PROGRAMA DE DOCTORADO EN BIOINGENIERÍA

CONSTRUCCIÓN Y VALIDACIÓN DE UN MODELO DE PREDICCIÓN DE RIESGO DEL TRASTORNO POR CONSUMO DE OPIOIDES DE PRESCRIPCIÓN: IMPACTO FARMACOGENÉTICO Y DEL SEXO

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INFORMA:

Que Dña. Mónica Escorial García ha realizado bajo mi supervisión el trabajo titulado **"Construcción y validación de un modelo de predicción de riesgo del Trastorno por Consumo de Opioides de Prescripción: impacto farmacogenético y del sexo"** conforme a los términos y condiciones definidos en su Plan de Investigación y de acuerdo con el Código de Buenas Prácticas de la Universidad Miguel Hernández de Elche, cumpliendo los objetivos previstos de forma satisfactoria para su defensa pública como Tesis Doctoral.

Lo que firmo para los efectos oportunos, en Alicante a 31 de mayo de 2023

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La presente Tesis Doctoral, titulada **"Construcción y validación de un modelo de predicción de riesgo del Trastorno por Consumo de Opioides de Prescripción: impacto farmacogenético y del sexo"** se presenta bajo la modalidad de Tesis Doctoral por compendio de las siguientes publicaciones que se encuentran recogidas en el ***Anexo VIII.***

Artículo 1. Mónica Escorial, Javier Muriel, Cesar Margarit, Jordi Barrachina, Cristian Carvajal, Domingo Morales y Ana M Peiró. Long-term deprescription in chronic pain and opioid use disorder patients: Pharmacogenetic and sex-differences. *Acta Pharmaceutica. 72 (2023)*.
Scimago (Scopus- Scimago Journal & Country Rank): 0.41 (Q2)
doi: *10.2478/acph-2023-0018*
Rank: Pharmacology, Toxicology and Pharmaceutics

Artículo 2. Javier Muriel, Jordi Barrachina, Guillermo del Barco, Carvajal Cristian, **Mónica Escorial**, César Margarit, Pura Ballester, Ana M Peiró. Impact of CYP2D6 genotype on opioid use disorder deprescription: an observational prospective study in chronic pain with sex-differences. *Frontiers in Pharmacology*. 14 (2023).
Scimago (Scopus- Scimago Journal & Country Rank): 1.06 (Q1)
doi: *10.3389/fphar.2023.1200430*
Rank: Medicine (Pharmacology)

Artículo 3. Mónica Escorial, Javier Muriel, Cesar Margarit, Laura Agulló, Domingo Morales y Ana M Peiró. Sex-Differences in Pain and Opioid Use Disorder Management: A Cross-Sectional Real-World Study. *Biomedicines.* 10(9) (2022): 2302.
Scimago (Scopus- Scimago Journal & Country Rank): 0.874 (Q1)
doi: *10.3390/biomedicines10092302*
Rank: Medicines (Miscellaneous)

Además, la siguiente relación de artículos se encuentra en fase revisión en revistas científicas, y, por lo tanto, no forman parte del compendio de publicaciones. Sin embargo, se presenta en este trabajo, así como recogida en el ***Anexo VIII***.

Artículo 4. Mónica Escorial, Javier Muriel, Laura Agulló, Thomas Zandonai, Cesar Margarit, Domingo Morales y Ana M Peiró. Clinical prediction of opioid use disorder in chronic pain patients: A case-control study with a pharmacogenetic approach. *The Clinical Journal of Pai*n. *En revisión*.
Scimago (Scopus- Scimago Journal & Country Rank): 0.79 (Q1)
Rank: Medicine (Anesthesiology and Pain Medicine)

Artículo 5. Mónica Escorial, Javier Muriel, Cesar Margarit, Laura Agulló, Thomas Zandonai, Ana Panadero, Domingo Morales y Ana M Peiró. Two-stage model for opioid use disorder; an innovative predictive model development and validation study. The Journal of Pain. En revisión.
Scimago (Scopus- Scimago Journal & Country Rank): 1.36 (Q1)
Rank: Medicine (Anesthesiology and Pain Medicine)

FINANCIACIÓN

La presente Tesis Doctoral ha recibido las siguientes ayudas:

1. "*VII Convocatoria de Ayudas para el Apoyo y Fomento de la Investigación*" para un contrato de personal predoctoral en I+D+i en el **Instituto de Investigación Sanitaria y Biomédica de Alicante** (ISABIAL, Alicante, España) "*Perfil de Riesgo de Adicción: un instrumento novedoso para proteger la salud de los atletas. Subestudio tramadol con perspectiva de género*". IP: Ana Peiró. Contratada Mónica Escorial (código 200311, 2020-2022). 48.000 €.
2. "*VIII Convocatoria de Ayudas para el Apoyo y Fomento de la Investigación*" de **ISABIAL** *"Diseño de un modelo de predicción de riesgo a dependencia a opioides de prescripción en el mundo real".* IP: Javier Muriel (código 2021-0383). 4.000 €.
3. "*VIII Convocatoria de Ayudas para el Apoyo y Fomento de la Investigación*" de **ISABIAL** *"Validación de un modelo de predicción de dependencia a opioides de prescripción".* IP: Mónica Escorial (código 2021-0046, 2021-2022). 3.800 €.
4. "*Convocatoria de Ayudas a la Investigación 2021*" de la **Fundación Bienvenida Navarro-Luciano Trípodi** (Alicante, España) *"Desarrollo y validación de un modelo de predicción de dependencia a opioides de prescripción".* IP: Javier Muriel (2021-2023). 2.400 €.
5. "*Ayudas de Incentivos a las Áreas" de* **ISABIAL** para la realización de una estancia predoctoral en un centro de investigación extranjero de excelencia, Centro de Psicofarmacología en el Hospital Diakonhjemmet de Oslo, Noruega (3 meses). IP: Ana Peiró (código UGP-22-172, 2022-2023). 2.500 €.

“No es la ausencia de miedo, es superarlo”

Emma Watson

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ABCB1	Gen codificante de la glicoproteína-p (en inglés, *ATP Binding Cassette Subfamily Member 1*)
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
ARNm	Ácido ribonucleico mensajero
AS	Puntuación de actividad enzimática CYP2D6 (en inglés, *Activity Score*)
CCAA	Comunidades Autónomas
CEIm	Comité Ético de la Investigación con Medicamentos
COIR	Código de Investigación Responsable
COVID-19	Enfermedad por coronavirus de 2019
COMM	Cuestionario *Current Opioid Misuse Measure*
COMT	Gen codificante de la enzima catecol-O-metiltransferasa
CPIC	Consorcio para la implementación clínica de la farmacogenética (en inglés, *Clinical Pharmacogenetics Implementation Consortium*)
CYP3A4	Gen codificante de la enzima del citocromo P450 (Isoforma 3A4)
CYP2D6	Gen codificante de la enzima del citocromo P450 (Isoforma 2D6)
DCNO	Dolor Crónico No Oncológico
DDEM	Dosis diaria equivalente de morfina
DHD	Dosis diarias definidas por cada 1000 habitantes
DSM-5	Manual diagnóstico y estadístico de los trastornos mentales (en inglés, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*)
EA	Eventos Adversos
EEUU	Estados Unidos
EFIC	Federación Europea del Dolor (en inglés, *European Pain Federation*)
EM	Metabolizador extensivo según CYP2D6 (en inglés, *Extensive metabolizer*)
EMA	Agencia Europea del Medicamento (en inglés, *European Medicines Agency*)
EVA	Escala Visual Analógica
GPSq	Cuestionario de evaluación del estado global de dolor (en inglés, *Global Pain Scale Questionnaire)*
HGUDrB	Hospital General Universitario Doctor Balmis de Alicante
IIS La Fe	Instituto de Investigación Sanitaria La Fe
IM	Metabolizador intermedio según CYP2D6 (en inglés, *Intermediate metabolizer*)
IP	Investigador Principal
ISABIAL	Instituto de Investigación Sanitaria y Biomédica de Alicante
NED	Neurofarmacología Aplicada al Dolor y Diversidad funcional
OMS	Organización Mundial de la Salud
OPRD1	Gen codificante del receptor opioide δ (en inglés, *Opioid Receptor δ*)
OPRK1	Gen codificante del receptor opioide κ (en inglés, *Opioid Receptor κ*)
OPRM1	Gen codificante del receptor opioide μ (en inglés, *Opioid Receptor μ*)

ORT	Cuestionario *Opioid Risk Tool*
OWS	Escala de abstinencia a opioides (en inglés, *Opioid Withdrawal Scale*)
PGx	Farmacogenética
PM	Metabolizador lento según CYP2D6 (en inglés, *Poor metabolizer*)
PTI	Plan terapéutico individualizado
QST	Test sensitivos cuantitativos (en inglés, *Quantitative Sensory Testing*)
RAM	Reacción Adversa a Medicamento
SEFC	Sociedad Española de Farmacología Clínica
SEFF	Sociedad Española de Farmacogenética y Farmacogenómica
SNS	Sistema Nacional de Salud
SAO	Síndrome de abstinencia a opioides
SNPs	Polimorfismos de un solo nucleótido (en inglés, *Single Nucleotide Polymorphism*)
SOAPP-R	Cuestionario *Screener and Opioid Assesment for Patients with pain Revised*
STROBE	*Strengthening the Reporting of Observational studies in Epidemiology*
TCO	Trastorno por consumo de opioides
TCOP	Trastorno por consumo de opioides de prescripción
TFM	Trabajo de Fin de Master
UCLM	Universidad de Castilla La Mancha
UDO	Unidad del Dolor
UGT2B7	Enzima UDP-glucuronosiltransferasa-2B7
UM	Metabolizador ultrarrápido según CYP2D6 (en inglés, *Ultrarapid metabolizer*)
UMH	Universidad Miguel Hernández de Elche
UPV	Universidad Politécnica de Valencia

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RESUMEN

Introducción: El Dolor Crónico No Oncológico (DCNO) supone un gran impacto en la calidad de vida, siendo la principal causa de uso de opioides. Dos de cada tres personas que lo padecen son mujeres. Es cierto que se han producido esfuerzos en innovación y desarrollo para mejorar el perfil de seguridad de los medicamentos opioides. Sin embargo, el **Trastorno por Consumo de Opioides de Prescripción (TCOP)** es una patología prevalente que requiere de **planes terapéuticos individualizados (PTI)** de deprescripción para prevenir el Síndrome de Abstinencia a Opioides (SAO). Más si cabe, cuando la evidencia está aportando marcadores farmacogenéticos trasladables al manejo del DCNO. **Objetivo:** Analizar los factores individuales, en casos de TCOP, implicados en la efectividad y seguridad a largo plazo de la deprescripción a opioides, focalizando en el impacto de la farmacogenética y en las diferencias por sexo como base para construir y validar un modelo de riesgo de TCOP. **Metodología:** Se realizaron tres estudios diferentes en pacientes ambulatorios con DCNO de la Unidad del Dolor que habían desarrollado un TCOP: **Proyecto 1:** Estudio retrospectivo de la efectividad y seguridad a largo plazo de un PTI de deprescripción de opioides (n=119) con análisis farmacogenético (genes del receptor opioide μ (*OPRM1*) y de la enzima *CYP2D6*) y subanálisis por sexo; **Proyecto 2**: Estudio prospectivo del impacto del fenotipo CYP2D6 (metabolizador lento, extensivo o ultrarrápido) sobre los resultados del PTI de deprescripción de opioides (n=138); **Proyecto 3**: Construcción y validación de un modelo de predicción de riesgo de TCOP (n=229), analizando las diferencias por sexo. **Resultados**: El PTI de deprescripción ambulatorio fue efectivo a largo plazo en un 49% de los casos, consiguiendo un aumento en el alivio del dolor y una disminución de eventos adversos (EA). Aquí, las mujeres mostraron un mayor nivel de deprescripción, pero con un mayor número de EA que los hombres. Los metabolizadores lentos obtuvieron una reducción significativamente mayor en la dosis de opioide, mientras que los ultrarrápidos presentaron un mayor número de EA y SAO que se correlacionó inversamente con la calidad de vida. El modelo de predicción de riesgo de TCOP ajustado y validado, comprendía 5 factores de riesgos (edad joven, situación laboral pobre y dosis diaria de opioides alta) y proporcionaba nueva información útil sobre otros factores de riesgo (baja calidad de vida, alelo mutante *OPRM1* y fenotipos extremos CYP2D6). La validación mostró unos resultados favorables de sensibilidad y especificidad con una discriminación y una bondad de ajuste aceptables. **Conclusiones:** El PTI de deprescripción fue efectivo a largo plazo en la mitad de los casos TCOP con diferencias interindividuales en relación a los marcadores farmacogenéticos y al sexo. El modelo de predicción de riesgo propuesto podría ayudar a identificar a pacientes que, siendo tratados a largo plazo con opioides, son más vulnerables a desarrollar TCOP.

ABSTRACT

Introduction: Chronic Non-Cancer Pain (CNCP) has a major impact on quality of life, being the leading cause of opioid use. Here, two out of three sufferers are women. There have been efforts in innovation and development to improve the safety profile of opioids. However, **Opioid Use Disorder (OUD)** is a prevalent pathology that requires **individualized therapeutic programmes (ITP)** of deprescription to prevent Opioid Withdrawal Syndrome (OWS). Even more, when the evidence is providing that pharmacogenetic markers can be implemented for pain management. **Objective:** To analyse the individual factors, in OUD cases, involved in the long-term effectiveness and safety of an opioid deprescription, focusing on the pharmacogenetics impact and sex-differences as a basis for developing and validating an OUD predictive model. **Methodology:** Three different studies were conducted at the Pain Unit on CNCP outpatients who had developed an OUD: **Project 1**: Retrospective study of the long-term effectiveness and safety of an opioid deprescribing ITP (n=119) with a pharmacogenetic analysis (*μ*-opioid receptor (*OPRM1*) and *CYP2D6* enzyme genes) and subanalysis by sex; **Project 2**: Prospective study of the CYP2D6 phenotype impact (poor, extensive or ultrarapid metabolizer) on the opioid deprescribing ITP outcomes (n=138); **Project 3**: Development and validation of an OUD predictive model (n=229), analysing differences by sex. **Results:** The ITP was effective at long term in 49% of cases, achieving a greater pain relief and lower AEs. Here, women showed a higher level of deprescription with a higher number of AEs than men. Poor metabolizers had a significantly greater reduction of opioid dose, while ultrarapid metabolizers had a higher number of AEs and OWS, which were also inversely correlated with quality of life. The adjusted OUD predictive model comprised 5 well-known risk factors (young age, poor employment status and high daily opioid dose) and provided new useful information of other risk factors (low quality of life, *OPRM1* mutant allele and extreme CYP2D6 phenotypes). Validation showed favourable sensitivity and specificity results and acceptable discrimination and goodness-of-fit. **Conclusions**: The ITP was effective at long term in half of the cases with interindividual differences in relation to pharmacogenetic markers and sex. The predictive model proposed could help to identify patients who are more vulnerable to develop OUD.

1. Introducción

1.1. Dolor Crónico No Oncológico (DCNO)

El dolor como síntoma universal sigue siendo uno de los primeros motivos de consulta médica y una de las grandes causas de pérdida de calidad de vida, más si cabe, tras la situación de confinamiento vinculado a la pandemia de COVID-19, donde cerca del 60% de las personas que vivían con dolor crónico no oncológico (DCNO) en España afirmaron un empeoramiento de su condición [1]. Según la *Organización Mundial de la Salud* (OMS), el dolor crónico afecta alrededor del 20% de la población mundial [2], aunque datos recientes norteamericanos apuntan hasta a un 25% [3].

En Europa esta prevalencia varía debido a los criterios utilizados en los estudios para definir el dolor crónico y la población estudiada, siendo la media del 19% y donde cerca del 34% clasificaba el dolor como intenso [4]. Esa cifra es similar en España que, según la *Encuesta Europea de Salud en España*, el dolor crónico lo padecen principalmente personas entre los 45 y los 54 años de edad y, mayoritariamente, mujeres (60%). Se estima que el coste total que ocasiona el dolor crónico en España es de 16.000 millones de euros anuales, lo que supone el 2.5% del PIB [5], siendo las patologías más prevalentes la artrosis (56%), el dolor lumbar (31%), el dolor cervical (27%) y la migraña o dolor de cabeza (5%); la mayor parte, de naturaleza mixta, siendo el dolor de origen neuropático en torno al 8-10% [6] (**Figura 1**).

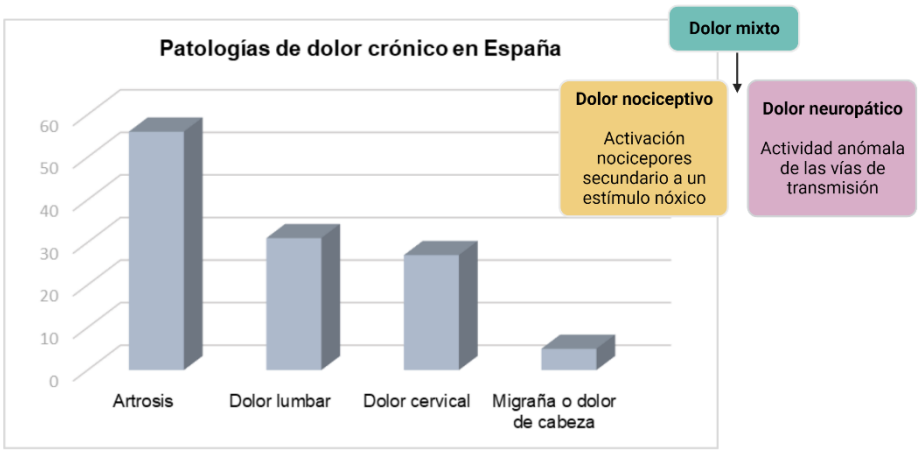

Figura 1. Prevalencia del dolor crónico en España según la etiología del dolor [6]. Elaboración propia.

En distintas revisiones y estudios epidemiológicos publicados se refleja la influencia del sexo y del género sobre la percepción y vivencia de los trastornos del dolor, en muchos de ellos, se observa que las mujeres tienen mayor riesgo de sufrir dolor crónico, a veces más grave y de más intensidad que los hombres [7], [8]. Asimismo, también se ha descrito un aumento de su prevalencia con la edad, siendo más alta en personas mayores de 65 años (**Figura 2**) [9].

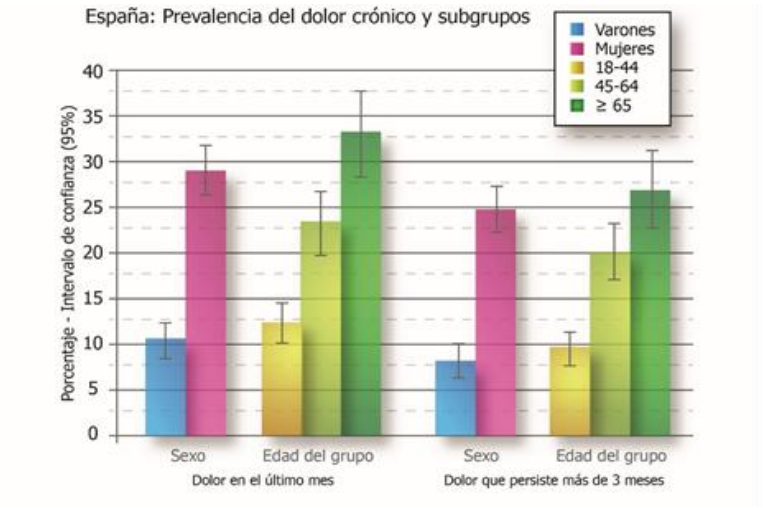

Figura 2. Prevalencia del dolor crónico en España según sexo y edad. Dueñas *et al*. [10].

A pesar de que en los últimos años se ha avanzado en el conocimiento del dolor, estudiando los mecanismos fisiopatológicos y los factores de riesgo, no se obtienen resultados satisfactorios deseados para quienes lo padecen. En un estudio de 2010 del *National Health and Wellness Survey*, realizado en 5 países europeos (Inglaterra, Francia, Alemania, Italia y España) junto con Japón y Estados Unidos (EEUU), se observó que el 46% tenía dolor a diario y el 80% de carácter intenso, que la adherencia a los tratamientos en los mejores casos estuvo en torno al 50%, la satisfacción con el tratamiento no superó el 50%, y que los/as pacientes con dolor intenso estaban en un 20% en situación de desempleo [11].

Por eso, conocer las características que definen a las personas que lo sufren es clave para poder dar soluciones más personalizadas, de la manera más ajustada posible. No obstante, en España hay 184 Unidades de Dolor (UDO) frente a 800 hospitales. De esta forma, 3 de cada 10 pacientes tienen que desplazarse geográficamente para ser atendidos. Asimismo, sólo el 18% de estas Unidades tienen la capacidad para abordar a los/as pacientes más complejos, de hecho, se estima que aproximadamente el 80% de la población con dolor moderado e intenso tiene un acceso insuficiente o nulo al tratamiento del dolor. Por estos motivos, se ha pedido que por cada millón de habitantes exista una unidad de referencia multidisciplinar y con acceso a terapias complejas [12].

1.1.1. Uso de Analgésicos Opioides de Prescripción

Los medicamentos opioides son una de las opciones farmacológicas más comunes usadas en el manejo sintomático del dolor [13]. Según el informe de la *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS) de 2021 [14], la utilización de opioides en España durante el periodo 2010-2021 se ha duplicado. Así, en 2022 el 16% de las personas de 15 a 64 años los ha consumido alguna vez en la vida, el 7% en los últimos 12 meses y el 4% en los últimos 30 días, más si cabe, el 57% de la población de entre 15 a 64 años que ha consumido analgésicos

opioides alguna vez en la vida declara que comenzó a tomarlos por dolor agudo [15]. En la **Tabla 1** se detallan los opioides principales utilizados en el tratamiento del dolor, sus mecanismos de acción y su porcentaje de uso en España en 2021.

Tabla 1. Principales opioides utilizados en el manejo del dolor en España [14].

Opioide	Mecanismo de acción	% DHD	Año Aprobación
Tramadol	Agonista del receptor opioide μ e inhibidor de la recaptación de noradrenalina (13) y serotonina (14).	19% (41%)[+]	1995[1]
Fentanilo	Agonista del receptor opioide μ y en menor medida del κ (15).	15%	1968[1]
Buprenorfina	Agonista parcial del receptor opioide μ y antagonista del receptor κ (16).	5%	1990-2000*
Tapentadol	Agonista del receptor opioide μ e inhibidor de la recaptación de noradrenalina (13).	4%	2011[2]
Oxicodona/Naloxona	La oxicodona actúa como agonista de los receptores opioides μ, δ y κ del cerebro, la médula espinal y órganos periféricos. La naloxona actúa como antagonista de estos receptores a nivel intestinal (17).	3%	2010[2]
Morfina	Agonista de los receptores opioides μ y en menor medida κ y δ (18).	2%	1980[1]

Nota: [1]Año aprobación FDA (Administración de Alimentos y Medicamentos de los Estados Unidos), [2]Año aprobación EMA (Agencia Europea de Medicamentos), *Años de aprobación en países europeos, [+]Porcentaje de DHD en formato tramadol y paracetamol. DHD: dosis diaria definidas por 1000 habitantes y día.

Según los datos anuales de 2020 de la *Junta Internacional de Fiscalización de Estupefacientes,* España es el tercer país con mayor consumo de fentanilo, sólo por detrás de EEUU y Alemania. Según el informe, el promedio de muertes relacionadas con los opioides en los 25 miembros de la *Organización para la Cooperación y el Desarrollo Económicos* sobre los que se disponía de datos aumentó en un 20% durante el período 2011–2016 [16]. Asimismo, cabe mencionar que se han observado diferencias en el consumo según el sexo, que se han mantenido durante los años. Las mujeres tienen un mayor consumo de analgésicos opioides en proporción a los hombres: un 8% de mujeres frente a un 6% de hombres en 2022.

En España, como se ha indicado previamente, el consumo de estos fármacos ha aumentado de forma general y se estiman unas tasas de uso indebido de opioides entre el 7% y el 54% [17]–[19], las cuales se asocian con costes sociales y sanitarios adicionales [20]. Uno de los riesgos asociados al uso de opioides a largo plazo, es la capacidad de inducir conductas aberrantes (incluyendo la adicción/dependencia y el uso indebido). En la **Tabla 2** se describen las conductas aberrantes más conocidas.

Tabla 2. Conductas aberrantes asociadas al consumo de medicamentos opioides [21].

Término	Definición
Uso indebido	Utilización con **fines extramédicos o por razones distintas a las que han motivado la prescripción**, con conductas como variar la dosis o la frecuencia, o compartirlos con terceras personas.
Uso aberrante	Usos **fuera de los límites del plan de tratamiento** establecido y acordado con el paciente al inicio del mismo. **Sugieren** la presencia de **abuso** a opioides.
Abuso	Mal uso que conlleva **consecuencias negativas para la salud,** o que se realiza para modificar o controlar el estado de ánimo de forma ilegal o perjudicial para uno mismo o para otros.
Dependencia	Necesidad **fisiológica** en la cual el organismo habituado a la presencia del opioide los necesita para su correcto funcionamiento. Es la **responsable de la aparición del síndrome de abstinencia** cuando se suspenden de forma brusca los fármacos opioides.
Adicción	Trastorno neurobiológico crónico que comporta tanto un uso aberrante del opioide como un **comportamiento social inadaptado.**
Pseudoadicción	Cambios de comportamiento similares a los/as pacientes con adicción verdadera, pero **secundarios a un tratamiento inadecuado del dolor.**

En el *Manual de Diagnóstico y Estadística de los Trastornos Mentales* (DSM-5) se introduce el término de "Trastorno por Consumo de Opioides" (TCO), fundiendo los términos abuso y adicción, y definiéndolo como un "**patrón problemático de uso de opioides que provoca un deterioro o malestar clínicamente significativo**" [22] (**Tabla 3)**. También aborda la utilización con fines extramédicos o por razones distintas a las que han motivado la prescripción, con conductas como variar la dosis o la frecuencia, o compartirlos con terceras personas, que es la definición de un uso inadecuado y que debe diferenciarse de otros conceptos. Como en la presente Tesis Doctoral se tratará el TCO de prescripción, nos referiremos a éste como "Trastorno por Consumo de Opioides de Prescripción" (TCOP).

Tabla 3. Criterios diagnósticos para el Trastorno por Consumo de Opioides (TCO) según el *Manual de Diagnóstico y Estadística de los Trastornos Mentales* (DSM-5).

Criterios diagnósticos
Patrón problemático de consumo de opioides que provoca un deterioro o malestar clínicamente significativo y que se manifiesta al menos por dos de los hechos en un plazo de 12 meses: 1. Se consumen opioides con frecuencia en cantidades superiores o durante un tiempo más prolongado del previsto. 2. Existe un deseo persistente o esfuerzos fracasados de abandonar o controlar el consumo de opioides. 3. Se invierte mucho tiempo en las actividades necesarias para conseguir opioides,

consumirlos o recuperarse de sus efectos.
4. Ansias o un poderoso deseo o necesidad de consumir opioides.
5. Consumo recurrente de opioides que lleva al incumplimiento de los deberes fundamentales en el trabajo, la escuela o el hogar.
6. Consumo continuado de opioides a pesar de sufrir problemas sociales o interpersonales persistentes o recurrentes, provocados o exacerbados por sus efectos.
7. El consumo de opioides provoca el abandono o la reducción de importantes actividades sociales, profesionales o de ocio.
8. Consumo recurrente de opioides en situaciones en las que provoca un riesgo físico.
9. Se continua con el consumo de opioides a pesar de saber que se sufre un problema físico o psicológico persistente o recurrente probablemente causado o exacerbado por ellos.
10. Tolerancia, definida por alguno de los siguientes hechos:
    a. Una necesidad de consumir cantidades cada vez mayores de opioides para conseguir la intoxicación o el efecto deseado.
    b. Un efecto notablemente reducido tras el consumo continuado de la misma cantidad de un opioide.

Nota: No se aplica cuando se consumen bajo supervisión médica.

11. Abstinencia, manifestada por alguno de los hechos siguientes:
    a. Presencia del síndrome de abstinencia característico de los opioides.
    b. Se consumen opioides (o alguna sustancia similar) para aliviar o evitar los síntomas de abstinencia.

Nota: No se aplica cuando se consumen bajo supervisión médica.

En EEUU, según los *Centros para el Control y la Prevención de Enfermedades* aproximadamente 69,000 personas murieron por sobredosis de opioides en 2020, aumentando el número de muertes en un 29% con respecto al año anterior [23]. Según el *Departamento de Salud y Servicios Humanos* de EEUU el costo económico total fue de 696 mil millones de dólares en 2018 [24], no obstante, aunque esta situación no se esté replicando en Europa, las dudas sobre su seguridad a largo plazo, la preocupación por su uso con fines extramédicos o por razones distintas a las que han motivado la prescripción, con consecuencias negativas para la salud, ha obligado a las autoridades sanitarias a implementar estrategias coordinadas para promover la prescripción segura y responsable, intentando mitigar sus riesgos [25].

1.1.2. Factores de Riesgo Conocidos para el TCOP

Dado el impacto sanitario tan negativo asociado con el TCOP, la estrategia más efectiva podría consistir en su prevención, es decir, identificar los casos de mayor vulnerabilidad a desarrollar TCOP. Para ello se han descrito algunos factores de riesgos como son: historia de abuso de sustancias, psicomorbilidad, edad joven y factores psicosociales y ambientales que favorecen el inicio y la mantención del consumo [26] (**Figura 3**).

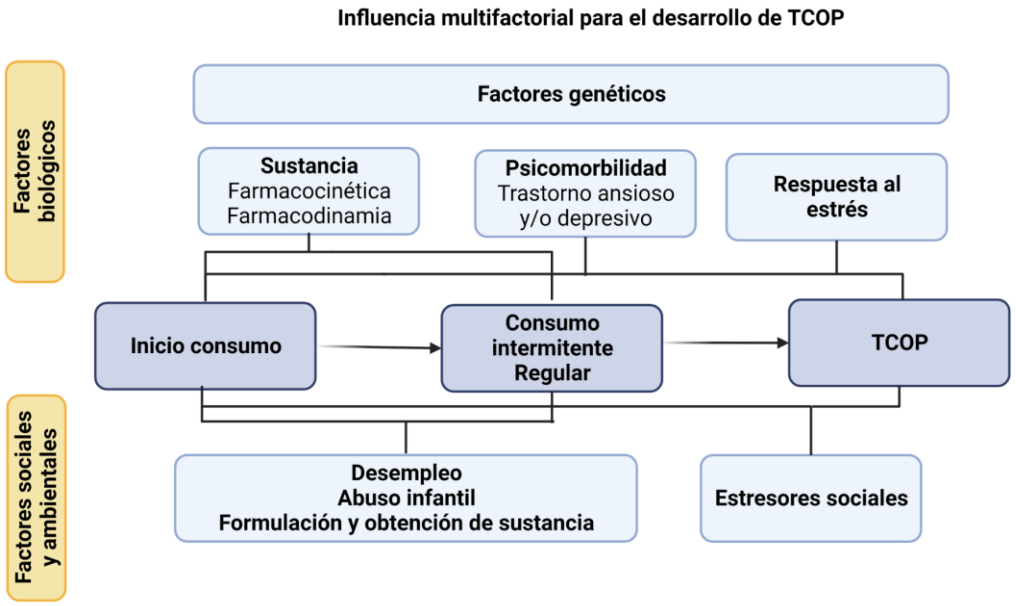

Figura 3. Influencia multifactorial para el Trastorno por Consumo de Opioides de Prescripción (TCOP). Imagen adaptada de Acuña *et al*. [27].

Existen diversos instrumentos que han sido desarrollados de forma específica para la valoración del riesgo de abuso de opioides previo del inicio del tratamiento. En estos instrumentos se evalúan diferentes dimensiones que se consideran como los principales factores de riesgo para el desarrollo del TCOP. Estos instrumentos son el *Opioid Risk Tool* (ORT) y *Screener and Opioid Assesment for Patients with pain Revised* (SOAPP-R) y son específicos para pacientes con dolor crónico. El cuestionario ORT se trata de un autoinforme compuesto por 5 ítems en el que se recogen las siguientes dimensiones: historia familiar y personal de abuso de sustancias, edad, episodios de abuso sexual en preadolescencia y presencia de trastornos psicológicos [28], [29]. En el caso del cuestionario SOAPP-R, es un autoinfome compuesto por 24 ítems que aborda la frecuencia relativa de un pensamiento o comportamiento durante los últimos 30 días. Las dimensiones evaluadas son comportamiento/antecedentes antisociales, historial de abuso de sustancias, comportamiento relacionado con los medicamentos, factores referentes a la relación médico-paciente, antecedentes psiquiátricos, dependencia emocional a los medicamentos para el dolor, cuidado personal, y problemas de estilo de vida [30]–[32].

