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OPRM1 influence on and effectiveness of an individualized treatment plan for prescription opioid use disorder patients

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Screening for opioid use disorder should be considered in chronic non-cancer pain (CNCP) patients with long-term use of opioids. The aim of our study was to assess the effectiveness of an individualized treatment plan (ITP) for prescription opioid dependence that included screening of pharmacogenetic markers. An observational prospective study was performed using prescription opioid-dependent CNCP outpatients ($n = 88$). Patients were divided into nonresponders, responders, or high responders according to their response to the ITP. Genotyping of *OPRM1* (A118G), *OPRD1* (T921C), *COMT* (G472A), *ABCB1* (C3435T), and *ARRB2* (C8622T) was performed by real-time PCR. Our ITP achieved a significant reduction of the morphine equivalent daily dose (MEDD) in 64% of responders, including 33% of high responders. Nonopioid medication or buprenorphine use was significantly higher at final versus basal visit. 118-AA *OPRM1* patients required significantly lower MEDD at basal and final visits. Our ITP showed effectiveness and security in reducing MEDD in opioid-dependent patients, with good conversion to buprenorphine that was more pronounced in 118-AA *OPRM1* patients.

Keywords: opioid; opioid use disorder; *OPRM1*; pharmacogenetics; chronic pain

Introduction

In the past two decades in the Western world, there has been an increasing use of opioids in chronic non-cancer pain (CNCP),[1] reflecting a major shift in the prescribing behaviors of physicians due to many factors, including increased awareness and diagnosis of chronic pain.[2,3] However, abuse[4] and dependence are associated with these high rates of opioid prescriptions.[5,6] Estimates suggest that dependence occurs in approximately 0.2–3% of patients with previous substance abuse history.[7] Underreporting of dependence remains an obstacle in determining its real incidence and is thus not accurately reflected in the information provided to prescribers in the summary product characteristics (SPCs). This results in only a small proportion of opioid dependence cases being described in the literature, which does not reflect everyday practice.[8]

Data about the side effects of long-term use of opioids continue to be scarce. Only a few randomized controlled trials directly comparing different opioids have been published; however, information about dependence profiles was not included.[9] Moreover, pharmacological pain management typically requires multiple drugs that can present synergistic or adjunctive effects and are usually prescribed at high doses. This overall drug profile is often overlooked and oversimplified in clinical trials.[10]

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The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines dependence as "a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation of a drug, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist."[11] Once detected, an opioid tapering individualized treatment plan (ITP) should be applied together with general recommendations that include: monitoring, opioid rotation, discontinuation of therapy, and prevention of opioid adverse drug reactions (ADRs).[12]

Some meta-analyses[13] have been performed to examine the heritability of drug use behavior and the genetic determinants of opioid dependence.[14–16] However, most of the patients have a dual pathology diagnosis as a methadone- or alcohol-addicted population.[17] The evidence from molecular genetic studies continues to be inconclusive; however, at least, three different factor categories have been associated by genome-wide and multigene association studies with vulnerability to developing a specific addiction once self-exposed. These factors are: (1) environmental factors, including cues conditioning, and external stressors and the stress they cause; (2) drug-induced factors that lead to a variety of molecular neurobiological changes resulting in altered behaviors; (3) and genetic factors, which represent approximately 40–60% of the risk of developing an addiction.[18]

In opioid treatments, a high variability in response has often been reported, with 10–30% of patients not responding due to either loss of efficacy or the presence of adverse events (AEs).[19,20] Recently, it has been demonstrated that some single nucleotide polymorphisms (SNPs) in key genes can play an important role in the interaction, distribution, and/or elimination of opioid drugs. Opioid receptor mu 1 (OPRM1) is the main target for opioid molecules. The most studied SNP in *OPRM1* is A118G (rs21799971), which leads to the loss of an N-glycosylation site in the extracellular region of the receptor.[21] Some studies have pointed out that carriers of the G allele required higher morphine or fentanyl doses to reach analgesia.[22,23] Other genes studied in this field encode for different opioid receptors (*OPRD1*), drug transporters (*ABCB1*), catecholamine degradation proteins (*COMT*), or for arrestin beta-2 (*ARRB2*), a protein that participates in agonist-mediated desensitization of G protein–coupled receptors and causes specific dampening of cellular responses to stimuli.

The present study was undertaken to (1) demonstrate the effectiveness of an ITP in prescription opioid-dependent patients; (2) analyze the pharmacological pain therapy safety profile in ambulatory Pain Unit patients, including dependence behavior and their response to the ITP; and (3) assess genetic factors that predict response to the ITP. In doing so, we wish to fill the current gaps in the literature and suggest practical ways in which clinicians could optimize opioid use in CNCP.

Materials and methods

Study design

An observational prospective study of prescription opioid dependence was conducted during 30 months, from May 2013 to December 2015, on CNCP patients receiving long-term opioid treatment at the pain unit of Alicante General Hospital and who were included sequentially by chronological order of visit. The study was approved by the Ethics Committee of Alicante Department of Health-General Hospital. Once the aim and confidentiality of the information obtained was explained to the patients and informed consent was obtained, the questionnaires were self-administered.

