INTERNATIONAL DOCTORAL THESIS

Prevalence and associated factors of the use of opioids in the treatment of chronic non-cancer pain. Perspective of the general Spanish population and the experience of patients.

Helena De Sola Perea

Cádiz (Spain) 2020

UCA Universidad de Cádiz

INTERNATIONAL DOCTORAL THESIS

Prevalence and associated factors of the use of opioids in the treatment of chronic non-cancer pain. Perspective of the general Spanish population and the experience of patients.

Helena De Sola Perea

Dissertation presented to obtain the doctorate degree in the Health Science program from the University of Cádiz.

DIRECTORS:

Dra. Inmaculada Failde Martínez and Dr. Alejandro Salazar Couso

Cádiz (Spain) 2020

"We are not isolated beings getting older; rather, we are parts of collective bodies that condition our health over and above individual characteristics."

"No somos seres aislados que envejecemos; más bien, somos partes de cuerpos colectivos que condicionan nuestra salud más allá y por encima de las características individuales"

Merlo J. (2011) Psychosocial Intervention 20, 109-118

“Context is something you swim in like a fish. You are in it. It is you”.

Dervin, B. (1997). Given a context by any other name: methodological tools for taming the unruly beast. 13-38

ACKOWNOLEDGEMENT 7
STRUCTURE OF THE THESIS 9
LIST OF SCIENTIFIC ARTICLES 10
LIST OF SCIENTIFIC COMMUNICATIONS 11
DISSEMINATION IN THE MEDIA 13
GLOSSARY 14
OPIOIDS MENTIONED THROUGHOUT THE THESIS 16
ABSTRACT 17
RESUMEN 21
INTRODUCTION 25
1. CHRONIC PAIN 25
1.1 Definition and classification 25
1.2 Epidemiology of chronic pain 26
1.3 Social and demographic determinants of chronic pain 27
1.4 Impact of chronic pain 28
1.5 Chronic pain and its pharmacological management 30
2. OPIOIDS 32
2. 1 A brief history of opioids 32
2.2 Recent history of opioids 33
2.3 The global burden of opioids 34
3. CHRONIC PAIN AND OPIOIDS 35
JUSTIFICATION 37
THE STORY LINE OF THE THESIS 38
OBJETIVES 39
GLOBAL AIM 39
SPECIFIC OBJETIVES 39
HYPOTHESIS AND RESEARCH QUESTION 40
METHODS 42
Study 1 42
Study 2 44
Study 3 45
Study 4 47
RESULTS 49

STUDY 1 50

Prevalence of therapeutic use of opioids in chronic non-cancer pain patients and associated factors: a systematic review and meta-analysis. 50

Table 1. Characteristics of the studies included in the systematic review. 68

Table 2. Prevalence of opioids' use and factors associated to opioid us in chronic pain population. 75

Table 3. Characteristics of the subgroups and results of the meta-analysis. 82

Figure legends 84

Supplementary material..... 87

STUDY 2 92

The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017. Differences between Spain and the United States. 92

Table 1A: Opioid-related deaths (ORD) in Spain in the period 2008-2012. 105

Table 1B: Opioid-related deaths (ORD) in Spain in the period 2013-2017. 106

Table 2A: Years of Live Lost (YLL) due to opioids in Spain in the period 2008-2012. 107

Table 2B: Years of Live Lost (YLL) due to opioids in Spain in the period 2013-2017..... 108

Figure legend..... 109

STUDY 3 112

Opioids in the Treatment of Pain. Beliefs, knowledge, and attitudes of the General Spanish population. Identification of subgroups through cluster analysis 112

Table 1. General characteristics of the population surveyed. 126

Table 2. Respondents' opinion associated with opioid use. 127

Table 3. Classification of the individuals into groups according to their opinions, beliefs and attitude towards opioids. 128

Table 4. Factors associated with the groups with the worst vision on opioids vs the group with a positive vision. 130

Figure legend..... 131

STUDY 4 132

Living with opioids: A qualitative study with patients with chronic low back pain. 132

Table 1. Characteristics of the sample 155

Table 2. Interview guide used for the semi-structured interviews. 156

Table 3. Quotations illustrating categories and theme. 157

GENERAL DISCUSSION 159

CONCLUSIONS 163

BIBLIOGRAPHY 165

ANNEXES 177

ACKOWNOLEDGEMENT

En primer lugar, quiero agradecer a mi directora de tesis Inmaculada Failde, por abrirme camino y guiarme en el mundo de la investigación. Gracias por darme la oportunidad y apostar por mí, con esa entrega y disposición que te caracteriza. Estos años han sido de trabajo y esfuerzo, pero sobre todo de aprendizaje y entusiasmo. Gracias por contagiarme el amor por la investigación. Asimismo, gracias por haberme dado la libertad y facilitarme los medios para la ejecución de esta tesis.