Por otro lado, se han desarrollado algunas herramientas de evaluación del uso inadecuado de los opioides, entre ellos, uno de los cuestionarios más utilizados es el *Current Opioid Misuse Measure (*COMM). Este instrumento está diseñado para evaluar el incumplimiento de la medicación en pacientes que están con tratamiento de opioides a largo plazo. Consta de 17 preguntas que recogen las siguientes dimensiones (1) signos y síntomas del uso indebido de drogas; (2) problemas emocionales/problemas psiquiátricos; (3) mala respuesta a los

medicamentos; (4) evidencia de uso de drogas ilícitas; (5) patrones de citas inconsistentes; y (6) uso indebido/abuso de medicamentos [33], [34].

1.2. Plan Terapéutico Individualizado de Deprescripción

La deprescripción farmacológica es un proceso que implica **la reducción gradual hasta el cese completo de la dosis de opioides**. Su objetivo es minimizar los riesgos asociados al uso prolongado de opioides, como la dependencia y la tolerancia, mejorando la calidad de vida [35]. Asimismo, debe evitar la aparición del Síndrome de Abstinencia a Opioides (SAO), el cual se caracteriza por la aparición de sudoración, náuseas, vómitos, temblores o insomnio, entre muchos otros [22]. Es por ello que, una vez confirmado el diagnóstico de TCOP, se debería de aplicar un Plan Terapeútico Individualizado (PTI) que consiga una deprescripción farmacológica, evitando la aparición de EA y SAO en el/la paciente. Este debe ser multidimensional, personalizado y consensuado, que incluya medidas farmacológicas, psicológicas y sociales, y que incluya visitas programadas, valorándose en conjunto con la actividad física y cambios en el estilo de vida del/la paciente [36].

De forma general, los tratamientos de deprescripción a opioides incluyen terapias basadas en agonistas opioides, incluyendo la rotación a opioides con mejor perfil de seguridad como la buprenorfina transdérmica. El PTI de la UDO del *Hospital General Universitario Dr Balmis de Alicante* (HGUDrB) suele utilizar de forma rutinaria la buprenorfina transdérmica y el tramadol como los fármacos de rotación [37]. Se utiliza la formulación transdérmica ya que supera los problemas que plantea la farmacocinética de los opioides orales (corta duración del efecto, escasa biodisponibilidad, entre otros) y favorece la liberación del fármaco a velocidad constante, logrando una analgesia eficaz a largo plazo y reduciendo los EA [38]. Asimismo, la alta afinidad de la buprenorfina por los receptores μ hace que tenga un efecto similar a los agonistas puros, pero con menor riesgo de desarrollar un TCOP [39]. De igual forma, también se ha sugerido el uso del tramadol por ser un opioide débil [40].

Cabe mencionar que el PTI en nuestro entorno logró un 64% de “respondedores” y entre éstos, un 53% de “altos respondedores”, reduciendo significativamente la dosis de opioide sin incremento del SAO. En la visita final, los participantes (53±13 años, 64% mujeres) presentaron un mayor porcentaje de prescripción de buprenorfina o retirada total de opioides (65%, $p<0.001$) sin empeoramiento en su dolor, calidad de vida y funcionalidad de lo/as pacientes [41].

1.3. Variabilidad Interindividual

Comprender las causas de la variabilidad interindividual en la efectividad y la toxicidad de las terapias para el dolor se ha convertido en una prioridad de investigación. Entre ellos, están las variantes genéticas implicadas en la farmacología de los analgésicos [42]. Esto muestra un cambio de paradigma de “una talla para todos” a una prevención y terapia de salud individualizada o adaptada a cada persona. Sin embargo, la traducción de los estudios

farmacogenéticos al "mundo real" sigue siendo escasa y, además de estos, existen otros factores extrínsecos o ajenos, como pueden ser el sexo, el ambiente en el que se desenvuelve o el consumo de alcohol o tabaco, que pueden influir en la respuesta del/de la paciente a la medicación prescrita. Estos factores junto con las características propias del individuo pueden condicionar y modificar la respuesta a los fármacos, tal y como se expone en la **Figura 4**.

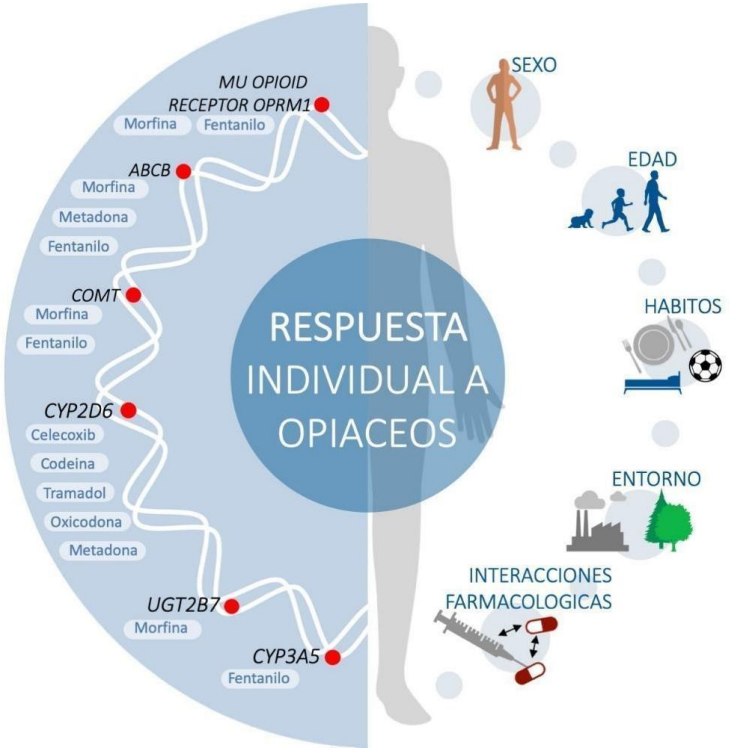

Figura 4. Factores intrínsecos y extrínsecos que pueden contribuir a la variabilidad interindividual a opiáceos. Imagen adaptada de Benjeddou and Peiró [43].

1.3.1. Marcadores Farmacogenéticos

La farmacogenética (PGx) se define como el uso de la información genética para guiar la selección y dosificación de fármacos con el fin de maximizar los efectos terapéuticos, mejorando los resultados y minimizando la toxicidad [44]. Hasta la fecha, más de 300 fármacos contienen información sobre biomarcadores genéticos y su relación con la exposición del fármaco, la variabilidad en la respuesta clínica, el riesgo de aparición de EA, la dosificación del fármaco, los mecanismos de acción y las dianas farmacológicas [45].

Entre los genes más estudiados en el ámbito del dolor, destacan dos grupos. Por una parte, los que codifican los receptores opioides, a través de cuya activación se produce la analgesia, siendo el principal el receptor opioide μ (gen *OPRM1*), y en menor medida los δ (gen *OPRD1*) y κ (gen *OPRK1*); y por otra parte, aquellos implicados en el metabolismo y/o eliminación de los opioides, ya estén vinculados con la familia de enzimas CYP450 (mayoritariamente *CYP2D6*), o los relacionados con la vía metabólica de la glucuronidación catalizada por la UDP-

glucuronosiltransferasa (*UGT2B7*). De igual forma, en este campo se ha estudiado el efecto del gen que codifica la enzima catecol-O-metiltransferasa (gen *COMT*), implicada en la degradación de catecolaminas y de la modulación del dolor, así como las variantes en el gen que codifica la glicoproteína-p (gen *ABCB1/MDR1*), las cuales podrían influir en el transporte y disponibilidad del fármaco opioide [46] (**Figura 5**).

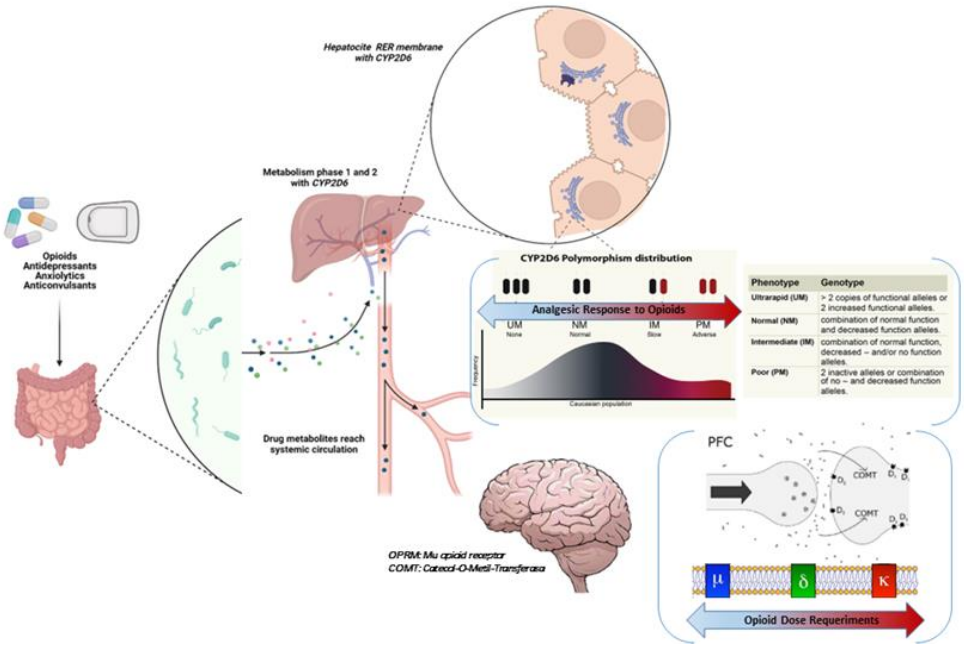

Figura 5. Marcadores farmacogenéticos de interés en la medicina del dolor. Imagen adaptada de Ballester *et al.* [47].

No obstante, en la última actualización de las guías clínicas para los opioides del Consorcio de Implementación Clínica de la Farmacogenética (CPIC) de 2021 se revisan sólo los genes *CYP2D6, OPRM1* y *COMT* [48] con mecanismos biológicamente plausibles para afectar a la respuesta de los opioides. De estos tres, finalmente se establecen guías clínicas para para el *CYP2D6* para los opioides codeína y tramadol, concluyendo una evidencia insuficiente para el caso de los genes *OPRM1* y *COMT* (**Figura 6**).

De esta forma, en los últimos tiempos se han dado pasos importantes para la implementación de la medicina personalizada como una estrategia sanitaria más en el *Sistema Nacional de Salud* (SNS). Hay una serie de iniciativas actuales en este contexto, como el que empezó en Extremadura en 2013 bajo el nombre de 'MedeA' para conocer la genética del paciente con el fin de evitar la aparición de eventos adversos (EA) y/o reacciones adversas de los medicamentos (RAM) [49].

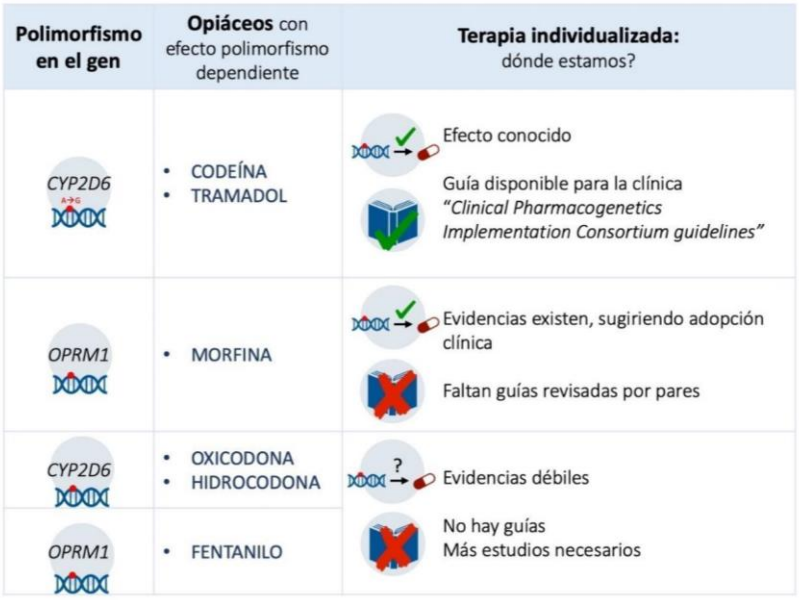

Figura 6. Variantes en genes clave de la farmacodinamia y farmacocinética de algunos fármacos opioides. Imagen adaptada de Owusu Obeng A *et al*. [50].

Gen del Citocromo CYP2D6 (*CYP2D6*)

En cuanto a su metabolismo, los opioides son sometidos a reacciones de fase 1 (reacciones de modificación p.e. morfina) y/o reacciones de fase 2 (reacciones de conjugación p.e. oxicodona). Las enzimas del citocromo P450 someten a los fármacos a las reacciones de fase 1, normalmente mediante reacciones de oxidación o hidrólisis, en las que intervienen principalmente las enzimas CYP3A4 y CYP2D6. La enzima CYP2D6 interviene en el metabolismo de aproximadamente el 25% de los medicamentos conocidos. Es relevante, sobre todo, por el uso concomitante de inhibidores de la enzima (p.e., paroxetina, fluoxetina y bupropión) o inductores (p.e., carbamazepina, fenobarbital y fenitoína), que podrían contrarrestar el efecto clínico o desencadenar efectos secundarios de los analgésicos [43], [47], [51].

Con más de 100 variantes alélicas conocidas y catalogadas, el gen *CYP2D6*, localizado en la posición 22q13.1, es altamente polimórfico con variaciones significativas en las frecuencias alélicas según el origen étnico. Estas variantes alélicas se originan como consecuencia de diferentes tipos de polimorfismos: polimorfismos de base única (SNPs) en la región codificante, promotora del gen (por ejemplo, CYP2D6*2, *4, o *17), inserciones o deleciones de una o más bases nitrogenadas (CYP2D6*3, *6, o *9, entre otros alelos) o la deleción completa del gen (CYP2D6*5) [52].

En un esfuerzo por estandarizar la actividad enzimática prevista de la enzima CYP2D6 en un individuo, se propuso la puntuación *Activity Score* (AS) para cada alelo, permitiendo la extrapolación del genotipo al fenotipo metabólico [53]. El resultado fenotípico resulta de la combinación de los distintos alelos (*2, *3, *4, *5, *6, *10, *17, *29, *35 y *41) y las variaciones

en el número de copias del gen (xN). Los alelos no funcionales (*3, *4, *5 y *6) otorgan un valor de 0; los alelos con actividad reducida tienen un valor de 0.25 para el caso de *10 y de 0.5 para los casos *17, *29 y *41. En cambio, los alelos con actividad normal (*1, *2 y *35) tienen un valor de 1; y, por último, los alelos con actividad incrementada (*1xN, *2xN, *35xN), que otorgan una puntuación de 2. Las frecuencias alélicas varían ampliamente según el grupo étnico y a través del cálculo del AS se agrupan y estiman los siguientes fenotipos CYP2D6: metabolizadores lentos (PM) con una puntuación de 0 (aproximadamente 1%-10% de los pacientes), metabolizadores intermedios (IM) con una puntuación >0 y <1,25 (aproximadamente 1%-13% de los pacientes), metabolizadores extensivos (EM) con una puntuación de 1,25 a 2,25 (aproximadamente 72%-88% de los pacientes), y metabolizadores ultrarrápidos (UM) con una puntuación de >2,25 (aproximadamente 1%-20% de los pacientes) [47], [54].

En este contexto, existe evidencia que apunta a que el metabolismo de diversos opioides podría ser más eficiente en sujetos UM, quienes presentarían mayores y más rápidos niveles sistémicos de la molécula activa, y, por lo tanto, requerirían de menores dosis analgésicas [55]. Sin embargo, este perfil sería más propenso a la toxicidad opioide, incluyendo la aparición de EA [56]. Por el contrario, los perfiles PM presentarían menores niveles del metabolito activo, lo que conduciría a falta de efectividad analgésica [57].

Asimismo, a la complejidad genética CYP2D6 se suma el efecto de factores no genéticos que contribuyen al fenotipo metabolizador. Por ejemplo, la actividad de la enzima CYP2D6 está regulada por una gran cantidad de factores fisiológicos (embarazo, entre otros), patológicos (enfermedad hepática, inflamación, entre otros), ambientales (tabaco, alcohol, entre otros) y epigenéticos [52]. En las mujeres se ha observado una mayor actividad de CYP2D6 entre los UM en comparación con los hombres, lo que sugiere que las diferencias biológicas subyacentes pueden contribuir a las diferencias en la actividad de CYP2D6 [58]. Asimismo, las hormonas sexuales se han estudiado como modificadores potenciales de la actividad de CYP2D6, sin embargo, todavía no se ha establecido ninguna una asociación clara entre la fase menstrual o el uso de anticonceptivos orales con la actividad de CYP2D6.

Gen del Receptor Opioide Mu (*OPRM1*)

El receptor opioide μ es la principal diana tanto de los opioides endógenos como de los utilizados clínicamente, y un importante mediador de la drogodependencia y de la depresión respiratoria inducida por opiáceos. Se han descrito más de 250 SNPs para el gen del receptor opioide μ (*OPRM1*), el cual se localiza en la posición 6q25.2. De entre todos los polimorfismos, la variante A118G (rs1799971) es la más común. Esta conduce a una sustitución de asparagina por aspartato en el aminoácido 40 (Asn40Asp), provocando una disminución de la expresión de ARNm y una reducción de las proteínas del receptor [59]. Este polimorfismo es responsable de la pérdida de un sitio N-glicosilación en el dominio extracelular del receptor, así como del aumento de la afinidad de unión, unas tres veces mayor, por la β-endorfina [60]. La prevalencia

de este polimorfismo se estima entre el 10-32%, variando según el grupo étnico. La frecuencia descrita para la población Afro-Americana es del 2%, para la caucásica del 8-30% y para la asiática del 50% [61].

En cuanto a la evidencia clínica, numerosos trabajos han descrito que los portadores del alelo G son más sensibles al dolor físico y presentan una eficacia reducida de los fármacos opioides en el tratamiento del dolor. De esta forma, se ha asociado la presencia de este alelo con un mayor requerimiento de dosis diaria equivalente de morfina (DDEM) para mantener el mismo nivel de analgesia que aquellos con la variante nativa [62]. Asimismo, el gen *OPRM1* desempeña un papel primordial en la regulación de la señalización opioide en el sistema de recompensa y en los efectos de refuerzo de una variedad de sustancias [63]. Diversos estudios lo han asociado significativamente con una mayor vulnerabilidad a desarrollar adicción a los opioides [64]–[66]. Se ha observado que el SNP rs1799971 regula la señalización opioide y la posterior liberación de dopamina en las regiones del sistema de recompensa de forma diferencial entre los individuos homocigotos para el alelo A en comparación con los portadores del alelo G [67]. Por ejemplo, se ha visto que los adultos portadores del alelo G experimentan más efectos agudos positivos del alcohol en comparación con los homocigotos para el alelo A [68], [69]. De esta forma, se ha sugerido que ser portador del alelo G puede representar un importante factor de riesgo para el abuso de sustancias.

Gen Catecol-O-metiltransferasa (*COMT*)

La enzima catecol-O-metiltranferasa (COMT) juega un papel importante en la degradación de catecolaminas, siendo un modulador clave de la neurotransmisión dopaminérgica y adrenérgica, y, como consecuencia, en la respuesta de señalización de recompensa a los opioides. La variante G472A es el polimorfismo más estudiado para este gen, localizado en la posición 22q11.21. Esta variante se traduce en un cambio de aminoácido de valina por metionina en la posición 158 (Val158Met) [70]. El alelo A se ha asociado con una menor actividad enzimática (hasta cuatro veces menos) y, como resultado, con mayores niveles prefrontales de dopamina, lo que resulta en menores niveles de encefalinas y, consecuentemente, a un mayor dolor [71].

Asimismo, diversos estudios han indicado una interacción entre las variantes de los genes *COMT y OPRM1* que pueden afectar a la analgesia. A nivel experimental, la combinación de la variante Met/Met con el genotipo nativo del *OPRM1* (AA) se ha asociado con un menor requerimiento de dosis opioide para alcanzar el alivio del dolor [50].

1.3.2. Traslación Farmacogenética según los Analgésicos Opioides

Tramadol

Uno de los analgésicos más prescritos a día de hoy en España es el tramadol, un agonista del receptor opioide μ. Este se administra en forma de profármaco que pasa a su metabolito activo (O-desmetiltramadol) por la O-desmetilación vía CYP2D6 [72].

Se ha descrito que los PM tienen concentraciones plasmáticas mucho más bajas del metabolito activo comparado con los EM, asociándolos con una menor respuesta analgésica. Por otro lado, en estudios farmacocinéticos se ha visto que los UM presentan mayores concentraciones del metabolito activo, con mayor analgesia, pero mayor EA. De esta forma, constituye uno de los dos fármacos, junto con la codeína, que presenta guías clínicas. En estas se recomienda evitar su uso en PM por falta de analgesia y en UM por riesgo de toxicidad [48].

Tapentadol

El tapentadol es un agonista del receptor opioide μ que se desarrolló para mejorar la efectividad analgésica y la seguridad terapéutica, reduciendo los EA gastrointestinales. Se metaboliza en el hígado mediante conjugación de fase II, predominantemente por la glucuronidación vía UGT2B7, aunque también por reacciones de oxidación de fase I a través de la enzima CYP2D6 dando lugar a hidroxitapentadol [73]. A día de hoy, si bien no existen recomendaciones a la hora de prescribir este medicamento, a partir de los resultados de nuestros estudios previos, se sugiere que tapentadol podría proporcionar buenos resultados clínicos a menor coste debido a la menor necesidad de dosis opioide y la menor incidencia de EA, pudiendo servir para optimizar la rotación de opioides [74].

Oxicodona

La oxicodona es un agonista opioide μ semisintético que se metaboliza principalmente a través de la enzima CYP3A4 a noroxicodona. No obstante, esta también es metabolizada a oximorfona por la vía CYP2D6 (aproximadamente el 11%), la cual tiene una afinidad 60 veces mayor por los receptores opioides μ [50].

Existen datos contradictorios sobre la asociación del fenotipo metabolizador de CYP2D6 con el efecto analgésico y la toxicidad de la oxicodona en estudios clínicos prospectivos [75], [76]. Debido a esto, y al pequeño tamaño muestral, especialmente para los fenotipos UM, a día de hoy no existen recomendaciones, aunque el CPIC desaconseja su uso como alternativa a la codeína en los UM y PM [48].

Otros opioides de interés

En el caso de otros opioides ampliamente empleados en la medicina del dolor como es el caso de la morfina, además de poseer actividad farmacológica por sí misma, genera por glucuronidación 2 metabolitos diferentes: mofina-6-glucurónido y morfina-3-glucurónido, principalmente a través de la enzima UGT2B7, y aunque existe cierta evidencia que sugiere asociaciones entre la configuración genética y su farmacocinética, su implementación clínica no

se ha establecido, siendo usada meramente a título informativo. En una situación similar se encuentra el fentanilo. Este medicamento es un potente analgésico metabolizado por la enzima CYP3A4 a norfentanilo, un metabolito inactivo [59], [77]. En su caso, no existe un consenso sobre un uso clínico que incorpore marcadores farmacogenéticos.

1.3.3. Impacto de las Diferencias por Sexo/Género

El sexo se refiere a un conjunto de factores biológicos relativos a los seres sexuados. Se asocia principalmente con el físico y las características fisiológicas. Así que, según la *Comisión Europea*, en su *Estrategia para la Igualdad de Género 2020* [78], cuando nos referimos al término «sexo» hacemos referencia a las características biológicas de mujeres y hombres, en términos de órganos reproductivos y funciones basadas en la fisiología y los cromosomas. Para la guía de la *Comisión Europea*, el género se refiere a la construcción sociocultural y política que determina las relaciones interpersonales de mujeres y hombres que otorgan beneficios y acceso a recursos (**Tabla 4**).

Tabla 4. Diferencias entre los conceptos de género y sexo [79].

GÉNERO	SEXO
● Roles ● Comportamientos ● Expresiones e identidades construidas socialmente de niñas, mujeres, niños, hombres y personas de género diverso	● Atributos biológicos de humanos y animales ● Características físicas, cromosomas, expresión génica, hormonas y anatomía

Diferencias por sexo en el DCNO

Muchas dolencias crónicas, incluido el dolor crónico, tienen un marcado predominio femenino [80]. Los datos presentes en la literatura sugieren que hombres y mujeres pueden diferir en su respuesta frente al dolor posiblemente debido a la diferente modulación del sistema opioide endógeno, inmune y por acción de las hormonas sexuales [81]–[85]. En especial, destaca el papel del estrógeno, cuya concentración y localización puede determinar la intensidad del dolor [86]. Se ha visto que las hormonas sexuales desempeñan un papel importante en la regulación del sistema inmunitario, ya que la testosterona suprime los linfocitos T proinflamatorios, mientras que el estrógeno tiene un efecto contrario [87]. No obstante, las diferentes narrativas entre pacientes de diferentes géneros también podrían suponer un factor diferencial y, por tanto, a tener en cuenta por parte del personal sanitario, que conlleve un esfuerzo diagnóstico y terapéutico diferente entre hombres y mujeres ante la misma necesidad sanitaria [88]. En el caso del mantenimiento del dolor, el diagnóstico incluso se puede llegar a confundir, como es el caso de la espondiloartritis, donde hay una diferencia de 2 años en el diagnóstico entre mujeres y hombres y se suele confundir con fibromialgia u otras patologías puesto que los síntomas relacionados con el dolor, en hombres y mujeres, incluida la sensibilidad al dolor, la respuesta a las terapias analgésicas y el riesgo de hiperalgesia inducida por opioides, también difieren [89].

Durante los últimos treinta años, la literatura médica ha mostrado diferencias significativas en la forma de presentar dolor crónico y en la respuesta analgésica entre hombres y mujeres [56], [90]. Hay estudios que muestran una diferencia significativa con una mayor tolerancia al dolor térmico por presión en las mujeres mediado por el receptor opioide κ [91]. Asimismo, las mujeres suelen presentar un mayor porcentaje de grasa corporal, lo que puede afectar al volumen de distribución de ciertos fármacos. También se ha visto que las mujeres suelen tener un aclaramiento más lento con respecto a los hombres [92]. En el caso de los hombres, se ha observado que tienen una mayor motilidad intestinal gástrica con respecto a las mujeres, pudiendo afectar a la concentración plasmática y absorción de los fármacos orales [93]. Además, se ha descrito una mayor expresión hepática de la glicoproteína-p en los hombres. Esta proteína está implicada en la resistencia a múltiples fármacos, dando lugar a una vida media de eliminación más corta de los fármacos [94]. En relación al patrón de tolerabilidad, se ha visto en varios estudios que existe una mayor prevalencia de eventos adversos gastrointestinales, psiquiátricos y neurológicos en las mujeres, algunos vinculados a fenotipos CYP2D6, pudiendo tener un mayor impacto en su calidad de vida [56], [95].

Estas diferencias por sexo podrían estar significativamente influenciadas por otros factores psicosociales como las estrategias de afrontamiento del dolor o la exposición temprana al estrés [96]. Asimismo, parece que los roles atribuidos al género podrían contribuir a las diferencias en la expresión del dolor (signos y síntomas), que se asociarían a diferencias en el manejo del dolor (diagnósticas, terapéuticas) y, por lo tanto, a una inequidad del sistema sanitario que podría ser evitable si aplicáramos la medicina con perspectiva de género [80].

Sesgos de Género en el DCNO

Algunos estudios muestran que el dolor se suele atribuir más a componentes psicológicos en las mujeres, teniendo ellas más probabilidades de recibir medicamentos ansiolíticos o antidepresivos que los hombres [97], siendo alarmante la alta tasa de co-prescripción de benzodiacepinas en las mujeres de nuestro país [98]. Estas diferencias de prescripción también podrían asociarse a mayores interacciones farmacológicas e influir en el peor perfil de tolerabilidad farmacológica observado en las mujeres [99], [100].

Un monográfico publicado recientemente por la Dra. Ruiz-Cantero orienta a que podría existir un retraso diagnóstico en 700 enfermedades en mujeres frente a hombres. Solo ocurría a la inversa en el caso de la osteoporosis, más invisibilizada en los hombres. Este retraso diagnóstico se explicó porque la sintomatología, entre ellos el dolor, era peor detectada y diagnosticada en las mujeres, afectando a su calidad de vida, e incrementando el gasto al sistema sanitario [101].

En resumen, cuando se trata de la salud, los roles, las normas y las relaciones de género pueden actuar como factores de protección o de riesgo para las mujeres y los hombres. Eso significa que debemos desarrollar las herramientas de investigación necesarias para estar en condiciones de detectar los factores que ponen a las mujeres y los hombres en riesgo y abordarlos con

intervenciones eficaces. En este contexto, en la **Tabla 5** se propone la incorporación del enfoque de género, así como los objetivos, estrategias y guías/directrices para ello; las técnicas y herramientas didácticas e información sobre instituciones de diferentes países, que cuentan con recursos accesibles para aplicar conceptos sobre enfoque de género en ciencias de la salud.

Tabla 5. Estrategias educativas, herramientas docentes e instituciones profesionales para la incorporación del enfoque de género en las titulaciones de ciencias de la salud [102].

Referencia	Aportación principal (país) y descripción
Evaluación de la incorporación del enfoque de género y guías	
Zelek B. Gender sensitivity in medical curricula. Can Med Assoc J. 1997;156:1297-300.	Directrices para evaluar la sensibilidad de género en el currículo de medicina (Canadá)
Phillips SP. Evaluating women's health and gender. Am J Obstet Gynecol. 2002;187:S22-4.	Metas y objetivos en salud de las mujeres y temas de género (Canadá), análisis con enfoque de género de las evidencias científicas, actitudes y capacidades
Verdonk P. Making a gender difference: case studies of gender mainstreaming in medical education. Med Teach. 2008;30:e194-201.	Objetivos a tener en cuenta para valorar el éxito al implementar el género en el currículo de medicina (Holanda)
Tenglein E. Discourses with potential to disrupt traditional nursing education: nursing teachers' talk about norm-critical competence. Nurs Inq. 2017;24:e12166.	Capacitación en perspectiva de género para el profesorado de enfermería (Suecia) Curso para mejorar las habilidades del profesorado de enfermería para identificar y cuestionar las normas sociales dominantes que afectan a los encuentros con pacientes, para utilizar dicha perspectiva en su enseñanza
Técnicas didácticas, materiales y evaluación	
Miller VM. Integrating topics of sex and gender into medical curricula - lessons from the international community. Biol Sex Differ. 2016;7 (Suppl 1):44.	Recursos para el desarrollo del currículo en perspectiva sexo-género (EEUU). Libros de texto y artículos que describen diseños metodológicos experimentales para incorporar la perspectiva sexo-género en las titulaciones de ciencias de la salud
Michela NJ. Feminist learning strategies in health professions education. Virtual Mentor. 2014;16:192-5.	Estrategias docentes desde un enfoque feminista para ciencias de la salud (EEUU). Aprendizaje cooperativo, estudios de casos, grupos reducidos

Lamont E. Understanding the art of feminist pedagogy: facilitating interpersonal skills learning for nurses. Nurse Educ Today. 2014;34:679-82	Estrategias docentes desde un enfoque feminista aplicado a enfermería (Reino Unido). Aprendizaje de competencias interpersonales y aplicación en el primer curso de la titulación
Instituciones profesionales con recursos accesibles para investigación y educación	
eGender platform (Alemania) http://egender.charite.de (requiere registro gratuito)	Plataforma con módulos formativos independientes sobre diferencias por sexo y género, y habilidades de comunicación, para facilitar la toma de decisiones por parte de profesionales de la salud
The Sex and Gender Medical Education Summit (EEUU) http://www.sgbmeducationsummit.org	Acceso a documentos de*The Sex and Gender Medical Education Summit* (2015)
The Sex and Gender Women's Health Collaborative (EEUU) www.sgwhc.org (Every cell has a sex, and all bodies are influenced by gender)	Centrado en la competencia sexo-género en los cuidados a las mujeres. Ofrece materiales específicos de sexo y género para adaptar en la educación y en la práctica clínica
The Gender Awakening Tool (Canadá) http://www.cwhn.ca/en/node/43342	Recursos para la inclusión de la perspectiva de género en la investigación. Casos en los que se muestran los beneficios de incluir sexo y género en salud, estrategias y guías para incluir sexo y género en investigación (básica, experimental, revisiones sistemáticas, buenas prácticas en investigación y listas de comprobación para cada paso del proceso de investigación)
Sex and Gender in Systematic Reviews: Planning Tool (EUU) http://methods.cochrane.org/equity/sex-and-gender-analysis	
Toolkit Gender in EU Funded Research (Unión Europea) https://publications.europa.eu/es/publication-detail/-/publication/c17a4eba-49ab-40f1-bb7b-bb6faaf8dec8	
The Center for Gender Medicine (CfGM), Karolinska Institutet (Suecia) http://ki.se/en/research/centre-for-gender-medicine	Primera institución europea con cursos web sobre salud y enfermedad con perspectiva de género
Institute of Gender and Health (IGH), Canadian Institutes of Health Research (Canadá) http://www.cihr-irsc.gc.ca/e/48641.html	Instituto dependiente del Gobierno de Canadá, con acceso a solicitud de fondos para investigación, seminarios, vídeos y módulos de capacitación*on-line*
Online Continuing Medical Education and Certificate Program in Sex and Gender Specific Health, Texas Tech University Health Sciences Center (EEUU) http://www.laurabushinstitute.org/cme/default.aspx	Programa de certificación para graduados/as en medicina, enfermería, farmacia y otras ciencias de la salud

Sex and gender specific health, Texas Tech University Health Sciences Center (EEUU) https://www.sexandgenderhealth.org/	Repositorio interprofesional y lugar de encuentro para debates sobre la contribución de sexo y género a la atención a la salud personalizada
Gender innovations, Stanford University (EEUU) https://genderedinnovations.stanford.edu	Aplicación del enfoque de género en la investigación e innovación científicas, en ciencias de la salud y en otras disciplinas

1.4. Modelos de Predicción Riesgo del TCOP

Actualmente, se está dando el salto desde modelos predictivos mediante métodos estadísticos tradicionales al uso de técnicas de *Machine Learning* [103]. Estas nuevas técnicas permiten generar modelos predictivos a través de la detección de patrones ocultos dentro de grandes conjuntos de datos a través de un proceso de dos fases: (1) entrenar un modelo con un conjunto de datos mediante una combinación de las predicciones individuales de cada clasificador; y, (2) evaluar su rendimiento con un conjunto de datos de prueba de forma que los errores de unas predicciones sean compensados por los aciertos de otras [104].

