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

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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

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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 pheno-types 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
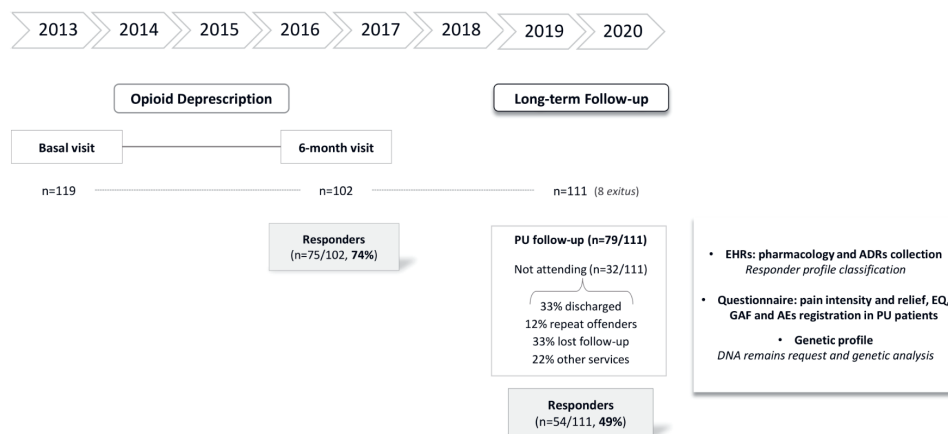

Fig. 1. Flow chart of the opioid depresscription and long-term follow-up (CI – informed consent, EHRs – electronic health records data, EQ – EuroQol-5D, GAF – global assessment of functioning, AEs – adverse events, ADRs – adverse drug reactions).

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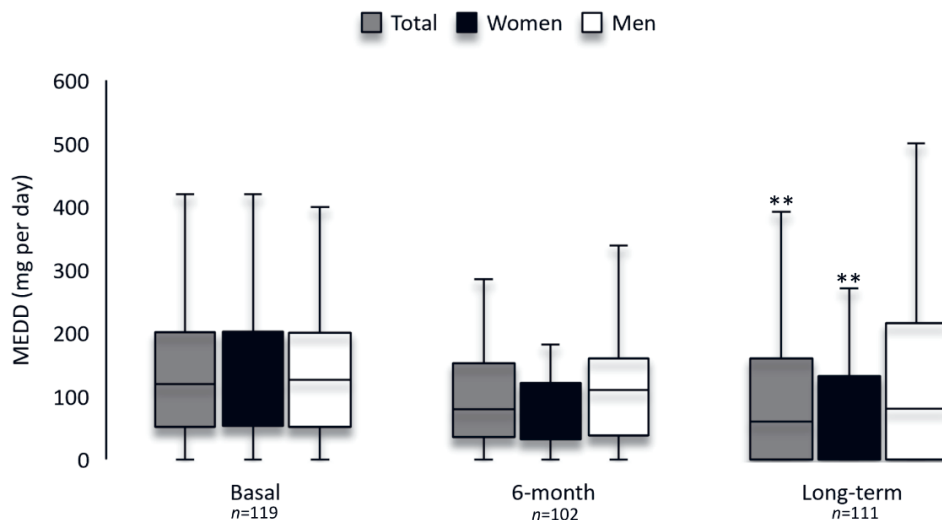
Fig. 2. Morphine equivalent daily dose [MEDD, mg per day), bars median (IQR)] per visit (basal, 6 months, long-term) and sex (all patients in grey, women in black, men in white colour). Statistically significant difference: **p < 0.001 comparing basal, 6-month and long-term visits.