Un trabajo de investigación es siempre fruto de ideas, proyectos y esfuerzos previos. Por ello, agradecer a la Universidad de Cádiz y a la Fundación Grünenthal, y en particular a Juan Antonio Micó, por fomentar y promover la investigación. A la Sociedad Española del Dolor y a la Fundación Española del Dolor que, tras acogerme como miembro, financiaron mi estancia predoctoral en el extranjero y posibilitaron con ello la mención internacional de mi tesis.

A mi querida amiga y compañera Bego Ojeda, la que me trajo de la mano al “Observatorio del Dolor”. Gracias por tu insistencia. Nunca un consejo de alguien ha tenido una repercusión tan importante y enriquecedora en mi vida. Gracias.

Alejandro Salazar, mi mentor y co-director. La vida es mucho más fácil con personas como tú. Desde el principio me has tenido entre tus quehaceres. Gracias por tu paciencia, dedicación y búsqueda de la perfección. Gracias por tus ganas de enseñarme y conseguir que herede algunas de tus muchas virtudes. Gracias porque sin duda, sin ti nada sería lo mismo.

A los compis del Observatorio, por hacer que el trabajo en equipo sea tan fácil y fructífero. María Dueñas, has marcado el camino para los que hemos venido detrás. Gracias por habernos aconsejado siempre desde la tranquilidad y la experiencia. Eres el ejemplo a seguir. A las “LeTris”, Patricia Ortega y Leticia del Reguero, por ser un revulsivo de espontaneidad, generosidad y ganas. Es genial tener compis y coleguis como vosotras. A Jose A. Moral, por abrirnos un campo de investigación diferente. Jenifer Palomo, gracias por la paciencia de aguantarme en este último tirón.

Al grupo de Salud Pública de Cádiz, por su compromiso y dedicación con la Salud Pública. En especial a Juan Antonio Córdoba, por haberme hecho la mejor recomendación que me podían hacer sobre el lugar de la estancia. A Antonio Escolar, por tu atención y tu cariño, por recordarme

para qué sirve lo que hacemos, y no perder el punto de mira. A Pepe Almenara, gracias por tus indicaciones cada vez que he necesitado ayuda en la parte burocrática, guiándome en todo el proceso del doctorado desde entrevista hasta el final.

To Miguel San Sebastian and Anna-Karin Hurtig for accepting and facilitating my pre-doctoral stay in The Epidemiology Department at Umeå University, Sweden. A Isabel Goicolea, ha sido un placer haber coincidido contigo en esta experiencia. Me has enseñado y mostrado un nuevo camino en la forma de hacer investigación, además, de ser un apoyo muy importante. A Amaia Maquibar, por tu disponibilidad y tu crucial trabajo en el desarrollo del que espero sea el primero de muchos trabajos juntas. To Anne, Ida, Parvin, Jennifer, Iratxe, Edwina, Yue, Chama… for welcoming me and making me feel at home. All of you turned my stay in Umeå into one of the most enriching experiences of my life. Not only professionally, but also personally.

A los participantes de los estudios de esta tesis por compartir generosamente sus experiencias. También a los médicos y enfermeras de la Unidad de Dolor en el Hospital Universitario "Puerta del Mar", por permitirnos ser parte de su equipo durante un período de tiempo, especialmente el Dr. José Manuel Trinidad.

A mis amigues, una pieza fundamental en mi vida. Es un orgullo rodearme de personas como vosotras, con las que es tan fácil ser tú misma. Gracias por los momentos de escucha y apoyo.

A la familia Perea, por estar siempre todos a una y, en especial a mis abuelos, por la dedicación y el amor que me han dado.

A mi familia política, por enseñarme que en la vida es todo cuestión de actitud y positividad.

A mis padres, mis cimientos, por vuestro esfuerzo constante en darme lo mejor, darme libertad de elección y confiar en mis decisiones. Sois un orgullo de padres. A mi hermano Elio, las ramas de un árbol pueden crecer en diferentes direcciones, pero nuestra raíz es una. Os quiero.