En base a esto, se ha solicitado un proyecto colaborativo nacional en el SNS (código IA_DEPOP) que pretende incorporar dichas técnicas para desarrollar un modelo predictivo de riesgo TCOP, que pueda ser asumido por el SNS, que sea fácilmente implementable, útil y aceptado por los profesionales prescriptores, tal y como se esquematiza en la **Figura 7**.

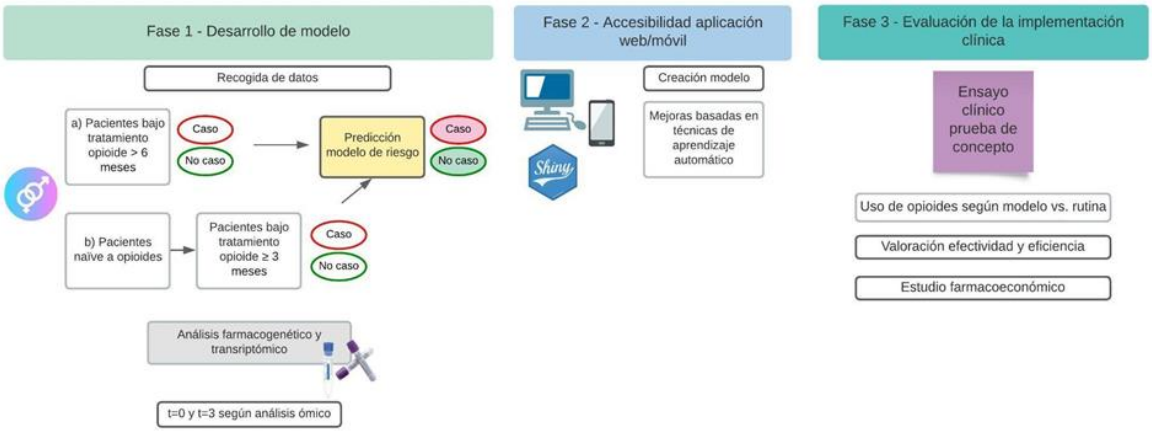

Figura 7. Proyecto diseñado para validar de modo multicéntrico y nacional de predicción de riesgo a desarrollar un Trastorno por Consumo de Opioides de Prescripción (TCOP). Elaboración propia.

Previa a su implementación, es necesario evaluar la efectividad y eficiencia del mismo. Para ello, se ha propuesto:

A) Evaluar la efectividad y eficiencia de la implementación del modelo y su posterior aplicación en poblaciones de pacientes con DCNO en el mundo real de las UDO en 6 Comunidades Autónomas (CCAA).

B) Predefinir las variables de evaluación, priorizando su relevancia clínica y sencillez para la recogida de los datos.

C) Realizar ensayos clínicos aleatorizados, que incluyan un análisis farmacoeconómico riguroso, y que evalúen además la utilidad clínica en el SNS.

En definitiva, el proyecto se ejecutaría dentro del propio sistema asistencial, lo que facilitará que sus conclusiones sean relevantes para el SNS y que pueda avanzar en un uso más eficiente de los medicamentos analgésicos en la Medicina del Dolor. Asimismo, el impacto sanitario y económico que supondría poder prescribir según este modelo de riesgo TCOP puede ser considerable.

2. Hipótesis y objetivos

2.1. Hipótesis

El uso de opioides para el DCNO se ha incrementado notablemente en las últimas décadas en España; y con ello, las dudas sobre su seguridad y el uso inadecuado. En este terreno, se han estudiado diferentes escalas de predicción de riesgo a desarrollar TCOP. Sin embargo, muchas no son específicas de pacientes con dolor crónico y/o no nos dan la información del riesgo cuando el uso de opioides es prolongado. También se han descrito determinados factores biológicos como el sexo y/o marcadores farmacogenéticos que podrían estar implicados en la farmacocinética, farmacodinamia, respuesta al tratamiento y el perfil de RAM de los opioides.

Se consideró que monitorizar a largo plazo a los pacientes que habían desarrollado TCOP y se habían sometido al PTI de la UDO aportaría más información acerca de los factores individuales implicados en la efectividad y la seguridad de la deprescripción ambulatoria de opioides. Asimismo, con la incorporación de los marcadores farmacogenéticos y del análisis de las diferencias por sexo se podría explicar mejor la variabilidad observada. Además, el desarrollo y la validación de un modelo de predicción de TCOP para esta población, que se pudiera incorporar en la rutina asistencial de UDO, podría servir al clínico para prevenir la aparición de este suceso y con ello, establecer una prevención más individualizada del TCOP.

2.2. Objetivos

Objetivo principal

Analizar los factores individuales, en casos de TCOP, implicados en la efectividad y seguridad a largo plazo de la deprescripción a opioides, focalizando en el impacto de la farmacogenética y en las diferencias por sexo como base para construir y validar un modelo de riesgo TCOP.

Objetivos secundarios

1. Evaluar la efectividad y seguridad de la deprescripción ambulatoria de opioides a largo plazo ante casos TCOP.
2. Evaluar el impacto de los marcadores farmacogenéticos y del sexo sobre la deprescripción de opioides a largo plazo.
3. Estudiar los factores de riesgo individuales de la TCOP para la construcción de un modelo de riesgo en nuestro medio.
4. Evaluar prospectivamente en la consulta UDO la validez del modelo de predicción de riesgo a desarrollar TCOP.

3. Materiales y métodos

3.1. Desarrollo de los Proyectos de Investigación

La presente Tesis Doctoral está formada por tres proyectos observacionales que han dado lugar a cuatro artículos y un quinto que se añade en el **Anexo VIII** como material suplementario:

1. **Proyecto 1** (DESOPI LONG, **Anexo I**) el cual está conformado por el Artículo 1 que evalúa la efectividad y seguridad del PTI a largo plazo (Artículo 1. DESOPI LONG).
2. **Proyecto 2** (DESOPI CYP, **Anexo II**) el cual está formado por el Artículo 2 que analiza el impacto del perfil metabolizador CYP2D6 (Art. DESOPI CYP, 2023).
3. **Proyecto 3** (preDESOPI, **Anexo III**), formado por 3 artículos: (1) Artículo 3 que analiza las diferencias por sexo (Art. preDESOPI Sex), (2) Artículo 4 en el que se construye un modelo de predicción a TCOP (en revisión, Art. preDESOPI Retro) y (3) Artículo 5 en el que se valida el modelo de predicción a TCOP (en revisión, ANEXO- preDESOPI Val).

Los seis proyectos se pueden revisar en la **Figura 8** que se muestra a continuación.

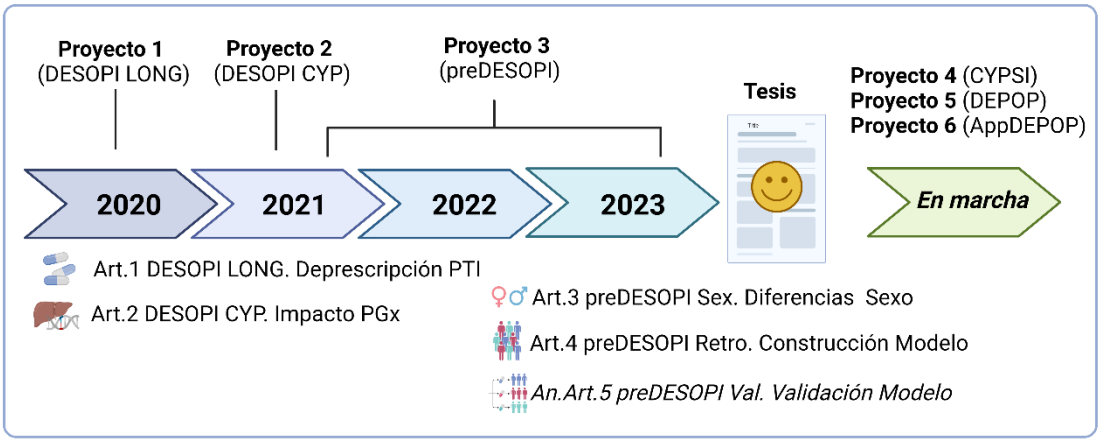

Figura 8. Cronograma de los proyectos de investigación que conforman la Tesis Doctoral (2020-2023). Elaboración propia con Biorender. PTI: Plan Terapéutico Individualizado. PGx: Farmacogenética.

Todos estos proyectos se desarrollaron en el seno del Grupo de Investigación de *Neurofarmacología aplicada al dolor* (grupo NED). Todos los participantes incluidos en sus estudios provinieron de la UDO del HGUDrB. A continuación, se describen los proyectos y los manuscritos vinculados con un esquema de cada uno que incluye sus características, comunicación de resultados y líneas futuras en la **Tabla 6**.

Tabla 6. Información y actividades resumidas de cada uno de los tres proyectos que conforman la presente Tesis Doctoral.

Proyecto 1	Deprescripción en pacientes con dependencia inducida a opioides: efectividad a largo plazo y validación de marcadores genéticos.
Código	DESOPI LONG
Promotora e IP	Dr. Ana María Peiró
Invest. colab.	D. Juan José Lozano, D. Carlos Arysti, D. Jordi Barrachina, **Dña. Mónica Escorial**
Aprobación CEIm	29 de enero de 2020. CEIm: PI2019/092 (***Anexo I***)
Artículo 1	**Mónica Escorial,** Javier Muriel, Cesar Margarit, Jordi Barrachina, Cristian Carvajal, Domingo Morales, Ana M Peiró. Long-term deprescription in chronic pain and opioid use disorder patients: Pharmacogenetic and sex-differences. Acta Pharm. 72 (2023): Aceptado.
Proyecto 2	Farmacogenética y metabolismo de fármacos analgésicos en pacientes con dependencia inducida por opioides.
Código	DESOPI CYP
Promotora e IP	Dr. Javier Muriel
Invest. colab.	Dr. César Margarit, Dra. María del Mar Inda, Dra. Ana María Peiró, D. Cristian Carvajal
Aprobación CEIm	12 de enero de 2018. CEIm: PI2017/97 (***Anexo II***)
Artículo 2	Javier Muriel, Jordi Barrachina, Guillermo del Barco, Carvajal Cristian, **Mónica Escorial**, César Margarit, Pura Ballester, Ana M Peiró. Impact of CYP2D6 genotype on opioid use disorder deprescription: an observational prospective study in chronic pain with sex-differences. *Frontiers in Pharmacology*. 14 (2023).
Líneas futuras	**Proyecto 4:** Analizar el impacto farmacológico del fenotipo CYP2D6 y del sexo en la co-prescripción de medicamentos psicótropos y analgésicos (CYPSI). IP: Mónica Escorial (***Anexo IV***).
Proyecto 3	Desarrollo y validación de un modelo de predicción de dependencia a opioides de prescripción.
Código	preDESOPI
Promotor e IP	Dr. Javier Muriel
Investigadores colaboradores	Dr. César Margarit, Dra. Ana María Peiró, Dr. Thomas Zandonai, **Dña. Mónica Escorial,** Dña. Iuliia Patrusheva
Aprobación CEIm	29 de abril de 2020. CEIm: PI2020-047. COIR: ADH.BIO.APP.MEG.23 (***Anexo III***)
Artículo 3	**Mónica Escorial**, Javier Muriel, Cesar Margarit, Laura Agulló, Domingo Morales, Ana M Peiró. Sex-Differences in Pain and Opioid Use Disorder Management: A Cross-Sectional Real-World Study. Biomedicines. 10(9) (2022): 2302.
Artículo 4	**Mónica Escorial,** Javier Muriel, Laura Agulló, Thomas Zandonai, Cesar Margarit, Domingo Morales y Ana M Peiró. Clinical prediction of opioid use disorder in chronic

	pain patients: A case-control study with a pharmacogenetic approach. *The Clinical Journal of Pai*n. *En revisión*.
Artículo 5	**Mónica Escorial**, Javier Muriel, Cesar Margarit, Laura Agulló, Thomas Zandonai, Ana Panadero, Domingo Morales y Ana M Peiró. Two-stage model for opioid use disorder; an innovative predictive model development and validation study. *The Journal of Pain. En revisión.*
Líneas futuras	**Proyecto 5:** Interacción sexo/género en la funcionalidad de pacientes con dolor crónico y dependencia a opioides de prescripción (DEPOP). Incluye un subproyecto (*Text mining*). IP: Ana Peiró (***Anexo V***). **Proyecto 6:** Desarrollo y presentación de una App como herramienta de estratificación de riesgo objetiva para prevenir la dependencia a los analgésicos opioides de prescripción a través de un modelo de riesgo basado en datos del mundo real (AppDEPOP). IP: Mónica Escorial. (***Anexo VI***).

CEIm: Comité Ético de investigación con medicamentos. COIR: Código de Investigación Responsable. EFIC: Federación Europea del Dolor IP: Investigador/a principal.

3.2. Variables Recogidas

A lo largo de los tres proyectos, se recogieron variables sociodemográficas, clínicas y farmacológicas, gran parte de las cuales están incorporadas en un nuevo cuestionario de evaluación del estado global de dolor (*Global Pain Scale Questionnaire,* GPSq*)*, diseñado, validado e implementado en la UDO-HGUDrB a través de las investigaciones previas de nuestro grupo [105] (**Anexo VII**). Las variables recogidas durante el desarrollo de los proyectos que conforman la Tesis Doctoral fueron las siguientes:

- **Datos sociodemográficos:** sexo (hombre/mujer), edad, situación laboral (sí/no: activo/a, jubilado/a, con incapacidad laboral (permanente o temporal), desempleado/a o amo/a de casa) e ingresos económicos mensuales (bajos ingresos- menos de 500 euros/mes, ingresos medios- entre 500 y 1000 euros/mes-, o altos ingresos- más de 1000 euros/mes).

- **Datos clínicos:** La intensidad y el alivio del dolor, así como la calidad de vida, se midieron mediante la Escala Visual Analógica (EVA) [106]. Cada escala consiste en una línea horizontal que va desde 0 (sin dolor/sin alivio) hasta 100 mm (máximo dolor/máximo alivio). El paciente debe seleccionar en el momento de la consulta la intensidad del dolor/alivio que siente con el tratamiento, respectivamente. El dolor se clasifica como leve (<40 mm), moderado (40 – <70 mm) e intenso (>70 mm). Asimismo, la calidad de vida se midió con la escala EuroQol-5D-3L [107] (número de registro: 48802, disponible en https://euroqol.org/), la cual también incluye una puntuación de utilidad (*Health Utility*) que mide cinco dimensiones (movilidad, autocuidado, actividades habituales, dolor/malestar y ansiedad/depresión) donde en cada una de ellas existen 3 niveles de gravedad (1, 2 o 3). Las puntuaciones oscilan entre el valor 1 (mejor estado de salud) y el 0 (la muerte), aunque existen valores negativos correspondientes a aquellos estados de salud que son valorados como peores que la muerte. Además, dentro de este

cuestionario se recogió el uso de recursos sanitarios (cualquier visita reciente al servicio de urgencias, hospitalización o cambios de fármacos por dolor y/o otras causas).

También se recogieron los EA más frecuentes relacionados con el uso de opioides a los que se referían los pacientes a través de una lista cerrada compuesta por: somnolencia, mareo, náuseas, vómitos, estreñimiento, picor, impotencia y disminución del deseo sexual, cambio de peso, cefalea, enrojecimiento, piel seca, boca seca, edema, depresión, insomnio, nerviosismo y falta de apetito. Además, se agruparon los EA por sistemas según el *Medical Dictionary For Regulatory Activities Terminology*- MedDRA (disponible en https://www.meddra.org) [108]. Asimismo, se registraron las RAM notificadas a la AEMPS.

Por otro lado, el SAO fue evaluado usando la Escala de Abstinencia a Opiáceos (*Opiate Withdrawal Scale*, OWS), la cual está compuesta por 32 signos y síntomas característicos y comunes en pacientes que presentan abstinencia a opioides. En este caso, cada ítem puntúa como 0 (ausente), 1 (leve), 2 (moderado) o 3 (severo) según el grado de manifestación de cada uno para cada paciente. El resultado se obtiene de la suma de la puntuación total de los 32 ítems (rango 0 - 96 puntos), en el cual, a mayor puntuación indica una mayor intensidad del SAO [109].

La presencia/ausencia de abusos previos de sustancias se realizó a partir de la revisión de los diagnósticos médicos, la historia clínica electrónica del/la paciente o cualquier visita a la Unidad de Conductas Adictivas.

- **Datos farmacológicos:** Se registró el uso de todos y cada uno de los fármacos prescritos y se contrastó con la historia clínica electrónica del/la paciente. Se registró el uso de analgésicos no opioides (es decir, paracetamol y metamizol), antiinflamatorios no esteroideos (AINES), opioides débiles (es decir, tramadol y codeína) y fuertes (es decir, fentanilo, oxicodona, tapentadol, buprenorfina, morfina, hidromorfona y metadona), y opioides de liberación inmediata. En las diferentes combinaciones de opioides, se estimó la DDEM oral utilizando las referencias disponibles [110]. También se recogió la prescripción de antidepresivos (es decir, amitriptilina, duloxetina y escitalopram), benzodiacepinas y neuromoduladores (es decir, pregabalina, lacosamida y gabapentina).

- **Datos genéticos:** a través del análisis genotípico de los SNPs de los genes *OPRM1* (rs1799971, A118G), *COMT* (rs4680, G472A) y *CYP2D6* (2, *3, *4, *5, *6, *10, *17, *29, *35, *41 y xN) se obtuvieron las diferentes combinaciones alélicas (nativa, heterocigótica o mutante). Para el caso del *CYP2D6*, se estimó el fenotipo metabolizador CYP2D6 (PM, EM o UM) de cada participante.

3.3. Aspectos Éticos

Los tres proyectos que conforman la presente Tesis Doctoral se llevaron de acuerdo al Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, el Comité de Ética en Investigación con Medicamentos (CEIm) del HGUDrB y el Registro Español de Estudios Clínicos, la Declaración de Helsinki (revisión 2013), las normas de Buena Práctica Clínica y la legislación vigente en España relativa a la realización de estudios observacionales (orden ministerial SAS/3470/2009). Estos proyectos se adhirieron a las guías STROBE de estudios observacionales.

Todos/as los/as pacientes incluidos/as leyeron y entendieron la hoja de información al paciente y cumplimentaron la hoja del consentimiento informado. Para la recogida de la muestra biológica (saliva) se firmó el consentimiento de donación al biobanco del HGUDrB para el almacenamiento del excedente de la muestra. Toda participación fue voluntaria, dando la posibilidad a los participantes de revocar su consentimiento en cualquier momento, sin necesidad de dar ninguna explicación al respecto y sin que supusiera ningún detrimento en su seguimiento clínico.

Toda la información recogida del paciente se trató según la Directiva 95/46/CE del Parlamento Europeo y del Consejo (24 de octubre de 1995), relativa a la protección de personas físicas en lo que respecta al tratamiento de datos personales, y a la Ley Orgánica 15/1999 del 13 de diciembre de Protección de Datos de Carácter Personal y el Real Decreto 1720/2007, del 21 de diciembre. Además, todos los datos se registraron en una base de datos electrónica, anonimizada, específica y exclusiva del estudio.

4. Resultados

4.1. Proyecto 1: DESOPI LONG

Los resultados de la presente Tesis Doctoral muestran que el PTI mantuvo su efectividad a largo plazo en casi la mitad de los sujetos, con un aumento significativo del alivio del dolor y una reducción de las RAM. Asimismo, se evidenció un diferente patrón de respuesta a largo plazo al igual que diferentes factores de riesgo y necesidades específicas según el sexo. A nivel farmacogenético, los PM mostraron las dosis más bajas de opioides.

4.1.1. Artículo 1- Deprescripción de Opioides

En primer lugar, la deprescripción a largo plazo mostró ser efectiva en el 49% de los pacientes (n=54/111), ya que estaban bajo una prescripción regular de opioides inferior a 50 mg/día (10 ± 17 mg/día) y no presentaban conductas aberrantes inducidas por opioides. Además, desde la visita final del PTI, se observó una reducción en la prescripción de opioides (89 vs. 66%, p<0.001) y de opioides de liberación inmediata (13 vs. 3%, p=0.02) a la vez que un aumento de analgésicos simples (11 vs. 35%, p<0.001), neuromoduladores (33 vs. 67%, p<0.001) y antidepresivos (22 vs. 55%, p<0.001), junto con un aumento significativo del alivio del dolor (40 ± 29 vs. 51 ± 25 mm, p = 0.01). Aquí, las mujeres consiguieron reducir más su DDEM a largo plazo (120 (49–203) vs. 53 (0–144) mg/día) que los hombres (126 (47–212) mg/día vs. 80 (0–256) mg/día) con un aumento en el uso de tramadol (17 vs. 3%, p=0.002) y neuromoduladores (70 vs. 51%, p=0.009). En el caso de los hombres, mostraron un mayor uso de fentanilo (29 vs. 13%, p=0.01) y opioides de liberación rápida (9 vs. 0%, p=0.003) que las mujeres.

Por otro lado, se observó una reducción del 8% en las RAM notificadas (11 vs. 3%, p=0.04) a pesar de un aumento significativo de los EA (6(2–8) vs. 9 (6–11), p<0.001). A largo plazo, se evidenció una mayor incidencia de piel seca (43 vs. 79 %, p<0.001), cambio de peso (31 vs. 56%, p<0.001), impotencia sexual (11 vs. 35%, p<0.001), boca seca (62 vs. 84%, p<0.001), mareo (25 vs. 46%, p=0.003), somnolencia (39 vs. 58%, p=0.01), estreñimiento (44 vs. 61%, p=0.02) y nerviosismo (41 vs. 56%, p=0.04). Respecto al sexo, las mujeres tuvieron mayor número de EA (6 (2–8) vs. 9 (6–11), p<0.001), observándose diferencias en el 40% de los EA recogidos.

Por último, nuestros datos mostraron que el alelo G del gen *OPRM1* estaba asociado con un mayor uso de tramadol (genotipo AA: 7 vs. portadores alelo G: 28%, p=0.01) y, en las mujeres, con un mayor cambio de peso (35 vs. 82%, p=0.01). Para el caso del fenotipo CYP2D6, los PM mostraron una DDEM más baja (PM: 27 ± 59 mg/día vs. EM-UM: 117 ± 140 mg/día, p<0.001), sin consumo entre las mujeres (PM: 0 vs. EM: 70 vs. UM: 63%, p=0.01). Por otro lado, en los hombres se asociaron los UM con los vómitos (PM: 0, EM: 0, UM: 100%, p<0.001).

4.2. Proyecto 2: DESOPI CYP

Durante el transcurso del PTI (n=138 comenzaron, n=117 finalizaron) se disminuyó el consumo de opioides a través de la reducción de la DDEM en un 67%. Aquí, un 42% de los pacientes alcanzaron la deprescripción total libre de opioides, sin que ello conllevase cambios en la aparición de SAO o en las variables clínicas analizadas.

Las características de esta población con TCOP fueron comparadas con las de otro grupo de pacientes con DCNO y uso prolongado de opioides, pero sin sospecha de TCOP (control, n=231). Aquí, los casos fueron casi 10 años más jóvenes (54 (13) vs 63 (14) años, p<0.001), y presentaron un mayor alivio del dolor, probablemente debido a un mayor consumo de DDEM (120 (80-200) vs. 40 (0-82) mg/día, p<0.001).

4.2.1. Artículo 2- Impacto PGx

En lo que respecta al impacto del perfil metabolizador, estimado a partir del genotipo del *CYP2D6* de cada paciente, se encontró una frecuencia de 6% PM, 85% EM y 9% UM en la población de estudio, sin que existieran diferentes frecuencias entre sexos ni respecto al grupo control.

Al inicio del PTI, los UM consumieron 3 veces menos DDEM para alcanzar la analgesia respecto a los PM-EM (40 (20-123) vs. 123 (80-226), p=0.04). Sin embargo, este resultado no se replicó cuando se seleccionaron exclusivamente los casos con uso de opioides con metabolismo mediado por CYP2D6. Por otra parte, al finalizar el PTI, los perfiles UM presentaron un aumento significativo de la sintomatología del SAO durante la deprescripción (46 (10) vs. 30 (20) puntos OWS, p=0,01), lo cual además se correlacionó inversamente con la calidad de vida tanto en hombres (r=-0,572 (-0.797 a -0.209), p=0.01) como en mujeres (r=-0.700 (-0.841 a -0.470), p<0.001). En la misma dirección, los UM reportaron un mayor número de EA (7 (6-11)) en comparación al resto de fenotipos (5 (2-7), p=0,02), presentando una mayor frecuencia de dolor de cabeza (100 vs. 33%, p=0.01), edema (50 vs. 9%, 255 p=0.02), boca seca (100 vs. 53%, p=0.03) y nerviosismo (86 vs. 38%, p=0.04), afectando principalmente a los sistemas gastrointestinal y general.

Se notificó la aparición de RAM en el 13% de la población a estudio, donde, en función del sexo, los hombres notificaron tres veces más que las mujeres (23 vs. 7%, p=0.02), así como una mayor frecuencia de AE de tipo sexual/reproductivo (25 vs. 4%, p=0.01), mientras las mujeres presentaron edema (15 vs. 0%, p=0.05), boca seca (63 vs. 33%, p=0.02) y nerviosismo (50 vs. 22%, p=0.029) en mayor proporción. A modo de resumen, el fenotipo CYP2D6 y el sexo del paciente pudo contribuir a un perfil diferencial de seguridad en los pacientes con DCNO y TCOP que se someten al PTI.

4.3. Proyecto 3: preDESOPI

Se desarrolló y validó internamente un modelo de predicción de TCOP en pacientes con DCNO y opioides a largo plazo a partir de datos retrospectivos (pacientes que habían participado en estudios previos del grupo con DCNO y opioides a largo plazo) y de nuevos datos prospectivos (pacientes con DCNO y opioides a largo plazo de UDO cuya información no se había utilizado previamente para el desarrollo del modelo) con una buena sensibilidad y especificidad (78% y 68%, respectivamente).

4.3.1. Artículo 3- Diferencias por Sexo

En este artículo se quiso identificar riesgos potenciales y necesidades específicas según el sexo del paciente a partir de los datos caso TCOP/control recogidos de los estudios previos del grupo NED.

En primer lugar, se observó que las mujeres estaban en un mayor porcentaje como amas de casa y presentaban una peor tolerabilidad con respecto a los hombres. Con respecto al grupo caso, las mujeres mostraron un mayor historial de abusos previos de sustancias (caso: 19 vs. control: 11%, p=0.03) junto con insomnio (52 vs. 35%, p=0.012), mientras que los hombres tuvieron una mayor prescripción de fentanilo (40 vs. 18%, p=0.002), RAM (24 vs. 12%, p=0.04), vómitos (20 vs. 4%, p=0.005) y picor (33 vs. 15%, p=0.02).

Por otro lado, en el grupo control se observaron mayores diferencias significativas según el sexo. Las mujeres eran mayores (66 (56–75) vs. 60 (49–73) años, p=0.001), estaban en un mayor porcentaje como amas de casa (7 vs. 0%, p=0.004) y tenían mayor prescripción de analgésicos simples (45 vs. 37%, p=0.039), tramadol (37 vs. 25%, p=0.001) y medicación psicotrópica (antidepresivos y benzodiacepinas) con respecto a los hombres. Además, tuvieron más visitas a urgencias (32 vs. 22%, p=0.02) con una peor tolerabilidad (5 (2–8) vs. 4 (2–6) EA, p=0.003), específicamente por vómitos, cambio de peso, piel seca, depresión y falta de apetito.

4.3.2. Artículo 4- Construcción del Modelo de Riesgo

En primer lugar, se analizaron los factores de riesgo en el paciente con DCNO bajo prescripción de opioides a largo plazo a partir del análisis entre casos (con TCOP, n=137) y controles (sin TCOP, n=669) para el posterior desarrollo de un modelo predictivo de TCOP. Aquí, se observó que los casos eran más jóvenes (54 ± 13 vs. 64 ± 14 años; p<0.001) con menores ingresos económicos (<500 euros/mes; 55 vs. 22%, p=0.02) y mayor incapacidad laboral (49 vs. 14%, p<0.001). Asimismo, tuvieron mayor historial de abusos previos de sustancias (principalmente al tabaco; 20 vs. 12%, p=0.03), DDEM (120 (72-217) vs. 60 (40-120) mg/día, p<0.001) y co-prescripción de fentanilo (32 vs. 19% p=0.002) con benzodiacepinas (50 vs. 36%, p<0.010). En cuanto a la tolerabilidad, el número de EA y RAM se mantuvieron similares, sin embargo, los

casos tenían mayor prevalencia de insomnio (51 vs. 33%, p=0.001). La distribución genética se mantuvo similar entre ambos grupos.

Para el desarrollo del modelo, se seleccionaron 16 variables en base a los siguientes criterios: significancia estadística (p<0.050), *effect size*, resultados previos del grupo y consenso de los investigadores sobre variables relevantes medibles. De esta forma, las variables incluidas en el modelo fueron las siguientes: edad, situación laboral (trabajador en activo e incapacidad laboral), historial de abuso previos de sustancias, uso de tramadol, DDEM, uso de opioides fuertes, uso de fentanilo, uso de benzodiacepinas, visitas a urgencias, vómitos, insomnio, EA de tipo psiquiátrico, genotipo *OPRM1* (AA y portadores del alelo G), genotipo *COMT* y fenotipo CYP2D6.

En base a la total disponibilidad de las variables elegidas, el modelo final se desarrolló en un tamaño muestral de 129 sujetos (n=27 casos y n=102 controles). Se construyó un modelo de regresión logística basado en las normas para el proceso de construcción de modelos [111]. La selección de las variables se hizo en base a los siguientes criterios: (1) AIC pequeño (no necesariamente el mínimo), (2) significancia estadística de las variables (p<0.050) e (3) interpretabilidad de los signos de los coeficientes (coherencia con la literatura científica). El modelo final seleccionó cinco factores de riesgo independientes: ζ = 1.633 - 0.072 edad + 2.012 incapacidad laboral + 0.006 DDEM -1.424 genotipo-AA *OPRM1* + 0.075 CYP2D6-PM + 3.172 CYP2D6-UM con valores óptimos de sensibilidad y especificidad (82% y 85%, respectivamente), discriminación (curva ROC, 0.89) y bondad de ajuste (test Hosmer-Lemeshow, p=0.87).

4.3.3. Anexo Artículo 5- Validación del Modelo de Riesgo

En este estudio, se incluyeron prospectivamente 100 sujetos de la UDO-HGUDrB para la validación del modelo. El principal motivo de consulta era la lumbalgia (67%, mayoritariamente por discopatía proveniente de una estenosis del canal medular). Esta nueva población prospectiva mantuvo diferencias significativas con respecto a la cohorte retrospectiva. En primer lugar, presentaba más dolor (70 (26) vs. 61 (28) mm, p=0.02). En segundo lugar, tenía mayor prescripción de analgésicos simples (63 vs. 34%, p<0.001), tramadol (45 vs. 22%, p<0.001) y benzodiacepinas (54 vs. 35%, p=0.005), pero menor DDEM (60 (33-108) vs. 80 (40-160) mg/día, p=0.04) y opioides de liberación rápida (10 vs. 24%, p=0.009). A nivel sociodemográfico, tenía mayores ingresos económicos (>1000 euros/mes, 42 vs. 13%, p=0.04) y un menor abuso previo de tabaco (71 vs. 96%, p=0.03).

