Online version at https://www.minervamedica.it

Minerva Anestesiologica 2024 Apr 12
DOI: 10.23736/S0375-9393.24.17864-9

ORIGINAL ARTICLE

Clinical prediction of opioid use disorder in chronic pain patients: a cohort-retrospective study with a pharmacogenetic approach

Mónica ESCORIAL [1, 2], Javier MURIEL [1], Laura AGULLÓ [1, 2], Thomas ZANDONAI [1, 3], César MARGARIT [4], Domingo MORALES [5], Ana M. PEIRÓ [1, 2] *

[1]Unit of Pharmacogenetics, Department of Clinical Pharmacology, Alicante Institute for Health and Biomedical Research (ISABIAL), Alicante, Spain; [2]Institute of Bioengineering, Miguel Hernández University, Elche, Spain; [3]Addiction Science Lab, Department of Psychology and Cognitive Science, University of Trento, Trento, Italy; [4]Pain Unit, Dr. Balmis General University Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL), Alicante, Spain; [5]Operations Research Center, Miguel Hernández University, Elche, Spain

*Corresponding author: Ana M. Peiró, Unit of Pharmacogenetics, Department of Clinical Pharmacology, Alicante Institute for Health and Biomedical Research (ISABIAL), c/ Pintor Baeza, 12, 03010 Alicante, Spain. E-mail: apeiro@umh.es

ABSTRACT

BACKGROUND: Opioids are widely used in chronic non-cancer pain (CNCP) management. However, they remain controversial due to serious risk of causing opioid use disorder (OUD). Our main aim was to develop a predictive model for future clinical translation that include pharmacogenetic markers.

METHODS: An observational study was conducted in 806 pre-screened Spanish CNCP patients, under long-term use of opioids, to compare cases (with OUD, N.=137) with controls (without OUD, N.=669). *Mu-opioid receptor 1 (OPRM1*, A118G, rs1799971) and *catechol-O-methyltransferase* (*COMT*, G472A, rs4680) genetic variants plus cytochrome P450 2D6 (CYP2D6) liver enzyme phenotypes were analyzed. Socio-demographic, clinical and pharmacological outcomes were also registered. A logistic regression model was performed. The model performance and diagnostic accuracy were calculated.

RESULTS: *OPRM1-AA* genotype and CYP2D6 poor and ultrarapid metabolizers together with three other potential predictors: 1) age; 2) work disability; 3) oral morphine equivalent daily dose (MEDD), were selected with a satisfactory diagnostic accuracy (sensitivity: 0.82 and specificity: 0.85), goodness of fit (P=0.87) and discrimination (0.89). Cases were ten-year younger with lower incomes, more sleep disturbances, benzodiazepines use, and history of substance use disorder in front of controls.

CONCLUSIONS: Functional polymorphisms related to *OPRM1* variant and CYP2D6 phenotypes may predict a higher OUD risk. Established risk factors such as young age, elevated MEDD and lower incomes were identified. A predictive model is expected to be implemented in clinical setting among CNCP patients under long-term opioids use.

(*Cite this article as:* Escorial M, Muriel J, Agulló L, Zandonai T, Margarit C, Morales D, *et al.* Clinical prediction of opioid use disorder in chronic pain patients: a cohort-retrospective study with a pharmacogenetic approach. Minerva Anestesiol 2024 Apr 12. DOI: 10.23736/S0375-9393.24.17864-9)

KEY WORDS: Chronic pain; Analgesics, opioid; Opioid-related disorders; Pharmacogenetics; Predictive value of tests.

Opioid use disorder (OUD) is defined as a problematic pattern of consume leading to clinically significant impairment or distress.[1] Rates for developing OUD in adults with chronic non-cancer pain (CNCP) change widely due to inconsistent criteria diagnosis and methodology differences. Through systematic reviews (N.=310,408),[2] OUD incidence varied from 0.2% (without prior history of substance use) to 5% (with a positive history) or, even higher, up-to 36%.[3] Here, there are numerous factors involved in the risk of developing OUD. Most of them are

registered in the Opioid Risk Tool,[4] which includes personal/family substance use disorders (SUD), psychiatric disorders and childhood trauma, taking into account sex-differences.

Nevertheless, there have been described some genetic variants that could contribute to the inter-individual variability observed in aberrant opioid related behaviors, predicting dose requirements, harmful or addictive potential.[5] For example, the *mu-opioid receptor 1* (*OPRM1*) polymorphism (A118G, rs1799971) has been associated with higher opioid consumption in postoperative patients[6] and potential opioid misuse behaviors.[7, 8] In the same line, CYP2D6 poor and ultra-rapid metabolizers are expected to hardly obtain any pain relief or higher toxicity, respectively.[9, 10] This could render a patient less sensitive to opioid analgesic effects and more prone to OUD. On the other hand, another motivating for SUD is *catechol-O-methyltransferase* (*COMT*) enzyme polymorphism (G472A, rs4680 Val158Met),[11] which has been described to impact on dopamine-mediated reward deficiency.[12]

Briefly, the aim of this study was to develop a predictive model for OUD in CNCP ambulatory patients, including actionable pharmacogenetic markers.

Materials and methods

Participants

A retrospective cohort study was designed and conducted from September 2020 to September 2021 at the Pain Unit (PU) of Dr. Balmis General University Hospital with outpatients (N.=1,589) previously included in three studies. We identify cases and controls, and retrospectively identify risk variables trying to analyze differences.[13]

The inclusion criteria were patients at least 18 years of age, chronic non-oncological musculoskeletal pain (moderate or severe pain lasting for six or more months) under long-term opioids (≥six months). They were excluded if presented oncologic pain or an opioid prescription <six months. All unidentifiable candidates, duplicated, or who did not meet the inclusion criteria were excluded, as well as patients under neuropathic pain, caused by damage in the somatosensory system, or nociceptive pain, caused by damage in the non-neural tissue were excluded. Neuropathic pain diagnosis included conditions such as trigeminal neuralgia, mononeuritis, and multiple sclerosis. Nociceptive pain diagnosis included conditions such as osteoarthritis, myalgia, myositis, carpal tunnel syndrome, and rheumatism. Subjects diagnosed with mixed pain (*i.e.* migraine, headache, cervicalgia, non-traumatic compartment syndrome) or other conditions that may or may not be pain-related (*i.e.* restless legs syndrome, cerebrovascular disease, paraplegia) were also excluded in the study.[14, 15]

Procedure

Cases

The case arm was composed of CNCP patients that met DSM-5 criteria for OUD and underwent a regular opioid tapering procedure at our PU. In brief, the opioid deprescription consisted of six clinical visits (inclusion visit as basal visit, one week, two weeks, one month, three months, and at six months as final visit) with an opioid rotation to tramadol and/or buprenorphine together with the tapering process, and a one-two weekly phone monitoring. A flexible dosing approach was used, with dose changes allowed during the study.[16]

Controls

The control arm was composed of CNCP patients from previous observational studies[17, 18] related to opioid pharmacovigilance that included pharmacogenetic markers as part of the research goals. The latter was suspended in January 2020 due to COVID-19 pandemic.