A Lola, por compartir y formar parte del mejor de mis proyectos. Gracias.

STRUCTURE OF THE THESIS

This thesis is presented as a compendium of publications. In the case of this thesis, four articles have been included.

In addition, it is intended to obtain the International Mention, which adds requirements such as writing some sections in both English and Spanish. Therefore, the structure of the thesis is as follows:

Firstly, we present the list of articles on which this thesis is based, showing the progress and the evolution in our work. Then, we continue with the list of scientific communications presented in national and international congresses, the glossary and the list of opioids mentioned throughout the thesis.

The abstract is presented in both English and Spanish.

The introduction presents an overview of all the topics covered in this thesis, without particularizing in each article. After this, there is a section presenting a justification of the thesis and its storyline. This section has been included for clarity in the presentation of the results and to explain the whole process carried out.

The objectives are presented as a global aim that agglutinates and summarizes the objectives of each article, serving as a general aim of the whole thesis. Subsequently, the specific objectives of each study are detailed. For coherence in the exposition, the hypotheses are also separated into the specific hypotheses of each study.

The methods and the results sections are also detailed for each of the four articles. Next, there is a general discussion of the combined results of the four articles. The final section presents the conclusions of the thesis as a whole. The bibliography covers all the references that have been cited in the common part of the thesis, while the specific bibliography of each article can be found in its corresponding section.

LIST OF SCIENTIFIC ARTICLES

This thesis is composed of the following articles:

1. Prevalence of therapeutic use of opioids in chronic non-cancer pain patients and associated factors: a systematic review and meta-analysis.
2. The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017. Differences between Spain and the United States.
   This paper was published in the journal *Current Medical Research and Opinion* with a Journal Impact Factor of 2.345, included in the second quartile of the category Medicine, General & Internal category of the Journal Citation Report SCI section
3. Opioids in the Treatment of Pain. Beliefs, Knowledge, and Attitudes of the General Spanish Population. Identification of Subgroups Through Cluster Analysis.
   This article was published in the *Journal of Pain and Symptoms Management*
   with a Journal Impact Factor of 3.378, included in the first quartile of the Health Care Sciences / Services category of the Journal Citation Report SCI section.
4. Living with opioids: A qualitative study with patients with chronic low back pain. This article was accepted to be published in the *Health Expectations* with a Journal Impact Factor of 2.847, included in the first quartile of the Health Care Sciences / Services category of the Journal Citation Report SCI section

LIST OF SCIENTIFIC COMMUNICATIONS

The communications to congresses resulting from this work are:

1. De Sola H, Maquibar A, Failde I, Salazar A, Palomo J, Goicolea I. Experiences of chronic pain patients with long-term opioid treatment. Oral Communication. XXXVII Reunión Anual de la Sociedad Española de Epidemiología (SEE) y XIV Congresso da Associação Portuguesa de Epidemiologia (APE) XVIII Congreso SESPAS. ISSN 0213-9111. Oviedo. From 3rd to 6th September 2019.

2. De Sola H, Dueñas M, Salazar Couso A, Ortega-Jiménez P, del Reguero L, Failde I. Prevalence of therapeutic use of opioids in chronic non-cancer pain patients and associated factors: a systematic review and meta-analysis. Poster. XXXVII Reunión Anual de la Sociedad Española de Epidemiología (SEE) y XIV Congresso da Associação Portuguesa de Epidemiologia (APE) XVIII Congreso SESPAS. ISSN 0213-9111. Oviedo. From 3rd to 6th September 2019.

3. Salazar A, M Soledad, De Sola H, Moral-Munoz JA, Dueñas M, Palomo J, Del Reguero L, I Failde. The evolution of opioid-related mortality and potential years of life lost in Spain from 2013 to 2016. Differences between Spain and the United States. Poster. XXXVII Reunión Anual de la Sociedad Española de Epidemiología (SEE) y XIV Congresso da Associação Portuguesa de Epidemiologia (APE) XVIII Congreso SESPAS. ISSN 0213-9111. Oviedo. From 3rd to 6th September 2019.

4. De Sola H, Salazar Couso A, Dueñas M, Ortega-Jiménez P, del Reguero L, Failde I. Perspectiva de la población joven (≤35 años) sobre el uso de opiáceos en el tratamiento del dolor. Poster. XV Congreso de la Sociedad Española del Dolor. Palma de Mallorca. From 24th to 26th May 2018.