De esta forma, el modelo desarrollado previamente en la cohorte retrospectiva (muestra 1) no se ajustó correctamente a la nueva cohorte (muestra 2) y, por ello, se planteó la construcción de un modelo de regresión logística en dos etapas (bietápico) que (1) clasificara a los pacientes y (2) estimara el riesgo TCOP. El modelo clasificador de pacientes incluyó nueve factores independientes: ζ = 0.242 – 1.950 trabajador activo– 1.740 incapacidad laboral– 3.976 desempleado + 0.004 DDEM + 3.493 opioides fuertes – 2.626 benzodiazepinas – 1.496 visitas a

urgencias + 2.289 EA psiquiátricos – 2.159 genotipo-GA *COMT* – 0.901 genotipo-GG *COMT*. Por otro lado, los modelos predictivos de riesgo TCOP finales fueron ζ = - 0.622 – 0.057 edad + 2.859 incapacidad laboral + 0.006 DDEM + 1.191 PM- CYP2D6 fenotipo + 3.299 UM- CYP2D6 para la muestra 1; y, ζ = - 1.713 – 0.032 EQ + 0.006 DDEM + 1.017 genotipo AG/GG-*OPRM1* para la muestra 2. Para la validación del modelo bietápico se calculó la sensibilidad y especificidad del mismo a partir del 20% de datos aleatorios extraídos de ambas muestras. Los valores obtenidos fueron óptimos (70% y 75%, respectivamente).

5. Discusión

5.1. Proyecto 1: DESOPI LONG

Los resultados muestran que la deprescripción ambulatoria a largo plazo permite reducir el uso de opioides prescritos con un incremento en el alivio del dolor. Asimismo, estos datos muestran las ventajas de incorporar en la rutina clínica un sistema de monitorización, ya que se vieron reducidas significativamente las RAM notificadas.

Nuestros resultados mostraron un aumento de EA a largo plazo (final PTI: 6 (2-8) vs. largo plazo: 9 (6-11), p<0.001), siendo la piel seca el EA más frecuente, seguido de cambio de peso, impotencia sexual, boca seca, mareos, insomnio, estreñimiento y nerviosismo. En diferentes revisiones entre opioides versus placebo, se ha observado un mayor riesgo de estreñimiento, somnolencia, fatiga, sofocos, sudoración, náuseas, prurito y vómitos [112]. Sin embargo, la falta de estudios que analicen los EA en pacientes con DCNO y TCOP representa una seria limitación para comparar nuestro patrón de tolerabilidad. No obstante, cabe resaltar que a pesar de que se comunicasen más EA, estos no fueron valorados con suficiente causalidad como RAM, disminuyendo las notificaciones hasta en un 8%. Ambos aspectos resaltan la importancia incorporar medidas de monitorización a largo plazo en las UDO, sobre todo, por el impacto de las RAM en la calidad de vida de los pacientes y por las señales que puedan detectarse y guiar a una efectiva deprescripción.

También, este estudio muestra la necesidad de incorporar el subanálisis por sexo y los marcadores farmacogenéticos (principalmente *CYP2D6*) del/la paciente con el fin de entender la variabilidad interindividual observada en la efectividad y seguridad del tratamiento. En primer lugar, los resultados del presente trabajo nos han permitido comprobar, pese a la limitación de contar con un tamaño muestral reducido, que la proporción de mujeres con diagnóstico de DCNO es mayor a la de hombres, como ya se ha observado en previos estudios [113], [114], siendo el porcentaje en nuestra Unidad del 68% con una edad media de 58 (13) años bajo un tratamiento multimodal analgésico.

En este estudio, se observa que las mujeres reducen significativamente la DDEM a largo plazo manteniendo una peor tolerabilidad con respecto a los hombres. La evidencia científica sugiere que los hombres y las mujeres responden de forma diferente al dolor debido a variaciones en la modulación del sistema opioide endógeno [115] o por el papel de las hormonas sexuales [116]–[118]. Estas diferencias en el dolor entre hombres y mujeres surgen alrededor de la pubertad. Aun así, la influencia hormonal sobre el dolor es compleja y puede depender de: (1) la dosis y el momento de exposición hormonal, (2) el tipo de dolor, (3) la presencia de múltiples factores hormonales y (4) el sitio de acción de las hormonas. Asimismo, cabe mencionar que se han observado diferencias por sexo en la distribución en los receptores opioides mu y delta en las

células piramidales del hipocampo [117], así como en el funcionamiento de la microglía [116], dependientes a los estadios hormonales.

Las diferencias observadas en la prescripción farmacológica también pudieron haber sido consecuencia de la normalización de los síntomas entre las mujeres y los profesionales sanitarios [119]. Existen varios estudios que demuestran que las mujeres reciben menos tratamiento para el dolor que los hombres. Esto se ha asociado a los estereotipos de género entre los profesionales de la salud, que atribuyen el dolor de las mujeres a un componente más psicológico que físico, o subestiman el mismo por las diferencias en la presentación que se da en algunas mujeres [81], [96]. Así, las mujeres presentaron un mayor consumo de benzodiacepinas. Este hecho coincide con la literatura científica, donde se ha descrito que las mujeres tienen más probabilidades que los hombres de ser prescritas ansiolíticos, sedantes e hipnóticos (hasta 3 veces más en el sur de Europa) [120]. También se ha explicado por una atribución más fácilmente de factores psicológicos en las mujeres con respecto a los hombres por parte de los profesionales de la salud [89].

Con respecto al peor patrón de tolerabilidad evidenciado en las mujeres, este pudo deberse a la co-prescripción de coadyuvantes para el tratamiento del dolor, los cuales pudieron haber aumentado la probabilidad de interacciones farmacológicas [121] y con ello, a la aparición de EA. No obstante, se necesitan más estudios que investiguen estos hallazgos.

En cuanto al impacto farmacogenético, nuestros resultados asociaron el alelo G con un mayor consumo de tramadol, pero no con mayor DDEM. En la literatura, ha sido previamente descrito que pacientes con dolor crónico portadores del alelo G requerían dosis más opioides más para conseguir el mismo alivio del dolor que los pacientes portadores del alelo A [122]–[126], sin embargo, estos resultados todavía no están dilucidados [127], [128], por lo que se necesitan investigaciones en cohortes más grandes que determinen el papel del mismo.

En el caso del fenotipo CYP2D6, es el único marcador farmacogenético del panel de opioides que sí dispone de guías clínicas para el tramadol y la codeína, con una evidencia menor para la oxicodona e hidrocodona. En nuestro estudio, se relacionó el fenotipo PM con una menor DDEM ($p<0.001$). Estos resultados coinciden con lo descrito anteriormente por la literatura en donde se observó que los pacientes PM, al tener una menor capacidad para metabolizar los opioides, su eliminación era más lenta y, por lo tanto, el consumo de opioides necesario era menor para lograr el mismo efecto analgésico [51], [77]. Por otro lado, con respecto a la seguridad farmacológica, solo se encontraron asociaciones significativas entre los fenotipos UM de los hombres con la presencia de vómitos. Los fenotipos UM pueden producir niveles más altos de metabolitos activos de los opioides, siendo más susceptibles a la aparición de EA. En algunos estudios de pacientes tratados con codeína y tramadol se observó que los fenotipos UM tenían un mayor riesgo de desarrollar vómitos y otros EA en comparación con los fenotipos EM [129], [130]. No obstante, se requieren de estudios con mayor tamaño muestral debido a la baja prevalencia de estas

variantes. De la misma forma, es necesario explorar las posibles interacciones farmacológicas con otros coadyuvantes empleados en el DCNO que puedan actuar como inhibidores CYP (p.e. paroxetina, fluoxetina o bupropión) o inductores (p.e. escitalopram o clobazam). Esto está empezando a ser analizada en profundidad como parte de nuestras nuevas investigaciones (resultados en fase de envío), ya que estos fármacos pueden actuar como sustratos y/o inhibidores de la enzima CYP2D6, condicionando los niveles de opioide activo y, por tanto, la posología a pautar por parte del facultativo [131]. Además, hay que tener en cuenta que la actividad enzimática CYP está regulada por factores fisiológicos (ciclo menstrual, embarazo, entre otros), ambientales (dieta, tabaco, alcohol, entre otros), patológicos (enfermedad hepática, inflamación, entre otros), y epigenéticos, lo que puede haber comprometido la interpretación fenotípica.

5.2. Proyecto 2: DESOPI CYP

A través del análisis del impacto del fenotipo metabolizador CYP2D6 sobre la deprescripción, los UM mostraron una peor tolerabilidad, que además se correlacionó con un mayor (y negativo) impacto sobre la calidad de vida.

Los hallazgos de este estudio orientan hacia estrategias de actuación en la práctica clínica cuando se detectan perfiles UM, especialmente relevantes en las poblaciones del sur de Europa y del norte de África donde existen mayores proporciones de UM [130]. En estas situaciones, es importante considerar el uso de fármacos analgésicos diferentes, como los que se metabolizan a través de una vía metabólica de fase II, para evitar un posible fracaso terapéutico. En este sentido, el tapentadol, aunque se metaboliza de forma residual a hidroxitapentadol inactivo (2%) por CYP2D6, se glucoronidiza en gran medida por la vía de fase II y no se espera variabilidad interindividual relacionada con CYP2D6 en la respuesta analgésica [132], lo que hace del tapentadol una alternativa a considerar. En la misma línea, se plantea que, una vez detectado el perfil UM, se establezca un plan de disminución y/o interrupción de opioides de forma individualizada, basado en guías clínicas, para tratar de prevenir la aparición de signos y síntomas del SAO [133]. Además, la detección de estos fenotipos podría ser crucial en una etapa temprana de TCOP para prevenir la aparición de EA frecuentes en opioides [134], así como el riesgo de reacciones potencialmente mortales en comparación con los EM [135].

Por tanto, estos resultados respaldan el interés clínico del genotipado en la deprescripción para identificar a pacientes con riesgo de analgesia insuficiente o de EA. No obstante, junto a futuros estudios que analicen el coste-efectividad de estos marcadores, es importante la necesidad de desarrollar guías clínicas como vehículo de ayudar para los prescriptores de opioides, que tengan en cuenta no sólo con CYP2D6, sino también con otras enzimas P450 (1A2, 2C9, 2C19 o B6).

Además, para comprender la variabilidad interindividual en términos de seguridad se realizó el análisis por sexo. En este sentido, se reportaron diferentes frecuencias de EA y RAM entre sexos.

A este respecto, los datos mostraron que las mujeres comunicaron más EA relacionados con los sistemas nervioso, gastrointestinal y general, y menos relacionados con la esfera sexual en comparación con los hombres, siendo las RAM menos frecuentes en las mujeres. Es necesario dilucidar estas diferentes tendencias de impacto relacionadas con la compleja interdependencia entre el sexo biológico y el género [136], [137].

Por último, este artículo sirvió también para sugerir la edad (más jóvenes) y las DDEM (más altas) como factores de riesgo de TCOP, lo que nos permitió considerar como prioritarias estas variables a la hora de realizar la construcción del modelo de predicción.

5.3. Proyecto 3: preDESOPI

Nuestro modelo nos reveló que los pacientes de menor edad, situación laboral pobre y alta DDEM fueron más vulnerables a desarrollar TCOP. Según el CDC, la edad promedio de los consumidores de opioides es de 52 (95% [IC] = 50-54) años, siendo los que más consumen el grupo de sujetos de entre 40-59 años [138], en su mayoría de forma lícita. Asimismo, un peor nivel educativo y condiciones económicas también se relacionaron con un mayor riesgo de desarrollar TCOP [139]. No obstante, el principal determinante descrito en el riesgo a desarrollar TCOP es la DDEM. Se ha expuesto que dosis diarias cercanas o mayores a 100 mg/día tienen un mayor riesgo en el desarrollo de TCOP que las dosis <50 mg/día [140]. Una encuesta de EEUU (n=1,229 sujetos) mostraba que el 80% de los pacientes con DDEM superiores a 50mg continuaban al menos 1 año con la prescripción a pesar de la inefectividad analgésica y los EA comunicados. Estos datos también muestran la dificultad de reducir la dosis de opioides entre los consumidores crónicos de opioides cuando están en dosis altas [141].

Nuestros datos muestran que los casos TCOP tuvieron un mayor uso concomitante de benzodiacepinas. La literatura ha descrito un aumento de la co-prescripción de benzodiacepinas con opioides en pacientes con dolor crónico. En un estudio de EEUU, encontraron que este uso concomitante había aumentado del 9% en 2001 al 17% en 2013 [142]. Diversos estudios han asociado el consumo simultáneo con un mayor riesgo de sobredosis y muerte [143], [144]. Esto se debe a que ambos fármacos causan depresión en el sistema nervioso central, pudiendo provocar una reducción en el ritmo respiratorio y con ello, contribuir a la desaturación de oxígeno. Es por ello, por lo que se recomienda limitar la prescripción sólo a pacientes para los que las opciones alternativas de tratamiento son inadecuadas.

Además, nuestro estudio evidencia una mayor prevalencia de sueño entre los casos TCOP. Existe evidencia que sugiere una relación entre la deficiencia del sueño y la TCOP [145], [146]. Los problemas de sueño se han correlacionado con los trastornos de ansiedad y estrés, lo que puede aumentar el riesgo de conductas aberrantes. Asimismo, algunos estudios han relacionado los trastornos del sueño con una mayor sensibilidad a los opioides [147], aumentando también

el riesgo de abuso y dependencia. De esta forma, este estudio indica la necesidad de incluir esta variable como marcador de calidad en este tipo de población.

Hasta la fecha, se han desarrollado guías clínicas farmacogenéticas para el fenotipo CYP2D6 en al menos 48 fármacos [52]. En general, los fenotipos UM y PM se han asociado con una menor respuesta analgésica, lo que puede contribuir al desarrollo de TCOP. Esto se debe porque los sujetos UM tienen una metabolización más rápida del fármaco opioide [58], mientras que, en el caso de los PM, se debe por la conversión nula de los metabolitos activos [148]. Por otro lado, las asociaciones del alelo G del gen *OPRM1* con la TCOP siguen sin ser concluyentes. Algunos estudios asocian la presencia del mismo con un mayor riesgo a desarrollar TCOP [64], [66], mientras que otros no han podido establecer ninguna asociación [127], [128]. De esta forma, es necesaria la realización de estudios farmacogenéticos que nos ayuden dilucidar esta evidencia.

Con respecto a las diferencias por sexo, entre los riesgos psicosociales que pueden empeorar el estado de salud de las mujeres, encontramos una significativa mayor dedicación a las tareas domésticas. Diversos estudios han evidenciado que las tareas domésticas pueden contribuir al dolor crónico y que reducir la carga de trabajo doméstico y mejorar las condiciones ergonómicas durante las tareas domésticas puede ayudar a reducir o prevenir el dolor crónico [149]. Asimismo, el malestar físico causado por la sobrecarga de trabajo doméstico, así como el estrés físico y mental derivado de la doble jornada laboral como empleadas y cuidadoras de toda la familia, exige nuevos estudios para identificar estrategias adecuadas de intervención y prevención [150].

Por otro lado, en este estudio se observan diferencias por sexo en los casos TCOP en relación a los abusos previos de sustancias y el uso de fentanilo. Se ha descrito que las mujeres son prescritas más frecuentemente fármacos ansiolíticos, sedantes e hipnóticos [151] y, que éstos tienen un efecto indirecto sobre el sistema de recompensa, pudiendo aumentar el riesgo de desarrollar TCOP en combinación con los opioides [152]. Por otro lado, la evidencia sugiere que los hombres son más sensibles que las mujeres a los efectos de abuso de los agonistas mu, como el fentanilo, aunque todavía estos datos no son concluyentes [153]. De esta forma, este estudio respalda la necesidad de adaptar el tratamiento en función del sexo, siempre considerando las diferencias interindividuales.

Así, las diferencias observadas pueden deberse a diversos factores, entre ellos, neuroanatómicos, hormonales y neuroinmunológicos, pero también psicológicos, sociales y culturales, los cuales deben analizarse en mayor profundidad. Nuestros resultados muestran que se debería de dejar de considerar a hombres y mujeres como un grupo homogéneo dado que la tolerabilidad subjetiva de los analgésicos difiere sustancialmente entre sexos.

En esta era de la medicina de precisión y la inteligencia artificial, la atención sanitaria podría beneficiarse de los predictores genéticos para estratificar a los pacientes en categorías de riesgo para la TCOP. Nuestros datos muestran que se podría identificar el 75% de los casos, mejorando

el seguimiento, ya que se podrían centrar los programas de prevención en aquellos sujetos con mayor riesgo.

6. Limitaciones y Líneas Futuras

6.1. Limitaciones

En primer lugar, la falta de aleatorización en los estudios observacionales pudo haber impedido cualquier asociación de causalidad. También, la baja prevalencia de las variantes genéticas pudo haber comprometido la potencia estadística y haber limitado los hallazgos. Por otro lado, la mayoría de los pacientes también tenían prescritos fármacos coadyuvantes relacionados con sus diversas comorbilidades, pudiendo haber contribuido de forma independiente en la aparición de EA. También, en el estudio DESOPI LONG, el tiempo de seguimiento varió entre los pacientes. En cualquier caso, no se observaron diferencias significativas analizándolo individualmente. Además, en este estudio la información clínica se recogió sólo en aquellos pacientes que acudían a la UDO, reduciendo el tamaño muestral y con una posible implicación en los resultados, especialmente en los hombres.

Por otra parte, cabe mencionar las limitaciones propias de los estudios retrospectivos como son la recogida de datos de diferentes periodos de tiempo y estudios, así como, la disponibilidad de ciertas variables en la historia clínica electrónica del paciente. En el caso del modelo de predicción, la incidencia relativamente baja de TCOP en nuestro entorno clínico podría haber evitado la detección de otros factores de riesgo potenciales. Asimismo, nuestro modelo se validó internamente en un número limitado de pacientes, lo que hace necesario su desarrollo en una cohorte mayor para mejorar el rendimiento y la precisión diagnóstica, así como, su validación externa para la generalización de los resultados. Por otro lado, el hecho de que el modelo desarrollado a partir de la muestra retrospectiva (primera muestra) no se ajustara a la muestra prospectiva (nueva muestra) puede atribuirse a (1) la naturaleza retrospectiva de la primera muestra, (2) la disponibilidad de datos para el modelo en la primera muestra, (3) el reclutamiento de pacientes en diferentes consultas de la UDO en la nueva muestra y (4) los cambios en las guías clínicas nacionales sobre la prescripción de opioides.

Se suman las barreras que surgen para la implementación de la PGx, y es que uno de los objetivos que persigue esta Tesis Doctoral es ayudar en la implementación de esta como una herramienta más en la práctica clínica. Además, actualmente son pocas las herramientas PGx empleadas en la práctica asistencial, limitadas a unos pocos genes, por lo que aún se deben de realizar grandes esfuerzos para conseguir su implantación. Junto con esto, otra amenaza es la situación tan precaria de la investigación a nivel nacional, debida en gran parte a la escasa financiación. Esto puede suponer un freno a las investigaciones y a la implantación de la PGx en la rutina clínica. Por último, otra debilidad de la presente Tesis Doctoral es la escasa financiación

que ha recibido para su desarrollo, lo que ha supuesto la búsqueda de alianzas externas, tanto públicas como privadas, para poder avanzar en las investigaciones.

Por otro lado, cabe señalar que los estudios de la presente Tesis Doctoral presentan también diferentes fortalezas. Primeramente, son trabajos realizados en pacientes del mundo real, lo que permite recoger información representativa de la población y proporciona más información útil para futuros estudios en el campo. Nuestros resultados muestran que investigar en mayor profundidad los determinantes genéticos, clínicos y sociales de la salud; la forma que tienen los pacientes y sus médicos de entender la salud/enfermedad, las vivencias y los estados emocionales que acompañan al dolor crónico, es fundamental para un mejor desarrollo de programas de prevención individualizados y manejo del dolor. Esto es destacable ya que, al fin y al cabo, cuando se realiza una investigación se pretende extrapolar al mundo real, cosa que no sucede en la mayoría de las investigaciones. Además, los estudios de esta Tesis Doctoral se han realizado desde una perspectiva personalizada, es decir, llevando a cabo un análisis genético y con un subanálisis de sexo en todos los estudios. Los resultados obtenidos permiten tener una mayor comprensión de la influencia que pueden ejercer factores individuales sobre el tratamiento, como pueden ser las diferencias genéticas en ciertos genes clave, o el sexo del paciente, tan importante en la regulación hormonal.

6.2. Relevancia, Aplicabilidad y Capacidad de Transferencia

El proyecto integra el objetivo común de consolidar el modelo de predicción como herramienta **relevante** y **aplicable**, permitiendo la individualización terapéutica y la mejora de la salud y la calidad de vida de los pacientes.

El proyecto ha pretendido dar respuesta a una **necesidad clínica** no cubierta, como es el disponer de herramientas que nos permitan anticipar el riesgo de desarrollar TCOP en una sociedad en la que el número de pacientes con dolor crónico, así como el uso de analgésicos opioides se ha duplicado en una década. Las comorbilidades asociadas e impacto negativo en la calidad de vida de este trastorno se suman a la **vulnerabilidad** de este tipo de paciente, que de por sí incluye una edad avanzada, insomnio, depresión, polimedicación y dependencia física, entre otras, lo que explica el **impacto social** que presenta el estudio. Además, existe un estigma asociado con el TCOP, que conlleva sentimientos de vergüenza y aislamiento, lo que dificulta aún más el debido seguimiento clínico del paciente. Esto puede revertirse aumentando el conocimiento de estas condiciones y abriendo oportunidades preventivas durante su manejo clínico.

6.2.1. Plataforma de Farmacogenética

Gracias a toda esta experiencia acumulada, en el año 2022 se pudo poner en marcha la Plataforma de Farmacogenética Aplicada a la Investigación (ISABIAL, ver: https://isabial.es/apoyo-cientifico-servicios-investigacion/farmacogenetica-aplicada-

investigacion/) presidida por la Dra. Peiró y coordinada por el Dr. Muriel desde donde se está colaborando con el Instituto de Investigación Sanitaria de la Fe de Valencia (IIS La Fe) (Proyecto SESGEN OMIC, código: AP2021-06, 2022) y la Universidad de Roma (Farmacocinética, Dra. Mercolini, Proyecto PKditos, código: 2022-0519, 2023).

Impacto en Salud

En relación al impacto en salud, el presente proyecto se orienta hacia la Medicina Predictiva centrada en el paciente, utilizando factores sociodemográficos (incluyendo la edad y el sexo), farmacológicos y clínicos junto a las características genéticas de los pacientes para tratar de prevenir complicaciones del manejo clínico de los pacientes con dolor crónico, como son la seguridad de los opioides, incluyendo el TCOP. Este hecho repercutirá de forma positiva en el manejo del paciente con DCNO y uso de analgésicos opioides, incluyendo su calidad de vida.

Consolidación de la Línea de Investigación

Esta línea se consolida con la concesión del proyecto IPharmPGx (PMP22/00055 2022-2025. 950.000€ (contrato de investigación), la colaboración con el Centro de Psicofarmacología del Hospital Diakonhjemmet de Oslo, Noruega y la organización de la Red Farmacovigilancia en diversidad cognitiva con un ensayo clínico testando la agomelatina.

Traslación Clínica/Social

Se están implementando guías clínicas con marcadores farmacogenéticos a nivel nacional desde la Sociedad Española de Farmacogenética y Farmacogenómica (SEFF). Asimismo, se ha generado un protocolo de análisis de casos de abuso a opioides junto con Farmacia de Atención Primaria (Proyecto Bencopi ISABIAL 2021-0458).

6.2.2. Plataforma Mujer y Dolor

Gracias a toda esta experiencia acumulada, en el año 2023 el grupo forma parte de la Plataforma "Mujer y Dolor" (ver: https://www.mujerydolor.es/). Esta es una iniciativa surgida de la inquietud de varios profesionales implicados en diferentes ámbitos de nuestra sociedad, constituyéndose como una asociación independiente con carácter social y científico, multidisciplinar, que tiene por objeto fomentar la sensibilización social para el estudio o investigación del dolor en la mujer en áreas relacionadas con la enfermedad, la violencia y la sociedad, a través de la participación de instituciones y profesionales que pongan su atención en el dolor crónico y sus consecuencias en la mujer.

Impacto en Salud

Incorporación de investigación cualitativa, testimonios (Proyecto Text Mining).

6.2.3. Uso de Técnicas de Inteligencia Artificial

La presente Tesis Doctoral inicia una nueva línea futura (ver punto 1.4, Proyecto IA_DEPOP) la cual pretende incorporar técnicas de Inteligencia Artificial para desarrollar un modelo predictivo de riesgo que pueda ser asumido por el SNS. El desarrollo de este tipo de herramienta ayuda a potenciar el eje entre investigación e industria y puede suponer una optimización en la eficiencia de los recursos económico-sanitarios que se requieren para el seguimiento y tratamiento de los casos de TCOP, así como para el resto de EA asociados al tratamiento del dolor (uso del servicio de urgencias, ingresos hospitalarios, aumento de la frecuencia de consultas, entre otras).

En resumen, tras los resultados obtenidos se abre un abanico de posibilidades para profundizar aún más en las líneas de investigación que se presentan (**Tabla 7**). En primer lugar, los datos obtenidos en estos estudios son de nuestra población, de pacientes que acuden a la UDO del HGUDrB para recibir tratamiento contra su dolor, los cuales se pueden extrapolar a la mayoría de nuestra población al ser una muestra representativa de la misma. Así, con los resultados obtenidos en los trabajos de nuestro grupo de investigación, se pretende implementar aquellos marcadores genéticos con alto nivel de evidencia en las guías terapéuticas como una nueva herramienta en la práctica clínica, además de tener en cuenta el sexo/género del/la paciente a la hora de prescribir un tratamiento específico o que resultados esperar con la terapia.

Tabla 7. Resumen líneas futuras, proyectos y colaboraciones surgidas.

LÍNEA FUTURA	PROYECTO	NUEVAS COLABORACIONES
Farmacogenética	- Desarrollo de guías clínicas - Grupo de Trabajo en SEFF: Regulación en farmacogenética y farmacogenómica. - Estancia Oslo: implementación PGx en la clínica.	Traslación a la cartera de servicios del SNS *2 papers en redacción* *2 guías clínicas en redacción SEFF (opioides con marcador PGx) y SNS (guía deprescripción opioide tras TCOP nacional)*
Otras ómicas: epigenética, metabolómica, trascriptoma	- Proyecto IA_DEPOP (solicitado PI_AES_2023, Código: PI23/00011)): *"Desarrollo e implementación, mediante el uso de técnicas de Inteligencia Artificial, de un modelo de predicción de riesgo del Trastorno por Consumo de Opioides de Prescripción".*	6 CCAA Alicante: ISABIAL-Hospital General Universitario Dr. Balmis de Alicante/UMH Barcelona: Parc Salut Mar Madrid: Hosp. La Princesa Sevilla: Hosp. Universitario Virgen Macarena y Hosp. Virgen del Rocío Ourense: Complejo Hosp. Universitario Albacete: Complejo Hosp. Universitario/Universidad de Castilla La Mancha (UCLM). Valencia: UPV

	-Proyecto SESGEN-OMIC (Código: AP2021-06) Inclusión epigenética: *"Ciencias ómicas aplicadas a la medicina del dolor con análisis de la interacción sexo/género".*	Colaboración IIS La Fe - UMH *1 paper en redacción*
Sexo	Proyecto SESGEN- ICI2020 (Código: ICI20/00146): "*Sesgos de género en la medicina del dolor: de las ómicas a la atención sanitaria".*	2 CCAA Valencia: IIS La Fe Zaragoza: Universidad de Zaragoza Colaboración UPV TFM Alba Gómez (Biotecnología) TFM Irene Muela (Medicina) *2 papers en redacción* *1 paper en revisión*
Farmacogenética y Sexo	Proyecto en colaboración con La Princesa (Código protocolo: PBC-GENDN-2019-01): "*Evaluación del sexo y marcadores farmacogenéticos en el manejo del dolor neuropático".*	Inclusión de valoración dolor QST
Modelo de predicción de riesgo TCOP	Proyecto IA_DEPOP (solicitado PI_AES_2023, Código: PI23/00011)): "*Desarrollo e implementación, mediante el uso de técnicas de Inteligencia Artificial, de un modelo de predicción de riesgo del Trastorno por Consumo de Opioides de Prescripción".*	6 CCAA Alicante: ISABIAL-Hospital General Universitario Dr. Balmis de Alicante/UMH Barcelona: Parc Salut Mar Madrid: Hosp. La Princesa Sevilla: Hosp. Universitario Virgen Macarena; Hosp. Virgen del Rocío Ourense: Complejo Hosp. Universitario Albacete: Complejo Hosp. Universitario-CHUA/ UCLM). Valencia: UPV
Aplicación al mundo del deporte	Proyecto AddiSport (Código: PI2020-251): "*Perfil de Riesgo de Adicción: un instrumento novedoso para proteger la salud de los atletas."* Proyecto PkDitos (Código: 2022-0519, en fase de evaluación CEIm): "*Validación de una técnica innovadora por microsampling para el*	Colaboración Pharmaco-Toxicological Analysis Lab – Universidad Alma Mater de Bolonia. TFG 2023 Fernando *2 papers en redacción*

	análisis farmacocinético de medicamentos".	
Inclusión control coadyuvantes analgésicos	Proyecto Bencopi (Código: 2021-0458): "*Revisión del impacto funcional de la co-prescripción de anticolinérgicos y benzodiacepinas en pacientes con dolor crónicos tratados con opioides".* Proyecto Duloxetina (Código: ICI21/00006l): "*Eficacia de duloxetina perioperatoria en pacientes con alto riesgo de desarrollar dolor crónico post-quirúrgico tras la cirugía de hernia inguinal: ensayo multicéntrico, aleatorizado y controlado".*	Colaboración Servicio de Farmacia de Atención Primaria *1 paper en redacción* Colaboración Hospital del Mar de Barcelona

CCAA: Comunidades Autónomas; SEFF: Sociedad Española de Farmacogenética y Farmacogenómica; ISABIAL: Instituto de Investigación Sanitaria y Biomédica de Alicante; UMH: Universidad Miguel Hernández de Elche; UPV: Universidad Politécnica de Valencia; IIS La Fe: Instituto de Investigación Sanitaria de La Fe de Valencia; TFM: Trabajo de Fin de Master; QST: Quantitative Sensory Testing; UCLM: Universidad de Castila La Mancha.

7. Conclusiones

1- La deprescripción de opioides ambulatoria fue efectiva en un 49% de los casos TCOP a largo plazo, consiguiendo un aumento en el alivio del dolor y una disminución de EA, con impacto farmacogenético y diferencias por sexo.

2- En su conjunto, las mujeres con DCNO y TCOP mostraron más antecedentes de abusos de sustancias y un menor uso de tramadol, mientras que los hombres presentaron una mayor prescripción de fentanilo, junto con un patrón diferente de EA, que incluye una mayor notificación de RAM frente a las mujeres. Existen datos que podrían indicar un retraso en la derivación a las UDO de las mujeres, que debería analizarse junto con el género.

3- Los pacientes con fenotipos CYP2D6 extremos presentaron un patrón de deprescripción diferente. Por un lado, los PM obtuvieron una reducción significativamente mayor en la DDEM; por otro, los UM mostraron un mayor número de EA y SAO durante la deprescripción ambulatoria de opioides. El fenotipo CYP2D6 podría ser un marcador predictivo en la deprescripción de opioides ante casos TCOP.

4 – El modelo comprendió factores de riesgo de TCOP previamente descritos (edad joven, situación laboral pobre y alta DDEM) y proporcionó nueva información útil acerca de otros factores de riesgo (baja calidad de vida, alelo G del gen *OPRM1* y fenotipos extremos CYP2D6).

5 – El modelo de predicción desarrollado se ajustó y se validó prospectivamente con una precisión diagnóstica satisfactoria. Esta herramienta podría identificar a los pacientes de alto riesgo, lo que permitiría concentrar los recursos médicos en un número limitado de pacientes.

7. Conclusions

1- Ambulatory long-term opioid deprescription was effective in 49% of TCOP cases, achieving a greater pain relief and lower AEs, with a pharmacogenetic impact and sex-differences.

2- Globally, women with CNCP and OUD showed a higher history of substance use and lower use of tramadol, while men presented a greater prescription of fentanyl, along with a different pattern of AEs, including higher ADRs. There is some evidence that indicates a delay in referrals in women, which should be analysed together with gender.

3- Patients with extreme CYP2D6 phenotypes presented a different deprescribing pattern. On the one hand, PMs obtained a significantly higher reduction of MEDD; on the other hand, UMs showed a higher number of AEs and OWS during the opioid deprescription. The CYP2D6 phenotype could be a predictive marker for opioid deprescribing.

4 – The model comprised well-known risk factors related to OUD (young age, low work status and high MEDD) and provide new useful information about other risk factors (low quality of life, OPRM-G allele and CYP2D6 extreme phenotypes).

5 - The predictive model was adjusted and prospectively validated with satisfactory diagnostic accuracy. This tool could identify high-risk patients, allowing medical resources to be applied on a limited number of patients.