Participants

A total of 88 participants from our hospital or surrounding areas that attended the pain unit were included in the study. Inclusion criteria were patients over 18 years old with CNCP, long-term use of opioids (>6 months), and a clinical profile indicating possible dependence behavior. To be included in the study, a diagnosis of prescription opioid dependence was performed according to DSM-5 diagnostic criteria.[11] Patients under 18 years old with oncologic pain or any psychiatric disorders that could interfere with the proper development of the study were excluded.

Individualized treatment plan

All prescription opioid-dependent patients followed an opioid tapering ITP in six clinical visits (basal, 1 week, 2 weeks, 1 month, 3 months, and at 6 months as final visit) that was designed, established, and executed according to national and international guidelines (Fig. 1).[24]

Four physicians (two anesthesiologists, one clinical pharmacologist, and one psychiatrist), one

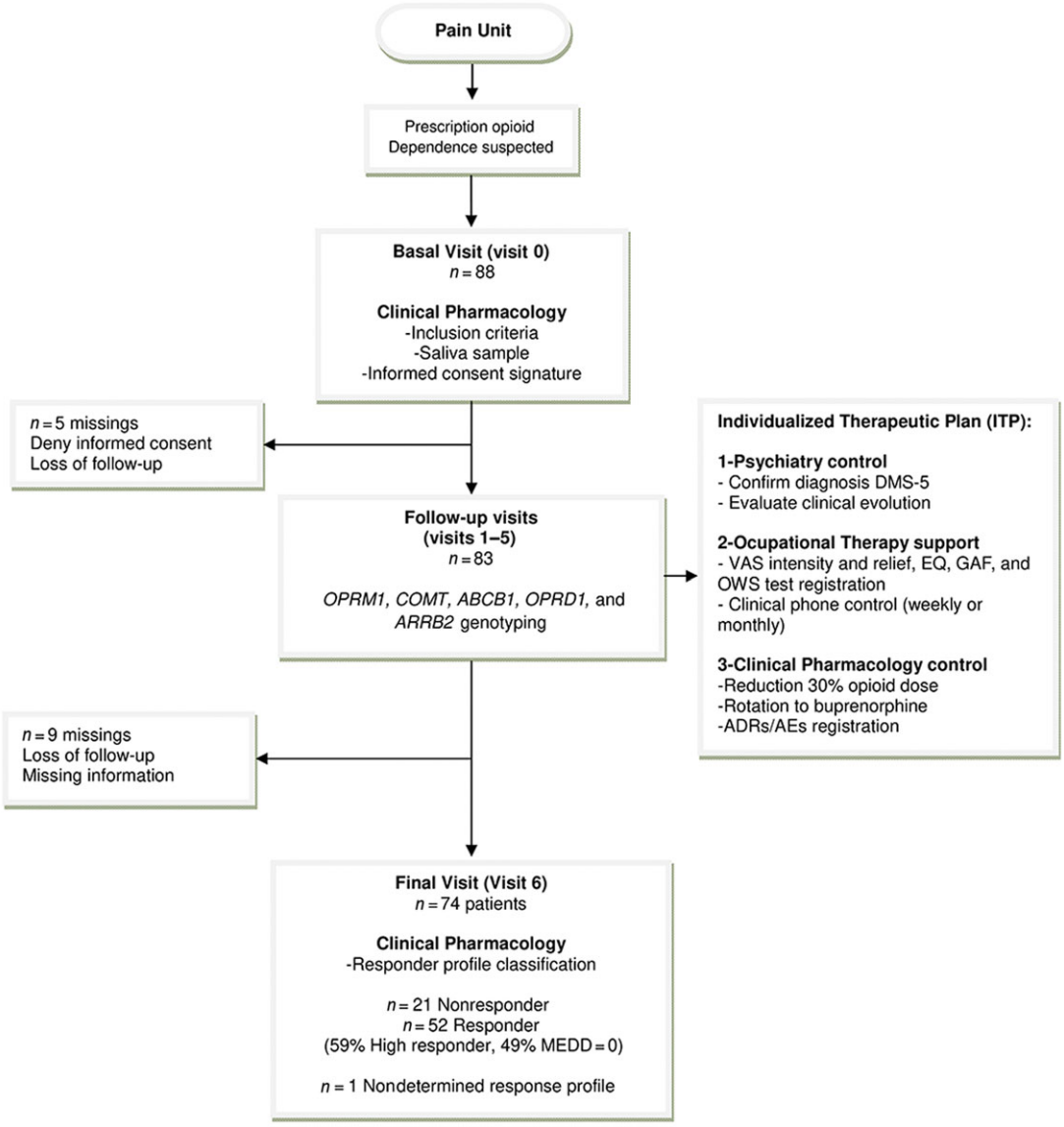

Figure 1. Study flowchart from basal to final individualized treatment plan (ITP) visits. VAS, visual analog scale; EQ, EuroQol quality of life scale; GAF, global assessment of functioning scale; OWS, opiate withdrawal scale; ADRs, adverse drug reactions; AEs, adverse events; MEDD, morphine equivalent daily dose.

nurse, and one occupational therapist trained in pain management assessed the patients.