Measures

Data were collected from basal visit of the original study database and were completed using Electronic Health Records (EHRs), which include medical diagnoses, medication use (strength, quantity and duration of therapy) and outcomes (*e.g.*, pain intensity, relief, comorbidities and adverse events).

Socio-demographic and clinical data

Sex (female/male), age, ethnicity and employment status (yes/no: active, retired, with work

disability-permanent or temporary, unemployed or homemaker) were collected. The cut-off points for monthly incomes were established according to the Spanish minimum interprofessional wage (€1000) and the minimum vital income (€500) to facilitate the translation to other countries. Thus, data was categorized in low incomes- less than €500, middle incomes- between €500-1000, or upper incomes- more than €1000.

The presence/absence (yes/no) of current and/or previous SUD (except opioid use), including tobacco, alcohol and illicit drugs, was collected from the EHRs through the review of medical diagnoses, narratives or any visit to the Addictive Behavior Unit.

Pain, relief, quality of life and any adverse events was collected at the time of the original study from basal visit where OUD was confirmed. Pain intensity and relief were measured with the Visual Analogue Scale (VAS).[19] This tool consists of a horizontal line ranging from 0 (lowest) to 100 mm (highest) where the patient indicates the intensity of pain or relief that he/she feels. 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). This scale also includes the Health Utility Score, which consisted of a questionnaire with five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) whose answers can be converted into scores anchored at 0 for death and 1 for perfect health.[20] In addition, a list including any emergency department (ED) visit, hospitalization, or drug changes recently due to pain or other causes, was registered.

Patients' reports of adverse events (AEs) were collected through a list with the most frequent adverse drug reactions (ADRs, selected according to opioids Summary of Product Characteristics frequency as "very common" and "common")[21] and a blank space to collect any other adverse event presented. In addition, patients were asked about any depression or anxiety symptom. They were also grouped by systems according to the Medical Dictionary For Regulatory Activities Terminology- MedDRA.[22, 23] ADRs related to the pain treatment and notified to the Spanish Agency of Medicines and Medical Devices were gathered through EHRs.

Pharmacological data

All and only prescribed drug use was collected from the original study database. Any missing data were gathered from the EHRs, which allows for reviewing drug prescriptions and is contrasted with patients interview information. Non-opioid analgesics (*i.e.*, paracetamol and metamizole), non-steroidal anti-inflammatory drugs (NSAIDs), weak (*i.e.*, tramadol and codeine) and strong opioids (*i.e.*, fentanyl, oxycodone, tapentadol, buprenorphine, morphine, hydromorphone and methadone), and immediate release opioids were registered. In different opioids' combinations, oral morphine equivalent daily dose (MEDD) was estimated using available references.[24] The prescription of antidepressants (*i.e.*, amitriptyline, duloxetine and escitalopram), benzodiazepines and neuromodulators (pregabalin and gabapentin) was also collected.

Genotyping data

DNA was extracted from saliva sample and stored at -20 °C prior to genotyping. All the technical information about the procedure can be found in genotyping procedure (Supplementary Digital Material 1: Supplementary Text File 1). Briefly, the genomic DNA was extracted and genotyped by the Real Time PCR Rotor Gene Q system (Qiagen, Hilden, Germany) with specific TaqMan MGB® probes (Applied Biosystems, Foster City, CA, USA) for each gene variant (*OPRM1*-rs1799971, *COMT*- rs4680 and *CYP2D6**2, *3, *4, *5, *6, *10, *17, *29, *35, *41, xN). For the *CYP2D6* gene, a standard estimation of its metabolic phenotype,[25] based on its enzymatic activity: null function (poor metabolizer, PM), normal function (extensive metabolizer, EM) and increased function (ultra-rapid metabolizers, UM),[26] was performed from its genotype.

Statistical analysis

Convenience sampling was considered to increase statistical power, resulting in a ratio of 1 case for 5 controls. This entailed selecting all available patients from historic database. Data

distribution was analyzed with the Kolmogorov-Smirnov Test using the Lilliefors correction method. Quantitative parametric data are presented as mean and standard deviation (SD), whilst the median and interquartile range (IQR) was used for not parametric data. Categorical data are expressed as percentages (%). We compared socio-demographic, clinical, pharmacological and genetic factors using χ^2 or Fisher's Exact Test for categorical variables and *t*-test or U Mann-Whitney test for continuous variables depending upon their distribution. Unadjusted odd ratio (ORs) and 95% confidence intervals (CI) were also calculated. Effect size measures were tested with Cramer's V test (V<0.2 small, 0.2<intermediate<0.6, and large effect>0.6) whereas for continuous variables was tested with Eta-squared test (η^2=0.01 small; η^2=0.06 intermediate and $\eta 2$ = 0.14 large effect) upon their distribution. To control MEDD as a potential confounder with OUD status, a linear regression model was conducted. Gene frequencies were compared using the chi-square χ^2 goodness-of-fit test. For the *OPRM1* genotype, the G-carriers were grouped as they presented a low allelic frequency.

Independent variables were selected for the model on the basis of the investigators' consensus on relevant measurable variables, the results of previous studies,[16, 27] the univariate analysis (P<0.05) and its effect size. A logistic regression model was constructed based on the standards for the model building process.[28] The selection of predictive variables was proposed by a backward stepwise selection. The final model selection was made according to two criteria:[1] small Akaike information criterion-AIC and[2] significance of the variables (P<0.05). Calibration (Hosmer-Lemeshow Goodness-of-fit statistic and calibration belt) and discrimination (*C*-statistic, area under the receiver operating curve) were measured to assess the model performance. The clinical usefulness was measured with the sensitivity and specificity. All statistical analyses were carried out using R (Version 3.2.0; GNU project, Cambridge, MA, US).

Results

A total of 1589 candidates were explored, whereof 443 were duplicated among the databases and 284 unidentifiable. Finally, 806 Caucasians patients (N.=137 cases and N.=669 controls) were pre-screened (Figure 1).

Socio-demographic and clinical outcomes

Characteristics of the participants and clinical variables are shown in Table I.