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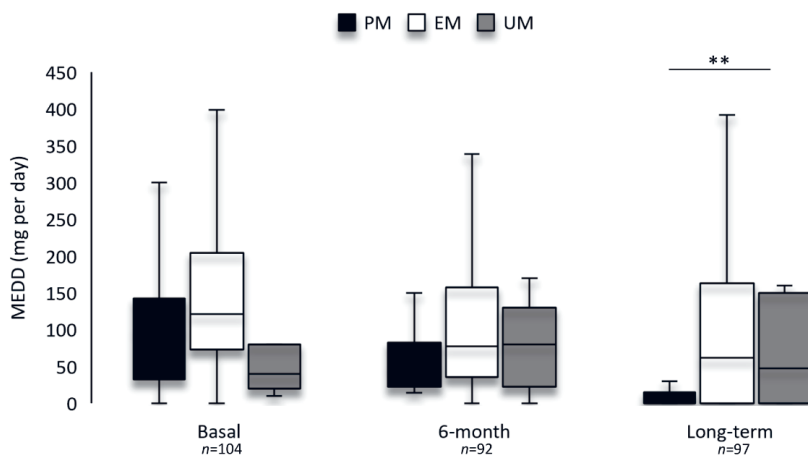
Fig. 3. Morphine equivalent daily dose [MEDD, bars median (IQR)] per visit and CYP2D6 phenotypes. Statistically significant difference: **$p < 0.001$ comparing CYP2D6 phenotype.

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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REFERENCES

1. E. A. Salsitz, Chronic pain, chronic opioid addiction: a complex nexus, *J. Med. Toxicol.* **12**(1) (2016) 54–57; https://doi.org/10.1007/s13181-015-0521-9

2. A. Schuchat, G. P. Guy, Jr. and D. Dowell, Prescription drug monitoring programs and opioid death rates-reply, *JAMA* **318**(20) (2017) Article ID 2045; https://doi.org/10.1001/jama.2017.16304

3. R. Lumish, J. K. Goga and N. J. Brandt, Optimizing pain management through opioid deprescribing, *J. Geront. Nurs.* **44**(1) (2018) 9–14; https://doi.org/10.3928/00989134-20171213-04

4. A. Owusu Obeng, I. Hamadeh and M. Smith, Review of opioid pharmacogenetics and considerations for pain management, *Pharmacotherapy* **37**(9) (2017) 1105–1121; https://doi.org/10.1002/phar.1986

5. B. S. Haerian and M. S. Haerian, OPRM1 rs1799971 polymorphism and opioid dependence: evidence from a meta-analysis, *Pharmacogenomics* **14**(7) (2013) 813–824; https://doi.org/10.2217/pgs.13.57

6. J. Muriel, C. Margarit, J. Barrachina, P. Ballester, A. Flor, D. Morales, J. F. Horga, E. Fernández and A. M. Peiró, Pharmacogenetics and prediction of adverse events in prescription opioid use disorder patients, *Basic Clin. Pharmacol Toxicol.* **124**(4) (2019) 439–448; https://doi.org/10.1111/bcpt.13155

7. G. Ruano and J. A. Kost, Fundamental considerations for genetically-guided pain management with opioids based on CYP2D6 and OPRM1 polymorphisms, *Pain Phys.* **21**(6) (2018) E611–E621.

8. V. Haufroid and P. Hantson, CYP2D6 genetic polymorphisms and their relevance for poisoning due to amfetamines, opioid analgesics and antidepressants, *Clin Toxicol.* (Philadelphia) **53**(6) (2015) 501–510; https://doi.org/10.3109/15563650.2015.1049355

9. 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 and T. C. Skaar, Clinical pharmacogenetics implementation consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy, *Clin. Pharmacol. Ther.* **110**(4) (2021) 888–896; https://doi.org/10.1002/cpt.2149

10. M. Matic, S. N. de Wildt, D. Tibboel and R. H. N. van Schaik, Analgesia and opioids: A pharmacogenetics shortlist for implementation in clinical practice, *Clin. Chem.* **63**(7) (2017) 1204–1213; https://doi.org/10.1373/clinchem.2016.264986

11. B. Planelles, C. Margarit, M. D. Inda, P. Ballester, J. Muriel, J. Barrachina, R. Ajo, M. D. Esteban and A. M. Peiró, Gender based differences, pharmacogenetics and adverse events in chronic pain management, *Pharmacogen. J.* **20**(2) (2020) 320–328; https://doi.org/10.1038/s41397-019-0118-9

12. K. Goodyear, C. L. Haass-Koffler and D. Chavanne, Opioid use and stigma: The role of gender, language and precipitating events, *Drug Alc. Depen.* **185** (2018) 339–346; https://doi.org/10.1016/j.drugalcdep.2017.12.037

13. M.-T. Ruiz-Cantero, M. Blasco-Blasco, E. Chilet-Rosell and A. M. Peiró, Gender bias in therapeutic effort: from research to health care, *Farm. Hospital* **44** (2020) 109–113.