All patients from the Pain Unit with potential abuse or misuse of opioids were directed to a clinical pharmacologist. At the basal visit, a clinical interview was performed to evaluate physical health, drug use, and medical history. Patients were informed of the goals of the study and informed consent was obtained. The same day, a psychiatrist performed the diagnosis of prescription opioid use disorder. Opioid rotation to tramadol/buprenorphine together with the tapering process (progressive withdrawal of rapid release opioids, rotation to buprenorphine/tramadol with opioid dose reduction, and pharmacological review for withdrawal of medication) then began. All clinical visits included psychiatric monitoring (personality analysis, risk behavior assessment, and medication use for

psychiatric symptoms if required), opioid rotation, or tapering control. Patients were closely followed in order to prevent opiate abstinence syndrome (OAS) or any other event associated with the discontinuation procedure (nervousness, insomnia, anxiety, gastrointestinal, among others) and individualized interventions were incorporated to palliate them. Furthermore, weekly control of all the patients was performed by an occupational therapist throughout the phone.

All questionnaires were compiled at each visit. At the end of the study, patients were categorized as nonresponder if (1) the patient dropped out of the ITP, (2) the diagnosis of prescription opioid dependence persisted according to DSM-5 criteria, (3) aberrant opioid use behavior persisted, or (4) the patient did not achieve at least a 30% reduction of the morphine equivalent daily dose (MEDD). The rest of the patients not fitting the nonresponder criteria were then categorized as responders. Within the responder group, a high responder subgroup was defined as patients who achieved a reduction of more than 50% of basal MEDD.

Data collected

All patients were interviewed at the first visit to collect demographic information and pain history (e.g., number of years with pain, pain location, and current pain medication).

Validated scales and questionnaires completed at each visit were used to evaluate the clinical situation for each patient. Pain intensity and relief were measured using the visual analog scale (VAS).[25] Both consist of a 100 mm horizontal line ranging from 0 (lowest) to 100 mm (highest), where the patient points on the line the intensity of pain or relief, respectively, that he or she feels. Quality of life was evaluated through the VAS-EuroQol Scale that consists of a 100 mm vertical line from 0 (the worst imaginable health status) to 100 mm (the best imaginable), where the patient points to his or her actual health status.[26]

OAS was evaluated using the validated opiate withdrawal scale, which is a questionnaire composed of 32 characteristic signs and symptoms common in opioid withdrawal patients.[27] Each item is rated as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe), depending on the degree manifested by the patient. Final scores range between 0 and 96 points, in increasing order of severity.

A global assessment of functioning was used to evaluate the psychological, social, and occupational functioning of the participants, excluding the activity alterations caused by physical limitations. It provides a score from 0 to 100 according to the global activity of the patient, with higher scores meaning a better level of activity and life.[28]

Drug use and adverse events

Analgesic (simple analgesics, tramadol, opioids, and adjuvants) use was obtained from the institution's electronic prescribing application. As the number of available opioid medications is increasing, it is necessary when comparing patients taking different agents to compare equivalent morphine doses. For this purpose, oral MEDD for the different opioids taken by a single patient was estimated using available references.[29] Use of gabapentin, pregabalin, duloxetine, non-steroidal anti-inflammatory drugs, other analgesics, or benzodiazepine was also registered.

To collect patients' AEs, a questionnaire with the list of the most frequent ADRs (selected according to opioid's SPC frequency as "very common" and "common")[30] and a blank field to add any other AEs was developed. In addition, all ADRs[31] related to the pharmacological pain treatment were collected and classified by the Medical Dictionary for Regulatory Activities (MedDRA, version 20.0) and Preferred Term.

Genotyping

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

Approximately 2 mL of saliva was collected in PBS-containing tubes. Genomic DNA was extracted with E.N.Z.A. Forensic DNA Kit (Omega bio-tek) was used according to manufacturer's instructions. Real-time polymerase chain reaction (RT-PCR) analysis was used for the identification of the *OPRM1* rs1799971, *OPRD1* rs2234918, *COMT* rs4680, *ABCB1* rs1045642, and *ARRB2* rs1045280 gene polymorphisms. All PCR amplifications were carried out in an RT-PCR Rotor Gene Q (Qiagen) using specific TaqMan MGB® probes (Applied Biosystems). Amplification parameters were as follows: pre-PCR 30 s at 60 °C, followed by 10 min initial denaturation at 95 °C, 45 cycles for 15 s at

95 °C, 60 s at 60 °C, and 30 s of final extension at 72 °C.

Statistical analyses

Quantitative parametric data are presented as mean ± standard deviation (SD), while median and interquartile range (IQR) were used for nonparametric data. The symbol "Δ" was used to point out value differences from basal to final visit. Comparisons for quantitative or categorical data between two groups were conducted using independent *t*-tests or chi-square (χ^2) tests (or Fischer exact test), respectively.