Cases were on average 10-year younger

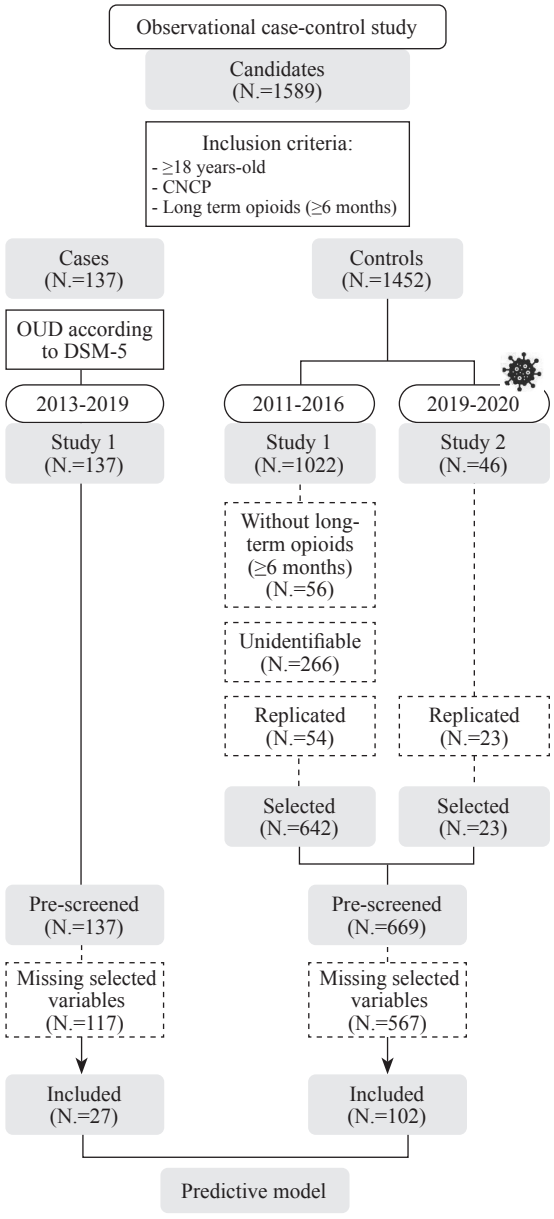


Figure 1.—Flow chart of patient selection for the development of the predictive model.

TABLE I.—*Socio-demographic and clinical analysis in controls and cases.*

	Controls (N.=669)	Cases (N.=137)	P value Effect size[a]	OR (95%CI)
Sex (% female)	66	64	0.69 0.02	0.92 (0.63 to 1.36)
Age (years old) (mean [SD])	64 (14)	54 (13)	<0.001*** 0.06	
Employment status (%)	(N.=331)	(N.=79)		
Retired	55	24	<0.001*** 0.24	0.26 (0.15 to 0.46)
Active	17	5	<0.01*** 0.14	0.26 (0.09 to 0.73)
Work disability	14	49	<0.001*** 0.35	6.20 (3.61 to 10.65)
Unemployed	10	3	0.04 0.11	0.24 (0.06 to 1.00)
Homemaker	4	19	<0.001*** 0.22	4.94 (2.30 to 10.61)
Incomes (%)[b]				
Less than €500	22	55	0.02 0.32	4.28 (1.39 to 13.21)
Between €500 to 1000	62	30	0.03 0.30	0.26 (0.08 to 0.81)
More than €1000	16	15	1.00 0	0.96 (0.22 to 4.16)
Clinical outcomes (mean [SD])				
Pain intensity (mm)	59 (28)	59 (27)	0.96 0	
Pain relief (mm)	35 (29)	37 (30)	0.58 0	
Quality of life (mm)	45 (23)	45 (24)	0.94 0	
Quality of life (Health Utility Score, mean [IQR])	0.45 (0.05 - 0.71)	0.17 (0.08 - 0.61)	0.85 0	
Health resources use (%)				
Emergency department visit	29	24	0.47 0.03	0.79 (0.44 to 1.43)
Hospitalization	13	7	0.28 0.05	0.52 (0.18 to 1.49)
Medication changes	38	36	0.88 0.01	0.92 (0.51 to 1.65)
Previous substance use disorder (SUD, %)	12	20	0.03 0.08	1.77 (1.09 to 2.85)
Tobacco	12	18	0.06 0.07	1.64 (0.99 to 2.70)
Alcohol	0.5	1	0.20 0.05	3.34 (0.55 to 20.18)
Illicit substances	0.3	1	0.42 0.03	2.49 (0.22 to 27.66)

*P value <0.05; **P value <0.001 for differences in controls vs. cases (higher value shaded and in bold).
[a]Effect size: Eta-squared (η^2=0.01 indicates a small effect; η^2=0.06 indicates an intermediate effect; η^2=0.14 indicates a large effect) and Cramer's V (V<0.2 small, 0.2<intermediate<0.6, and large effect>0.6); [b]the cut-off points for monthly incomes were established according to the Spanish minimum interprofessional wage (€1000) and the minimum vital income (€500).

(cases *vs.* controls, 54±13 *vs.* 64±14 years old; P<0.001/η^2=0.06), homemakers (90% females in both groups; 19% *vs.* 4%, P<0.001/V=0.22) or with work disability (49% *vs.* 14%, P<0.001/V=0.35). Additionally, cases had significant lower incomes (55% *vs.* 22%, P=0.02/V=0.32) and higher positive history of SUD (mostly smoking, 20% *vs.* 12%, P=0.03). In contrast, controls were active workers (17% *vs.* 5%, P<0.01) or retired (55% *vs.* 22%, P<0.001/V=0.24) with middle in-

comes (62% *vs.* 30%, P=0.03/V=0.30). The rest of the clinical outcomes remained similar among groups.

Pharmacological and safety outcomes

Pharmacological data are shown in Table II.

Cases had two-time higher MEDD (cases *vs.* controls, 120 [72-217] *vs.* 60 [40-120] mg/day, P<0.001/η^2=0.06), specifically due to a 13% higher use of fentanyl (32% *vs.* 19%, P<0.01) and a 16% of buprenorphine (19% *vs.* 3%, P<0.001).

All this was accompanied by a 14% higher use of benzodiazepines (50% *vs.* 36%, P<0.01/V=0.25) and a 16% lower use of tramadol (17% *vs.* 33%, P<0.001). In terms of tolerability, the median number of AEs and ADRs remained similar in both groups. However, cases suffered an 18% more sleep disturbance (51% *vs.* 33%, P<0.01) and 11% less constipation (39% *vs.* 50%, P=0.04) as can be seen at Table III. No other significant differences were observed when grouped by systems (Supplementary Digital Material 2: Supplementary Table I).