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9. ANEXOS

ANEXO I- Proyecto 1: APROBACIÓN ÉTICA (DESOPI LONG)

GENERALITAT VALENCIANA

ALACANT HOSPITAL GENERAL DEPARTAMENT DE SALUT

COMITÉ DE ÉTICA PARA LA INVESTIGACIÓN CON MEDICAMENTOS DEL DEPARTAMENTO DE SALUD DE ALICANTE – HOSPITAL GENERAL

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Teléfono: 965-913-952
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Ref. CEIm: PI2019/092 Ref. ISABIAL: 190255

INFORME DEL COMITE DE ETICA PARA LA INVESTIGACION CON MEDICAMENTOS

Reunidos los miembros del Comité de Ética para la Investigación con medicamentos del Departamento de Salud de Alicante – Hospital General, en su sesión del día 29 de enero de 2020 (Acta 2020-01), y una vez estudiada la documentación presentada por **Dra. Ana Peiró Peiró** del Servicio de Farmacología clínica del Hospital General Universitario de Alicante, tiene bien a informar que el proyecto de investigación titulado **"Desprescripción en pacientes con dependencia inducida a opioides: efectividad a largo plazo y validación de marcadores genéticos. Código DESOPI LONG. (versión 1.0 de 4 de marzo de 2019)** se ajusta a las normas deontológicas establecidas para tales casos.

Y para que conste a los efectos oportunos, firmo la presente en Alicante con fecha 29 de enero de 2020.

GENERALITAT VALENCIANA · DPTO. DE SALUD DE ALICANTE · COMITÉ DE ÉTICA PARA LA INVESTIGACIÓN CON MEDICAMENTOS · HOSPITAL GENERAL · Conselleria de Sanitat Universal i Salut Pública

Fdo. Dr. Luis Manuel Hernández Blasco
Secretario Técnico CEIm Departamento de Salud de Alicante – Hospital General

ANEXO II- Proyecto 2: APROBACIÓN ÉTICA (DESOPI CYP)

GENERALITAT VALENCIANA

ALACANT HOSPITAL GENERAL DEPARTAMENT DE SALUT

(Ref. CEIC PI2017/97)

INFORME DEL COMITE ETICO DE INVESTIGACION CLINICA

Reunidos los miembros del Comité Ético de Investigación Clínica del Hospital General Universitario de Alicante, en su sesión del día 20 de Diciembre de 2017, y una vez estudiada la documentación presentada por **D. Javier Muriel Serrano,** Investigador pre-doctoral del Grupo NED-Isabial del Hospital General Universitario de Alicante, tiene bien a informar que el proyecto de investigación titulado **"Farmacogenética y metabolismo de fármacos analgésicos en pacientes con dependencia inducida por opioides",** se ajusta a las normas deontológicas establecidas para tales casos.

Y para que conste a los efectos oportunos, firmo la presente en Alicante con fecha doce de Enero de dos mil dieciocho.

Fdo. Mayte Domenech Varón
Secretaria del CEIC

ANEXO III- Proyecto 3: APROBACIÓN ÉTICA (preDESOPI)

APROBACIÓN ÉTICA CEIM (PI2020/047, 2020)

GENERALITAT VALENCIANA

ALACANT HOSPITAL GENERAL
DEPARTAMENT DE SALUT

COMITÉ DE ÉTICA PARA LA INVESTIGACIÓN CON MEDICAMENTOS DEL DEPARTAMENTO DE SALUD DE ALICANTE - HOSPITAL GENERAL
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Ref. CEIm: PI2020-047 - Ref. ISABIAL: 200078

INFORME DEL COMITE DE ETICA PARA LA INVESTIGACION CON MEDICAMENTOS

Reunidos los miembros del Comité de Ética para la Investigación con medicamentos del Departamento de Salud de Alicante – Hospital General, en su sesión del día 29 de Abril de 2020 (Acta 2020-04), y una vez estudiada la documentación presentada por **D. Javier Muriel Serrano** del Servicio de Unidad del dolor del Hospital General Universitario de Alicante, tiene bien a informar que el proyecto de investigación titulado **"Desarrollo y validación de un modelo de predicción de dependencia a opioides de prescripción"**, se ajusta a las normas deontológicas establecidas para tales casos.

Y para que conste a los efectos oportunos, firmo la presente en Alicante con fecha 15 de Mayo de 2020.

GENERALITAT VALENCIANA • Conselleria de Sanitat Universal i Salut Pública • DPTO DE SALUD DE ALICANTE • COMITÉ DE ÉTICA PARA LA INVESTIGACIÓN CON MEDICAMENTOS HOSPITAL GENERAL

Fdo. Dr. Luis Manuel Hernández Blasco
Secretario Técnico CEIm Departamento de Salud de Alicante – Hospital General

INFORME OFICINA INVESTIGACIÓN RESPONSABLE (230315103209, 2022)

INFORME DE EVALUACIÓN DE INVESTIGACIÓN RESPONSABLE

Elche, a 15/03/2023

Director/a	Ana María Peiró Peiró
Codirectores/as	Ana María Peiró Peiró
Estudiante	Mónica Escorial García
Programa de doctorado	Bioingeniería
Título de la tesis doctoral	Desarrollo y validación de un modelo de predicción de dependencia a opioides de prescripción (Código: Pre-Desopi)
Tipo de actividad	Adherido a un proyecto autorizado
Evaluación Riesgos Laborales	**No procede**
Evaluación Ética	**No procede**
Código provisional	**230315103209**
Código de Investigación Responsable (COIR)	**ADH.BIO.APP.MEG.23**
Caducidad	**8 años***

***Importante: La caducidad de las autorizaciones de tesis, basadas en la adhesión a un proyecto de investigación, están condicionadas a la vigencia de la autorización de dicho proyecto en este sentido: todas las actividades de la tesis que tengan implicaciones ético-legales deberán realizarse mientras dicho proyecto esté vigente. Dicho de otro modo, sólo podrán realizarse actividades de carácter intelectual una vez el proyecto al que se adhiere haya caducado.**

Se considera que la presente actividad no supone riesgos laborales adicionales a los ya evaluados en el proyecto de investigación al que se adhiere. No obstante, es responsabilidad del tutor/a informar y/o formar al estudiante de los posibles riesgos laborales de la presente actividad.

La necesidad de evaluación ética del trabajo titulado: **Desarrollo y validación de un modelo de predicción de dependencia a**
opioides de prescripción (Código: Pre-Desopi) ha sido realizada en base a la información aportada en el formulario online: "Solicitud Código de Investigación Responsable (COIR)", habiéndose determinado que no requiere ninguna evaluación adicional. Es importante destacar que si la información aportada en dicho formulario no es correcta este informe no tiene validez.

Por todo lo anterior, se autoriza la realización de la presente actividad.

Atentamente,

Alberto Pastor Campos
Secretario del CEII
Vicerrectorado de Investigación

Domingo L. Orozco Beltrán
Presidente del CEII
Vicerrectorado de Investigación

ANEXO IV- Proyecto 4: APROBACIÓN ÉTICA (CYPSI)

COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS DEL DEPARTAMENTO HOSPITAL GENERAL UNIVERSITARIO DE ALICANTE
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Ref. CEIm: 2022-158 - Ref. ISABIAL: 2022-0278

DICTAMEN DE ESTUDIO EOm NO Prospectivo

Dr. Luis Manuel Hernández Blasco, Secretario del Comité Ético de Investigación con Medicamentos del Hospital General Universitario de Alicante.

CERTIFICA

Que este Comité ha evaluado la propuesta del promotor Mónica Escorial García *para el investigador principal Mónica Escorial García de* ISABIAL, para que se realice el estudio:

TÍTULO	Impacto farmacológico del fenotipo CYP2D6 y del sexo en la coprescripción de medicamentos psicótropos y analgésicos
PROMOTOR	Mónica Escorial García
CODIGO DEL PROTOCOLO	CYPSI
VERSION DEL PROTOCOLO	1
FECHA DEL PROTOCOLO	12 diciembre 2022
HOJA DE INFORMACION AL PACIENTE (Versión y fecha)	Aprobada Exención de HIP y CI

Y tomando en consideración las siguientes cuestiones:

-La pertinencia del estudio, teniendo en cuenta el conocimiento disponible, así como los requisitos del Real Decreto 957/2020, de 3 de Noviembre, por el que se regulan los estudios observacionales con medicamentos de uso humano y el Real Decreto 1344/2007, de 11 de octubre, por el que se regula la farmacovigilancia de medicamentos de uso humano.

-Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto, teniendo en cuenta los beneficios esperados.

-El seguro o la garantía financiera previstos son adecuados.

-El procedimiento para obtener el consentimiento informado, incluyendo la hoja de información para los sujetos versión de (día/mes/año), modificación nº ... versión (día/mes/año), y el plan de reclutamiento de sujetos previstos son adecuados, así como las compensaciones previstas para los sujetos por daños que pudieran derivarse de su participación en el ensayo.

-La capacidad del investigador y sus colaboradores son apropiados para llevar a cabo el estudio.

-Las instalaciones y medios disponibles son apropiados para llevar a cabo el estudio.

COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS DEL DEPARTAMENTO HOSPITAL GENERAL UNIVERSITARIO DE ALICANTE
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- y Miembro Lego:

- D. José Diego Espadas Ruiz, Miembro de la Asociación AFA (Asociación de Alzheimer de Alicante) Alicante.

Lo que firmo en Alicante

Firmado por Luis Manuel Hernandez Blasco - 21424371D el 22/12/2022 10:09:16

Fdo.: D. Luis Hernández Blasco

ANEXO V- Proyecto 5: APROBACIÓN ÉTICA (DEPOP)

REGISTRO CEIM (2022-003 Ref.: 2021-0509, DEPOP)

ISABIAL
INSTITUTO DE INVESTIGACIÓN SANITARIA Y BIOMÉDICA DE ALICANTE
De la investigación a la calidad asistencial

D. José Sánchez Payá, como Director Científico del Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL),

CERTIFICA que

El/la **Dr./Dra. *Ana Mª Peiró Peiró,*** ha presentado el proyecto de investigación titulado: ***"Interacción sexo/género en la funcionalidad de pacientes con dolor crónico y dependencia a opioides de prescripción" – 2021-0091,*** al Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), que toda la documentación aportada está siendo evaluada por los órganos que correspondan de este (Comisión de Investigación, CEIm, etc.) y que a la mayor brevedad posible se dispondrá de una resolución respecto a este.

Y para que conste, lo firmo en Alicante con fecha 23 de septiembre de 2021.

22116003P JOSE SANCHEZ (R: G42641308)

ISABIAL
INSTITUTO DE INVESTIGACIÓN SANITARIA Y BIOMÉDICA DE ALICANTE
CIF G42641308

ANEXO VII- GLOBAL PAIN STATE QUESTIONNAIRE (GPSq)

Nombre y apellidos: _____ Género:_____
Edad: _____ Peso (kg): _____ Fecha: ___/_____/_____

CUESTIONARIO DE ESTADO DE DOLOR

Global Pain State questionnaire (GPSq)

DOLOR	
Señale sobre la línea horizontal donde mejor se describa el **dolor** que siente ahora 0 ——— 10	MARQUE CON UNA CRUZ □ 4 - Extremadamente intenso □ 3 - Intenso □ 2 - Moderado □ 1 - Suave □ 0 - Ninguno

ALIVIO	
Señale sobre la línea horizontal donde mejor se describa el **alivio** que siente ahora 0 ——— 10	MARQUE CON UNA CRUZ □ 4 - Extremadamente aliviado □ 3 - Intenso □ 2 - Moderado □ 1 - Suave □ 0 - Ninguno

SÍNTOMAS DESDE LA ÚLTIMA CONSULTA			
□ Somnolencia	□ Impotencia sexual	□ Boca seca	□ Otros (indicar):
□ Mareos	□ Disminución deseo sexual	□ Edema	
□ Náuseas	□ Cambio de peso	□ Depresión	
□ Vómitos	□ Dolor de cabeza	□ Insomnio	
□ Estreñimiento	□ Enrojecimiento piel	□ Nerviosismo	
□ Picor	□ Piel seca	□ Falta de apetito	

SI ESTOS SÍNTOMAS HAN MOTIVADO		
	Por su DOLOR	Por OTRAS causas
Ir a urgencias	□ SÍ □ NO	□ SÍ □ NO
Ingreso en el hospital	□ SÍ □ NO	□ SÍ □ NO
Cambio de medicación	□ SÍ □ NO	□ SÍ □ NO

Nombre y apellidos: _____ Fecha: ___/_____/____

CUESTIONARIO DE ESTADO DE DOLOR

Global Pain State questionnaire (GPSq)

ESTADO DE SALUD	
La respuesta de cada apartado que mejor describa su estado de salud en el día de hoy:	Señale sobre la línea vertical donde mejor se describa su estado de salud hoy
Movilidad □ No tengo problemas para caminar □ Tengo algunos problemas para caminar □ Tengo que estar en la cama **Cuidado personal** □ No tengo problemas con el cuidado personal □ Tengo algunos problemas para lavarme o vestirme □ Soy incapaz de lavarme o vestirme **Actividades cotidianas** (p. ej. Trabajar, estudiar, hacer las tareas domesticas, actividades familiares o durante el tiempo libre) □ No tengo problemas para realizar mis actividades cotidianas □ Tengo algunos problemas para realizar mis actividades cotidianas □ Soy incapaz de realizar mis actividades cotidianas **Dolor/malestar** □ No tengo dolor ni malestar □ Tengo moderado dolor o malestar □ Tengo mucho dolor o malestar **Ansiedad/depresión** □ No estoy ansioso ni deprimido □ Estoy moderadamente ansioso o deprimido □ Estoy muy ansioso o deprimido **Comparado con mi estado general de salud durante los últimos 12 meses, mi estado de salud de hoy es:** □ Mejor □ Igual □ Peor	El mejor estado de salud imaginable 100 90 80 70 60 50 40 30 20 10 0 El peor estado de salud imaginable

OCUPACIÓN ACTUAL: □ Trabajador en activo □ Parado □ Jubilado □ Ama de casa

INGRESOS ECONÓMICOS: □ Menos de 500 € □ Entre 500-1000 € □ Más de 1000 €

Muchas gracias por completarla, dásela al personal facultativo

ANEXO VIII- COMPENDIO DE PUBLICACIONES Y PUBLICACIONES EN REVISIÓN

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Original research paper

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 phenotypes and MEDD were detected. p-value ≤ 0.050 was considered statistically significant. In multiple testing, the Bonferroni correction was adjusted. All statistical analyses were carried out using the system for statistical computation R (Version 3.2.0).

RESULTS AND DISCUSSION

Participants

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

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

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

Demographic, clinical and therapeutic outcomes

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

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

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

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

Therapeutic safety pattern

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

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

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

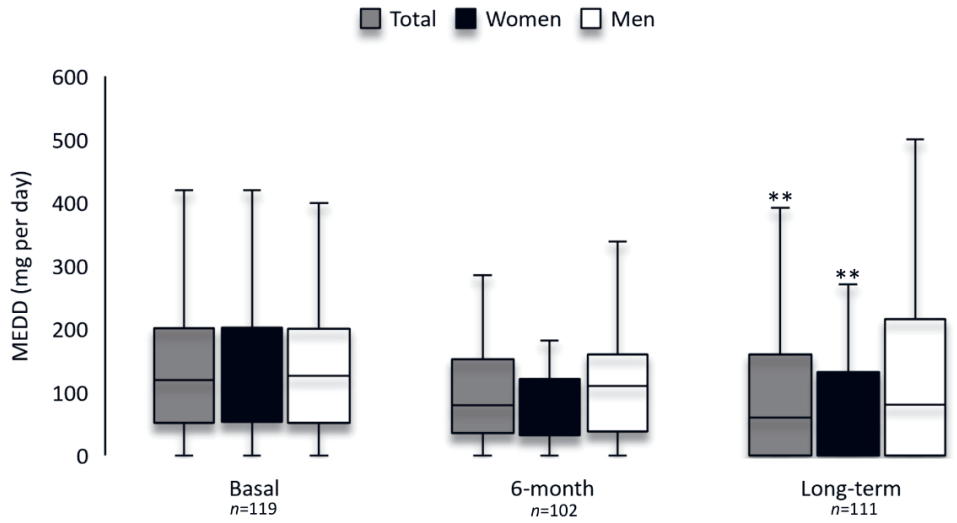

Fig. 2. Morphine equivalent daily dose [MEDD, mg per day), bars median (IQR)] per visit (basal, 6 months, long-term) and sex (all patients in grey, women in black, men in white colour). Statistically significant difference: $^{**}p < 0.001$ comparing basal, 6-month and long-term visits.

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).

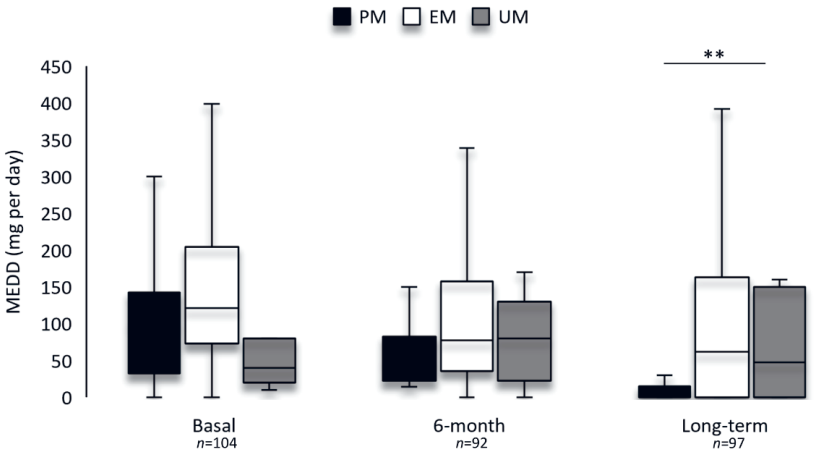

Fig. 3. Morphine equivalent daily dose [MEDD, bars median (IQR)] per visit and CYP2D6 phenotypes. Statistically significant difference: $^{**}p < 0.001$ comparing CYP2D6 phenotype.

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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Author's contributions. – Javier Muriel and Mónica Escorial contributed with the data collection, pharmacogenetics and statistical analysis and drafting of the manuscript. Jordi Barrachina and Cristian Carvajal contributed with the data collection and the pharmacogenetics analysis. Domingo Morales contributed with the statistical analysis. César Margarit contributed with the study design, data interpretation and drafting of the manuscript. Ana M. Peiró supervised and helped with all the parts. All authors have discussed the results and have commented on the manuscript.

Conflict of interest. – None.

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Impact of CYP2D6 genotype on opioid use disorder deprescription: an observational prospective study in chronic pain with sex-differences

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Introduction: Opioid deprescription is the process of supervised tapering and safe withdrawal when a potentially inappropriate use is detected. This represents a challenge in chronic non-cancer pain (CNCP) patients who may respond differently to the procedure. Our aim was to analyze the potential impact of CYP2D6 phenotypes and sex on the clinical and safety outcomes during an opioid use disorder (OUD) tapering process.

Methods: A prospective observational study was conducted on CNCP ambulatory OUD patients (cases, n = 138) who underwent a 6-month opioid dose reduction and discontinuation. Pain intensity, relief and quality of life (Visual analogue scale, VAS 0–100 mm), global activity (GAF, 0–100 scores), morphine equivalent daily doses (MEDD), analgesic drugs adverse events (AEs) and opioid withdrawal syndrome (OWS, 0–96 scores) were recorded at basal and final visits. Sex differences and CYP2D6 phenotypes (poor (PM), extensive (EM) and ultrarapid (UM) metabolizers based on CYP2D6*1, *2, *3, *4, *5, *6, *10, *17, *41, 2D6*5, 2D6 × N, 2D6*4 × 2 gene variants) were analyzed.

Results: Although CYP2D6-UM consumed three-times less basal MEDD [40 (20–123) mg/day, p = 0.04], they showed the highest number of AEs [7 (6–11), p = 0.02] and opioid withdrawal symptoms (46 ± 10 scores, p = 0.01) after deprescription. This was inversely correlated with their quality of life (r = –0.604, p < 0.001). Sex-differences were evidenced with a tendency to a lower analgesic tolerability in females and lower quality of life in men.

Discussion: These data support the potential benefits of CYP2D6-guided opioid deprescription, in patients with CNCP when OUD is detected. Further studies are required to understand a sex/gender interaction.

KEYWORDS

CYP2D6, sex-differences, opioid use disorder, deprescription, chronic pain, pharmacogenetics

1 Introduction

The current international analgesic landscape is characterized by a significant global increase in the use of prescription opioid (Upp and Waljee, 2020; Di Gaudio et al., 2021). In fact, 15.2% of the adult Spanish population admits having used opioid analgesics, at some point in their lives (Spanish Observatory on Drugs and Addictions OEDA, 2021), with observed differences in the use and the presence of any opioid use disorder (OUD) between sexes (McHugh et al., 2018). This problematic opioid use has resulted in formulation of practice-specific guidelines as a mechanism to curb current trend (National Academies of Sciences and and Medicine, 2017). In this context, research shows that patients in severe pain despite use of high-dose opioids may experience significant improvement in pain relief and functioning, when their opioid is tapered to a lower, safer dose (Kahan et al., 2011), improving adherence and reducing drug-seeking behaviors (Becker et al., 2018).

Current evidence suggests potential genetic factors that could be used to predict one's risk of opioid misuse or a problematic use (Singh et al., 2021), harmful (Muriel et al., 2019) or addictive potential (Linares et al., 2014). There is some evidence suggesting CYP2D6 enzyme, responsible for the metabolism of tramadol, codeine and oxycodone, may be more efficient at ultra-rapid metabolizer (UM) synthesizing endogenous opioids (Zahari and Ismail, 2014), experience quicker and higher systemic levels of the active metabolites and therefore, to require lower analgesic doses (Candiotti et al., 2009). However, UM subjects will be prone to higher mu-opioid-related toxicity and a higher risk of adverse events (AEs) (Lopes et al., 2020). In contrast, CYP2D6 poor metabolizers (PMs) would tend to have lower levels of the active metabolites (Haufroid and Hantson, 2015), which may result in reduced analgesic efficacy (Lötsch et al., 2004; Zahari and Ismail, 2014). This could have special impact for females who generally exhibit a lower opioid tolerability in comparison to males (Planelles et al., 2020), which can be turned into differences in opioid´s clearance (Anderson, 2008). Here, scarce data on the effect of sex on the CYP2D6 activity exist, and except for some data related to menstrual cycle influence (Tamminga et al., 1999), explicit recommendations derived through a validated process have not yet been formulated (He et al., 2015).

In this sense, there is increasing evidence in humans and laboratory animals for sex differences in processes of reward and addictive behavior, withdrawal, craving, and relapse due to psychostimulants and opioids (Becker and Chartoff, 2018). In fact, women are more likely to refer and be diagnosed with acute and chronic pain and to be prescribed these drugs in significantly greater numbers than men (Goetz et al., 2021). Although several reports have documented risk factors for opioid use following treatment discharge, yet few have assessed sex differences in long-term opioid use in chronic non-cancer pain (CNCP) management (Cragg et al., 2017; National Academies of Sciences and and Medicine, 2017; Davis et al., 2021).

The primary goal of the present study was to evaluate the impact of CYP2D6 phenotypes and sex influence on OUD deprescription ambulatory CNCP patients. As a primary hypothesis, it was considered that CYP2D6-UM metabolizers would show a different clinical outcome pattern when compared to the other groups, as would be also observed between sexes.

2 Materials and methods

2.1 Study design and selection of participants

This manuscript adheres to the applicable STROBE guidelines. This prospective observational pharmacogenetic study followed the current Declaration of Helsinki and European Medicines Agency Guidelines for Good Clinical Practice and was approved by the Ethics Committee of The General University Hospital of Alicante. Written informed consent was obtained from all participants prior to their inclusion in the study.

All the CNCP consecutive patients with confirmed OUD who underwent a 6-month opioid deprescription (cases, n = 138) by clinical practice at the Pain Unit (PU, General University Hospital of Alicante, Alicante, Spain) from May 2013 to May 2019 were included under the inclusion criteria prior to deprescription: 1) patients aged 18 years or older; 2) with CNCP and long-term opioid use (>6 months); 3) OUD diagnosis according to diagnostic DSM-5 criteria (American Psychiatric Association, 2013) as confirmed by a psychiatrist; and 4) informed consent granted. All the cases were followed-up prospectively for opioid dose reduction and discontinuation. A control group of 231 participants who had previously participated in observational studies from the same setting which were under opioids for chronic pain and no OUD suspicion (Margarit et al., 2019) was included to explore potential differences in terms of sociodemographic, clinical, pharmacological and CYP2D6 phenotypes in comparison to the cases.

2.2 Description procedure

The deprescription program was designed, established and executed according to national and international guidelines (Fernández-Miranda, 2007). OUD was defined as a problematic pattern of opioid use that causes significant impairment or distress according to the criteria in the DSM-5 (American Psychiatric Association, 2013). Here, a monitored opioid rotation to tramadol/buprenorphine together with the tapering process (progressive opioid withdrawal through a rotation with dose-reduction and control of any withdrawal symptoms) was conducted through consecutive clinical visits along 6 months (Muriel et al., 2019; Muriel et al., 2018). Depending on the patients' clinical status they were fully rotated to buprenorphine/tramadol from their basal prescriptions or stayed on their basal prescriptions but lower doses with tramadol as rescue medication. Basal MEDD was ideally 20%–30% reduced at each clinical visit (follow-up visits (1, 2 weeks, 1 and 3 months) and a final visit at 6 months) starting with the total withdrawal of quick-release opioids. Any precipitated opioid withdrawal symptom was carefully monitoring at each clinical visit. Effectiveness, as primary outcome, was considered when neither OUD nor any aberrant opioid use behavior was observed together with a morphine equivalent daily doses (MEDD) reduction minimum of 30% from basal levels - as a clinically meaningful reduction in dose (Perez et al., 2020) - or opioid discontinuation.

2.3 Clinical data collection

Demographic characteristics (age, sex) and clinical variables were collected using validated questionnaires and scales completed at each of the patients' visit. Pain intensity and relief were measured using the Visual Analogue Scale (VAS) (McCormack et al., 1988). Both VAS scales consist of a 100 mm horizontal line ranging from 0 (lowest) to 100 mm (highest). Similarly, VAS-EuroQol Scale (EQ) was used for quality of life assessment (EuroQol, 1990). Opiate Withdrawal Scale (OWS, 0–96 scores) is a questionnaire composed of 32 common symptoms in opioid withdrawal patients (Bradley et al., 1987) rated using scores of 0 (absent) to 3 (severe). The Global Assessment of Functioning (GAF, 0–100 scores) scale was used to assess patient's psychological, social, and work activity independently from the activity alterations caused by physical limitations. Higher score meaning a better level of activity and life (Jones et al., 1995).

2.4 Drug use and adverse events

Opioid and co-adjuvant medications were strictly prescribed by clinical judgement by the physician without any experimental decision. Use of opioid and non-opioid analgesics, NSAIDs, antidepressants (duloxetine), anxiolytics (benzodiazepines) and neuromodulators (pregabalin and gabapentin) was obtained from EHRs. MEDD were estimated using the available opioids equivalent doses (Pergolizzi et al., 2008) and classified as being low (MEDD<100 mg/day) or high (MEDD≥100 mg/day), given the potential increased dose-dependent side-effects (Chapman et al., 2010; Dunn et al., 2010). In addition, MEDD was calculated and analyzed separately in those patients with use of CYP2D6-mediated opioids (oxycodone, hydrocodone, tapentadol, codeine and tramadol).

To assess the tolerability, a questionnaire with the list of the most frequently occurring AEs (according to the opioids' summary of product characteristics, including "very common" and "common" listings) (Boiarkina and Potapov, 2014) and a blank field to add any other, was used to record patients' occurrence of AEs (Barrachina et al., 2021). In addition, all ADRs (Wisher, 2012) were collected and classified using the Medical Dictionary for Regulatory Activities (MedDRA, version 20.0) and the Preferred Terms.

2.5 *CYP2D6* genotyping

Approximately 2 mL of saliva was collected in PBS containing tubes. Genomic DNA was extracted using an E.N.Z.A. Forensic DNA Kit (Omega bio-tek), according to the manufacturer's instructions. Genetic analysis was based in usual PCR-methods following the instructions of the Consortium of Pharmacogenetics (CEIBA) and the pharmacogenomics iberoamerican network (RIBEF) for the analysis of samples. XL-polymerase chain (XL-PCR) analysis was used for identification of duplications and deletions (Dorado et al., 2005). These XL-PCR amplifications were carried out in a Mastercycler 384 (Eppendorf, AG, Hamburg, Germany). After the genotype was stablished, the different variants were converted to an Activity Score (AS), which indicated the enzyme's activity level (null, reduced, normal, increased) (Gaedigk et al., 2008). Presence of SNP *3, *4, *5 or *6 represents an AS of 0, which means a null enzyme activity. Variants *10, *17 and *41 are associated with an AS of 0.5 and *1, *2 and *35 with an AS of 1, representing reduced and normal enzyme activity levels, respectively. Presence of duplications *1xN, *2xN or *35xN suppose an increased enzyme activity level (AS = 2). According to previous classifications, if the AS resulting from the combination of both alleles was zero, the subject was considered as PM; if ranges from 0.5 to 2 as EM; and above 2 as UM (Naranjo et al., 2016).

2.6 Statistical analyses

Based on the observational prospective nature of the study and to the inclusion limited by the low frequency of patients with an OUD, a convenience sample was proposed. As an estimated prevalence of 3.2% of OUD was detected in our setting (Muriel et al., 2018). Out of an average of 915 patients/year who visit our PU, 30 potentially eligible subjects per year were expected. Due to the missing or refusing to participate (almost 20%), approximately 24 patients were expected annually. To complement the analysis, a control group from our previous study was proposed. As the condition/event (OUD) is infrequent (<10% prevalence), a complete series of controls was included to achieve a superior number of controls (ratio 2:1).

Data distribution was analyzed using Kolmogorov-Smirnov normality test. Quantitative parametric data are presented as mean (SD) while median (IQR) was used for non-parametric data and discrete variables. Categorical data are expressed by percentages. Comparisons of continuous data between two groups were conducted using a *t*-test for parametric data, meanwhile for non-parametric, U Mann-Whitney test was used. When analyzing categorical data between two groups, Fischer's exact test was performed. For the analyses of the three metabolic phenotypes, ANOVA test was performed for parametric continuous data and Kruskal-Wallis for non-parametric. In this case, Chi-square test was used for categorical analyses. *t*-test and/or U Mann-Whitney (for PM vs. EM/UM, EM vs. PM/UM and UM vs. PM/EM) were performed too. Gene by sex interaction was explored by invoking a regression model. All the obtained variables included a separate description and analysis by sex.

The Pearson correlation coefficient (r) and its 95% confidence intervals (CI) were calculated to analyze the correlation between opioid withdrawal and quality of life. Two groups (subjects included between 2013–2015 and 2016–2019) were compared to determine if deprescription outcomes changed over time. The MEDD difference between groups was expressed using the Hodges-Lehmann estimator shift with the 95% CI. In the assumption of missing completely at random, complete case (or available case) analysis was performed. A $p \leq 0.05$ was considered statistically significant. In all cases, multiple testing was adjusted using Bonferroni correction. All statistical analyses were carried out using R (3.2.0 version) software.

3 Results

A total of 138 patients (65% female) with an OUD were recruited and enrolled in the ambulatory opioid deprescription. Fifteen percent (n = 21) of the patients were lost to follow-up (n = 18 did not attend follow-up visits, n = 2 no biological

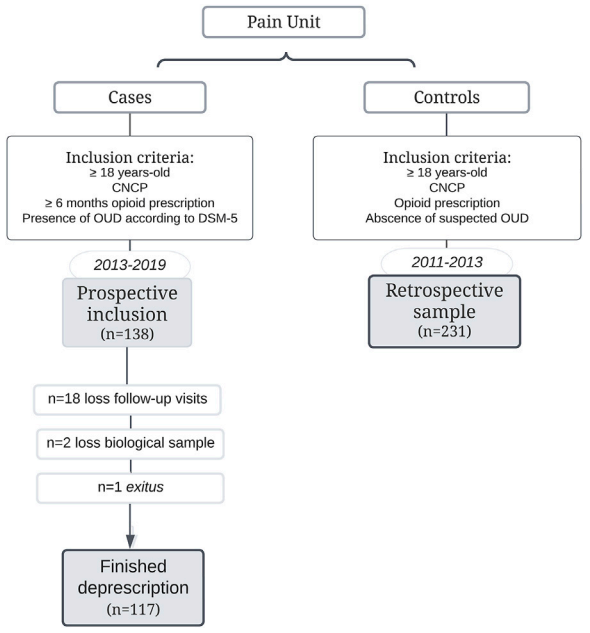

FIGURE 1
Flow Chart of patients with OUD (cases) along 6 years at Pain Unit and the control group included in the study.

samples, and $n = 1$ death due to intestinal pneumatosis) with 117 (66% female), of them completing the program. Data from a total of 231 subjects (64% female) were included as a control group (Figure 1).

At basal visit, cases showed a moderate basal chronic VAS pain intensity (60 (27) mm) and quality of life [45 (24) mm], with mild relief [37 (29) mm] and a mean of [32 (19) OWS scores]. No differences based on the inclusion period or between visits during deprescription were found in these outcomes. Here, patients evidenced "some mild symptoms or difficulties in social, interpersonal relationships or occupational functioning, but generally functioning pretty well" due GAF 71 (15) scores.