5. De Sola H, Salazar A, Dueñas M, Failde I. La visión de la población general española sobre el uso de los opiáceos en el tratamiento del dolor. Identificación de subgrupos de individuos a través de análisis cluster. Poster. XXXV Reunión Anual de la Sociedad Española de Epidemiología (SEE) y XII Congresso da Associação Portuguesa de Epidemiologia (APE). ISSN 0213-9111. Barcelona. From 6th to 8th September 2017.

6. De Sola H. Perspectiva de la población general española sobre el uso de los opiáceos en el tratamiento del dolor. Identificación de subgrupos de individuos a través de análisis clúster. Jornadas Doctorales EDUCA y EIDEMAR. Poster. Escuela de Doctorado Universidad de Cádiz. Cádiz. 4 December 2017.

7. Failde I, De Sola H, Salazar A, Dueñas M, Ojeda B, Sánchez-Magro I. Beliefs, opinions, and attitudes towards the use of opioids. A nationwide study in the Spanish general population. Poster. The 16th World Congress on Pain. Yokohama. Japan. From 26th to 30th September 2016.

8. De Sola H, Salazar A, Dueñas M, Failde I. Creencias, opiniones y actitudes de la población general hacia el uso de opiáceos en el tratamiento del dolor: resultados preliminares de una encuesta nacional. Poster. XIII Congreso de la Sociedad Española de DOLOR. Pamplona. From 1st to 4th June 2016.

DISSEMINATION IN THE MEDIA

1. Güell O. (22th October 2019). Las sobredosis de opioides causan más de 1.000 muertes al año en España. *El País.* Retrieved from https://elpais.com/sociedad/2019/10/20/actualidad/1571601031_438955.html

2. Cáceres C. (7th August 2018). La morfina es el opiáceo más conocido por los españoles, según un estudio. *Diario médico*. Retrieved from https://www.diariomedico.com/salud/la-morfina-es-el-opiaceo-mas-conocido-por-los-espanoles-segun-un-estudio.html

3. (15th June 2018). El 4% de los adultos con dolor crónico toma opiáceos. *Diario de Cádiz*. P. 16. Retrieved from https://www.diariodecadiz.es/cadiz/adultos-dolor-cronico-toma-opiaceos_0_1254774705.html

4. (15th June 2018). Perspectiva y opinión de los españoles sobre los opioides. Página web Universidad de Cádiz. uca.es/noticia/investigadores-de-la-uca-analizan-las-creencias-conocimientos-y-actitudes-de-la-poblacion-espanolafrente-a-los-opioides.

GLOSSARY

Abuse persistent or sporadic excessive drug use unrelated to acceptable medical practice.

Adherence the extent to which a person's behavior agrees with the recommendations from a health care provider.

Addiction a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Analgesic a medicine that reduces pain.

Dependence a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Diversion the movement of controlled drugs from licit to illicit distribution channels or to illicit use.

Long-term opioid therapy (LTOT) The use of opioids on most days for more than 3 months.

Misuse any use outside of prescription parameters, including misunderstanding of instructions, self-medication of sleep, mood, or anxiety symptoms, and compulsive use driven by an opioid use disorder.

Morphine a potent opiate analgesic drug frequently used in medicine.

Opiate the origin of the opium substance; that is, substances extracted from the capsule of the opium plant. The active opiates found in the opium poppy are morphine, codeine, thebaine and papaverine. By extension, the chemical products derived from morphine, such as oxycodone and hydrocodone, are also called opiates.

Opioid commonly referred to as prescription opioids, medications that have been used to treat moderate to severe pain. Analgesic agents used to designate endogenous or exogenous substances that have a similar effect to morphine on the central nervous system; they can be natural or synthetic.

Overuse to use more drugs than prescribed by the doctor.

Pain intensity term used interchangeably with pain severity and referring to the level of pain experienced and reported by the patient.

Pain severity see “Pain intensity”.

Prolonged-release or extended-release (formulation) are mechanisms used in tablets (pills) and capsules to dissolve a drug over time in order to be released more slowly and steadily into the bloodstream while having the advantage of being taken at less frequent intervals than immediate-release formulations of the same drug.

Tolerance a reduction in the sensitivity to a pharmacological agent following repeated administration. As a consequence, increased doses are required to produce the same magnitude of effect.

Withdrawal syndrome the occurrence of a complex syndrome of uncomfortable symptoms or physiological changes caused by an abrupt discontinuation or decrease in a dosage after repeated administration of a pharmacological agent. Withdrawal syndrome can also be caused by the administration of an antagonist.