Genetic prevalence

Genetic information was available in the 67% of the total sample (N.=538) corresponding to 80% cases (N.=109) and 64% controls (N.=429). As it can be seen in Supplementary Digital Material 3: Supplementary Table II, genotypes were: *OPRM1* (AA: 63%, AG: 35%, GG: 2%), *COMT* (GG: 25%, GA: 49%, AA: 26%) and CYP2D6 (PM: 6%, EM: 88%, UM: 6%) without any sig-

TABLE II.—*Pharmacological analysis in controls and cases.*

	Controls (N.=669)	Cases (N.=137)	P value Effect size[a]	OR (95% CI)
Non-opioid analgesics (%)	43	38	0.34 0.03	0.83 (0.57 to 1.21)
NSAIDs (%)	16	14	0.61 0.02	0.85 (0.50 to 1.43)
Tramadol (%)	33	17	<0.001*** 0.13	0.42 (0.26 to 0.67)
MEDD (mg/day, median (IQR))	60 (40-120)	120 (72-217)	<0.001*** 0.06	
Strong opioids (%)	86	95	<0.001*** 0.10	3.06 (1.39 to 6.76)
Fentanyl (%)	19	32	<0.001*** 0.12	2.00 (1.32 to 3.01)
Oxycodone (%)	37	33	0.43 0.03	0.84 (0.57 to 1.25)
Tapentadol (%)	33	25	0.09 0.06	0.69 (0.45 to 1.05)
Buprenorphine (%)	3	19	<0.001*** 0.25	7.02 (3.84 to 12.82)
Morphine (%)	6	7	0.56 0.02	1.26 (0.61 to 2.58)
Hydromorphone (%)	1	1	1.00 0.07	0.71 (0.09 to 5.79)
Methadone (%)	0.1	0	1.00 0.02	1.65 (0.07 to 40.62)
Immediate release opioids (%)	18	16	0.62 0.02	0.85 (0.51 to 1.41)
Neuromodulators (%)	45	52	0.16 0.05	1.32 (0.91 to 1.92)
Antidepressants (%)	39	46	0.15 0.05	1.33 (0.92 to 1.94)
Benzodiazepines (%)	36	50	<0.001*** 0.11	1.76 (1.21 to 2.56)

MEDD: morphine equivalent daily dose; NSAIDs: non-steroidal anti-inflammatory drugs.
*P value<0.05; **P value<0.001 for differences in controls vs. cases (higher value shaded and in bold).
[a]Effect size: Eta-squared (η^2=0.01 indicates a small effect; η^2=0.06 indicates an intermediate effect; η^2=0.14 indicates a large effect) and Cramer's V (V<0.2 small, 0.2<intermediate<0.6, and large effect>0.6)

TABLE III.—*Safety variables description in controls and cases.*

	Controls (N.=623)	Cases (N.=93)	P value Effect size[a]	OR (95% CI)
Adverse Events (median (IQR))	5 (2-7)	5 (2-7)	0.58 0	
Sleepiness (%)	38	35	0.73 0.02	0.91 (0.58 to 1.44)
Dizziness (%)	31	35	0.34 0.04	1.24 (0.79 to 1.97)
Nausea (%)	21	28	0.14 0.06	1.44 (0.88 to 2.36)
Vomiting (%)	8	13	0.10 0.07	1.82 (0.92 to 3.57)
Constipation (%)	50	39	0.04*** 0.08	0.63 (0.40 to 0.98)
Itching (%)	19	28	0.05 0.07	1.64 (1.00 to 2.69)
Sexual dysfunction (%)	13	8	0.13 0.06	0.52 (0.23 to 1.17)
Loss of libido (%)	22	25	0.59 0.02	1.15 (0.69 to 1.93)
Weight change (%)	30	33	0.55 0.02	1.17 (0.73 to 1.85)
Headache (%)	30	31	0.81 0	1.06 (0.66 to 1.69)
Skin redness (%)	17	9	0.06 0.08	0.47 (0.22 to 1.01)
Dry skin (%)	33	30	0.56 0.02	0.86 (0.54 to 1.38)
Dry mouth (%)	58	52	0.22 0.05	0.76 (0.49 to 1.18)
Edema (%)	13	12	1.00 0	0.94 (0.48 to 1.84)
Depression (%)	31	34	0.55 0.03	1.18 (0.74 to 1.86)
Sleep disturbance (%)	33	51	<0.01*** 0.13	2.09 (1.35 to 3.25)
Nervousness (%)	40	44	0.43 0.03	1.19 (0.77 to 1.85)
Loss of appetite (%)	24	29	0.30 0.04	1.29 (0.80 to 2.09)
Adverse drug reactions suspected (%)	16	18	0.53 0.02	1.16 (0.72 to 1.87)

*P value<0.05; **P value<0.001 for differences in controls *vs.* cases (higher value shaded and in bold).
[a]Effect size: Eta-squared (η^2=0.01 indicates a small effect; η^2=0.06 indicates an intermediate effect; η^2=0.14 indicates a large effect) and Cramer's V (V<0.2 small, 0.2<intermediate<0.6, and large effect>0.6)

nificant difference in the distribution between cases and controls.

Risk factors and predictive model for OUD

The data availability of all the independent variables chosen to enter the model limited the number of subjects for which the model was developed. Thus, 129 subjects (N.=27 cases (20%) and N.=102 controls (15%)) were included in the model as can be seen in Figure 1.

A total of sixteen independent variables were selected, as seen in Supplementary Digital Material 4: Supplementary Table II, according to the established criteria (see in Statistical Analysis), to enter the model. Variables were age, employment status (active and work disability), prior SUD, tramadol use, MEDD, strong opioids use, fentanyl use, benzodiazepines use, ED -due to pain and other causes-, vomiting, sleep disturbance, MedDRA psychiatric, *OPRM1* genotype (AA, AG/GG), *COMT* genotype (GG, GA and AA) and CYP2D6 phenotypes (PM, EM and UM).

TABLE IV.—*Independent opioid use disorder (OUD) risk predictors selected in the logistic model.*

		β-coefficients	95% CI	Std. Error	z-value	Pr (>|z|)[a]
Intercept		1.633	-1.32 to 4.63	1.489	1.097	0.27
Age		-0.072	-0.13 to -0.03	0.025	-2.884	<0.01
Work disability		2.012	0.86 to 3.25	0.604	3.331	<0.01
MEDD		0.006	0.00 to 0.01	0.002	2.633	<0.01
OPRM1 (AG/GG)		-1.424	-2.90 to 0.17	0.684	-2.083	0.04
CYP2D6	PM	0.075	-3.21 to 2.56	1.375	0.054	0.96
	UM	3.172	1.33 to 5.23	0.972	3.265	<0.01

MEDD: morphine equivalent daily dose; PM: poor metabolizer; UM: ultra-rapid metabolizer
[a]P value associated with the z-value.