Observed gene frequencies were compared to what were expected using the χ^2 goodness-of-fit test and the Hardy–Weinberg proportion. Due to the low number of homozygotes for some polymorphisms, patients were grouped for analyses as carriers or noncarriers, where carriers are defined as participants who tested positive for the presence of the allelic variants (dominant model).

To estimate the risk for responding associated with *OPRM1* A118G, *COMT* G472A, *ABCB1* C3435T, *OPRD1* T921C, and *ARRB2* C8622T, the odds ratio (OR) was calculated using logistic regression analysis before and after adjustment for other factors (age, sex, and MEDD). For interaction analyses, genotypes were also classified into dichotomous variables according to dominant models. Effect sizes were calculated for all the comparisons. For the *t*-test analyses, Cohen's *d* and Hedge's *g* values were calculated. For the χ^2 and Fisher's exact tests, the OR and 95% confidence interval (95% CI) are provided. For the different regression analyses, f^2 and R^2 values are given. A P value < 0.05 was considered statistically significant. In all cases, multiple testing was adjusted using Bonferroni's correction. All statistical analyses were carried out with the R software (version 3.2.0).

Results

Throughout the 30-month study period, a total of 2744 pain patients were nursed at our Pain Unit, of which 80% presented CNCP and 86% of them were under opioid treatment. A total of 88 out of 1887 CNCP patients under long-term opioid treatment were diagnosed for prescription opioid dependence by DSM-5 criteria. Data were not collected from five patients due to several reasons (refused to participate in the study, dropped out, did not understand the questionnaires, or similar). Figure 1 shows the flowchart from the basal visit to the final visit at 6 months.

Study participant characteristics were representative of patients who are typically seen at our hospital Pain Unit. According to the criteria detailed in the Methods, 64% of the patients were categorized as responders and 30% as nonresponders. Six percent of patients could not be categorized due to lack of information. In the nonresponders group, 70% did not reach a 30% reduction of MEDD and 21% presented persistent aberrant opioid use behavior. The remaining 9% presented unavailable data from basal or final MEDD but were categorized as nonresponders by clinical criteria. In the responder group, 52% of the patients achieved an MEDD reduction greater than 50% and were categorized as high responders. Also, a total of 45% achieved opioid tapering before the end of the ITP (mean ± SD, 3 ± 2 months).

Descriptive and clinical data

A summary of the descriptive, clinical, and pharmacological data of the study participants is presented in Tables 1 and 2. Patients (53 ± 13 years old, 64% females, 100% Caucasian) presented a moderate pain intensity (55 ± 27 mm), low pain relief (39 ± 30 mm), and moderate quality of life (47 ± 23 mm) and functionality (71 ± 15 scores). None of them showed OAS (32 ± 19 scores).

At the end of the ITP, pain intensity was significantly lower in responders versus nonresponders (50 ± 30 versus 66 ± 23 mm, $P = 0.027$, $d = 0.601$, $g = 0.561$). No differences between the responder and nonresponder groups were found for pain relief, quality of life, functionality, and OAS.

The high responder group presented significantly lower pain intensity (40 ± 31 versus 63 ± 22 mm, $P = 0.011$, $d = 0.852$, $g = 0.818$), higher quality of life (52 ± 21 versus 33 ± 15 mm, $P = 0.009$, $d = 0.898$, $g = 0.853$), and lower OAS (25 ± 18 versus 43 ± 16 scores, $P = 0.008$, $d = 1.066$, $g = 1.022$) relative to the rest of the responders at the final visit (Table 2). No other clinical differences were found in each group.

Pharmacological data

A summary of pharmacological data is presented in Tables 1 and 2. Basal MEDD was 167 ± 179 mg/day, with most patients under fentanyl (37%) or oxycodone (18%) treatment. Other analgesics

Table 1. Descriptive characteristics, clinical variables, and medication use

	Total population		Nonresponder		Responder	
	Basal visit ($n = 83$)	Final visit ($n = 74$)	Basal visit ($n = 25$)	Final visit ($n = 21$)	Basal visit ($n = 53$)	Final visit ($n = 52$)
Age (years)	53 ± 13	50 ± 15	54 ± 12			
Gender (% female)	64%	52%	66%			
VAS intensity (mm)	55 ± 27	54 ± 29	61 ± 23	**66 ± 23**$^{\#}$	53 ± 27	**50 ± 30**$^{\#}$
VAS relief (mm)	39 ± 30	40 ± 30	31 ± 25	29 ± 24	44 ± 32	44 ± 32
EQ (mm)	47 ± 23	46 ± 23	43 ± 22	40 ± 26	49 ± 23	48 ± 21
OWS (scores)	32 ± 19	33 ± 21	36 ± 22	35 ± 26	30 ± 18	32 ± 20
GAF (scores)	71 ± 15	69 ± 14	68 ± 13	67 ± 13	73 ± 16	70 ± 15
MEDD (mg/day)	**167 ± 179***	**87 ± 104***	193 ± 172	**176 ± 121**$^{\#\#}$	**128 ± 118***	**50 ± 69**$^{*\ \#\#}$
Pain medication (%)						
Without opioids or with buprenorphine	**22****	**65****	26	**29**$^{\#\#}$	**20****	**82**$^{**\ \#\#}$
Fentanyl transdermal	**37****	**11****	44	**29**$^{\#\#}$	**35****	**4**$^{**\ \#\#}$
Hydromorphone	0	3	0	10	0	0
Morphine	4	7	0	5	7	8
Oxycodone	3	1	4	5	2	0
Oxycodone/naloxone	**18***	**4***	17	10	**17***	**0***
Tapentadol	16	8.5	9	14	20	6
Other analgesics	**22***	**6***	27	5	19	6
NSAIDs	6	1	9	5	5	0
Tramadol/paracetamol	15	25	18	14	17	29
Tramadol	24	33	43	35	17	31
Coaduvants (%)						
Pregabaline	**39****	**10****	**50***	**5***	**36***	**13***
Gabapentine	**26***	**45***	29	57	20	39
Duloxetine	30	29	42	33	29	27
Benzodiazepine	36	34	46	**57**$^{\#}$	24	**23**$^{\#}$