OPIOIDS MENTIONED THROUGHOUT THE THESIS

	Drugs	Route of administration
Weak Opioids	Tramadol	- Oral forms: solid or liquids. - Parenteral administration (injection)
	Buprenorphine	- Sublingual tablets - Transdermal patch
Strong Opioids	Tapentadol	- Oral forms: Prolonged-release or immediate-release tablets
	Oxycodone	- Oral forms: Prolonged-release or immediate-release tablets - Parenteral administration
	Fentanyl	- Tablets to suck - Sublingual tablet - Oral tablet - Transdermal patch - Nasal spray.
	Morphine	- Prolonged-release tablets - Parenteral administration (injection)

ABSTRACT

Aims

The general aim of this thesis was to study the situation of opioid treatments for chronic non-cancer pain (CNCP). The specific aims were: first, to determine and synthesize the prevalence of the therapeutic use of opioids in patients with CNCP, and to analyze the factors associated with their use through a systematic review of the literature and a meta-analysis; second, to investigate the evolution of opioid-related mortality and potential years of life lost in the general population in Spain from 2008 to 2017 and to compare the results by gender and age with the United States; third, to describe the current perspective of the Spanish population toward opioid use in the treatment of pain and to identify groups of individuals based on their point of view on these drugs; and finally, to explore the experiences of patients with chronic non-malignant low back pain in Spain undergoing long-term treatment (>3 months) with opioids.

Methods

In the first study of the thesis, a systematic review of the current literature and meta-analysis were performed using two databases (PubMed and SCOPUS). For this purpose, original cross-sectional studies published in English or Spanish between 2009 and 2019 with the main objective of determining the prevalence of opioid use in CNCP patients were included. Search terms and search strategies were adapted to each database. The articles included in the meta-analysis were stratified according to the source of the sample, the type of pain, and the duration of the opioid treatment.

The second paper of the thesis is a descriptive study using retrospective annual data from 2008 to 2017 in the general population of Spain and the United States. Information on the population and opioid-related deaths stratified by age and sex was obtained from the Spanish National Statistics Institute and from the Centers for Disease Control and Prevention (CDC) WONDER Multiple Cause of Death Database, according to the ICD-10 codes. Years of life lost, crude and standardized mortality rates were calculated and compared with the results in US.

The third article included in the thesis is a cross-sectional study carried out on a nationwide representative sample of 1,299 Spanish adults. Data and information about beliefs, knowledge, fears, opinions and, attitudes towards the use of opioids were collected via a computer assisted telephone interview (CATI). A descriptive analysis of the variables studied and a cluster analysis were performed to identify groups of people based on these parameters. In addition, a

multinomial logistic regression model was developed to analyze the variables related to the clusters.

Finally, in the last part of the thesis, a qualitative study was performed using semi-structured interviews. Recruitment and data collection were conducted from April to October 2018. Fifteen participants were recruited from the Pain Clinic in Hospital Puerta del Mar. Inclusion criteria for the study were: adults suffering from chronic non-malignant low back pain and receiving long-term treatment (>3 months) with opioids. We conducted interviews until very similar experiences were described in the last interviews as in the previous ones. A constructionist perspective was adopted. The interviews were analyzed by the qualitative content method described by Graneheim and Lundman, and developed categories and themes discussed in the light biomedicalization theoretical framework.

Results

In the first article, we identified that of the 1062 potential articles found in the systematic review, 23 studies fulfilled the inclusion criteria. In the general population, the prevalence of long-term (>3 months) opioid use was 2.3% (95%CI:1.5%-3.6%), the prevalence of short-term opioid use was 7.3% (95%CI:4.3%-11.9%), and 5.8% among people with chronic low back pain (95% CI:0.5% - 45.5%). The prevalence of opioid use among patients from the health records or medical surveys was 41% (95%CI:23.3%-61.3%). Finally, in patients with musculoskeletal pain, the prevalence was 20.5% (95%CI:12.9%-30.9%) and 24.5% among patients with fibromyalgia (95%CI:22.9%-26.2%). A higher prevalence of opioid use was observed among the following groups: men; younger people; patients receiving prescriptions of different types of drugs; smokers and patients without insurance or with non-commercial insurance. In addition, non-white and Asian patients were less likely to receive opioids than non-Hispanic white patients.