14. S. S. Asl, A. Roointan, H. Bergen, S. Amiri, P. Mardani, N. Ashtari, R. Shabani and M. Mehdizadeh, Opioid receptors gene polymorphism and heroin dependence in Iran, *Basic Clin. Neurosci.* **9**(2) (2018) 101–106; https://doi.org/10.29252/nirp.bcn.9.2.101

15. P. Bach and D. Hartung, Leveraging the role of community pharmacists in the prevention, surveillance, and treatment of opioid use disorders, *Addict. Sci. Clin. Pract.* **14**(1) (2019) Article ID 30 (11 pages); https://doi.org/10.1186/s13722-019-0158-0

16. S. Sarkar, R. Lal, M. Varshney and Y. P. S. Balhara, Tramadol for maintenance in opioid dependence: A retrospective chart review, *J. Opioid Manag.* **13**(5) (2017) 329–334; https://doi.org/10.5055/jom.2017.0401

17. R. K. Lanier, A. Umbricht, J. A. Harrison, E. S. Nuwayser and G. E. Bigelow, Evaluation of a transdermal buprenorphine formulation in opioid detoxification, *Addiction* (Abingdon) **102**(10) (2007) 1648–1656; https://doi.org/10.1111/j.1360-0443.2007.01944.x

18. J. Muriel, C. Margarit, B. Planelles, M. J. Serralta, C. Puga, M. D. Inda, E. Cutillas, D. Morales, J. F. Horga and A. M. Peiró, OPRM1 influence on and effectiveness of an individualized treatment plan for prescription opioid use disorder patients, *Ann. N. Y. Acad. Sci.* **1425**(1) (2018) 82–93; https://doi.org/10.1111/nyas.13735

19. E. von Elm, D. G. Altman, M. Egger, S. J. Pocock, P. C. Gøtzsche and J. P. Vandenbroucke, The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies, *J. Clin. Epidemiol.* **61**(4) (2008) 344–349; https://doi.org/10.1016/j.jclinepi.2007.11.008

20. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed., Washington, D.C. 2013.

21. J. Fernández-Miranda, *Guide to the Treatment of Opioid Dependence*, Socidrogalcohol, Palma de Mallorca 2007, p. 118.

22. S. Mercadante, A. Casuccio, F. Fulfaro, L. Groff, R. Boffi, P. Villari, V. Gebbia and C. Ripamonti, Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study, *J. Clin. Oncol.* **19**(11) (2001) 2898–2904; https://doi.org/10.1200/jco.2001.19.11.2898

23. S. H. Jones, G. Thornicroft, M. Coffey and G. Dunn, A brief mental health outcome scale-reliability and validity of the global assessment of functioning (GAF), *Br. J. Psych.* **166**(5) (1995) 654–659; https://doi.org/10.1192/bjp.166.5.654

24. H. M. McCormack, D. J. Horne and S. Sheather, Clinical applications of visual analogue scales: a critical review, *Psychol. Med.* **18**(4) (1988) 1007–1019.

25. R. A. Moore and H. J. McQuay, Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids, *Arthr. Res. Ther.* **7**(5) (2005) R1046–R1051; https://doi.org/10.1186/ar1782

26. J. Barrachina, J. Muriel, C. Margarit, B. Planelles, P. Ballester, M. Richart-Martínez, E. Cutillas, T. Zandonai, D. Morales and A. M. Peiró, Global pain state questionnaire: Reliability, validity, and gender gap, *Arch. Intern. Med. Res.* **4** (2021) 91–113; https://doi.org/10.26502/aimr.0061

27. P. Mozzicato, MedDRA An overview of the medical dictionary for regulatory activities, *Pharm. Med.* **23**(2) (2009) 65–75; https://doi.org/10.1007/BF03256752