Cases were a mean of almost 10 years younger [54 (13) vs. 63 (14) years, $p < 0.001$], with a higher basal pain relief [37 (29) vs. 18 (13) mm, $p < 0.001$] probably due to a higher MEDD [120 (80–200) vs. 40 (0–82) mg/day, $p < 0.001$, difference Hodges-Lehmann: −80; 95% CI of the difference (−90 to −58)] at basal visit (Table 1).

3.1 Opioid deprescription

Clinical and pharmacological data of the total case population and classified by the CYP2D6 metabolic phenotypes is shown in Table 2.

Opioid deprescription was effective in 76% of the cases with a 42% of opioid discontinuation after tapering without differences due to sex. Total median MEDD was 67% significantly reduced with a final consumption of 40 (0–80) mg/day [$p < 0.001$, difference Hodges-Lehmann: −80 (−83 to −40)]. In consonance, the percentage of patients with a high MEDD level (>100 mg/day) decreased significantly from 55% to 27% ($p < 0.001$) without differences due to sex. Interestingly, cases included in later time period (2016–2019) showed a significant lower final MEDD [0 (0–80) mg/day] compared to those included in early time-period (2013–2015) [60 (0–160) mg/day, $p = 0.02$] (Supplementary Table S1).

3.2 *CYP2D6* phenotype

Metabolic CYP2D6 phenotypes were classified as 6% PM, 85% EM and 9% UM according to their genotype without differences in frequency between sexes (females 6% PM, 84% EM and 78% UM) or compared with the control group (5% PM, 89% EM and 6% UM). Allelic frequencies of *CYP2D6* variants can be seen in Supplementary Table S2.

Here, UM phenotypes showed a significantly lower three-times MEDD compared to PM-EMs [40 (20–123) vs. 123 (80–226), $p = 0.04$, difference Hodges-Lehmann: −63 (−140 to 0)]. However, when only CYP2D6 metabolism mediated opioids were selected,

TABLE 1 Sociodemographic, clinical, pharmacological and tolerability variables in cases (basal visit) and controls.

Basal visit	Cases ($n = 138$)	Controls ($n = 231$)	p-value[†]
Sex (female, %)	65	64	1.00
Age (years, mean (SD))	54 (13)	**63 (14)****	**<0.001**
Pain Intensity (VAS, 0–100 mm, mean (SD))	60 (27)	56 (31)	0.09
Pain relief (VAS, 0–100 mm, mean (SD))	**37 (29)****	18 (13)	**<0.001**
Quality of life (EQ, 0–100 mm, mean (SD))	45 (24)	45 (14)	1.00
Total MEDD (mg/day, median (IQR))	**120 (80–200)****	40 (0–82)	**<0.001**
AEs (median (IQR))	**5 (2–8)***	3 (1–6)	**0.03**
ADRs (%)	13	21	0.07

[†]Cases vs. controls comparisons using using *t*-test and U Mann-Whitney test for continuous parametric and non-parametric data, respectively, and Fisher's exact test for categorical data (significant $p < 0.05$ in bold).
*$p < 0.05$, **$p < 0.01$ (highest value in bold). VAS, visual analogue scale; EQ, VAS, EuroQol Scale (0–100 mm); AEs, adverse events; ADRs, adverse drug reactions; IQR, interquartile range, expressed in parenthesis as P25 and P75.

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TABLE 2 Demographic and pharmacological variables, in total population and classified by *CYP2D6* metabolic phenotype.

Variables		Cases (basal, *n* = 138; final, *n* = 117)	*CYP2D6* phenotype			*p*-value[†]
			PM (*n* = 7, 6%)	EM (*n* = 98, 85%)	UM (*n* = 10, 9%)	
Age [years, mean (SD)]		54 (13)	47 (12)	54 (13)	59 (14)	0.17
Sex (female, %)		65	71	65	80	0.61
Deprescription Responder (%)		76	80	76	89	0.66
Final opioid use (%)		58	80	55	56	0.55
Total MEDD [mg/day, median (IQR)]	*Basal*	120 (80–200)	120 (60–233)	123 (80–229)	**40 (20–123)**[+]	0.11
	Final	**40 (0–120)***	40 (7–65)	**40 (0–120)***	80 (0–150)	0.92
CYP2D6 opioid mediated MEDD [mg/day, median (IQR)]	*Basal*	40 (6–100)	40 (6–100)	40 (6–100)	40 (6–100)	0.81
	Final	**20 (0–43)****	20 (0–43)	**20 (0–43)****	20 (0–43)	0.64
High MEDD (>100 mg/day) (%)	*Basal*	55	60	59	22	0.10
	Final	**27** **	0	**30****	33	0.33
Pain Intensity [VAS, 0–100 mm, mean (SD)]	*Basal*	60 (27)	63 (22)	61 (27)	62 (29)	0.96
	Final	59 (27)	47 (6)	58 (29)	62 (21)	0.44
Pain Relief [VAS, 0–100 mm, mean (SD)]	*Basal*	37 (29)	28 (31)	36 (30)	42 (31)	0.62
	Final	40 (28)	57 (21)	41 (30)	39 (22)	0.53
Quality of life [EQ, 0–100 mm, mean (SD)]	*Basal*	45 (24)	38 (26)	46 (25)	46 (21)	0.73
	Final	43 (22)	52 (8)	43 (23)	36 (12)	0.46
Opioid Withdrawal [OWS, 0–96 score, mean (SD)]	*Basal*	32 (19)	35 (25)	32 (18)	33 (29)	0.91
	Final	32 (20)	10 (0)	30 (20)	**46 (10)**[+]	**0.03**
Global Functionality [GAF, 0–100 score, mean (SD)]	*Basal*	71 (15)	74 (17)	70 (14)	80 (21)	0.48
	Final	69 (16)	90 (0)	69 (16)	69 (13)	0.40
Use of non-opioid adjuvants (%)						
Neuromodulators	*Basal*	48	50	52	**0**[+]	0.05
	Final	49	40	49	**11**[+]	0.09
Duloxetine	*Basal*	18	33	22	17	0.53
	Final	23	20	25	11	0.91
NSAIDs	*Basal*	8	0	7	0	0.63
	Final	5	0	4	0	0.52
Simple analgesics	*Basal*	25	17	27	33	0.80
	Final	13	40	12	0	0.09
Benzodiazepines	*Basal*	36	17	40	33	0.52
	Final	37	20	38	22	0.85

[†]Comparisons between PM, vs. EM, vs. UM, were performed using ANOVA, or Kruskal-Wallis test for continuous parametric and non-parametric data, respectively and Chi-square test for categorical data.

+*$p < 0.05$, **$p < 0.01$ basal vs. final (lowest value in bold) using *t*-test or U Mann-Whitney test for parametric and non-parametric data, respectively$p < 0.05$ UM vs. PM/EM (UM, value in bold and shaded in grey) using *t*-test or Fisher's exact test for continuous or categorical data, respectively. PM, poor metabolizer; EM, extensive metabolizer; UM, ultrarapid metabolizer; MEDD, morphine equivalent daily dose; CYP-Opioids, Opioids subject to metabolism by CYP2D6; VAS, visual analogue scale; EQ, VAS, EuroQol Scale (0–100 mm); OWS, opiate withdrawal scale; GAF, global assessment of functioning; IQR, interquartile range, expressed in parenthesis as P25 and P75.

no differences between CYP2D6 phenotypes and consumed MEDD were observed. What's more, CYP2D6-UMs presented a lower rate of neuromodulators use in comparison to the other phenotypes in both basal and final visits (0% vs. 51%, $p = 0.03$ and 11% vs. 49%, $p < 0.04$, respectively) with no differences between sex or time period.

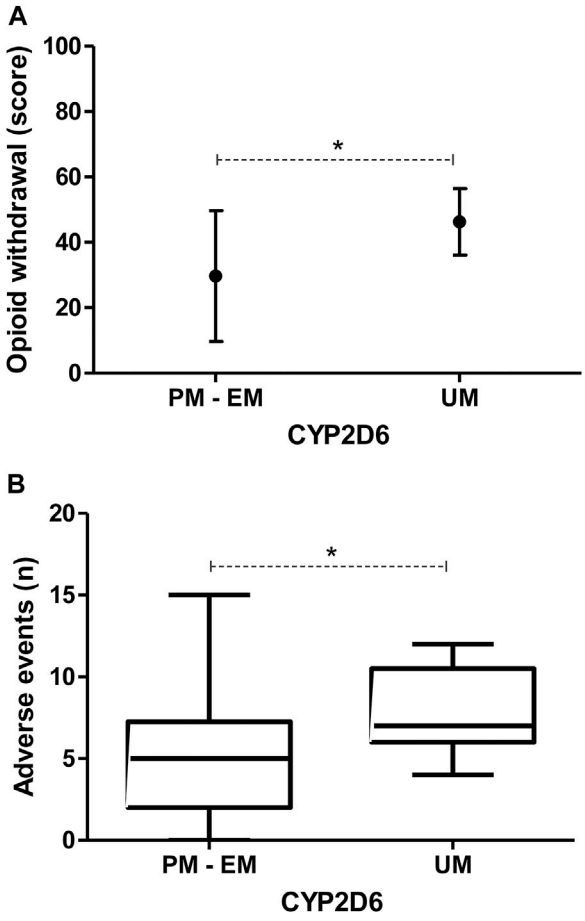

FIGURE 2
Final **(A)** opioid withdrawal scores (mean ± SD) and **(B)** total number of adverse events (boxplots) by *CYP2D6* metabolizer phenotype (PM, Poor Metabolizer; EM, Extensive Metabolizer; UM, Ultrarapid Metabolizer), showing a significant increase of both variables in UM. *p*-values <0.050 are represented with an asterisk.

3.3 Opioid deprescription outcomes and *CYP2D6* phenotype

At final visit, even though a significant reduction in MEDD and opioid use was reached, most of the clinical outcomes remained stable without any significant changed after opioid deprescription or cessation. Only men showed a non-significant reduction of quality of life [basal vs. final, 49 (24) vs. 38 (23) mm, $p = 0.05$] while women remained stable [43 (24) vs. 46 (21) mm, $p = 0.43$].

Related to CYP2D6, UMs subjects (Figure 2A) showed a 3-4-fold increase in opioid withdrawal (46 (10) in comparison to the other phenotypes [30 (20) OWS scores, $p = 0.01$] with a significant inverse correlation with levels of quality of life, both in males [$r = -0.572$ (−0.797 to −0.209), $p = 0.01$] and females [$r = -0.700$ (−0.841 to −0.470), $p < 0.001$] (Supplementary Figure S1) at final visit. What´s more, PMs final functionality clearly improves to a mean of 90 GAF scores, which means "absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities. socially effective, generally satisfied with life, no more than everyday problems or concerns." Whilst, UM decrease to 69 GAF scores, which means "some mild symptoms or difficulty in social, occupational, interpersonal relationships."

3.4 Adverse events

A median of 5 (2–8) AEs per patient were reported in cases, being the most prevalent dry mouth, sleep disturbance, constipation and nervousness (present in >40% of the patients), while controls showed a lower frequency of AEs [3 (1–6) AEs/patient, $p = 0.01$] (Table 1). Cases included in 2016–2019 showed a significant lower frequency of AEs [6 (4–9) vs. 2 (0–5), $p < 0.001$] compared to those included earlier (2013–2015) (Supplementary Table S1). Furthermore, a total of 13% of the cases presented some suspected ADR (ratio 60 AEs: 1 ADR) during the deprescription, mainly psychiatric or reproductive system's disorders.

Data related to AEs by CYP2D6 metabolic phenotype are shown in Table 3. Here, UMs showed a significantly higher mean of 7 (6–11) AEs/patient in comparison to the others phenotypes [5 (2–7) AEs/patient, $p = 0.02$], with higher frequencies of headache (100% vs. 33%, $p = 0.01$), edema (50% vs. 9%, $p = 0.02$), dry mouth (100% vs. 53%, $p = 0.03$) and nervousness (86% vs. 38%, $p = 0.04$) (Figure 2B and Supplementary Figure S2A). In accordance, UMs showed higher gastrointestinal (PM: 0 vs. EM: 71 vs. UM: 100, $p = 0.01$) and general (0% vs. 9% vs. 50%, $p = 0.01$) systems' disorders. No gene-sex interactions by regression model were found in those variables where CYP2D6 metabolic phenotypes showed differences (data not shown).

Related to sex, women reported a higher frequency of edema (15% vs. 0%, $p = 0.05$), dry mouth (63% vs. 33%, $p = 0.02$) and nervousness (50% vs. 22%, $p = 0.029$). Meanwhile, men retained sexual impotence issues at a significantly higher rate than females (25% vs. 4%, $p = 0.01$) mostly due to erectile dysfunction (Supplementary Figure S2B). What´s more, ADRs notified were three times higher in men than in women (23% vs. 7%, $p = 0.02$).

4 Discussion

Ambulatory opioid deprescription was effective in 76% of participants, where 42% ceased their opioid use. Here, CYP2D6-UMs showed the worst tolerability and high quality of life impact. Different frequencies of adverse events between sexes were reported that together with age and opioid dose could contribute to opioid dependence vulnerability.

This article also identifies priorities for monitoring younger, higher MEDD consumers with low tolerability CNCP patients who showed any misuse behavior. Current recommendations warn about a significant increase in OUD risk when the MEDD exceeds 90 mg/day (Busse et al., 2017; Webster, 2017). In our cases, a younger age and a higher median MEDD were found to be potential risk factors. Once OUD is detected, individualized decreasing dose regimen and/or opioid discontinuing is proposed based on clinical guidelines, which prevents the onset of withdrawal signs and symptoms (Nafziger and Barkin, 2018), as

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TABLE 3 Adverse events frequency at basal and final visit and analysis by metabolic phenotype.

Adverse events (%)	Visit	*CYP2D6* phenotype			*p*-value[†]
		PM (*n* = 7, 6%)	EM (*n* = 98, 85%)	UM (*n* = 10, 9%)	
Total (Median (IQR))	*Basal*	4 (2–10)	6 (3–8)	7 (3–14)	0.57
	Final	2 (0–3)	5 (2–8)	**7 (6–11)**[+]	**0.02**
Dry mouth	*Basal*	40	57	71	0.55
	Final	0	55	**100**[+]	**0.01**
Sleep disturbing	*Basal*	40	52	71	0.52
	Final	33	55	71	0.52
Constipation	*Basal*	40	45	57	0.81
	Final	0	48	43	0.26
Nervousness	*Basal*	40	42	57	0.73
	Final	0	40	**86**	**0.02**
Dizziness	*Basal*	40	**43**[*]	43	0.99
	Final	0	23	43	0.32
Headache	*Basal*	60	26	57	0.09
	Final	33	33	**100**[+]	**0.01**
Depression	*Basal*	40	34	43	0.88
	Final	0	39	75	0.05
Drowsiness	*Basal*	40	31	29	0.91
	Final	33	34	57	0.49
Weight change	*Basal*	0	35	43	0.24
	Final	0	28	17	0.49
Dry skin	*Basal*	20	31	43	0.70
	Final	0	38	67	0.14
Nausea	*Basal*	40	26	14	0.60
	Final	0	18	29	0.57
Itchy	*Basal*	40	25	43	0.49
	Final	0	27	43	0.37
Lack of appetite	*Basal*	20	28	43	0.65
	Final	0	23	57	0.09
Loss of libido	*Basal*	20	28	29	0.92
	Final	33	30	14	0.68
Vomiting	*Basal*	0	9	14	0.70
	Final	0	8	0	0.69
Edema	*Basal*	0	11	14	0.70
	Final	0	9	**50**	**0.01**
Skin redness	*Basal*	20	8	14	0.58
	Final	0	9	33	0.16

(Continued on following page)

TABLE 3 (*Continued*) Adverse events frequency at basal and final visit and analysis by metabolic phenotype.

Adverse events (%)	Visit	*CYP2D6* phenotype			*p*-value[†]
		PM (*n* = 7, 6%)	EM (*n* = 98, 85%)	UM (*n* = 10, 9%)	
Sexual dysfunction	*Basal*	0	9	0	0.54
	Final	0	14	0	0.49

[†]Comparisons between PM, vs. EM, vs. UM, for each visit were performed using ANOVA, or Kruskal-Wallis test for parametric and non-parametric data, respectively (significant $p < 0.05$ and highest value in bold). Multiple testing was adjusted with Bonferroni Correction where a *p*-value<0.017 was significant (+ highest value in bold and shaded in grey).
*$p < 0.05$ in basal vs. final (highest value in bold) using Fisher's exact test. PM, poor metabolizer; EM, extensive metabolizer; UM, Ultrarapid Metabolizer. IQR, interquartile range, expressed in parenthesis as P25 and P75.

happened in our case. Additionally, our data demonstrates that UM phenotypes showed 3–4 times increased opioid withdrawal and higher AEs numbers that could be crucial at an early OUD stage (Planelles et al., 2019) or increasing the risk of life-threatening reactions compared to regular metabolizers (Haufroid and Hantson, 2015). In our setting, 42% completed the program without opioid prescription. Here, adherence monitored by qualitative urine drug testing and/or gas chromatography mass spectrometry as confirmatory quantitative testing could be considered (Nafziger and Barkin, 2018).

The study provides clear directions that would lead to changes in clinical practice. As a primary hypothesis, it was considered that CYP2D6-UM phenotypes patients with an OUD would show a different clinical outcome pattern when deprescribing, mainly due to a worse safety profile. The potential benefits of using CYP2D6 phenotype could be especially relevant in southern European and Northern African populations that have higher proportions of UM (Kirchheiner et al., 2008). In these situations, when PM or UM are detected, it is important to consider using different analgesic drugs, such as those which are metabolized through a phase II metabolic pathway, in order to avoid a possible therapeutic failure. Here, oxymorphone immediate- and/or sustained-release formulations could be considered in countries where they are available. For its part, tapentadol, while being residually metabolized to inactive hydroxytapentadol (2%) by CYP2D6, it is largely glucoronidated via phase II and interindividual CYP2D6-related variability in the analgesic response is not expected (Barbosa et al., 2016), which makes tapentadol an alternative to consider.

This study aims to demonstrate the clinical interest of genotyping when deprescribing in order to identify patients at risk of insufficient analgesia or adverse events. In this way, there is also a need to carry out studies that analyze the cost-effectiveness of genetic testing when genotyping is included in these procedures. Along with this, it is important the need to develop clinical guidelines as a vehicle to assist the providers of opioids, in order to detect a potential issue not only with *CYP2D6,* but also with other P450 enzymes (*1A2, 2C9, 2C19* or *B6*).

Also, the need to implement pain research with a sex perspective is necessary to understand interindividual variability in terms of safety. Still, the remarkable female predominance in our study merits further attention. Nearly two thirds of our patients were adult women, given that female predominance in our CNCP population has been previously highlighted (Planelles et al., 2020). Furthermore, data showed that females communicated more AEs related to nervous, gastrointestinal and general systems, and less related to the sexual sphere in comparison to men, being third-less frequent ADRs in females (Muriel et al., 2019). Even more, surprisingly, men expressed a lower quality of life after opioid deprescription, while those of the women remained stable after deprescription. These different trends of impact related to the complex interdependence between biological sex and gender need to be elucidated (Becker and Chartoff, 2018; Rogers et al., 2020) because other factors (stress, depression, anxiety, responses to pain related to avoidance, coping) can have a greater impact on disability and quality of life, than on pain, *per se* (Sinha, 2008; Goodyear et al., 2018).

Some limitations should be taken under consideration. First, a convenience sample of patients attending a single pain clinic was established, along with this, a power analysis was not performed in order to know the best scenario to detect differences between groups. Furthermore, the total number of extreme phenotype subjects studied was relatively small. All this can compromise the power of statistical analyses, which may have made it difficult to detect significant differences between groups. Second, an 80% of UM were females, it would be difficult to assess the effect of CYP2D6 on the observed clinical outcome. Even more, drug inhibition or induction effects on CYP2D6 should be deeply analyzed (Kosten and Baxter, 2019), because it can condition the level of MEDD reduction (Smith et al., 2019). Furthermore, pharmacological data was obtained from EHRs and potential mismatches between the patients' intake and prescribed doses could exist. Other drugs or interventions less commonly used in our setting such as tricyclic antidepressant, cannabinoid or nerves block should be explored in further analyses. Third, with basal and final visit data available, it is preferable to analyze the repeatedly measured data together instead of separate statistical tests, but the low frequency of extreme phenotype subjects limited its execution. Finally, since the inclusion period was long and substantial changes could have occurred, such as increased physician experience in deprescribing and/or new indications for available drugs, among others, subjects included in 2013–2015 and those in 2016–2019 were compared to determine if deprescription outcomes changed over time. Here, statistical significance was not reach for deprescription response, but lower MEDD (51% of the subjects ended with no opioids) combined with a welcome lower frequency of AEs were observed while clinical variables remained stable, strongly suggesting an improvement in the deprescription procedure over time.

In conclusion, CYP2D6 metabolizer phenotypes may contribute to differential and improved opioid deprescription in CNCP. Sex

may play a relevant role in the tolerability when deprescribing. Further studies considering these potential genetics, as well as sex/gender differences could help to understand the interindividual variability in real-world patients.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of The General University Hospital of Alicante. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JM, JB, CM, and AP conceived and designed the study. JM, JB, GD, CC, and PB conducted most of the experiments. JM, JB, and ME carried out data analysis and wrote the manuscript. GD and CC participated in collecting data and helped to draft the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1200430/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Opioid withdrawal and quality of life inverse correlation after deprescription programme in OUD males and females.

SUPPLEMENTARY FIGURE S2
Percentage of Adverse Events at final visit classified by: **(A)** CYP2D6 metabolic phenotype (PM, Poor Metabolizer; EM, Extensive Metabolizer; UM, Ultrarapid Metabolizer); **(B)** Sex-differences (F, female, M, male). *p*-values <0.050 are represented with an asterisk.

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Article

Sex-Differences in Pain and Opioid Use Disorder Management: A Cross-Sectional Real-World Study

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Abstract: (1) Background: It is essential to focus attention on sex-specific factors which are clinically relevant in pain management, especially with regards to opioid use disorder (OUD) risk. The aim of this study was to explore potential sex-differences in chronic non-cancer pain (CNCP) outpatients. (2) Methods: An observational cross-sectional study was conducted under CNCP outpatients with long-term prescribed opioids (n = 806), wherein 137 patients had an OUD diagnosis (cases, 64% females) and 669 did not (controls, 66% females). Socio-demographic, clinical, and pharmacological outcomes were analyzed. (3) Results: Female controls presented an older age and less intensive pain therapy but higher psychotropic prescriptions and emergency department visits compared to male controls. Meanwhile, cases demonstrated a younger age, higher work disability, double morphine equivalent daily dose, and benzodiazepine use compared with controls. Here, female cases showed an 8% greater substance use disorder (OR 2.04 [1.11–3.76]) and 24% lower tramadol use, while male cases presented a 22% higher fentanyl use (OR 2.97 [1.52–5.81]) and reported the highest number of adverse drug reactions (24%, OR 2.40 [1.12–5.16]) compared with controls. (4) Conclusions: An OUD individual risk profile was evidenced with sex-differences to take into consideration to design equal prevention programs.

Keywords: opioid use disorder; sex-differences; chronic non-cancer pain; gender disparities; pain management; prevention programs

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1. Introduction

Chronic pain is one of the leading causes of medical consultation among adults and the main cause of abandonment of their daily activity [1]. It is estimated that 19% of Europeans suffer from chronic pain [2], resulting in important emotional, social, and economic consequences for the patient and his/her environment. Likewise, it is a major health problem associated with great costs and consumption of health resources (around 2.5% of the Spanish GDP) [3]. Normally, it is accompanied by a wide range of comorbidities and risk factors for other adverse health outcomes [4]. It has been demonstrated that women are more vulnerable for developing and maintaining musculoskeletal pain than men [5,6]. Findings from the literature suggest that women are more likely to be prescribed opioids for non-medical use [7], often with higher emotional and affective distress [8] compared with men. As opioid prescription is the usual therapy for CNCP, the question can be raised: Are females at a different risk for developing an opioid use disorder (OUD) than men?

Whilst it is important to clearly distinguish between sex and gender, we also need to understand the mechanisms and pathways underlying the trends we observe, as well as how sex and gender intersect with other factors such as age, income, social status, education, employment, genetics, or personal health practice, and contribute to our health and overall health outcome [9]. There is limited information on sex-differences in OUD risk factors. In general, a young age, past or current substance use, untreated psychiatric disorders, preadolescent sexual abuse, and social or family environments that encourage misuse constitute some of the OUD risk factors previously described [10–12]. Nevertheless, the limited presence of women in clinical trials and the lack of stratification by sex -mostly restricted to binary comparisons lacking data on gender dynamics raises questions related to sex-differences [13,14]. In this regard, our aim was to identify potential sex-specific risks and needs in CNCP patients using long-term prescribed opioids. The exploratory nature of this study would help to understand sex-differences in OUD risk for a future gender perspective analysis and allow for more equal clinical assessment and treatments.

2. Materials and Methods

2.1. Study Design

A cross-sectional study was conducted under CNCP outpatients with long-term prescribed opioids (≥6 months) from September 2020 to September 2021 at the Pain Unit (PU) of the Alicante General Hospital. The study is under the umbrella of a master protocol approved by the Ethics Committee of Alicante General Hospital (PI2020-047).

2.2. Participants

A total of 137 patients with OUD (cases) were included from an opioid tapering procedure routinely developed at PU [15] under the following inclusion criteria: adults (>18 years old) with CNCP under long-term prescribed opioids (≥6 months) and a clinical diagnosis of OUD Controls data (n = 669) were obtained from two concomitant observational studies [16,17] with same inclusion criteria except OUD diagnosis. All variables were collected from their original database and, if needed, they were completed using Electronic Health Records (EHRs), which allows for reviewing medical diagnoses, outcomes, and medication use.

2.3. Measures

OUD was diagnosed by a psychiatric expert in pain according to DSM-5 [18] as part of an established opioid tapering procedure [15]. The patient had to meet at least two of the criteria specified in the manual to consider he/she had an OUD.

The independent variable for all of the analysis was the sex of the patient (female/male).

Other socio-demographic characteristics such as age, employment status (active, retired, work disability, unemployed or homemaker) and income (low income as less than €500, middle income as between €500 and 1000, and upper income as more than €1000) were also registered.

A Global Pain State questionnaire [18] measuring, qualitatively, pain, relief, and quality of life was collected at the time of the original interview. Pain intensity and relief were measured using the Visual Analogue Scale (VAS) [19]. Both consist of a horizontal line ranging from 0 (lowest) to 100 mm (highest), where the patient points on the line to the intensity of pain or relief that he/she feels, respectively. Quality of life was evaluated through the EuroQol-5D scale that consists of a VAS (vertical line from 0 (the worst imaginable health status) to 100 mm (the best imaginable) where the patient indicates his/her actual health status. To collect patients' reports of adverse events (AEs), the most frequent adverse drug reactions (ADRs, selected according to opioids Summary of Product Characteristics frequency as "very common" and "common") [20], and any other AEs presented, were collected as present/absent. They consisted of the following: sleepiness, dizziness, nausea, vomiting, constipation, itchiness, sexual dysfunction, loss of libido, weight change, headache, skin redness, dry skin, dry mouth, edema, depression, sleep

disturbance, nervousness and loss of appetite. In addition, patients were asked about any depression or anxiety symptoms they had. Likewise, all ADRs related to the pain treatment were registered [21]. The presence of history of prior substance use disorder (including tobacco, alcohol and illicit drugs) were registered through the review of medical diagnoses, narratives or any visit to the Addictive Behaviour Unit.

The use (yes/no) of simple analgesics (i.e., paracetamol and metamizole), non-steroidal anti-inflammatory drugs (NSAIDs), and opioids use (i.e., tramadol, codeine, fentanyl, oxycodone, tapentadol, buprenorphine, morphine, hydromorphone and methadone), along with immediate release opioids prescription were registered. In different combinations of opioids, oral morphine equivalent daily dose (MEDD) was estimated using available references [22]. The prescription of antidepressants (i.e., amitriptyline, fluoxetine, escitalopram, and duloxetine), benzodiazepines, and neuromodulators (pregabalin and gabapentin) was also collected.

2.4. Statistical Analysis

Convenience sampling was considered based on the prevalence of OUD diagnosis in our regular clinical routine at PU. Data distribution was analysed with the Kolmogorov-Smirnov test using the Lilliefors correction method. Quantitative parametric data are presented as mean (standard deviation (SD)) whilst the median (interquartile range (IQR)) was used for non-parametric data. Categorical data are expressed as percentages (%). Comparisons of socio-demographic, clinical, pharmacological and safety data were evaluated depending upon their distribution. Bivariate odds ratio (OR) and 95% confidence intervals (CIs) were also calculated. Collinearity between categorical variables was tested depending upon their distribution. Here, results were analyzed by groups (men or women, cases vs. controls) or by sex (i.e., control or cases, men vs. women). A p-value < 0.05 was considered statistically significant. Analyses were carried out using R (Version 3.2.0; the GNU project, Cambridge, MA, USA) and GraphPad Prism (Version 5.0, Dotmatics, Boston, MA, USA).

3. Results

A total of 1452 potential control candidates were explored, whereof 783 were excluded due to patients being duplicated between the studies or not meeting the inclusion criteria. All participants included (Figure 1) were referred to our PU for regular pain management mostly due to somatic pain (85%). Non-specific low back pain was the most common type (associated with radiculopathy, spinal stenosis, or another specific spinal cause), followed by knee pain and other musculoskeletal pain (hip pain or due to other cervical joint dysfunctions).

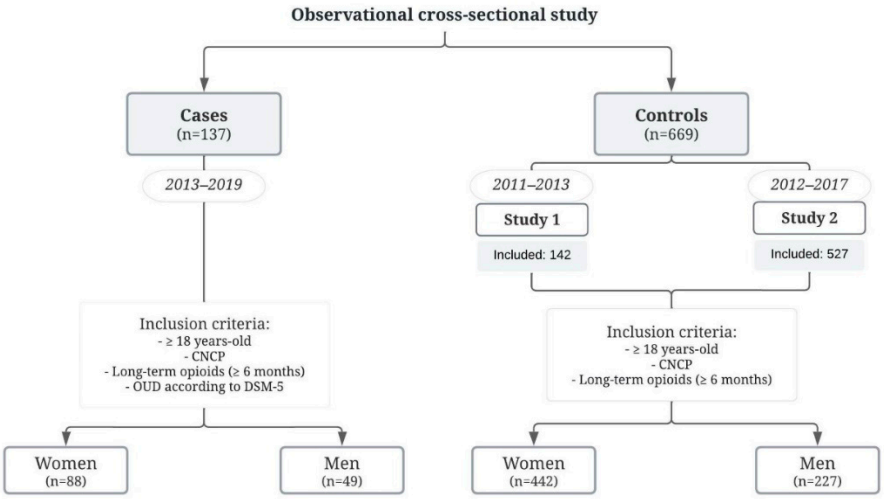
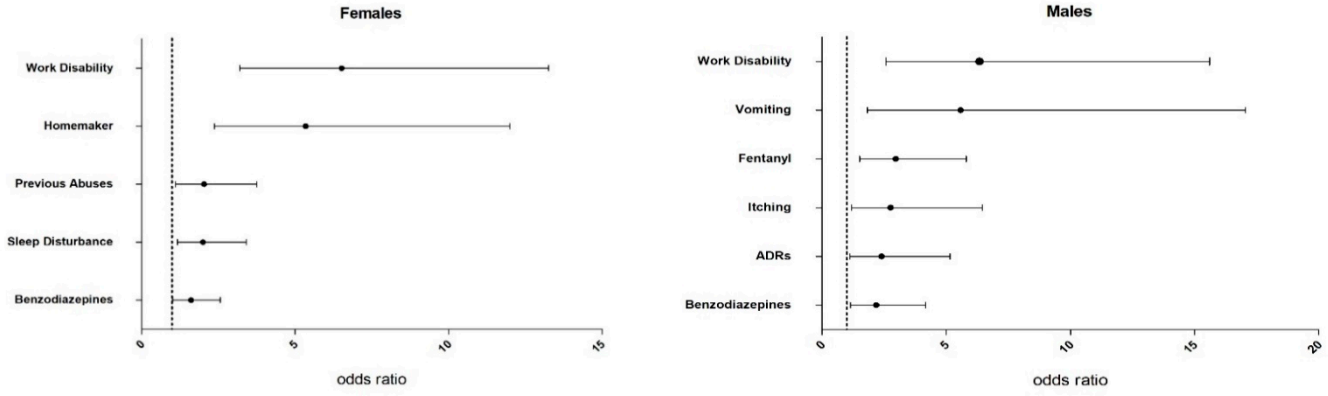


Figure 1. Flow chart of the patient selection for the study. CNCP, chronic non-cancer pain; OUD, opioid use disorder.

3.1. Socio-Demographic and Clinical Outcomes

A summary of the characteristics of the participants and clinical variables are shown in Tables 1 and 2. Meanwhile, Figure 2 shows the odds ratios and 95% confidence intervals for risk factors in females (Figure 2a) and males (Figure 2b).