The results of the second study showed that the crude rate of opioid-related deaths per 10^5 inhabitants has changed from 1.68 in 2008 to 2.25 in 2017 in Spain, with around 30,000 years of life lost per year. The most affected groups were middle-aged men and women over 65, and the main cause of death was accidental poisoning. The standardized rates per 10^5 inhabitants across the years were between 1.19 and 1.62 in Spain and between 11.17 and 20.68 in the US population.

In the analysis of the beliefs, fears, opinions and attitude towards opioids analyzed in the third article in the general Spanish population, three groups of subjects were identified: a group with a positive point of view (N=448) composed of people >65 years who would accept a treatment if prescribed and were less fearful of these drugs; a group with a moderate point of view (N=337) formed of younger subjects with university education, and who were better informed about opioids, afraid of these drugs (OR=2.67), and more frequently associated them with drowsiness (OR=2.58), nausea (OR=3.04), and tolerance (OR=2.16); a third group with a negative point of view (N=468), with a lower educational level who would more often reject treatment with opioids, and were more afraid of them (OR=3.95), considering that they may not be able to stop the treatment (OR=3.04) and that the opioids may produce tolerance (OR=3.03).

Finally, in the analysis of the experiences of people with chronic pain (CP) taking opioids, described in the fourth article, we developed one overarching theme - living with opioids: dependence and autonomy while seeking relief - which crosscut three categories: 1) The long pathway to opioids due to the invisibility of pain, 2) Opioids: from blind date to a long-term relationship and 3) What opioids cannot fix. The results show that the long and difficult process to obtain effective treatment was a fundamental part of the struggle to cope with pain, involving long-term relationships with the health system. The two first categories refer to the journey participants made to get a diagnosis and treatment with opioids, and their experiences during this long and difficult process, which was quite unique for each person. The third category describes the circumstances and situations experienced by the patients before and after the painful episode started, and how these influenced the whole process.

Conclusions

The results obtained in the different studies lead to the following conclusions:

- The prevalence of opioid use in patients with CNCP varies depending on the duration of treatment and the population analyzed, with higher prevalence in clinical studies based on health registries and occasional users. Age, race, and the access to the health service delivery system and its characteristics are the factors most related to the use of opioids.
- Regarding opioid-related mortality, an opioid overuse crisis does not seem a likely scenario in Spain. However, it is a social problem that requires special health surveillance, particularly in middle-aged men and women over 65.

- The different perspectives of patients regarding the use of opioids to treat pain should be taken into consideration by physicians when designing strategies to inform patients about the treatment of pain with opioids. This should promote their correct use, and prevent their misuse in particular.
- The experiences of patients should be considered to a greater extent by healthcare professionals when giving information about opioids and setting treatment goals. Greater consideration of the social determinants of health that affect chronic pain experiences might lead to more effective solutions to chronic pain.

RESUMEN

Objetivo

El objetivo general de esta tesis fue estudiar la situación de los tratamientos con opioides en pacientes con Dolor Crónico No Oncológico (DCNO). Para ello, en primer lugar, realizamos una revisión sistemática de la literatura y un meta-análisis para determinar y sintetizar la prevalencia del uso terapéutico de opioides en pacientes con DCNO, así como los factores asociados a su uso. En segundo lugar, nos planteamos investigar la evolución de la mortalidad relacionada con los opioides y los años potenciales de vida perdidos en la población general española entre 2008 y 2017, compararlos por género y edad y con los Estados Unidos. El tercer objetivo, fue describir la perspectiva de la población española sobre el uso de opioides en el tratamiento del dolor, e identificar grupos de individuos en función de su punto de vista con respecto a estos medicamentos. Finalmente, nos propusimos explorar las experiencias de pacientes con dolor lumbar crónico no oncológico bajo tratamiento de larga duración (>3 meses) con opioides.

Metodología

En el primer estudio de la tesis se realizó una revisión sistemática de la literatura y un meta-análisis utilizando dos bases de datos (PubMed y SCOPUS). Con este objetivo, se incluyeron artículos originales publicados en inglés o español entre 2009 y 2019 con un diseño transversal, cuyo objetivo principal era conocer la prevalencia del uso de opioides en pacientes con DCNC. Los términos y las estrategias de búsqueda se adaptaron a cada una de las bases de datos. Los artículos que se incluyeron en el meta-análisis se agruparon según la procedencia de los datos de la muestra, el tipo de dolor y la duración del tratamiento con opioides.