According to the logistic regression model, an individual's risk of OUD might be calculated as $e^{\zeta}/(1+e^{\zeta})$, where the linear predictor $\zeta=b_0+b_1x_1+b_2x_2+\ldots+b_px_p$, contains five independent risk factors. In other words, $\zeta = 1.633 - 0.072$ age+2.012 work disability+0.006 MEDD -1.424 *OPRM1* genotype (AG/GG)+0.075 CYP2D6 phenotype (PM)+3.172 CYP2D6 phenotype (UM) (Table IV). The optimal values for specificity and sensitivity (0.85 and 0.82, respectively) were obtained with a cut-off point of 0.29. The *C*-statistic indicated a satisfactory model discrimination (0.89). The model's ability to accurately predict the likelihood of developing OUD was measured with the test Hosmer-Lemeshow (P=0.87) and with the calibration belt (Supplementary Digital Material 5: Supplementary Figure 1), which indicated an adequate model fit.

Discussion

Our results describe pharmacogenetic factors that could help to determine why some patients seem more vulnerable than others to opioid AEs such as OUD. The most important genes coding for receptor of opioids (*OPRM*) and CYP liver enzyme (CYP2D6) were associated with OUD risk together with younger ages, work disability and higher MEDD. All this evidence could provide a better understanding of OUD that, together with other clinical data (histories or motivation of abuse, psychiatric illness or co-medications), could be the key to support tapering strategies in the outpatient setting.

The present study provides clear directions in clinical practice. To date, pharmacogenomic clinical guidelines for at least 48 CYP2D6-substrate drugs have been developed by prominent pharmacogenomics societies, which contain therapeutic recommendations based on CYP2D6-predicted categories of metaboliser phenotype.[9] CYP2D6- UMs can experience quicker and higher systemic levels of the active metabolites and therefore, require lower analgesic doses.[29] Besides, these subjects are prone to higher mu-opioid-related toxicity and a higher risk of side-effects.[30] In contrast, CYP2D6- PMs tend to have lower levels of the active metabolites, which may result in reduced analgesic efficacy.[31-33] Thus, patients at high-risk with dysfunctional *CYP2D6* could best managed with non-opioids.[26]

Additionally, *OPRM1* A118G variant can affect the downstream effects of the opioids in a long-term use. In various clinical scenarios, patients with the *ORPM1* wild type A allele, rather than the mutant G allele, appeared more sensitive to opioid medications.[26, 34] Our results would support pharmacogenetic test implementation in Health's Systems,[35] especially in population with greater prevalence of UMs (*i.e.* Southern European and Northern African).[25]

Here, the basal status of metabolism could be influenced by genetics, age, environmental factors, disease stage, ongoing medications and sex interaction.[36] For example, both genetic variants can be turned into differences in opioid´s clearance[33] what could have special impact in females, who generally exhibit a lower opioid tolerability or sensitivity to pain in front of males.[33, 37] Nevertheless, there is weak evidence related to menstrual cycle influence on the CYP2D6 activity,[38, 39] and, explicit recommendations derived through a validated process have not yet been formulated.[40]

On the other hand, our results do not consider the different metabolism related to each opioid

prescribed;[41] or even, the risk of dysfunction was not calculated from the frequency of the alleles with null function for *CYP2D6*, and from the low function polymorphism for *OPRM1*.[42] However, the fact that genetic distribution was not significantly different between cases and controls, highlights the need of taking into consideration other factors, needing studies with larger populations.[43] In fact, there are some active drugs that don't need to pass through the liver to be active, but there are others whose active metabolites after liver pass and activation may be more powerful than the primary drug.

What's more, according to literature our data show that patients with younger age, work disability and high opioid doses were more vulnerable for OUD. In fact, incident opioid overdoses have been related to educational attainment and having received social welfare, in a retrospective study based on Swedish national register data.[44] Besides, an US survey (N.=1229) showed 80% of CNCP patients under ≥50 mg MEDD continued higher-dose opioid use for 1 year, regardless of reported problems, concerns, side effects, pain reduction, or perceived helpfulness. These results suggest the difficulty of reducing opioid dose among chronic higher-dose opioid users.[45]

Furthermore, our study evidences that homemaker dedication, greater use of benzodiazepines and sleep disturbance were more frequent in cases compared to controls. Nowadays, women are more likely than men to be prescribed benzodiazepines – up to 3 – times higher in front of males in South Europe[46] – and to be diagnosed with sleep disorders with worse sleep quality.[47] In this context, some clinical studies demonstrated that poor sleep – a prevalent factor to prescribe anxiolytics – [48] leads to negative affect, which can contribute to opioid use problems, due to its interaction with the reward processing.[49]

Limitations of the study

Finally, there are some limitations in this study that need to be acknowledged. Due to the retrospective design - from different studies and time periods –we have to be aware of the recall bias or missing data because important information may not have been collected in the first place. Thus, the data collection of some variables such as prior SUD or OUD diagnosis could have been limited by the lack of reporting information in EHRs. What´s more, this study only includes CNCP patients with an OUD diagnosed in our clinical PU setting as cases, and trying to improve statistical power, it was decided to include the maximum number of patients available. Thus, the relatively poor incidence could have avoided us to detect other potential risk factors. In this way, internal and external validation is needed for data generalization. Nevertheless, the fact that psychiatric AEs and pain intensity were not significantly associated with OUD falls in line with several other studies, which have shown that when controlling psychological factors (*i.e.*, negative affect, catastrophizing), pain intensity is not so strongly associated with OUD.[50] On the other hand, the higher prevalence of buprenorphine observed among cases could be an expected finding since patients with OUD are often prescribed buprenorphine prior to the opioid tapering procedure. Finally, the bias of the metabolism of afferents opioids as CYP2D6 (tramadol, oxycodone, codeine, antidepressant –mostly inhibitors), UGT2B7 (morphine, fentanyl) and CYP3A4 (benzodiazepines, buprenorphine) should be controlled in future studies trying to obtain more homogeneous groups orientated to one pharmacogenetic marker (*i.e. ORPM1*).

Conclusions

Functional polymorphisms related to *OPRM1* variant and CYP2D6 phenotypes may predict a higher OUD risk. Thus, pharmacogenetic information plus young age, socio-economic data and high opioid doses could help to identify patients at high-risk of developing an OUD when they have persistent opioid use. This could allow healthcare practitioners to take prevention measures when chronic opioid exposure is needed. Future prospective validation of the developed model is expected for clinical translation.