$^{*}P < 0.050$ is in bold font, $^{**}P < 0.001$ for basal versus final visit.

$^{\#}P < 0.050$ is in bold font, $^{\#\#}P < 0.001$ for basal nonresponder versus basal responder or final nonresponder versus final responder.

Note: Data are presented as mean ± standard deviation or as percentage (%).

VAS, visual analog scale (0–100 mm); EQ, VAS EuroQol scale (0–100 mm); OWS, opiate withdrawal scale (0–96 scores); GAF, global assessment of functioning (0–100 scores); MEDD, morphine equivalent daily dose (mg/day); SD, standard deviation; NSAIDs, non-steroidal anti-inflammatory drugs.

(tramadol, benzodiazepines, anticonvulsants, and/or duloxetine) were prescribed in more than 20% of the patients.

After 6 months of the ITP, MEDD was significantly reduced to 87 ± 104 mg/day ($P = 0.007$, $d = 0.556$, $g = 0.584$) and the percentage of patients using buprenorphine or nonopioid medication was significantly higher (22% versus 65%, $P < 0.001$, OR = 0.111, 95% CI = 0.049–0.250). Furthermore, upon ITP, the percentage of patients using gabapentin was higher (26% versus 45%, $P = 0.047$, OR = 0.417, 95% CI = 0.182–0.952), while there was a decrease in the percentage of patients using fentanyl (37% versus 11%, $P < 0.001$, OR = 4.622, 95% CI = 1.925–11.10), oxycodone (18% versus 4%, $P = 0.015$, OR = 4.911, 95% CI = 1.335–18.07), other simple analgesics (22% versus 6% $P = 0.020$, OR = 4.714, 95% CI = 1.312–16.94), or pregabalin (39% versus 10%, $P = 0.001$, OR = 5.667, 95% CI = 2.080–15.45) (Table 1).

Basal MEDD was similar between the responder and nonresponder groups. However, the prescribed MEDD was significantly reduced after ITP in the responder group and was significantly lower versus nonresponders at final visit (50 ± 69 versus 176 ± 121 mg/day, $P < 0.001$, $d = 1.276$, $g = 1.420$, respectively). As expected, high responders showed the lowest MEDD at the final visit (15 ± 36 mg/day, $P < 0.001$, $d = 1.628$, $g = 1.711$).

Also, responders showed a significantly higher of use of nonopioid treatment or buprenorphine than nonresponders (82% versus 29%, $P < 0.001$, OR = 0.090, 95% CI = 0.027–0.296), reducing the use of fentanyl by 25% and the use of benzodiazepines at final visit by 34%. The use of pregabalin was significantly lower at the end of the ITP in both

Table 2. Descriptive characteristics, clinical variables, and medication use between normal and high responders at final visit

Individualized treatment plan Final visit (Mean ± SD)	Normal responder ($n = 18$)	High responder ($n = 27$)	P value
Age (years)	57 ± 12	53 ± 12	0.264
Gender (% female)	61	70	0.538
VAS intensity (mm)	**63 ± 22***	**40 ± 31***	**0.011***
VAS relief (mm)	36 ± 26	45 ± 34	0.344
EQ (mm)	**35 ± 15***	**52 ± 21***	**0.009***
OWS (scores)	**43 ± 16***	**25 ± 18***	**0.008***
GAF (scores)	66 ± 14	74 ± 14	0.145
MEDD (mg/day)	**109 ± 73***	**15 ± 36***	**< 0.001***

*$P < 0.050$ is in bold font.

VAS, visual analog scale (0–100 mm); EQ, VAS EuroQol scale (0–100 mm); OWS, opiate withdrawal scale (0–96 scores); GAF, global assessment of functioning (0–100 scores); AEs, adverse events; MEDD, morphine equivalent daily dose (mg/day); SD, standard deviation.

the responders (Δ23%, $P = 0.032$, OR = 3.844, 95% CI = 1.177–12.56) and nonresponders (Δ45%, $P = 0.005$, OR = 20.00, 95% CI = 1.994–200.6).