Controls were older than cases, even more in females (66 (56–75) years old) who were the oldest group (vs. female cases: 53 (45–65) years old, $p < 0.001$; vs. male controls: 53 (45–65), $p = 0.001$). Thus, controls were more retired than cases (females: 56% vs. 22%, $p < 0.001$; males: 53% vs. 28%, $p = 0.032$), whilst the latter presented higher prevalence of work disability (females: 9% vs. 41%, $p < 0.001$, OR 6.52 [3.21–13.27] and males: 22% vs. 64%, $p = 0.009$, OR 6.34 [2.57–15.61]) (Figure 2a,b). Females presented the highest household tasks dedication, even more in cases (27% vs. 7% in controls, $p < 0.001$; OR 5.35 [2.38–12.00]), being 7-times higher than men in both groups. What's more, a significant 8% greater of SUD was found in female cases relative to controls (19% vs. 11%, $p = 0.029$; OR 2.04 [1.11–3.76]).



(**a**) (**b**)

Figure 2. Odds ratio (OR) with 95% confidence intervals (95% CI) of risk factors for females (**a**) and males (**b**). ADRs, adverse drug reactions.

Table 1. Socio-demographic analysis by sex.

	Women		**Men**		**Women**	**Men**	**Controls**	**Cases**
	Controls 442 (66%)	**Cases** 88 (64%)	**Controls** 227 (34%)	**Cases** 49 (36%)	♀CONTROLS vs. ♀CASES *	♂CONTROLS vs. ♂CASES *	♀CONTROLS vs. ♂CONTROLS	♀CASES vs. ♂CASES *
Age (years old) (med (IQR))	**66 (56–75) ***	53 (45–65)	60 (49–73)	53 (45–61)	<0.001 **0.074**	<0.001 0.042	0.001 0.018	0.636 0.087
Employment status (%)								
Active	19	6	13	4	0.022 0.136	0.191 0.127	0.273 0.067	1.000 0.050
Retired	56	22	53	28	<0.001 **0.277**	0.032 0.199	0.550 0.039	0.584 0.079
Work disability	9	41	**22** *	64	<0.001 **0.229**	0.009 **0.242**	0.003 0.168	0.062 **0.221**
Unemployed	9	4	12	0	0.271 0.075	0.070 0.164	0.555 0.036	0.537 0.120

Table 1. *Cont.*

	Women		Men		Women	Men	Controls	Cases
Homemaker	**7 ***	**27 ***	0	4	<0.001 **0.264**	0.212 0.168	0.004 0.148	0.014 **0.291**
Income (%)								
Less than €500	31	60	6	40	0.106 0.177	0.128 **0.411**	0.071 **0.285**	0.617 0.175
Between €500–1000	62	27	63	40	0.055 **0.336**	0.611 0.194	1.000 0	0.613 0.127
More than €1000	7	13	31	20	0.596 0.107	1.000 0.107	0.079 **0.322**	1.000 0.081

* The values for the *p*-value are shown first and then for the effect size. [1] In grey higher value for differences between controls vs. cases in women/men (*p*-value < 0.05). [2] * *p*-value < 0.05 for differences between women vs. men in controls/cases (higher value in bold). [3] Effect size: Eta-squared (η^2 = 0.01 indicates a small effect; η^2 = 0.06 indicates a medium effect; η^2 = 0.14 indicates a large effect), Cohen's D (small: 0.2, intermediate: 0.5, and large effect: 0.8) and Cramer's V (small < 0.2, 0.2 < intermediate < 0.6, and large effect > 0.6). [4] From medium effect marked in bold.

Table 2. Clinical analysis by sex.

	Women		Men		Women	Men	Controls	Cases
	Controls 442 (66%)	**Cases** 88 (64%)	**Controls** 227 (34%)	**Cases** 49 (36%)	♀CONTROLS vs. ♀CASES *	♂CONTROLS vs. ♂CASES *	♀CONTROLS vs. ♂CONTROLS	♀CASES vs. ♂CASES *
Clinical Outcomes (mean (SD))								
Pain intensity (VAS, 0–100 mm)	60 (28)	60 (28)	57 (28)	59 (26)	0.999 0	0.909 0	0.319 0.002	0.753 0.001
Pain relief (VAS, 0–100 mm)	35 (29)	38 (30)	33 (29)	34 (29)	0.566 0.001	0.854 0	0.277 0.002	0.480 0.004
EQ (VAS, 0–100 mm)	44 (23)	42 (24)	45 (23)	50 (24)	0.364 0.002	0.302 0.004	0.654 0	0.116 0.021
Substance Use Disorder (SUD, %)								
Previous SUD	11	19	16	21	0.029 0.101	0.399 0.051	0.063 0.075	1.000 0.015
Tobacco	10	17	15	19	0.061 0.086	0.515 0.040	0.058 0.074	0.818 0.019
Alcohol	0.2	2	1	0	0.072 0.102	1.000 0.040	0.267 0.046	0.538 0.091
Illicit substances	0.5	0	0	2	1.000 0.028	0.175 0.131	0.551 0.039	0.356 0.116

* The values for the *p*-value are shown first and then for the effect size. [1] EQ: EuroQol scale (0–100 mm); VAS: Visual Analogue Scale (0–100 mm). [2] In grey higher value for differences between controls vs. cases in women/men (*p*-value < 0.05). [3] * *p*-value < 0.05 for differences between women vs. men in controls/cases (higher value in bold). [4] Effect size: Eta-squared (η^2 = 0.01 indicates a small effect; η^2 = 0.06 indicates a medium effect; η^2 = 0.14 indicates a large effect), Cohen's D (small: 0.2, intermediate: 0.5, and large effect: 0.8) and Cramer's V (small < 0.2, 0.2 < intermediate < 0.6, and large effect > 0.6). [5] From medium effect marked in bold.

3.2. Pharmacological Outcomes

Pharmacological outcomes are shown in Tables 3 and 4.

In control group, sex-differences were observed as females had a greater 8% use of simple analgesics (45% vs. 37% in males, p = 0.039), 12% of tramadol (37% vs. 25%,

$p = 0.001$), along with greater psychotropic drugs use (11%-antidepressants (42% vs. 31%, $p = 0.006$), 14%-benzodiazepines (41% vs. 27%, $p < 0.001$)) and emergency room visits (32% vs. 22%, $p = 0.017$) compared with males. In contrast, males presented a 6% greater use of morphine (10% vs. 4% in females, $p = 0.005$) and a 13% of neuromodulators prescription (54% vs. 41%, $p = 0.002$).

In cases, both sexes doubled their MEDD (120–163 mg/day, $p < 0.001$) compared to controls. As seen in Figure 2, they also presented a 17–15% higher buprenorphine and 12–14% benzodiazepines prescription (females: OR 1.62 [1.02–2.57] and males: OR 2.19 [1.15–4.17]). In contrast, a 24% lower use of tramadol (13% vs. 37% in controls, $p < 0.001$) was shown in female cases and a 22% greater fentanyl use (40% vs. 18%, $p = 0.002$; OR 2.97 [1.52–5.81]) was observed in male cases compared to controls.

Table 3. Analgesic analysis by sex.

	Women		**Men**		**Women**	**Men**	**Controls**	**Cases**
	Controls 442 (66%)	**Cases** 88 (64%)	**Controls** 227 (34%)	**Cases** 49 (36%)	♀CONTROLS vs. ♀CASES *	♂CONTROLS vs. ♂CASES *	♀CONTROLS vs. ♂CONTROLS	♀CASES vs. ♂CASES *
Simple analgesics	**45** *	37	37	40	0.157 0.065	0.741 0.026	0.039 0.081	0.712 0.036
Tramadol	**37** *	13	25	25	<0.001 0.194	1.000 0	0.001 0.128	0.093 0.157
MEDD (mg/day) (med (IQR))	60 (40–120)	120 (60–200)	60 (40–116)	163 (80–250)	<0.001 0.049	<0.001 **0.078**	0.853 0	0.313 0.008
Fentanyl	19	28	18	40	0.083 0.077	0.002 0.198	0.755 0.014	0.179 0.123
Oxycodone	35	36	42	29	0.903 0.006	0.106 0.102	0.064 0.073	0.568 0.066
Tapentadol	35	30	29	17	0.390 0.039	0.106 0.106	0.140 0.058	0.102 0.146
Buprenorphine	3	20	4	19	<0.001 **0.266**	0.001 **0.227**	0.497 0.027	1.000 0.009
Morphine	4	8	**10** *	6	0.160 0.069	0.587 0.046	0.005 0.112	1.000 0.033
Hydromorphone	1	1	0.4	0	1.000 0.006	1.000 0.028	0.433 0.043	1.000 0.064
Immediate release opioids	18	15	19	17	0.642 0.025	0.840 0.018	0.805 0.018	0.671 0.027

* The values for the *p*-value are shown first and then for the effect size. [1] MEDD: morphine equivalent daily dose. [2] In grey higher value for differences between controls vs. cases in women/men (*p*-value < 0.05). [3] * *p*-value < 0.05 for differences between women vs. men in controls/cases (higher value in bold). [4] Effect size: Eta-squared ($\eta^2 = 0.01$ indicates a small effect; $\eta^2 = 0.06$ indicates a medium effect; $\eta^2 = 0.14$ indicates a large effect), Cohen's D (small: 0.2, intermediate: 0.5, and large effect: 0.8) and Cramer's V (small < 0.2, 0.2 < intermediate < 0.6, and large effect > 0.6). [5] From medium effect marked in bold.

Table 4. Pharmacological and health use analysis by sex.

	Women		**Men**		**Women**	**Men**	**Controls**	**Cases**
	Controls 442 (66%)	**Cases** 88 (64%)	**Controls** 227 (34%)	**Cases** 49 (36%)	♀CONTROLS vs. ♀CASES *	♂CONTROLS vs. ♂CASES *	♀CONTROLS vs. ♂CONTROLS	♀CASES vs. ♂CASES *
NSAIDs	16	14	16	15	0.632 0.026	1.000 0.015	1.000 0	1.000 0.015
Neuromodulators	41	48	**54** *	60	0.235 0.055	0.521 0.044	0.002 0.122	0.277 0.108
Antidepressants	**42** *	51	31	36	0.158 0.062	0.499 0.040	0.006 0.107	0.146 0.134

Table 4. *Cont.*

	Women		Men		Women	Men	Controls	Cases
Benzodiazepines	**41** *	53	27	45	0.044 0.089	0.022 0.146	<0.001 0.137	0.469 0.078
Health Resources Use data (%)								
Emergency department visits	**32** *	22	22	28	1.000 0	0.217 0.105	0.017 0.106	0.768 0.069
Hospitalisation	5	3	5	5	1.000 0.034	1.000 0	1.000 0.010	1.000 0.056
Medication changes	31	32	29	35	0.848 0.009	0.606 0.043	0.677 0.022	1.000 0.027

* The values for the *p*-value are shown first and then for the effect size. [1] NSAIDs: non-steroidal anti-inflammatory drugs. [2] In grey higher value for differences between controls vs. cases in women/men (p-value < 0.05). [3] * p-value < 0.05 for differences between women vs. men in controls/cases (higher value in bold). [4] Effect size: Eta-squared (η^2 = 0.01 indicates a small effect; η^2 = 0.06 indicates a medium effect; η^2 = 0.14 indicates a large effect), Cohen's D (small: 0.2, intermediate: 0.5, and large effect: 0.8) and Cramer's V (small < 0.2, 0.2 < intermediate < 0.6, and large effect > 0.6). [5.] From medium effect marked in bold.

3.3. Safety Outcomes

Analgesic drug tolerability is shown in Table 5 and Figure 2.

Women presented a higher number of AEs in both groups, being the highest (median of 6 AEs/patients) in female cases. In fact, ADRs were significantly greater in female controls than men (18% vs. 12%, p = 0.035). On the contrary, although male cases presented the lowest number of AEs (3 (1–6) AEs/patient), they doubled the male controls' ADRs (24% vs. 12%, p = 0.039; OR 2.40 [1.12–5.16]).

Table 5. Safety variables description by sex.

	Women		Men		Women	Men	Controls	Cases
	Controls 413 (66%)	**Cases** 63 (68%)	**Controls** 210 (34%)	**Cases** 30 (32%)	♀CONTROLS vs. ♀CASES *	♂CONTROLS vs. ♂CASES *	♀CONTROLS vs. ♂CONTROLS	♀CASES vs. ♂CASES *
Adverse Drug Reactions	**18** *	15	12	24	0.541 0.035	0.039 0.138	0.035 0.083	0.173 0.121
Adverse Events (med (IQR))	**5 (2–8)** *	**6 (3–8)** *	4 (2–6)	3 (1–6)	0.335 0.002	0.547 0.001	0.003 0.014	0.042 0.044
Sleepiness	38	41	38	23	0.580 0.026	0.156 0.099	1.000 0	0.109 0.175
Dizziness	33	**43** *	26	20	0.155 0.069	0.653 0.044	0.066 0.076	0.038 **0.223**
Nausea	23	29	17	27	0.346 0.042	0.212 0.081	0.097 0.071	1.000 0.021
Vomiting	**9** *	10	4	20	1.000 0.005	0.005 **0.215**	0.036 0.088	0.192 0.146
Constipation	51	40	48	37	0.104 0.079	0.328 0.076	0.447 0.031	0.823 0.029
Itching	21	25	15	33	0.417 0.036	0.022 0.157	0.105 0.069	0.464 0.083
Sexual dysfunction	8	5	**25** *	13	0.603 0.039	0.247 0.089	<0.001 **0.236**	0.207 0.152
Loss of libido	20	21	27	33	0.865 0.007	0.510 0.051	0.087 0.087	0.206 0.138

Table 5. *Cont.*

	Women		Men		Women	Men	Controls	Cases
Weight change	**36** *	40	19	20	0.575 0.027	0.806 0.013	<0.001 0.178	0.065 0.195
Headache	32	33	26	27	0.885 0.010	1.000 0	0.141 0.060	0.634 0.067
Skin redness	17	6	16	13	0.035 0.110	1.000 0.023	0.704 0.021	0.267 0.116
Dry skin	**38** *	35	24	20	0.677 0.023	0.818 0.030	<0.001 0.145	0.157 0.152
Dry mouth	61	59	54	37	0.783 0.015	0.117 0.114	0.103 0.067	0.075 **0.206**
Edema	13	**17** *	11	0	0.432 0.041	0.089 0.123	0.444 0.034	0.014 **0.253**
Depression	**35** *	40	23	23	0.482 0.033	1.000 0	0.002 0.124	0.162 0.161
Sleep disturbance	35	52	28	47	0.012 0.119	0.053 0.138	0.058 0.079	0.661 0.054
Nervousness	42	**52** *	35	27	0.135 0.070	0.415 0.060	0.101 0.067	0.026 **0.242**
Loss of appetite	**28** *	33	16	20	0.455 0.039	0.603 0.034	0.001 0.132	0.227 0.137

* The values for the *p*-value are shown first and then for the effect size. [1] In grey higher value for differences between controls vs. cases in women/men (*p*-value < 0.05). [2] * *p*-value < 0.05 for differences between women vs. men in controls/cases (higher value in bold). [3] Effect size: Eta-squared (η^2 = 0.01 indicates a small effect; η^2 = 0.06 indicates a medium effect; η^2 = 0.14 indicates a large effect), Cohen's D (small: 0.2, intermediate: 0.5, and large effect: 0.8) and Cramer's V (small < 0.2, 0.2 < intermediate < 0.6, and large effect > 0.6). [4] From medium effect marked in bold.

Among reported cases, females presented 23% more dizziness (43% vs. 20% in males, $p = 0.038$), 17% edema (17% vs. 0%, $p = 0.014$), and 25% nervousness (52% vs. 27%, $p = 0.026$) compared to males. They suffered 17% more sleep disturbance compared to controls (52% vs. 35% in female controls, $p = 0.012$; OR 2.00 [1.18–3.42]). Meanwhile, in male reported cases, 16% higher vomiting (20% vs. 4%, $p = 0.005$; OR 5.58 [1.83–17.05]) and 18% itching (33% vs. 15%, $p = 0.022$; OR 2.77 [1.19–6.46]) rates were observed compared to controls. On the other hand, in the control group, females suffered 5% more vomiting (9% vs. 4% in males, $p = 0.036$), 17% weight change (36% vs. 19% males, $p < 0.001$), 14% dry skin (38% vs. 24% males, $p < 0.001$), 12% depression (35% vs. 23% males, $p = 0.002$), and 12% loss of appetite (28% vs. 16% males, $p = 0.001$) rates relative to males. Only sexual dysfunction was higher in males (25%) in comparison with females (17%, $p < 0.001$).

4. Discussion

Younger age, work disability, opioid doses higher than 120 mg/day of morphine equivalent daily dose and benzodiazepine use were found significantly higher in cases compared to controls (similarly for both sexes). Nevertheless, sex-differences in cases were found related to prior SUD, opioid prescription and tolerability. Thus, the use and dose of opioids should be carefully monitored in patients with these underlying factors.

Our data have shown known socio-economic risk factors along with co-medication of high doses of opioids and benzodiazepines [23,24]. However, sex-based differences were observed due to prior SUD [25] and fentanyl prescription [26]. Women have been described to report greater receipt of prescriptions for anxiolytics, sedatives or hypnotics, what could contribute to an OUD [27]. Other clinical evidence suggest that men are more sensitive than women to the abuse-related effects of mu-opioid agonists, as fentanyl, although

preclinical studies differ from this evidence [28]. These findings support sex-based tailoring of treatment, but any tailoring should also consider person-level differences [29].

Greater and different pain treatment intensity in females might be a consequence of the normalization of pain symptom between women and family doctors, which may also lead to delays in pain diagnosis or referrals to a PU [30]. In this way, these potential diagnosis and therapeutics delays should be deeply analyzed in terms of biopsychosocial mechanisms, adjusting for confounding by gender, as they may underlie these sex-differences, and considerations for future research should be discussed [31,32]. Besides, among the psychosocial risks that can worsen the state of health of women, we find a significant higher dedication to household tasks. The physical discomfort caused by the overload of domestic work, as well as the physical and mental stress resulting from the double working day as employees and as caregivers for the whole family, calls for further studies to identify appropriate intervention and prevention strategies [33].

The worse analgesic tolerability in females -related to gastrointestinal and nervous systems- and 10% more emergency department visits, falls in line with previously published scientific literature [34–37]. However, in spite of male cases having the lowest number of AEs, they arose the highest ADRs notification. These sex-differences are not fully elucidated [38]. Possible multifaceted factors seem to be associated. These include neuroanatomical, hormonal, neuroimmunological, but also psychological plus other social and cultural factors which need to be deeper analyzed (along with a gender perspective). In this way, studies should no longer consider men and women as a homogeneous group, given that subjective painkillers' tolerability substantially differs between sexes [17,39].

The exploratory nature of the study has permitted us to establish differences between women and men in some intersectional factors such as age. However, it did not allow us to collect essential information that would enable us to link, for example, whether this fact was caused by a delayed diagnosis in women [40,41]. For this reason, it is essential to consider potential gender stereotypes threats that could affect our varied experiences and overall health [42].

There are some limitations in this study that need to be acknowledge. First, the sample size was limited by a "convenience sample" due to the low incidence of OUD. Secondly, although the control group came from the same setting, it was composed by subjects from different studies. Moreover, most patients were under other non-opioid centrally acting drugs related to their diverse comorbidities, which might have independently contributed to the observed side-effects. This could introduce a bias mediated by several other variables, such as socio-demographics, that could be more relevant than pain status [43,44]. What's more, the higher prevalence of buprenorphine among cases could be part of the beginning of medication assisted therapy, prior to the derivation to the PU for the opioid tapering procedure. The data collection of some variables such as prior SUD could have been limited by the poor documentation from healthcare professionals. Nevertheless, this information was gathered through medical diagnoses, narratives, and Addictive Behavior Unit visits. All in all, this study helps to create more information about the needs of these patients to design more equal prevention programs.

5. Conclusions

In light of the above information, sex-differences in pain management and OUD risk have been observed. A deeper analysis of sex-gender interactions may be needed to understand disparities in potential diagnosis delays, analgesic prescription, safety pattern and healthcare resources use. Hence, further research is needed to refine these results and explore potential gender disparities in order to optimize individual pain and OUD management.

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Clinical prediction of opioid use disorder in chronic pain patients: A case-control study with a pharmacogenetic approach.

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Abstract:	Objectives 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 analysed. 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 10-year younger with lower incomes, more sleep disturbances, benzodiazepines use and history of substance use disorder in front of controls. Discussion 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.

Table 1

Table 1. 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))				

			0.96
Pain intensity (mm)	59 (28)	59 (27)	0

Pain relief (mm)	35 (29)	37 (30)	0.580	
Quality of life (mm)	45 (23)	45 (24)	0.940	
Quality of life (Health Utility Score, mean (IQR))	0.45 (0.05 - 0.71)	0.17 (0.08 - 0.61)	0.850	
Health resources use (%)				
Emergency department visit	29	24	0.470.03	0.79 (0.44 to 1.43)
Hospitalisation	13	7	0.280.05	0.52 (0.18 to 1.49)
Medication changes	38	36	0.880.01	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	0.060.07	1.64 (0.99 to 2.70)
Alcohol	0.5	1	0.200.05	3.34 (0.55 to 20.18)
Illicit substances	0.3	1	0.420.03	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 (η2 = 0.01 indicates a small effect; η2 = 0.06 indicates an intermediate effect; η2 = 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).*

Table 2

Table 2. 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	0.85 (0.51 to 1.41)

			0.02	
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 (η2 = 0.01 indicates a small effect; η2 = 0.06 indicates an intermediate effect; η2 = 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 3

Table 3. 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)	0.580	
Sleepiness (%)	38	35	0.730	0.91 (0.58 to 1.44)
Dizziness (%)	31	35	0.340	1.24 (0.79 to 1.97)
Nausea (%)	21	28	0.140	1.44 (0.88 to 2.36)
Vomiting (%)	8	13	0.100	1.82 (0.92 to 3.57)
Constipation (%)	50	39	**0.040**	0.63 (0.40 to 0.98)
Itching (%)	19	28	0.050	1.64 (1.00 to 2.69)
Sexual dysfunction (%)	13	8	0.130	0.52 (0.23 to 1.17)
Loss of libido (%)	22	25	0.590	1.15 (0.69 to 1.93)
Weight change (%)	30	33	0.550	1.17 (0.73 to 1.85)
Headache (%)	30	31	0.810	1.06 (0.66 to 1.69)
Skin redness (%)	17	9	0.060	0.47 (0.22 to 1.01)
Dry skin (%)	33	30	0.560	0.86 (0.54 to 1.38)
Dry mouth (%)	58	52	0.220	0.76 (0.49 to 1.18)

Edema (%)	13	12	0.05 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 for differences in controls vs. cases (higher value shaded and in bold).*

[a]Effect size: Eta-squared (η2 = 0.01 indicates a small effect; η2 = 0.06 indicates an intermediate effect; η2 = 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 4

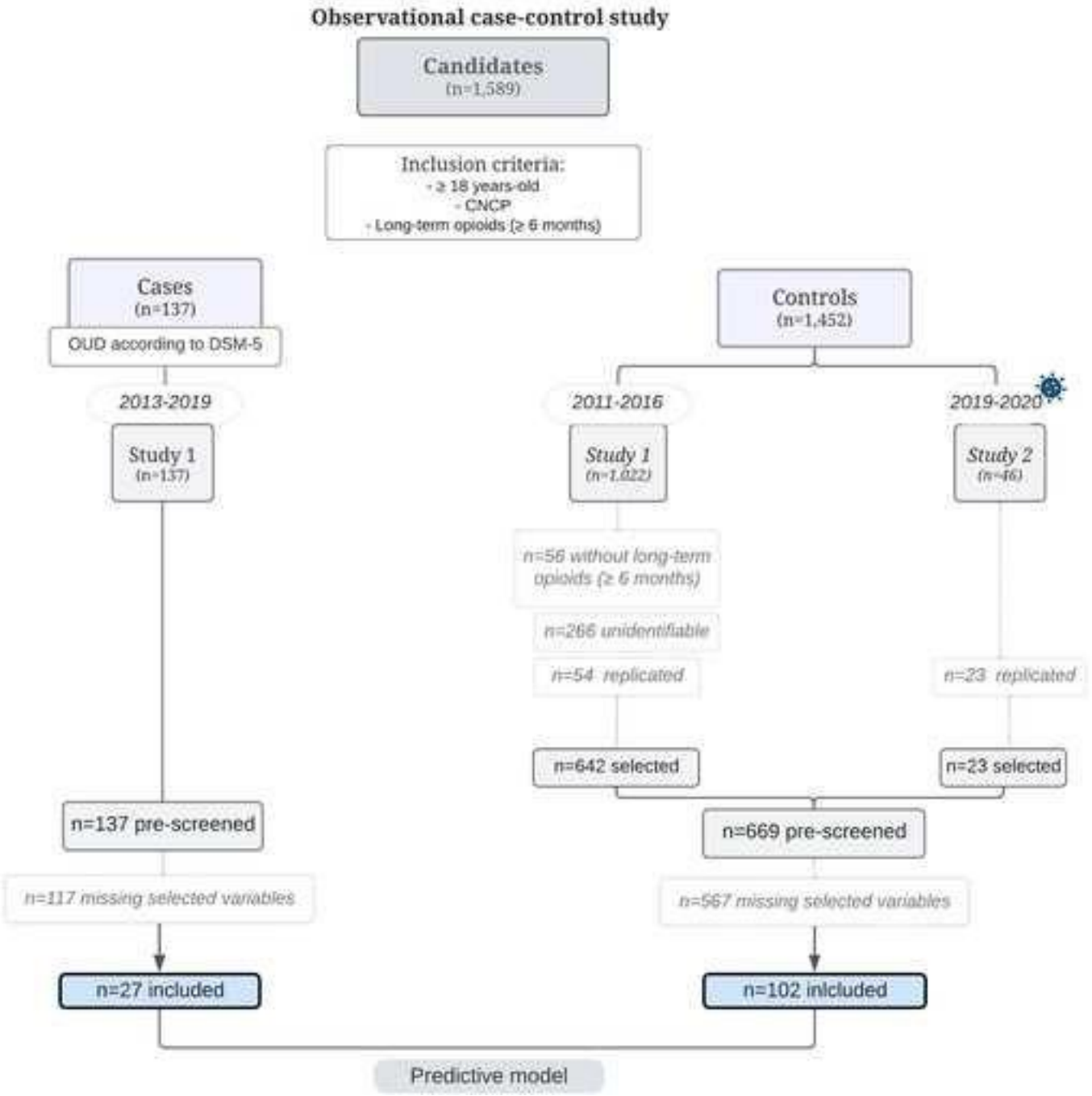
Table 4. Independent opioid use disorder (OUD) risk predictors selected in the logistic model.

	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
CYP2D6 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.*

Figure 1



Clinical prediction of opioid use disorder in chronic pain patients: A case-control study with a pharmacogenetic approach.

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ABSTRACT

Objectives: 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 analysed. 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 10-year younger with lower incomes, more sleep disturbances, benzodiazepines use and history of substance use disorder in front of controls.

Discussion: 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.

Keywords: opioid use disorder, pharmacogenetics, opioid, predictive model, chronic pain

INTRODUCTION

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 behaviours, 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 post-operative patients (6) and potential opioid misuse behaviours (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 case-control 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. The inclusion criteria were patients at least 18 years of age, CNCP (moderate or severe pain lasting for six or more months) under long-term opioids (≥6 months). They were excluded if presented oncologic pain or an opioid prescription <6 months. All unidentifiable candidates, duplicated, or who didn't meet the inclusion criteria were excluded. All the patients' selection of both arms (case or control) was made according to the same characteristics.

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, 1 week, 2 weeks, 1 month, 3 months, and at 6 months as final visit) with an opioid rotation to tramadol and/or buprenorphine together with the tapering process, and a 1-2 weekly phone monitoring. A flexible dosing approach was used, with dose changes allowed during the study (13).

Controls

The control arm was composed of CNCP patients from previous observational studies (14,15) 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 Behaviour 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) (16). 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 (17). In addition, a list including any emergency department (ED) visit, hospitalisation, 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") (18) 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 (19,20). 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 (21). 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, Supplemental Digital Content 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 (22), based on its enzymatic activity: null function (poor metabolizer, PM), normal function (extensive metabolizer, EM) and increased function (ultra-rapid metabolizers, UM) (23), was performed from its genotype.

Statistical Analysis

Convenience sampling was considered to increase statistical power. This entailed selecting all available patients from historic database. Data distribution was analysed 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 $\chi 2$ or Fisher's exact test for categoricalvariables 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 ($\eta 2 = 0.01$ small; $\eta 2 = 0.06$ 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 $\chi 2$ 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 (13,24), 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 (25). 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).

Ethics

The Institutional Review Board approved the study (code: PI2020-047) where procedures were carried out in accordance with the Declaration of Helsinki.

Written informed consent was waived due to the retrospective nature of the study. This manuscript adheres to the applicable STROBE guidelines.

RESULTS

A total of 1,589 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 (Fig. 1).

Socio-demographic and Clinical outcomes

Characteristics of the participants and clinical variables are shown in Table 1.

Cases were on average 10-year younger (cases vs. controls, 54 ± 13 vs. 64 ± 14 years old; $p<0.001$ / $\eta^2 = 0.06$), 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 incomes (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 2.

Cases had 2-time higher MEDD (cases vs. controls, 120 (72-217) vs. 60 (40-120) mg/day, $p<0.001$ / $\eta^2 = 0.06$), 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 3. No other significant differences were observed when grouped by systems (Table S1, Supplemental Digital Content 2).

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 at Table S2, Supplemental Digital Content 3, 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 significant 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 at Fig 1.

A total of sixteen independent variables were selected, as seen at Table S3, Supplemental Digital Content 4, 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).

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, ζ = 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 4). 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 (Fig. S1, Supplemental Digital Content 5), 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 adverse events 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 (26). Besides, these subjects are prone to higher mu-opioid-related toxicity and a higher risk of side-effects (27). In contrast, CYP2D6- PMs tend to have lower levels of the active metabolites, which may result in reduced analgesic efficacy (28,29). (30). Thus, patients at high-risk with dysfunctional *CYP2D6* could best managed with non-opioids (23).

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 (23,31). Our results would support pharmacogenetic test implementation in Health's Systems (32), especially in population with greater prevalence of UMs (i.e. Southern European and Northern African) (22).

Both genetic variants can be turned into differences in opioid´s clearance (30) what could have special impact in females, who generally exhibit a lower opioid tolerability or sensitivity to pain in front of males (30,33). Nevertheless, there is weak evidence related to menstrual cycle influence on the CYP2D6 activity (34,35), and, explicit recommendations derived through a validated process have not yet been formulated (36). On the other hand, 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 (37).

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 (38). Besides, an US survey (n=1,229) 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 (Thielke et al., 2014).

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 (40)- and to be diagnosed with sleep disorders with worse sleep quality (41). In this context, some clinical studies demonstrated that poor sleep –a prevalent factor to prescribe anxiolytics- (42) leads to negative affect, which can contribute to opioid use problems, due to its interaction with the reward processing (43).

Finally, there are some limitations in this study that need to be acknowledged. Due to the retrospective design, - from different studies and time periods - the data collection of some variables such as prior SUD or OUD diagnosis could have been limitedby 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. 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 generalisation. 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 (44). 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.

CONCLUSIONS

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.

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FIGURE LEGENDS

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

Fig. S1. Predicted probabilities and observed opioid use disorder (OUD) frequencies in the population.

Supplemental Digital Content

1. Genotyping procedure

2. Table S1

3. Table S2

4. Table S3

5. Figure S1

Figure S1

Two-stage model for opioid use disorder: an innovative predictive model development and validation study.

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Abstract:	Early detection alternatives are required to help clinicians to identify patients requiring more intensive monitoring to prevent developing opioid use disorder (OUD). In the current study, we aimed to validate prospectively a predictive model for OUD in chronic non-cancer pain (CNCP) patients under long-term opioids. An innovative two-stage predictive model was developed from a retrospective (n=129) and non-overlapping prospective (n=100) cohorts of real-world CNCP outpatients. All subjects were under any opioid prescription for at least 6 months. Socio-demographic, clinical and pharmacological outcomes were registered. 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 also analysed. The model performance and diagnostic accuracy were calculated. The two-stage model comprised risk factors related to OUD (younger age, low work status and high MEDD) and provide new useful information about other risk factors (low quality of life, OPRM-G allele and CYP2D6 extreme phenotypes). The validation showed a satisfactory accuracy (70% specificity and 75% sensitivity) for our predictive model with acceptable discrimination and goodness of fit. Our study presents a newly developed and internally validated model for predicting OUD, allowing clinicians to focus medical resources.
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Two-stage model for opioid use disorder: an innovative predictive model development and validation study.