What is known

- Opioids are widely used to treat CNCP, but they can lead to OUD in some patients.

• Some genetic variants could influence in inter-individual variability observed in addiction to opioids.

What is new

• *OPRM1* and *CYP2D6* phenotypes can lead to a higher risk of opioid use disorder.

• Young age, high MEDD and lower incomes were risk factors in opioid use disorder.

• Our predictive model is expected to be implemented in clinical setting and help to identify patients with a higher risk.

References

1. American Psychiatric Association. Diagnostic and Statitical Manual of Mental Disorder (DSM-V). Arlington: American Psychiatric Association; 2016.

2. Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. Br J Anaesth 2018;120:1335–44.

3. Jantarada C, Silva C, Guimarães-Pereira L. Prevalence of Problematic Use of Opioids in Patients with Chronic Noncancer Pain: A Systematic Review with Meta-analysis. Pain Pract 2021;21:715–29.

4. Cheatle MD, Compton PA, Dhingra L, Wasser TE, O'Brien CP. Development of the Revised Opioid Risk Tool to Predict Opioid Use Disorder in Patients with Chronic Nonmalignant Pain. J Pain 2019;20:842–51.

5. Crist RC, Reiner BC, Berrettini WH. A review of opioid addiction genetics. Curr Opin Psychol 2019;27:31–5.

6. Zhou H, Rentsch CT, Cheng Z, Kember RL, Nunez YZ, Sherva RM, *et al.*; Veterans Affairs Million Veteran Program. Association of OPRM1 Functional Coding Variant With Opioid Use Disorder: A Genome-Wide Association Study. JAMA Psychiatry 2020;77:1072–80.

7. Mura E, Govoni S, Racchi M, Carossa V, Ranzani GN, Allegri M, *et al.* Consequences of the 118A>G polymorphism in the OPRM1 gene: translation from bench to bedside? J Pain Res 2013;6:331–53.

8. Kong X, Deng H, Gong S, Alston T, Kong Y, Wang J. Lack of associations of the opioid receptor mu 1 (OPRM1) A118G polymorphism (rs1799971) with alcohol dependence: review and meta-analysis of retrospective controlled studies. BMC Med Genet 2017;18:120.

9. Taylor C, Crosby I, Yip V, Maguire P, Pirmohamed M, Turner RM. A Review of the Important Role of CYP2D6 in Pharmacogenomics. Genes (Basel) 2020;11:1295.

10. Dean L. Codeine Therapy and CYP2D6 Genotype. Med Genet Summ. 2012;1–3.

11. Huang X, Wang C, Zheng L, Ren L, Jin T, Yu Z, *et al.* Significant Association of the Catechol-O-Methyltransferase Gene Polymorphism (rs4680) and Opioid Use Disorder in Asian Populations, but not Caucasian Populations: A Meta-analysis. Genet Test Mol Biomarkers 2022;26:316–23.

12. Crist RC, Li J, Doyle GA, Gilbert A, Dechairo BM, Berrettini WH. Pharmacogenetic analysis of opioid dependence treatment dose and dropout rate. Am J Drug Alcohol Abuse 2018;44:431–40.

13. Song JW, Chung KC. Observational studies: cohort and case-control studies. Plast Reconstr Surg 2010;126:2234–42.

14. Goldenberg DL, Clauw DJ, Palmer RE, Clair AG. Opioid Use in Fibromyalgia: A Cautionary Tale. Mayo Clin Proc 2016;91:640–8.

15. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database Syst Rev 2013;2013:CD006146.

16. Muriel J, Margarit C, Planelles B, Serralta MJ, Puga C, Inda MD, *et al.* OPRM1 influence on and effectiveness of an individualized treatment plan for prescription opioid use disorder patients. Ann N Y Acad Sci 2018;1425:82–93.

17. Planelles B, Margarit C, Ajo R, Sastre Y, Muriel J, Inda MD, *et al.* Health benefits of an adverse events reporting system for chronic pain patients using long-term opioids. Acta Anaesthesiol Scand 2019;63:248–58.

18. Barrachina J, Margarit C, Muriel J, López-Gil S, López-Gil V, Vara-González A, *et al.* Oxycodone/naloxone versus tapentadol in real-world chronic non-cancer pain management: an observational and pharmacogenetic study. Sci Rep 2022;12:10126.

19. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med 1988;18:1007–19.

20. Herdman M, Badia X, Berra S. El EuroQol-5D: una alternativa sencilla para la medición de la calidad de vida relacionada con la salud en atención primaria. Aten Primaria 2001;28:425–30.

21. AEMPS-CIMA. Online information center of medicines of Spanish Agency of Medicines and Health Products (AEMPS-CIMA); 2021.

22. MedDRA®. Introductory Guide MedDRA Version 23.1. 2020.

23. Wisher D. Martindale: The Complete Drug Reference. 37th Edition. J Med Libr Assoc 2012;100:75.

24. Pergolizzi J, Böger RH, Budd K, Dahan A, Erdine S, Hans G, *et al.* Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract 2008;8:287–313.

25. Naranjo ME, de Andrés F, Delgado A, Cobaleda J, Peñas-Lledó EM, LLerena A. High frequency of CYP2D6 ultrarapid metabolizers in Spain: controversy about their misclassification in worldwide population studies. Pharmacogenomics J 2016;16:485–90.

26. Ruaño G, Kost JA. Fundamental considerations for genetically-guided pain management with opioids based on CYP2D6 and OPRM1 polymorphisms. Pain Physician 2018;21:E611–21.

27. Margarit C, Roca R, Inda MD, Muriel J, Ballester P, Moreu R, *et al.* Genetic Contribution in Low Back Pain: A Prospective Genetic Association Study. Pain Pract 2019;19:836–47.

28. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35:1925–31.

29. Candiotti KA, Yang Z, Rodriguez Y, Crescimone A, Sanchez GC, Takacs P, *et al.* The impact of CYP2D6 genetic

polymorphisms on postoperative morphine consumption. Pain Med 2009;10:799–805.

30. Lopes GS, Bielinski SJ, Moyer AM, Black Iii JL, Jacobson DJ, Jiang R, *et al.* Sex Differences in Associations Between CYP2D6 Phenotypes and Response to Opioid Analgesics. Pharm Genomics Pers Med 2020;13:71–9.

31. Zahari Z, Ismail R. Influence of Cytochrome P450, Family 2, Subfamily D, Polypeptide 6 (CYP2D6) polymorphisms on pain sensitivity and clinical response to weak opioid analgesics. Drug Metab Pharmacokinet 2014;29:29–43.

32. Lötsch J, Skarke C, Liefhold J, Geisslinger G. Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives. Clin Pharmacokinet 2004;43:983–1013.