Drug use and adverse events reported by patients

A summary of AEs reported by patients is presented in Table 3. Patients reported a total of 1665 AEs among 359 total visits of the study, with a median of 6.5 (IQR: 4–9) AEs per patient. The most common AEs reported at baseline were dry mouth (66% of the patients), sleep disruption (53%), constipation (51%), and depression (50%). No significant differences were found in the distribution and total number of AEs reported between the total population, responders, and nonresponders at the basal and final visits. However, high responders presented a significant reduction at final visit in constipation ($P = 0.027$, OR = 6.400, 95% CI = 1.338–30.62), drowsiness ($P = 0.014$, OR = 7.500, 95% CI = 1.493–37.67), depression ($P = 0.032$, OR = 6.667, 95% CI = 1.376–32.29), nausea ($P = 0.002$, OR = 30.00, 95% CI = 2.793–322.3), vomiting ($P = 0.001$, OR = 52.56, 95% CI = 2.442–1131), sexual disturbance ($P = 0.008$, OR = 5.042, 95% CI = 1.562–16.27), and total number of AEs ($P = 0.036$, $d = 0.710$, $g = 0.714$) compared to the rest of responders (Table 3).

A total of 14% of the patients presented a suspected ADR during the study follow-up, without any significant differences between responder and nonresponder groups (12% versus 17%, $P = 0.742$).

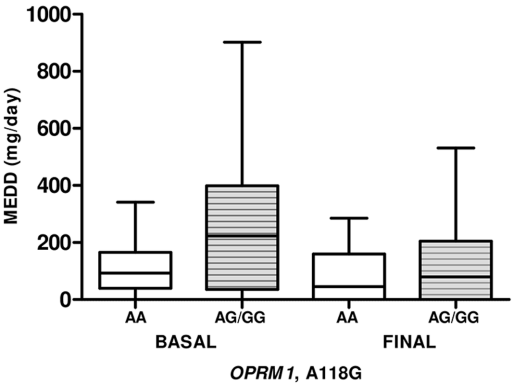

Figure 2. Morphine equivalent daily dose (MEDD) requirement at basal and final individualized treatment plan (ITP) visits, according to the *OPRM1* A118G genotype. Error bar, minimum to maximum.

Genotype

Genotypic and allelic frequencies are presented in Table S1 (online only). All the polymorphisms analyzed were in Hardy–Weinberg equilibrium, with the exception of the *ARRB2* gene. The minor allele frequencies were: 15% for *118G* ($P = 1.000$); 54% for *472A* ($P = 0.639$); 52% for *3435T* ($P = 0.486$); 47% for *921C* ($P = 0.639$); and 50% for *8622T* ($P = 0.000$).

MEDDs related to different *OPRM1* genetic models at the basal and final visits are shown in Figure 2 and Table 4. In the total population, a need for an increased MEDD was observed in patients carrying the *OPRM1* G allele. No other influence was found for any other polymorphism in our study.

Table 3. Adverse events reported by patients related to long-term use of opioids

AEs (%)	Total population		Nonresponder	Responder			
Visit	Basal	Final	Final	Total Final	Normal Final	High Final	*P* value Normal versus high
Constipation	51	45	58	43	**67***	**24***	**0.027***
Dry mouth	66	66	77	64	78	57	0.419
Drowsiness	39	48	55	45	**75***	**29***	**0.014***
Sleep disruption	53	57	54	60	58	67	0.716
Dizziness	36	30	25	30	50	19	0.105
Nervousness	44	52	67	49	50	57	1.000
Sexual disturbance	32	30	27	32	**58***	**21***	**0.008***
Nausea	24	22	17	24	**60***	**5***	**0.002***
Depression	50	54	69	50	**77***	**33***	**0.032***
Dry skin	44	49	73	43	56	38	0.443
Weight change	38	34	25	38	40	33	1.000
Headache	36	44	46	45	55	43	0.712
Vomiting	14	12.5	0	17	**56***	**0***	**0.001***
Itching	42	35	46	32	50	29	0.423
Redness	16	15	18	14	0	19	0.287
Edema	10	19	9	22	22	14	0.622
Loss of appetite	30	31	27	32	50	29	0.423
Total AEs mean ± SD	6.5 ± 3.8	6.3 ± 3.7	6.9 ± 3.8	6.2 ± 3.7	**7.7 ± 3.8***	**5.3 ± 2.9***	**0.036***

*$P < 0.050$ is in bold font.
AEs, adverse events; SD, standard deviation.

Further analysis of MEDD requirement and *OPRM1* genotype according to different genetic models was performed. A need for increased MEDD in A/G–G/G relative to A/A was found in the dominant model ($P = 0.018$, $d = 0.690$, $g = 0.737$) and in A/G relative to A/A–G/G in the overdominant model ($P = 0.020$, $d = 0.669$, $g = 0.731$) at the basal visit. MEDD increased with the number of G alleles, at a 95% CI. In the same way, at the final visit, the codominant model showed a need for increased MEDD in the A/G and G/G genotypes relative to A/A ($P = 0.032$, $R^2 = 0.097$). In the recessive model, the G/G genotype required a higher MEDD relative to A/A–A/G ($P = 0.032$). In a binary logistic regression analysis, the *118G* allele was not associated with a risk for being responder, before or after adjustment for age and sex ($P = 0.166$, 95% CI = –1.741 to 0.306), nor for being a high responder ($P = 0.089$, 95% CI = –2.262 to 0.106).

