per day, $p < 0.001$) (Fig. 3). In PM women were evidenced for no opioid use (PM: 0 % *vs*. EM: 70 % *vs*. UM: 63 %, $p = 0.008$) (Table SIV). As regards AEs, men with UM phenotypes suffered vomiting (PM: 0 %, EM: 0 % and UM: 100 %, $p < 0.001$) (Table SII). Future studies should take into account *CYP3A4* gene variants, as its genotype is associated with OUD withdrawal symptoms (48), as well as drug-drug-gene interactions such as CYP2D6 inhibitors (duloxetine, bupropion, fluoxetine, paroxetine) or inducers (escitalopram or clobazam) (49, 50).

Limitations of the study and future lines

First, the lack of randomization or any other instrument variable approach precludes the ability to make any causal inference. Secondly, the time of long-term assessment varies between patients, making a heterogeneous group to evaluate. In any case, no significant

differences were observed when analysing them individually. The scarce number of extreme phenotype subjects in our study may have compromised the statistical power. Further studies should include larger sample sizes to confirm this evidence. Additionally, long-term clinical information was only available for those patients who continued attending the PU, reducing the sample size, especially in men, and with a possible implication for AEs registration.

What's more, pharmacists often report a lack of information and clinical connection to other healthcare professionals as a barrier to the successful monitoring of problematic opioid use. Research has shown community pharmacists can play an important role in delivering evidence-based services to care for opioid-related risk. Thus, medical prescribers, pharmacists, and other healthcare providers are encouraged to work closely together to identify the best possible solution and outcome for each patient (51). In this way, specific approaches – access to EHRs, lab studies and other relevant data – should facilitate pharmacists to provide more comprehensive and careful oversight of OUD in pain management (52).

CONCLUSIONS

Long-term opioid deprescription was achieved in 49 % of the patients, with an increase of pain relief and a reduction of ADRs. Sex differences and a pharmacogenetic influence were detected in long-term deprescription effectiveness and tolerability. Successful OUD prevention programmes should include physicians, prescribers, pharmacists and other healthcare providers in a multidisciplinary PU team. What's more, further studies should include different genetically admixed populations and other variables such as hormonal status or gender issues to confirm and expand these observations.

Acronyms, abbreviations, symbols. – ADRs – adverse drug reactions, AEs – adverse events, AS – activity score, CNCP – chronic non-cancer pain, EHRs – electronic health records, EM – extensive metabolizer, EuroQol-5D – quality of life scale, GAF – global assessment of functioning scale, IQR – interquartile range, MEDD – morphine equivalent daily dose, NSAIDs – non-steroidal anti-inflammatory drugs, OUD – opioid use disorder, PM – poor metabolizer, PU – pain unit, UM – ultra-rapid metabolizers, VAS – visual analogue scale.

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