En la segunda parte de la tesis llevamos a cabo un estudio descriptivo utilizando datos anuales retrospectivos de mortalidad relacionada con los opioides de 2008 a 2017 en población general española y Estados Unidos. La información sobre la población y las muertes relacionadas con los opioides estratificadas por edad y sexo se obtuvieron del Instituto Nacional de Estadística de España y de la Base de datos de causas múltiples de muerte WONDER de los Centros para el Control y la Prevención de Enfermedades (CDC), de acuerdo con los códigos ICD-10. Se calcularon los años de vida perdidos y se aportan tanto en tasas de mortalidad brutas y estandarizadas y se comparan con los resultados en los Estados Unidos.

En la tercera parte de la tesis, realizamos un estudio de corte transversal a nivel nacional en una muestra representativa de 1.299 adultos españoles. Los datos fueron recolectados a través de entrevistas telefónicas asistida por ordenador (CATI) sobre las creencias, conocimientos,

miedos, opiniones y actitudes hacia el uso de opioides. Se realizó un análisis descriptivo de las variables estudiadas, un análisis clúster para identificar grupos de personas basados en estos parámetros y un modelo de regresión logística multinomial para analizar las variables relacionadas con cada grupo de individuos.

Finalmente, en la última parte de la tesis, realizamos un estudio cualitativo, usando entrevistas semi-estructuradas. El reclutamiento y la recolección de los datos se llevaron a cabo entre abril y octubre de 2018. Los datos fueron recogidos a través de 15 entrevistas a pacientes de la Unidad de Dolor en el Hospital Puerta del Mar. El criterio de inclusión para el estudio fue: adultos que sufrían dolor lumbar crónico no maligno y tomaban un tratamiento de larga duración con opioides. Se realizaron entrevistas hasta que en las últimas entrevistas se describían experiencias muy similares a las entrevistas previas. Se adoptó una perspectiva constructivista. Se realizó un análisis del contenido cualitativo tal y como describen Graneheim and Lundman, y se desarrollaron categorías y temas que fueron discutidos en el marco teórico de la biomedicalización.

Resultados

De los 1062 potenciales artículos encontrados en la revisión sistemática, 23 cumplieron los criterios de inclusión. A partir de la información analizada, se observó que, en población general, la prevalencia del uso de opioides de larga duración (>3 meses) fue 2.3% (IC 95%: 1.5% -3.6%) y la prevalencia del uso de opioides de tratamientos de corta duración fue 7.3% (IC 95%: 4.3% -11.9%). En los datos de los pacientes provenientes de registros sanitarios o encuestas médicas, la prevalencia fue 41% (IC 95%: 23.3% -61.3%). Finalmente, en pacientes con dolor musculoesquelético, la prevalencia fue 20.5% (IC 95%: 12.9% -30.9%) y en pacientes con fibromialgia, 24.5% (95%CI: 22.9%-26.2%). Además, se observó un mayor uso en hombres, en jóvenes, en pacientes que tienen prescritos diferentes tipos de medicamentos, en fumadores y en pacientes sin seguro o con seguro médico no comercial. Además, los pacientes no blancos y los pacientes asiáticos tenían menos probabilidades de recibir opioides que los pacientes blancos no hispanos.

Entre los resultados obtenidos en el segundo manuscrito, la tasa bruta de mortalidad relacionadas con los opioides por cada 10^5 habitantes ha cambiado de 1.68 en 2008 a 2.25 en 2017 en España, con alrededor de 30.000 años de vida perdidos por año. Los grupos más afectados fueron hombres de mediana edad y mujeres mayores de 65 años. La principal causa de muerte fue el envenenamiento accidental. Las tasas estandarizadas por 10 ^ 5 habitantes a

lo largo de los años se situaron entre 1.19 y 1.62 en España y entre 11.17 y 20.68 en la población de los Estados Unidos.

Respecto a los resultados obtenidos en el tercer artículo, en el que se analizan las creencias, miedos, opiniones y actitudes hacia los opioides en la población española general, destaca que se identificaron tres grupos de sujetos de acuerdo a su perspectiva sobre los opioides. Un grupo con un punto de vista positivo (N = 448) compuesto por personas >65 años que aceptarían un tratamiento con opioides si se lo recetaran y que tenían menos miedo a tomar estos medicamentos; un grupo con un punto de vista moderado (N = 337) formado por sujetos más jóvenes con educación universitaria, mejor informados sobre los opioides, temerosos de estos fármacos (OR = 2.67), y que lo asociaban con más frecuencia con somnolencia (OR = 2.58), náuseas (OR = 3.04) y tolerancia (OR = 2.16); un tercer grupo con un punto de vista negativo (N = 468), que se caracterizaba por tener un nivel educativo más bajo, que rechazaría con mayor frecuencia un tratamiento con opioides en el caso de que se lo recetaran, más miedo de tomarlos (OR = 3.95), considerando que es posible no ser capaces de detener el tratamiento (OR = 3.04) y que producen tolerancia (OR = 3.03).