Influence on OAS

A linear regression of the descriptive, clinical, and genotypic parameters performed at the final visit is presented in Table 5 and Table S2 (online only). Linear regression analysis showed a positive significant association of OAS with pain intensity ($P = 0.001$, $f^2 = 0.316$), and a negative association with pain relief ($P = 0.002$, $f^2 = 0.266$), quality of life ($P < 0.001$, $f^2 = 0.631$), and functionality ($P < 0.001$, $f^2 = 0.399$) in the total population and in the responder group, but not with MEDD, age, gender, or genotype (Table 5).

In a multiple regression analysis, a significant association between OAS and quality of life was found in the total population ($P = 0.005$) and responders ($P = 0.023$) (Table S2, online only).

Discussion

This study shows that our ITP achieved a significant reduction of MEDD requirement in opioid-dependent patients without inducing OAS, while keeping a moderate pain intensity, relief, quality of life, and functionality. At the final visit, the use of nonopioid medication or buprenorphine was significantly higher in ITP responders than in nonresponders, with a better tolerability profile in high responder patients.

Opioids are not considered first-line medications for the treatment of CNCP. However, when

Table 4. Morphine equivalent daily dose (MEDD) at basal and final individualized treatment plan (ITP) visits, as related to different *OPRM1* genetic models

Individualized treatment plan	Basal visit			Final visit (6 months)		
OPRM1	*n*	MEDD (mg/day) (mean ± SE)	*P* value	*n*	MEDD (mg/day) (mean ± SE)	*P* value
Codominant						
A/A	27	120 ± 18	0.060	49	73 ± 11	**0.032***
A/G	17	249 ± 61		20	114 ± 31	
G/G	1	206 ± 0		1	308 ± 0	
Dominant						
A/A	27	120 ± 18	**0.018***	49	73 ± 11	0.064
A/G–G/G	18	247 ± 58		21	123 ± 31	
Recessive						
A/A–A/G	44	170 ± 27	0.846	69	84 ± 12	**0.032***
G/G	1	206 ± 0		1	308 ± 0	
Overdominant						
A/A–G/G	28	123 ± 18	**0.020***	50	77 ± 12	0.191
A/G	17	249 ± 61		20	114 ± 31	
log-Additive						
0,1,2			**0.027***			**0.025***

*$P < 0.05$ is in bold font.
SE, standard error.

alternative treatment modalities do not provide adequate analgesia, an opioid trial might be indicated. In this context, screening for dependence should be a part of the complete CNCP care for patients with long-term use of opioids, especially when certain signs or symptoms can suggest a prescription opioid dependence. In certain circumstances, drug-seeking behavior might be due to insufficient analgesia and could be falsely interpreted as addiction.[32] We found a total of 88 patients (4%) with opioid prescription dependence out of 1887 patients treated at the Pain Unit during 30 months, a percentage similar to previous reports.[7]

Due to the need to deal in the real world with outpatients with opioid dependence, we designed a structured ITP as a multidisciplinary method and a drug abuse or misuse screening approach. Pain Unit ambulatory patients presented a diagnosis of prescription opioid dependence with different behavior than for other recreational drug–dependent profiles. Our data showed that once the ITP was completed and the MEDD was reduced 30–50%, pain intensity significantly decreased without presenting OAS, and high responders showed a significantly better tolerability profile, mostly related to a decrease of gastrointestinal (constipation, nausea, and vomiting) and neurological (drowsiness and depression) AEs. Thus, ITP was effective in improving patient management in terms of achieving a better control of the pharmacological pain therapy, enhancing their health status with less AEs, and better pain control in responder patients.

In one study that used data from a large commercial health plan, long-term opioid versus no opioid prescription was associated with increased risk for diagnosis of opioid abuse or dependence.[33] These rates ranged from 0.7% with low-dose therapy (MEDD of 1–36 mg/day, OR 14.9 (95%CI, 10.4–21.5)) to 6% with high-dose therapy (MEDD ≥120 mg/day, OR 122.5 (CI, 72.8–206.0)), compared with 0.004% with no opioids.[34] Our data for opioid abuse or dependence were similar to the data for high-dose therapy, probably because our basal MEDD was 167 ± 179 mg/day, which is within this high-dose range. In fact, the responder group achieved a significantly lower final MEDD than nonresponders (50 ± 69 versus 176 ± 121 mg/day).