33. Anderson GD. Gender differences in pharmacological response. Int Rev Neurobiol 2008;83:1–10.

34. Bauer IE, Soares JC, Nielsen DA. The role of opioidergic genes in the treatment outcome of drug addiction pharmacotherapy: A systematic review. Am J Addict 2015;24:15–23.

35. Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, *et al.* Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther 2021;110:888–96.

36. Smith HS. Opioid metabolism. Mayo Clin Proc 2009;84:613–24.

37. Sato H, Droney J, Ross J, Olesen AE, Staahl C, Andresen T, *et al.* Gender, variation in opioid receptor genes and sensitivity to experimental pain. Mol Pain 2013;9:20.

38. Tamminga WJ, Wemer J, Oosterhuis B, Weiling J, Wilffert B, de Leij LF, *et al.* CYP2D6 and CYP2C19 activity in a large population of Dutch healthy volunteers: indications for oral contraceptive-related gender differences. Eur J Clin Pharmacol 1999;55:177–84.

39. Hägg S, Spigset O, Dahlqvist R. Influence of gender and oral contraceptives on CYP2D6 and CYP2C19 activity in healthy volunteers. Br J Clin Pharmacol 2001;51:169–73.

40. He ZX, Chen XW, Zhou ZW, Zhou SF. Impact of physiological, pathological and environmental factors on the expression and activity of human cytochrome P450 2D6 and implications in precision medicine. Drug Metab Rev 2015;47:470–519.

41. Ballester P, Muriel J, Peiró AM. CYP2D6 phenotypes and opioid metabolism: the path to personalized analgesia. Expert Opin Drug Metab Toxicol 2022;18:261–75.

42. Ruano G, Kost JA. Fundamental Considerations for Genetically-Guided Pain Management with Opioids Based on CYP2D6 and OPRM1 Polymorphisms. Pain Physician 2018;21:E611–21.

43. Berrettini W. A brief review of the genetics and pharmacogenetics of opioid use disorders. Dialogues Clin Neurosci 2017;19:229–36.

44. Dahlman D, Ohlsson H, Edwards AC, Sundquist J, Håkansson A, Sundquist K. Socioeconomic correlates of incident and fatal opioid overdose among Swedish people with opioid use disorder. Subst Abuse Treat Prev Policy 2021;16:73.

45. Thielke SM, Turner JA, Shortreed SM, Saunders K, Leresche L, Campbell CI, *et al.* Do patient-perceived pros and cons of opioids predict sustained higher-dose use? Clin J Pain 2014;30:93–101.

46. McHugh RK, Geyer RB, Chase AR, Griffin ML, Bogunovic O, Weiss RD. Sex differences in benzodiazepine misuse among adults with substance use disorders. Addict Behav 2021;112:106608.

47. He H, Tang J, Liu T, Hao W, Liao Y. Gender Differences in Sleep Problems Among Drug Users. Front Psychiatry 2020;11:808.

48. Monti J. Primary and Secondary Insomnia: Prevalence, Causes and Current Therapeutics. Curr Med Chem Nerv Syst Agents. 2004;4:119–37.

49. Fathi HR, Yoonessi A, Khatibi A, Rezaeitalab F, Rezaei-Ardani A. Crosstalk between Sleep Disturbance and Opioid Use Disorder: A Narrative Review. Addict Health 2020;12:140–58.

50. Martel MO, Edwards RR, Jamison RN. The relative contribution of pain and psychological factors to opioid misuse: A 6-month observational study. Am Psychol 2020;75:772–83.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding

This study was funded by Alicante Institute for Health and Biomedical Research [code: UGP 21-116], Navarro-Luciano Tripodi Foundation Research Grant (2021), and Spanish Clinical Pharmacology Society [code: 2022 Research Award].

Authors' contributions

Mónica Escorial helped with the methodology, formal analysis, investigation, writing, and with funding acquisition; Javier Muriel helped with the conceptualization, methodology, writing and editing; Laura Agulló helped with the formal analysis, investigation and writing; Thomas Zandonai helped with the conceptualization, investigation and writing; César Margarit helped with the conceptualization, methodology, writing and supervision; Domingo Morales helped with the resources, writing and supervision; Ana M Peiró helped with the conceptualization, methodology, writing, funding acquisition, resources and supervision. All authors read and approved the final version of the manuscript.

History

Article first published online: April 12, 2024. - Manuscript accepted: January 19, 2024. - Manuscript revised: December 22, 2023. - Manuscript received: October 30, 2023.

SUPPLEMENTARY DIGITAL MATERIAL 1

Genotyping procedure

The lab procedure consisted of DNA extraction, performed using E.N.Z.A. Forensic DNA kit (Omega Bio-tek, Norcross, GA, USA), and *OPRM1* (rs1799971, A118G) and *COMT* (rs4680, G472A) variants genotyping using the Real-Time PCR Rotor-Gene Q system (Qiagen, Hilden, Germany) through specific TaqMan MGB® probes (Applied Biosystems, Foster City, CA, USA). Amplification parameters were as follows: pre-PCR section 10 minutes at 95 ºC, 40 cycles for 15 seconds denaturation at 92 ºC, and 1 minute final extension at 60 ºC. As regards the *CYP2D6* genotype, the following SNPs were analysed: *2D6*2*, *2D6*3*, *2D6*4*, *2D6*5*, *2D6*6*, *2D6*10*, *2D6*17*, *2D6*29*, *2D6*35*, *2D6*41*, *2D6xN*. Genetic analysis were made according to the instructions of the Consortium of the Pharmacogenetics and Pharmacogenomics Ibero-American network based on Dorado P et al., 2005. XL-polymerase chain reaction (XL-PCR) analysis was used for the identification of duplications and deletions. These XL-PCR amplifications were carried out on a Mastercycler 384 (Eppendorf, Hamburg, 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 based on Gaedgik A et al., 2007. The SNPs *3, *4, *5, *6 have an AS of 0, which means null enzyme activity. Variants *10, *17, *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, respectively. Duplications *1xN, *2xN, *35xN are associated with greater enzyme activity (AS=2). Metabolic phenotypes were based on the AS of both alleles: (1) AS=0 corresponds to the absence of enzymatic activity (poor metabolizer, PM), (2) AS= 0.5 to 2 coincides with normal enzymatic activity (extensive metabolizer, EM), and (3) AS≥2 when increased enzymatic activity (ultra-rapid metabolizer, UM).

SUPPLEMENTARY DIGITAL MATERIAL 2

Supplementary Table I.—Description of adverse events grouped by Medical Dictionary For Regulatory Activities Terminology (MedDRA) systems in controls and cases.