28. W. Häuser, B. Morlion, K. E. Vowles, K. Bannister, E. Buchser, R. Casale, J.-F. Chenot, G. Chumbley, A. M. Drewes, G. Dom, L. Jutila, T. O'Brien, E. Pogatzki-Zahn, M. Rakusa, C. Suarez-Serrano, T. Tölle and N. Krčevski Škvarč, European clinical practice recommendations on opioids for chronic noncancer pain – Part 1: Role of opioids in the management of chronic noncancer pain, *Eur. J. Pain* **25**(5) (2021) 949–968; https://doi.org/https://doi.org/10.1002/ejp.1736

29. C. Taylor, I. Crosby, V. Yip, P. Maguire, M. Pirmohamed and R. M. Turner, A review of the important role of CYP2D6 in pharmacogenomics, *Genes* **11**(11) (2020) Article ID 1295 (22 pages); https://doi.org/10.3390/genes11111295

30. A. Llerena, P. Dorado, R. Ramírez, I. González, M. Alvarez, E. M. Peñas-Lledó, B. Pérez and L. R. Calzadilla, CYP2D6 genotype and debrisoquine hydroxylation phenotype in Cubans and Nicaraguans, *Pharmacogen. J.* **12**(2) (2012) 176–183; https://doi.org/10.1038/tpj.2010.85

31. A. Gaedigk, S. D. Simon, R. E. Pearce, L. D. Bradford, M. J. Kennedy and J. S. Leeder, The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype, *Clin. Pharmacol. Ther.* **83**(2) (2008) 234–242; https://doi.org/10.1038/sj.clpt.6100406

32. P. Dorado, M. Cáceres, E. Pozo-Guisado, M. L. Wong, J. Licinio and A. Llerena, Development of a PCR-based strategy for CYP2D6 genotyping including gene multiplication of worldwide potential use, *BioTechniques* **39**(Suppl. 10) (2005) S571–S574; https://doi.org/10.2144/000112044

33. M. E. G. Naranjo, F. de Andrés, A. Delgado, J. Cobaleda, E. M. Peñas-Lledó and A. LLerena, High frequency of *CYP2D6* ultrarapid metabolizers in Spain: controversy about their misclassification in worldwide population studies, *Pharmacogen. J.* **16**(5) (2016) 485–490; https://doi.org/10.1038/tpj.2016.47

34. J. Mennis, G. J. Stahler and M. J. Mason, Risky substance use environments and addiction: A new frontier for environmental justice research, *Int. J. Environ. Res. Public Health* **13**(6) (2016) Article ID 607 (15 pages); https://doi.org/10.3390/ijerph13060607

35. M. Gosch, B. Böhmdorfer, U. Benvenuti-Falger, P. Dovjak, B. Iglseder, M. Lechleitner, R. Otto, R. E. Roller and U. Sommeregger, [Polypharmacy and pain treatment], *Wien. Med. Wochenschr.* **160**(11–12) (2010) 286–292; https://doi.org/10.1007/s10354-010-0788-z

36. A. I. Henche Ruiz, Problematic use of prescription opioid drugs: Classification and effective treatments, *Med. Clin.* **152**(11) (2019) 458–465; https://doi.org/https://doi.org/10.1016/j.medcli.2018.10.008

37. M. D. Cheatle, P. A. Compton, L. Dhingra, T. E. Wasser and C. P. O'Brien, Development of the revised opioid risk tool to predict opioid use disorder in patients with chronic nonmalignant pain, *J. Pain* **20**(7) (2019) 842–851; https://doi.org/10.1016/j.jpain.2019.01.011

38. C. Els, T. D. Jackson, D. Kunyk, V. G. Lappi, B. Sonnenberg, R. Hagtvedt, S. Sharma, F. Kolahdooz and S. Straube, Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane reviews, *Cochrane Database Syst. Rev.* **10**(10) (2017) Cd012509; https://doi.org/10.1002/14651858.CD012509.pub2

39. L. Hazell and S. A. Shakir, Under-reporting of adverse drug reactions: a systematic review, *Drug Safety* **29**(5) (2006) 385–396; https://doi.org/10.2165/00002018-200629050-00003

40. M. Gombert, P. Ballester, A. Segura and A. M. Peiró, Introducing sexual dysfunction in mental care, *Expert Opin. Drug Safety* **20**(1) (2021) 69–79; https://doi.org/10.1080/14740338.2020.1849135