Buprenorphine seemed an appropriate rotation opioid in our ITP. In previous studies, buprenorphine was found to be more effective than clonidine in ameliorating withdrawal symptoms and similar

Table 5. Linear regression of descriptive, clinical, and genotype parameters with OWS scores for the total population and nonresponder and responder groups at the last visit

	Total population ($n = 74$)			Nonresponder ($n = 21$)			Responder ($n = 52$)			High responder ($n = 27$)		
	r Pearson	*P* value	95% CI, slope	*r* Pearson	*P* value	95% CI, slope	*r* Pearson	*P* value	95% CI, slope	*r* Pearson	*P* value	95% CI, slope
VAS intensity	**0.490**	**0.001***	1.53–5.24	0.432	0.212	–4.76 to 18.30	**0.557**	**0.001***	1.69–5.46	0.390	0.109	–0.62 to 5.54
VAS relief	**–0.458**	**0.002***	–4.70 to –1.18	–0.310	0.384	–10.70 to 4.60	**–0.512**	**0.002***	–4.80 to –1.22	**–0.570**	**0.014***	–5.41 to –0.72
EQ	**–0.622**	**<0.001***	–0.80 to –0.35	–0.504	0.167	–1.24 to 0.26	**–0.678**	**<0.001***	–0.85 to –0.37	**–0.578**	**0.012***	–1.04 to –0.15
GAF	**–0.534**	**<0.001***	–0.80 to –0.35	–0.426	0.219	–2.29 to 0.61	**–0.579**	**<0.001***	–1.12 to –0.37	–0.428	0.087	–1.02 to 0.08
MEDD	0.148$^{\#}$	0.344	–0.05 to 0.08	–0.374$^{\#}$	0.287	–0.04 to 0.14	0.251$^{\#}$	0.160	–0.05 to 0.16	–0.184$^{\#}$	0.464	–0.29 to 0.19
Age	–0.055	0.719	–0.60 to 0.41	–0.157	0.666	–1.76 to 1.19	–0.004	0.982	–0.57 to 0.56	0.013	0.959	–0.78 to 0.82
Gender (male)	0.033	0.832	–11.59 to 14.33	–0.253	0.481	–52.53 to 27.03	0.124	0.479	–9.26 to 19.31	0.052	0.837	–20.57 to 25.07
OPRM1 (G allele)	0.156	0.306	–6.59 to 20.52	0.094	0.796	–45.69 to 36.19	0.249	0.149	–4.01 to 25.29	0.380	0.120	–4.74 to 37.53

$^{\#}$ *r* of Spearman (instead of Pearson); * $P < 0.050$ is in bold font.
VAS, visual analogue scale (0–100 mm); EQ, VAS EuroQol scale (0–100 mm); GAF, global assessment of functioning (0–100 scores); MEDD, morphine equivalent daily dose (mg/day); 95% CI, slope 95% confidence interval.

to methadone, but removing withdrawal symptoms more quickly.[35] However, no randomized trial evaluated opioid abuse, addiction, or related outcomes with long-term opioid therapy versus placebo or nonopioid therapy. In fact, a higher variability exists in the proposed long-term use monitoring systems.[36]

The most studied SNP in the mu opioid receptor is a nucleotide substitution in the N-terminal region of the receptor at position 118 (A118G) that results in the loss of a putative N-glycosylation site. This substitution could lead to alterations in *OPRM1* expression[37] that might confer protection from opioid toxicity.[38,39] A study on mRNA expression in postmortem brain tissue reported a 10-fold reduction in protein levels in subjects carrying the G allele. Furthermore, lower surface receptor expression and decreased forskolin-induced receptor activation have been identified in cell systems expressing the G allele.[40] It seems logical therefore that receptor function will be reduced in subjects with G allele and this might confer protection from opioid toxicity at therapeutic levels. Identification of genetic mutations that alter the functional activity of *OPRM1* might explain interindividual differences in responses in populations with dependence[41,42] and in opioid dose requirements.[22,43] In our population, patients with the 118-AA *OPRM1* genotype required significantly lower MEDD at basal and final visits, consistent with published data.

Alternatively, sex differences in drug abuse have been shown as an influential factor,[44] with reports of men being between two and three times more likely to have a drug abuse/dependence disorder than females.[45] In our study, females represented 64% of the total population with prescription opioid dependence, similar to the female frequency at the Pain Unit. The response to ITP was similar in both genders. We found that OAS was only influenced by pain, quality of life, and functionality, but not by MEDD, age, genotype, or gender.

Screening for dependence should always be done at the beginning of the treatment. Stratifying patients into risk categories for opioid abuse or dependence would make easier for a clinician to determine individualized treatment strategies.[46] More research is needed to develop improved therapies and treatment routes for optimum pain relief and to prevent the development of central sensitization. Staff meetings could be helpful in establishing treatment goals, facilitating compliance, and coordinating multidisciplinary teams. This information might be useful for identifying and minimizing preventable ADRs, generally enhancing the ability of prescribers to manage opioid in CNCP ADRs more effectively.[3,47]

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Supporting information

Additional supporting information may be found in the online version of this article.

Table S1. Genotype (*OPRM1, COMT, ABCB1, OPRD1,* and *ARRB2)* and allelic frequency in total population.

Table S2. Multiple regression from different clinical, demography, and genetic factors with OWS test for total population, nonresponder, responder, and high responder groups at last visit.

Competing interests

All authors declare no competing interests.

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