MedDRA Systems	**Controls** (n=623)	**Cases** (n=93)	**p-value** **Effect size[a]**	**OR (95% CI)**
Gastrointestinal (%)	76	69	0.16 0.06	0.70 (0.44-1.13)
Nervous (%)	64	66	0.73 0.01	1.09 (0.69-1.73)
Psychiatric (%)	62	70	0.17 0.05	1.41 (0.88-2.25)
Integumentary (%)	42	46	0.50 0.03	1.17 (0.76-1.81)
Complementary (%)	30	33	0.55 0.02	1.17 (0.73-1.85)
Metabolism (%)	24	29	0.30 0.04	1.29 (0.80-2.09)
Reproductive (%)	13	8	0.13 0.06	0.52 (0.23-1.17)
General (%)	13	12	1.00 0.01	0.94 (0.48-1.84)

MedDRA: Medical Dictionary for Regulatory Activities Terminology.

[a]Effect size: Eta-squared ($\eta 2 = 0.01$ indicates a small effect; $\eta 2 = 0.06$ indicates an intermediate effect; $\eta 2 = 0.14$ indicates a large effect) and Cramer's V (V<0.2 small, 0.2<intermediate<0.6, and large effect>0.6).

SUPPLEMENTARY DIGITAL MATERIAL 3

Supplementary Table II.—Genetic distribution in controls and cases.

	Controls (n=429)	**Cases** (n=109)	**p-value** **Effect size[a]**	**OR (95% CI)**
OPRM1 (A118G, %)				
AA	62	67	0.38 0.04	1.26 (0.81 to 1.96)
AG	36	32	0.50 0.03	0.85 (0.55 to 1.34)
GG	3	1	0.48 0.05	0.35 (0.05 to 2.76)
COMT (G472A, %)				
GG	27	17	0.06 0.09	0.55 (0.31 to 1.01)
GA	47	55	0.20 0.06	1.37 (0.87 to 2.17)
AA	26	28	0.69 0.02	1.11 (0.67 to 1.85)
CYP2D6 Phenotypes (%)				
Poor Metabolizer	6	6	1.00 0	1.02 (0.40 to 2.58)
Extensive Metabolizer	89	85	0.39 0.05	0.72 (0.38 to 1.38)
Ultra to rapid Metabolizer	5	9	0.25 0.07	1.75 (0.74 to 4.11)

[a]Effect size: Cramer's V (V<0.2 small, 0.2<intermediate<0.6, and large effect>0.6).

SUPPLEMENTARY DIGITAL MATERIAL 4

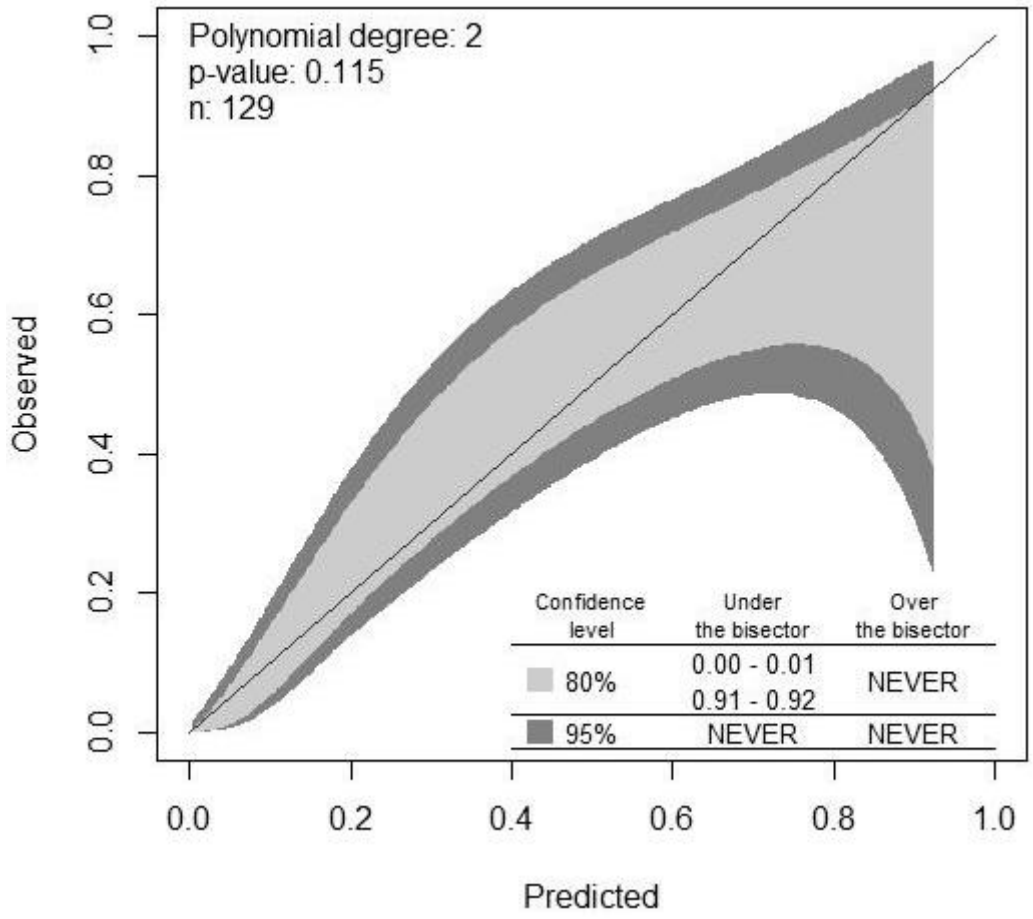
Supplementary Table III.—Justification for the inclusion of specific predictors in the model.

	Selection Criteria
Socio-demographic	
Age (years)	p<0.05
Active work status	p<0.05
Work disability	p<0.05
Prior SUD	p<0.05
Pharmacological	
Tramadol	p<0.05
MEDD	p<0.05
Opioids	p<0.05
Fentanyl	p<0.05
Benzodiazepines	p<0.05
Clinical	
Emergency department visits	Investigators' consensus
Vomiting	Investigators' consensus
Sleep disturbance	p<0.05
MedDRA Psychiatric	Investigators' consensus
Genetic	
OPRM1 (A118G)	Investigators' consensus and previous results
COMT (G472A)	Investigators' consensus and previous results
CYP2D6 Phenotypes	Investigators' consensus and previous results

MEDD: morphine equivalent daily dose; MedDRA: Medical Dictionary for Regulatory Activities; SUD: substance use disorder.

.

SUPPLEMENTARY DIGITAL MATERIAL 5



Supplementary Figure 1.—Predicted probabilities and observed opioid use disorder (OUD) frequencies in the population.