41. L. LeResche, K. Saunders, S. Dublin, S. Thielke, J. O. Merrill, S. M. Shortreed, C. Campbell and M. R. Von Korff, Sex and age differences in global pain status among patients using opioids long term for chronic noncancer pain, *J. Women Health* **24**(8) (2015) 629–635; https://doi.org/10.1089/jwh.2015.5222

42. M. Noble, J. R. Treadwell, S. J. Tregear, V. H. Coates, P. J. Wiffen, C. Akafomo, K. M. Schoelles and R. Chou, Long-term opioid management for chronic noncancer pain, *Cochrane Database Syst. Rev.* No. 1 (2010) CD006605; https://doi.org/10.1002/14651858.CD006605.pub2

43. N. Kozlov and H. T. Benzon, Role of gender and race in patient-reported outcomes and satisfaction, *Anesthesiol. Clin.* **38**(2) (2020) 417–431; https://doi.org/10.1016/j.anclin.2020.01.012

44. F. K. H. Sørup, R. Eriksson, D. Westergaard, J. Hallas, S. Brunak and S. E. Andersen, Sex differences in text-mined possible adverse drug events associated with drugs for psychosis, *J. Psychopharmacol.* (Oxford) **34**(5) (2020) 532–539; https://doi.org/10.1177/0269881120903466

45. E. Mura, S. Govoni, M. Racchi, V. Carossa, G. N. Ranzani, M. Allegri and R. H. van Schaik, Consequences of the 118A>G polymorphism in the OPRM1 gene: translation from bench to bedside?, *J. Pain Res.* **6** (2013) 331–353; https://doi.org/10.2147/jpr.s42040

46. K. Blum, M. Oscar-Berman, Z. Demetrovics, D. Barh and M. S. Gold, Genetic addiction risk score (GARS): molecular neurogenetic evidence for predisposition to reward deficiency syndrome (RDS), *Mol. Neurobiol.* **50**(3) (2014) 765–796; https://doi.org/10.1007/s12035-014-8726-5

47. L. Dean and M. Kane, *Codeine Therapy and* CYP2D6 *Genotype*, in *Medical Genetics Summaries* (Eds. V. M. Pratt, S. A. Scott, M. Pirmohamed, B. Esquivel, M. S. Kane, B. L. Kattman and A. J. Malheiro), National Center for Biotechnology Information, Bethesda (MD) 2012, p. 25.

48. E. B. Ettienne, A. Ofoegbu, M. K. Maneno, J. Briggs, G. Ezeude, S. Williams, C. Walker and E. Chapman, Pharmacogenomics and opioid use disorder: clinical decision support in an African American cohort, *J. Nat. Med. Assoc.* **111**(6) (2019) 674–681; https://doi.org/10.1016/j.jnma.2019.09.006

49. M. A. Bahar, D. Setiawan, E. Hak and B. Wilffert, Pharmacogenetics of drug-drug interaction and drug-drug-gene interaction: a systematic review on CYP2C9, CYP2C19 and CYP2D6, *Pharmacogenomics* **18**(7) (2017) 701–739; https://doi.org/10.2217/pgs-2017-0194

50. C. R. Fulton, Y. Zang, Z. Desta, M. B. Rosenman, A. M. Holmes, B. S. Decker, Y. Zhang, J. T Callaghan, V. M. Pratt, K. D. Levy, B. T. Gufford, P. R. Dexter, T. C. Skaar and M. T. Eadon, Drug-gene and drug-drug interactions associated with tramadol and codeine therapy in the INGENIOUS trial, *Pharmacogenomics* **20**(6) (2019) 397–408; https://doi.org/10.2217/pgs-2018-0205

51. G. Cochran, J. Bruneau, N. Cox and A. J. Gordon, Medication treatment for opioid use disorder and community pharmacy: Expanding care during a national epidemic and global pandemic, *Subst. Abuse* **41**(3) (2020) 269–274; https://doi.org/10.1080/08897077.2020.1787300

52. National Institute on Drug Abuse (NIDA), *Cooperation Between Physicians and Pharmacists May Improve Treatment for Patients with Opioid Use Disorder, 2021*; https://nida.nih.gov/news-events/nida-notes/2021/11/cooperation-between-physicians-and-pharmacists-may-improve-treatment-for-patients-with-opioid-use-disorder; last access date September 20, 2022