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Abstract

Early detection alternatives are required to help clinicians to identify patients requiring more intensive monitoring to prevent developing opioid use disorder (OUD). In the current study, we aimed to validate prospectively a predictive model for OUD in chronic non-cancer pain (CNCP) patients under long-term opioids. An innovative two-stage predictive model was developed from a retrospective (n=129) and non-overlapping prospective (n=100) cohorts of real-world CNCP outpatients. All subjects were under any opioid prescription for at least 6 months. Socio-demographic, clinical and pharmacological outcomes were registered. *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 also analysed. The model performance and diagnostic accuracy were calculated. The two-stage model comprised risk factors related to OUD (younger age, low work status and high MEDD) and provide new useful information about other risk factors (low quality of life, *OPRM*-G allele and CYP2D6 extreme phenotypes). The validation showed a satisfactory accuracy (70% specificity and 75% sensitivity) for our predictive model with acceptable discrimination and goodness of fit. Our study presents a newly developed and internally validated model for predicting OUD, allowing clinicians to focus medical resources.

Perspective: This article presents an innovative predictive model for opioid use disorder chronic non-cancer pain outpatients under long-term opioid prescription. This model could identify patients at high-risk with satisfactory accuracy, providing new useful information about risk factors.

Keywords: opioid use disorder, predictive model, chronic non-cancer pain, chronic opioid use

INTRODUCTION

Opioid analgesics are recognized as a legitimate medical therapy for selected patients with severe chronic non-cancer pain (CNCP) that does not respond to other therapies [1]. However, opioids are associated with risks that include aberrant drug related behaviours and opioid use disorder (OUD) in up to 20% of the regular opioid prescriptions [2]. OUD is detailed in DSM-5 as an unsuccessful effort to cut down or control use, social problems, and a failure to fulfil major role obligations [3]. This situation strongly contributes to clinician reluctance to manage pain using opioids. Thus, clinical tools and greater understanding and better assessment are needed to properly screen, and monitor patients under long-term opioid prescriptions.

There is not enough understanding of the inter-individual variability in analgesic administration and aberrant opioid related behaviours [4,5]. Scientific literature has indicated that genetic variation of *mu-opioid receptor 1* (*OPRM1*, A118G, rs1799971) may contribute to inter-individual differences in morphine consumption [6,7]. Polymorphisms associated with the metabolization process of opioid drugs, as CYP2D6 polymorphism, can be also very relevant in opioid titration (recommendation grade A). *Cathecol-O-methyltransferase* (*COMT*, G472A) is another genetic variation most frequently analysed gene in the pain scenario as it has been associated with highest pain score and opioid consumption in the postoperative setting [8].

In our Pain Unit (PU), a predictive model for OUD was developed from a retrospective cohort of patients under chronic use of opioids [9,10]. This model included these actionable pharmacogenetic markers and other variables such as age, employment status and equivalent morphine daily dose (MEDD). In this way, the aim of this study

was to internally validate the model, in real-world CNCP outpatients, for its clinical translation. We also examined the characteristics of routinely ambulatory CNCP patients under long-term use of opioids.

MATERIALS AND METHODS

Study design and participants

An observational transversal study was conducted at the PU of Dr. Balmis General University Hospital. The study was approved by the Institutional Review Board (code PI2020-047) where procedures were carried out in accordance with the Declaration of Helsinki. Enrolment began in September 2021 and ended in July 2022. All patients included were ≥18 years old with CNCP (moderate or severe pain lasting for six or more months) under long-term opioids (≥6 months). The exclusion criteria were: oncologic pain, opioid prescription <6 months and prior inclusion in the retrospective cohort (model development). Informed consent was obtained from all subjects involved in the study. The data that support the findings of this study are available from the corresponding author upon reasonable request. This manuscript adheres to the applicable STROBE guidelines.

Procedure

All subjects enrolled were attended by the research staff for data and saliva sample collection. The outcomes were collected through validated scales and questionnaires and completed through Electronic Health Records (EHRs), which include medical diagnoses, medication use (strength, quantity and duration of therapy) and outcomes (e.g., comorbidities). After data collection, patients followed their routine clinical visit. Here, a medical doctor (anaesthesiologist or clinical pharmacologist experts on pain) assessed the probability of OUD based on DSM-5 criteria [11].

Outcomes

Socio-demographic, clinical data, prescribed analgesic use and medical history were collected at the time of the enrolment. Sex (female/male), age, employment status (yes/no: active, retired, with work disability-permanent or temporary, unemployed or homemaker) were registered. 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 were categorized in low incomes- less than €500, middle incomes- between €500-1000 or upper incomes- more than €1000.

The presence/absence of current and/or previous substance use disorder (SUD) (except opioid use) related to tobacco, alcohol or other illicit drugs were collected through the review of medical diagnoses, narratives or any visit to the Addictive Behaviour Unit.

Pain intensity and relief, and quality of life were measured using the Visual Analogue Scale (VAS) [12] included in the Global Pain State questionnaire [13]. The VAS for each indicator consists of a 100 mm horizontal line ranging from 0 (lowest) to 100 mm (highest). Specifically, quality of life was measured with the EuroQol-5D-3L scale (registration number: 48802, available at https://euroqol.org/), which also includes a Health Utility Score [14] (five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; scores from 0 for death to 1 for perfect health). In addition, the health resources use (any recently emergency department (ED) visit, hospitalisation or drug changes due to pain and other causes) was registered.

All and only prescribed drug use was registered and contrasted with EHRs, which allows for reviewing drug prescriptions. Non-opioid analgesics (i.e., paracetamol and metamizole), non-steroidal anti-inflammatory drugs (NSAIDs), weak (i.e., tramadol and

codeine) and strong opioids use (i.e., fentanyl, oxycodone, tapentadol, buprenorphine, morphine, hydromorphone and methadone), and immediate release opioids were registered. In different opioids' combinations, oral MEDD was estimated using available references [15]. The prescription of antidepressants (i.e., amitriptyline, duloxetine and escitalopram), benzodiazepines and neuromodulators (i.e., pregabalin, lacosamide, gabapentin) were also collected.

What´s more, 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") [16] 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 (available at https://www.meddra.org) [17,18].

Pharmacogenetic analysis

Approximately 2 ml of saliva was collected in tubes containing 6 ml of PBS. Once the saliva sample was taken, it was stored at -80 ºC until its processing. Genomic DNA was extracted using E.N.Z.A. forensic DNA kit (Omega Bio-Tek Inc., USA) following the manufacturer's instructions. The following gene variants were genotyped: *OPRM1* (rs1799971), *COMT* (rs4680) and *CYP2D6**2, *3, *4, *5, *6, *10, *17, *29, *35, *41, xN 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 ºC, 40 cycles for 15 seconds denaturation at 92 ºC, and 1 minute final extension at 60 ºC.

As regards the CYP2D6 genotype, genetic analysis was based on the usual PCR-

methods following the instructions of Consortium of the Pharmacogenetics and Pharmacogenomics Ibero-American network [19] for the analysis of samples. 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).

The combination of *CYP2D6* alleles is used to determine a patient's diplotype. Each allele is assigned an activity score (AS) ranging from 0 to 1 (e.g., 0 for no function, 0.25 or 0.5 for decreased function, and 1 for normal function) [20]. Alleles *3, *4, *5, *6 (AS= 0) have null function, while *10 (AS= 0.25) and *17, *29, *41 (AS= 0.5) a reduced function. Alleles *1, *2, *35 (AS= 1) and duplications *1xN, *2xN, *35xN (AS= 2) have normal and greater function, respectively. If an allele contains multiple copies of a functional gene, the value is multiplied by the number of copies present. Thus, the CYP2D6 activity score is the sum of the values assigned to each allele. The CYP2D6 activity score can be translated into a standardized phenotype classification: null function (poor metabolizer, PM), normal function (extensive metabolizer, EM) and increased function (ultra-rapid metabolizers, UM) [21].

Statistical Methods

Sample size

It was expected to have 20 cases and 100 controls from the PU for 11 months based on the inclusion rate of cases in the previous study [9]. We anticipate withdrawals, incomplete data, or losses to teleassistance instead of PU visits, shrinking the targeted enrolment to 100 patients.

Statistical analysis

We compared all the outcomes between the retrospective cohort (Sample 1) and

the new cohort (prospective cohort, Sample 2) using $\chi 2$ or Fisher's exact test for categorical variables and t-test or U Mann-Whitney test for continuous variables, depending upon their distribution. Here, data distribution was analysed with the Kolmogorov-Smirnov test using the Lilliefors correction method. Quantitative parametric data (pain intensity, relief and quality of life) are presented as mean and standard deviation (SD), whilst the median and interquartile range (IQR) was used for not parametric data (age, quality of life- Health Utility Score, MEDD, AEs). Categorical data (sex, employment status, incomes, prior SUD, health resource use, drug use, AEs and genotypes) are expressed as percentages (%). Gene frequencies were compared using the chi-square $\chi 2$ goodness-of-fit test. For the *OPRM1* genotype, the G-carriers were grouped as they presented a low allelic frequency.

We applied the logistic regression model previously developed from the Sample 1 (Table S1) to calculate the risk of each individual as follows: $e^{\zeta}/(1+e^{\zeta})$, 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, ζ = 1.633 - 0.072 age + 2.012 work disability + 0.006 MEDD -1.424 *OPRM1* genotype (AG/GG) + 0.075 PM CYP2D6 phenotype + 3.172 UM CYP2D6 phenotype.

An adjustment of the predictive model was conducted. In this way, a two-stage model was proposed for: (1) classifying patients in Sample 1 or 2, and (2) predicting OUD risk in each Sample (1 and 2). Here, independent variables were selected for the model on the basis of the investigators' consensus on relevant measurable variables, the results of previous studies [9,10] and the univariate analysis ($p<0.05$). Three logistic regression models were constructed based on the standards for the model building process [22]. The model selection followed two criteria: (1) small Akaike information criterion-AIC and (2) significance of the variables. Non-significant variables were considered if their coefficients were interpretable. A 20% of random sample was extracted from each Sample

(1 and 2) for the internal validation of the model. This percentage was considered in order to estimate more accurately the clinical usefulness (sensitivity and specificity). Calibration (Hosmer-Lemeshow Goodness-of-fit statistic) and discrimination (*C*-statistic, area under the receiver operating curve) were measured to assess the model performance. All statistical analyses were carried out using R (Version 3.2.0; the GNU project, Cambridge, MA, USA) and GraphPad Prism (Version 5.0, Dotmatics, Boston, MA, USA).

RESULTS

Participants

Sample 1 corresponds to the retrospective cohort of patients (n=129) included in our previous studies [9,10]. Sample 2 corresponds to the new prospective cohort of patients (n=100) recruited, following the detailed inclusion criteria. Three subjects were missing due to insufficient sample for the pharmacogenetic analysis (2 for full analysis and 1 for CYP2D6 analysis) (Figure 1). All patients enrolled, attended our PU for regular CNCP management due to lumbalgia (67%, mostly for disc disease pain from spinal canal stenosis with or without a radicular or myofascial pain component), knee pain (gonalgia) and other musculoskeletal pain (i.e., arthralgia and cervical joint dysfunctions).

Outcomes

A middle age (63-65 years old), predominantly females (67-70%), retired (50-40%) with a 18-25% of previous SUD (mostly tobacco 71-96%) were the main characteristics of the population included. Half (53-67%) presented middle incomes, however, a higher prevalence of upper incomes (42% vs. 13%, p=0.04) and lower tobacco use (71% vs. 96%, p=0.03) was evidenced in Sample 2, as seen at Table 1.

Patients of prospective cohort (Sample 2) suffered higher pain intensity (70 (26) vs. 61 (28) mm, p=0.02) with near double use of non-opioid analgesics (63% vs. 34%, p<0.001) and tramadol (45% vs. 22%, p<0.001). However, less MEDD (median (IQR), 60 (33-108) vs. 80 (40-160) mg/day, p<0.01) and immediate-release opioids prescription (10% vs. 24%, p<0.01), but higher benzodiazepines use (54% vs. 35%, p<0.01) was observed in front of retrospective cohort (Sample 1). A different oxycodone, tapentadol and buprenorphine use was also observed between Samples. Besides, the number of AEs reported (2 (1-3) vs. 6 (3-8), p<0.001) were significantly lower in Sample 2 (Table S2).

Model performance

Due to the differences observed between Sample 1 and 2, the logistic regression model previously developed from Sample 1 didn't present a good sensitivity (fewer false negatives, 14%) in the new cohort of patients (Sample 2). In this way, a two-stage model was proposed for the adjustment of the developed model (Figure 2).

A total of nineteen independent variables were selected according to the established criteria (see in Statistical analysis) and entered in the logistic regression models as candidate predictors: age, employment status (active, work disability and unemployed), prior SUD, pain intensity, quality of life, tramadol use, MEDD, strong opioids use, fentanyl use, benzodiazepines use, ED visits, vomiting, sleep disturbance, psychiatric AEs, *OPRM1* genotype (AA, AG/GG), *COMT* genotype (GG, GA and AA) and CYP2D6 phenotypes (PM, EM and UM) (Table 2).

Firstly, a logistic regression model was developed to classify patients in Sample 1 or 2 (Table 3). This model included nine independent factors: $\zeta = 0.242 - 1.950$ active $- 1.740$ work disability $- 3.976$ unemployed $+ 0.004$ MEDD $+ 3.493$ strong opioid use $- 2.626$ benzodiazepines use $- 1.496$ ED visits $+ 2.289$ psychiatric AEs $- 2.159$ *COMT*

genotype (GA) – *0.901* COMT genotype (GG). Here, the cut-off point (*c*=0.57) presented the optimal values for specificity (0.86) and sensitivity (0.85).

Secondly, two logistic regression models were developed to estimate OUD risk in each Sample. The newly developed model for Sample 1 (Table 4) included four independent factors: ζ = - 0.622 – 0.057 age + 2.859 work disability + 0.006 MEDD + 1.191 PM CYP2D6 phenotype + 3.299 UM CYP2D6 phenotype. Here, the optimal values of specificity (0.82) and sensitivity (0.94) were obtained with a cut-off point of 0.18. The *C*-statistic indicated a satisfactory model discrimination (0.86). The model's ability to accurately predict the likelihood of developing OUD was measured with the test Hosmer-Lemeshow (p=0.26), which indicated a limited model fit.

The predictive model for Sample 2 (Table 5) included three independent factors: ζ = - 1.713 – 0.032 quality of life + 0.006 MEDD + 1.017 *OPRM1* genotype (AG/GG) with an optimal cut-off point of 0.19 for satisfactory specificity (0.78) and sensitivity (0.73). The *C*-statistic indicated a satisfactory model discrimination (0.86). The Hosmer-Lemeshow (p=0.36) showed a limited model fit.

Model validation

The sensitivity and specificity in the 20% of random sample of the classifier model were satisfactory (0.78 and 0.68, respectively) with a cut-off point of 0.35. The predictive models presented adequate sensitivities (0.75 both) and specificities (0.81 and 0.57, respectively) for a cut-off point of 0.08 (Sample 1) and 0.10 (Sample 2). In this way, the two-stage model presented on average 70% of specificity and 75% of sensitivity.

DISCUSSION

We have developed and internally validated a predictive model as a screening tool that can classify CNCP patients at risk for OUD when they are under long-term opioids. This tool consisted of a two-stage model which comprised well-documented risk factors related to OUD (younger age, low work status and high MEDD) and provide more useful information about other risk factors (low quality of life, *OPRM*-G allele and CYP2D6 extreme phenotypes). This model could help to identify patients who should be monitored closely or who may benefit from preventive interventions. Our innovative predictive model is expected to be applicable in the clinical setting and in national-level surveillance due to its readily identifiable and easily calculable nature.

One of the novel features of the study is the inclusion of genetic variables in the predictive model, which is lacking in many prior tools, including the Opioid Risk Tool. In this era of precision medicine and artificial intelligence, healthcare could benefit from such studies that utilise genetic predictors to stratify patients into risk categories for OUD [23]. What´s more, while previous studies have developed predictive models with databases from specific populations (e.g., a veterans' health administration database) [24,25], our model used regular CNCP patients from an ambulatory PU data. By focusing preferentially on patients at high-risk, 75% of cases could be identified, saving time and resources for evaluating patients.

Our model requires an extra effort due to genetic variants analysis. Clinical guidelines have been established and recommend *CYP2D6* genotype testing prior prescription of tramadol or codeine, as it has been associated with failure of pain treatment in PM (limited conversion to active metabolites) and higher risk of AEs in UM [21]. In the case of *OPRM1*, numerous studies have associated the mutant variant (118G) with OUD

risk as they have observed a lower receptor expression in the membrane [26,27]. In this way, pharmacogenetic testing would help to elucidate genetic polymorphisms impacting OUD development and management, and allow healthcare providers to individualize prevention strategies [28].

It is well recognized that MEDD is a major determinant for developing an OUD [29]. Experts has agreed that lower dosages of opioids could reduce the risk for opioid use disorder and overdose [3]. Here, daily doses close to or greater than 100 mg/day are at the higher risk than dosages <50 mg/day. Yang S. Liu et al. [30] developed and validated an OUD risk predictive model, through machine learning, in 316,039 patients from a national healthcare database, where one of the ten top-ranked predictors was MEDD with a good accuracy of 86%. Nevertheless, they lacked a clear indicator for treated OUD, and the model interpretability needed further validation with more traditional statistical approaches.

Data reveal that opioid crisis disproportionally impacts some specific populations, such as people with low incomes, with past or current substance abuse and untreated psychiatric disorders [1]. Our data reveal that younger ages with more vulnerable work status can condition OUD, together with low quality of life. The latter has been previously linked with SUD [31]. Thus, recognising and measuring it in clinical practice should also improve the outcomes in patients with OUD.

Limitations

These results need to be interpreted with caution due to their limitations. Firstly, our model has been internally validated in a limited number of patients, what makes necessary to test it in a large cohort of patients to improve the model performance and diagnostic accuracy. Secondly, the fact the model developed from Sample 1 didn't fit

Sample 2 can be attributed to the (1) retrospective data collection nature of Sample 1, (2) data availability for the model in Sample 1, (3) recruitment of patients from different doctor consultations in Sample 2 and (4) national clinical guidelines changes. Thirdly, the relatively poor incidence of OUD in our setting could have avoided us to detect the causality and other potential risk factors. Also, it is not clear how strong the genetic factors are compared to other factors in predicting OUD. Besides, the use of a self-reported questionnaire could have generated a systematic bias, conditioning the fact psychiatric AEs were not predictors. Prior SUD was registered from the EHRs, which is limited by the missing information reported by clinicians. However, it has been reported that the prevalence of this outcome is lower in prescribed opioid users [32]. Finally, it should be externally validated in different data sources or in specific subgroups of patients to ensure generalizability in different settings.

CONCLUSION

We have newly developed and internally validated an innovative model for predicting in a real-world setting. This tool could identify high-risk patients, allowing healthcare providers focus medical resources on a limited number of patients. To ensure the clinical usefulness of the model, further internal and external validation is needed.

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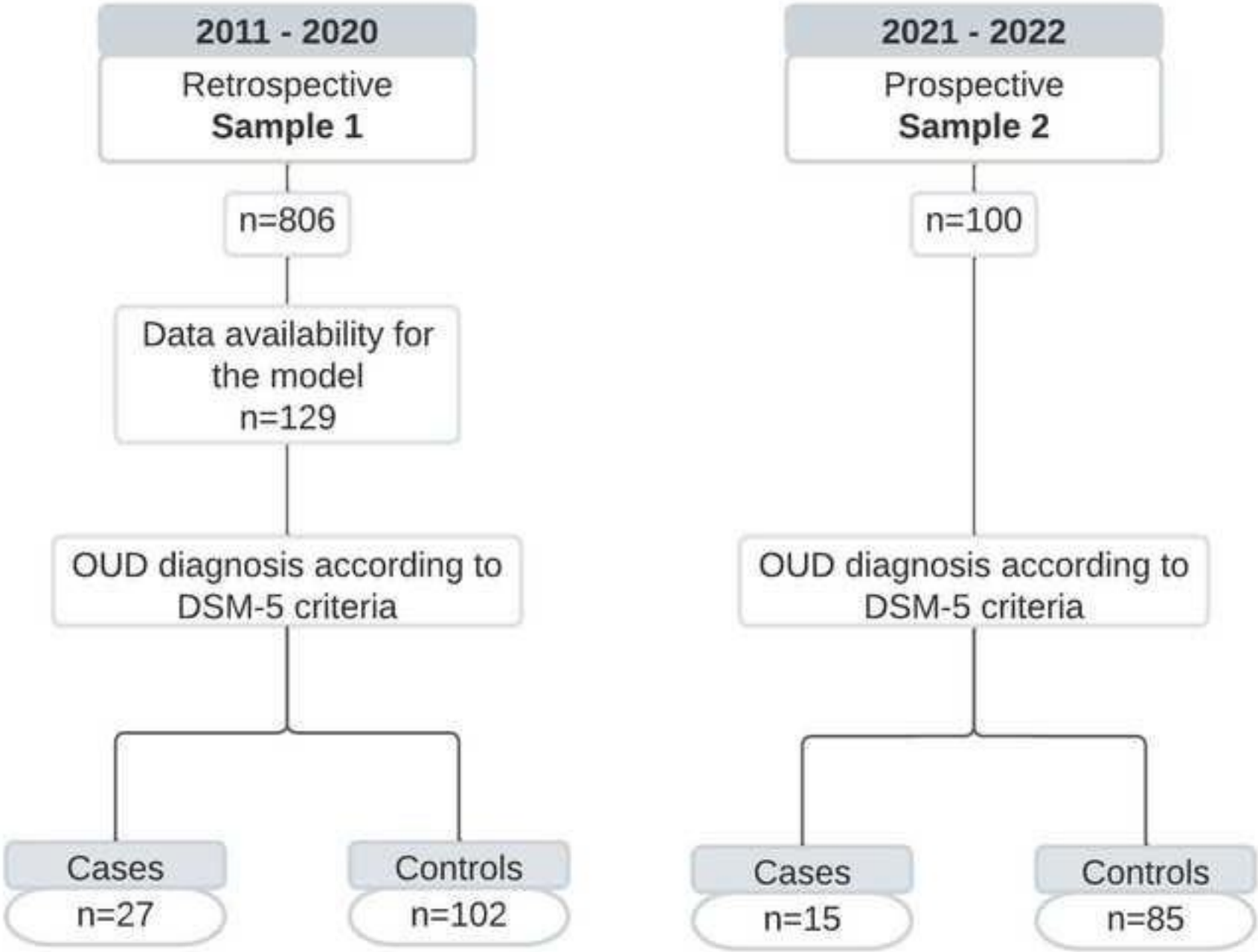
FIGURE LEGENDS

Figure 1. Flow chart of the patients included in a real-world Pain Unit setting.

Figure 2. Two-stage model for opioid use disorder (OUD): (1) Patient classification in Sample 1 or 2 and (2) OUD risk estimation based on the patient's characteristics (Sample 1 or 2).



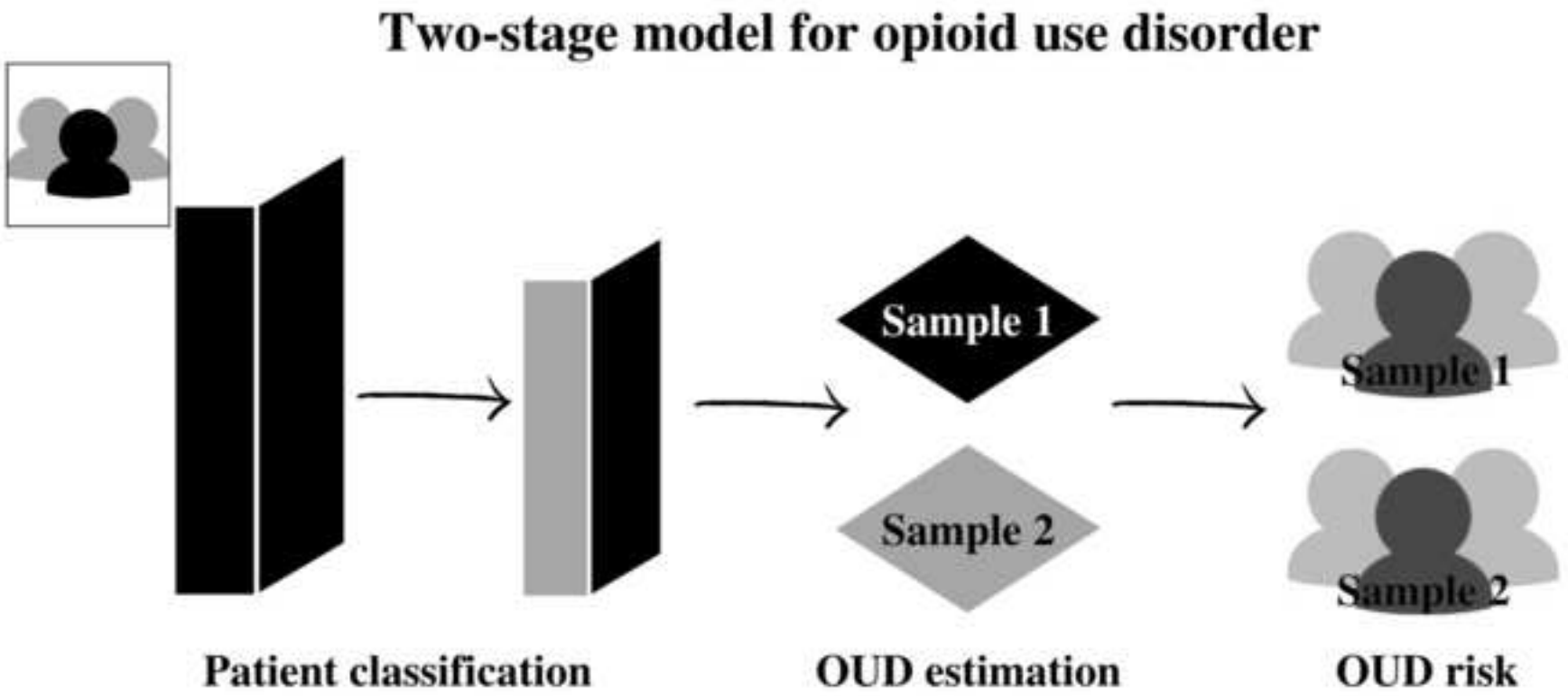


Table 1. Socio-demographic, clinical and pharmacological characteristics of Samples 1 and 2.

	Retrospective **Sample 1** (n=129)	Prospective **Sample 2** (n=100)
Sex (% female)	67	70
Age (years old) (mean (SD))	63 (52 - 72)	65 (52 - 73)
Employment status (%)		
Active	15	13
Retired	50	40
Work disability	21	26
Unemployed	7	6
Homemaker	7	15
Previous SUD (%)	18	25
Tobacco	**96***	71
Alcohol	4	25
Illicit substances	0	4
Incomes (%)		
Less than €500	20	5
Between €500 to 1000	67	53
More than €1000	13	**42***
Clinical outcomes (mean (SD))		
Pain intensity (VAS, mm)	61 (28)	**70 (26)***
Pain relief (VAS, mm)	38 (31)	41 (31)
Quality of life (VAS, mm)	46 (24)	46 (28)
Health Utility (0-1 score) (median (IQR))	0.514 (0.113-0.732)	0.252 (0.051-0.648)
Health resource use (%)		
Emergency room visits	30	42
Hospitalisations	14	25
Medication changes	50	51
Drug prescription (%)		
Non-opioid analgesics	34	**63***
NSAIDs	17	22
Tramadol	22	**45***
MEDD (mg/day) (median (IQR))	**80 (40 - 160)***	60 (33 - 108)
Oxycodone	**67***	14
Fentanyl	15	24
Tapentadol	11	**37***
Buprenorphine	3	**22***
Morphine	3	3
Hydromorphone	1	0
Immediate release opioids	**24***	10
Neuromodulators	52	60
Antidepressants	50	46
Benzodiazepines	35	**54***

NSAIDs: non-steroidal anti-inflammatory drugs; MEDD: morphine equivalent daily dose, VAS: visual analogue scale, SUD: substance use disorder.

***p-value<0.05 comparing Sample 1 vs. Sample 2*

Table 2. Justification for the inclusion of specific predictors in the model.

Variable	Selection Criteria
Socio-demographic	
Age	p<0.05 in Sample 1
Active	p<0.05 in Sample 1
Work disability	p<0.05 in Sample 1
Unemployed	p<0.05 in Sample 2
ED visit	Investigators' consensus and previous results [23]
Prior SUD	p<0.05 in Sample 1
Clinical	
Pain Intensity	p<0.05 in Sample 2
Quality of life	p<0.05 in Sample 2
Psychiatric AEs	Investigators' consensus and previous results [24]
Vomiting	Investigators' consensus
Sleep disturbance	p<0.05 in Sample 1
Pharmacological	
Tramadol	p<0.05 in Sample 1
Strong Opioids	p<0.05 in Sample 1
MEDD	p<0.05 in both Samples
Fentanyl	p<0.05 in both Samples
Benzodiazepines	Investigators' consensus and previous results [25]
Genetic	
OPRM1 Genotype	Investigators' consensus and previous results [9, 26]
COMT Genotype	Investigators' consensus and previous results [9, 26]
CYP2D6 Phenotype	Investigators' consensus and previous results [27]

AEs: adverse events, ED: emergency department visits due to pain and other causes, MEDD: morphine equivalent daily dose, SUD: substance use disorder.

Table 3. The logistic regression model chosen to classify patients in Sample 1 or 2.

		β-coefficients	95% CI	Std. Error	z-value	Pr (>|z|)[a]
Intercept		0.242	-1.53 to 1.95	0.873	0.277	0.782
Active		-1.950	-3.65 to -0.35	0.831	-2.347	0.019
Work disability		-1.740	-3.05 to -0.54	0.633	-2.750	0.006
Unemployed		-3.976	-5.71 to -2.51	0.809	-4.914	<0.001
MEDD		0.004	-0.00 to 0.01	0.003	1.515	0.130
Strong opioids		3.493	2.05 to 5.24	0.803	4.349	<0.001
Benzodiazepines		-2.626	-3.94 to -1.50	0.617	-4.254	<0.001
ED visits		-1.496	-2.64 to -0.45	0.552	-2.707	0.007
Psychiatric AEs		2.289	1.21 to 3.52	0.583	3.929	<0.001
COMT	GA	-2.159	-3.60 to -0.89	0.686	-3.147	0.002
	GG	-0.901	-2.56 to 0.70	0.824	-1.094	0.274

AEs, adverse events, ED: emergency department, MEDD: morphine equivalent daily dose
[a]p-value associated with the z-value.

Table 4. Independent opioid use disorder risk predictors selected in Sample 1.

		β-coefficients	95% CI	Std. Error	z-value	Pr (>|z|)[a]
Intercept		-0.622	-4.77 to 2.99	1.933	-0.322	0.748
Age		-0.057	-0.12 to 0.00	0.032	-1.798	0.072
Work disability		2.860	1.33 to 4.78	0.848	3.373	<0.001
MEDD		0.006	0.00 to 0.01	0.003	2.444	0.015
CYP2D6	PM	1.191	-2.19 to 3.90	1.442	0.826	0.409
	UM	3.299	0.82 to 5.97	1.255	2.628	0.009

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

Table 5. Independent opioid use disorder risk predictors selected in Sample 2.

	β-coefficients	**95% CI**	**Std. Error**	**z-value**	**Pr (>|z|)[a]**
Intercept	-1.713	-3.35 to -0.31	0.759	-2.256	0.024
Quality of life	-0.032	-0.06 to -0.01	0..014	-2.302	0.021
MEDD	0.005	-0.00 to 0.01	0.004	1.394	0.163
OPRM1 (AG/GG)	1.017	-0.36 to 2.56	0.727	1.400	0.162

MEDD: morphine equivalent daily dose [a]p-value associated with the z-value.

Table S1. Original model developed from Sample 1.

		β-coefficients	**95% CI**	**Std. Error**	**z-value**	**Pr (>|z|)[a]**
Intercept		1.633	-1.32 to 4.63	1.489	1.097	0.273
Age		-0.072	-0.13 to -0.03	0.025	-2.884	0.004
Work disability		2.012	0.86 to 3.25	0.604	3.331	0.001
MEDD		0.006	0.00 to 0.01	0.002	2.633	0.008
OPRM1 (AG/GG)		-1.424	-2.90 to 0.17	0.684	-2.083	0.037
CYP2D6	PM	0.075	-3.21 to 2.56	1.375	0.054	0.957
	UM	3.172	1.33 to 5.23	0.972	3.265	0.001

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

Table S2. Safety characteristics of Samples 1 and 2.

	Retrospective **Sample 1** (n=129)	Prospective **Sample 2** (n=100)
(%)		
Adverse Events (median (IQR))	**6 (3 – 8)***	2 (1 – 3)
Sleepiness	**55***	14
Dizziness	**32***	8
Nausea	**22***	9
Vomiting	**11***	3
Constipation	**63***	38
Itching	22	15
Sexual dysfunction	**11***	3
Loss of libido	**25***	10
Weight change	**40***	7
Headache	**36***	18
Skin redness	**24***	3
Dry skin	**42***	10
Dry mouth	**65***	39
Edema	**17***	6
Depression	**33***	9
Sleep disturbance	**39***	26
Nervousness	**47***	16
Loss of appetite	**29***	7

***p-value<0.05 comparing sample 1. vs. sample 2*

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	Tables
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*9-10*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.