Finalmente, en el análisis de los resultados obtenidos en el cuarto artículo sobre las experiencias de personas con DC que toman opioides, se obtuvo un tema principal: "Vivir con opioides: dependencia y autonomía mientras se busca alivio al dolor", que engloba tres categorías: 1) "El largo camino hacia los opioides debido a la invisibilidad del dolor", 2) opioides: de una cita a ciegas a una relación duradera y 3) "Donde los opioides no llegan". Los resultados muestran que la búsqueda de un tratamiento efectivo es fundamental en la lucha para mitigar el dolor, conllevando una larga relación con el sistema de salud. Las dos primeras categorías se refieren al largo y difícil proceso que hacen los participantes para obtener un diagnóstico y tratamiento con opioides, y sus experiencias durante esta búsqueda larga y difícil, que es única para cada persona. La tercera categoría describe las circunstancias y situaciones experimentadas por los pacientes antes y después del comienzo del episodio doloroso, y cómo han influido en todo el proceso.

Conclusiones

En vista de los resultados obtenidos en los diferentes estudios, se pueden extraer las siguientes conclusiones:

- La prevalencia del uso de opioides en pacientes con DCNO varía según la duración del tratamiento y la población analizada, con una mayor prevalencia en estudios clínicos basados en registros de salud y en pacientes con un tratamiento de corta duración. La edad, la raza, el

acceso y las características del sistema de sanitario son los factores más relacionados con el uso de opioides.

- Una crisis debida de uso excesivo de opioides no parece que sea un escenario probable en España. Sin embargo, es un problema social que requiere una vigilancia especial, particularmente en hombres de mediana edad y mujeres mayores de 65 años.

- El médico debe tener en cuenta las distintas perspectivas de los pacientes respecto al uso de opioides al diseñar estrategias para informarlos sobre el tratamiento del dolor con opioides. Esto debería servir para promover su uso correcto, especialmente evitando su mal uso.

- Las experiencias de los pacientes deben ser consideradas en mayor medida por los profesionales de la salud al aportar información sobre los opioides y establecer objetivos de tratamiento. Una mayor consideración de los determinantes sociales de la salud que afectan las experiencias de dolor crónico podría conducir a soluciones más efectivas en su tratamiento.

INTRODUCTION

1. CHRONIC PAIN

1.1 Definition and classification

Pain is a complex, multidimensional phenomenon that is defined by the International Association for the Study of Pain (IASP) as a "distressing experience associated with actual or potential tissue damage, with sensory, emotional, cognitive, and social components" [1]. In its acute form, pain is useful as it enables the protection of the physical well-being of an organism. By contrast, chronic pain (CP) exceeds the role of a warning signal and becomes a threat in itself [2]. As such, CP is no longer considered a symptom or a nerve impulse, but a disease itself, becoming the sole or predominant clinical problem in some patients [1].

CP is, by its nature, a disease which is difficult to evaluate and assess with physical explorations or complementary techniques. Therefore, it has been defined in terms of duration. Hence, the clinical history of the patient has a relevant role in the diagnosis. Although there is a non-specific set of cut-off scores to consider pain as chronic, the most recognized definition is set by the IASP, defining CP as a pain that persists or recurs for longer than three months [3]. However, this definition of CP does not include the specific characteristics of pain, such as frequency, taxonomy, intensity or severity, necessary for better patient care and to facilitate the comparison of research outcomes [4].

For the first time, the 11th Revision of the International Classification of Diseases (ICD-11) recognizes codes of CP in a systematic classification, representing an opportunity to improve the assessment of pain and treatment throughout all health care systems [5]. It includes seven main codes; one code for "chronic primary pain," where chronic pain is the disease, and six codes for chronic secondary pain syndromes, where pain is developed in the context of another disease. "Chronic primary pain" is defined as chronic pain in one or more anatomical regions and is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) and functional disability (interference in daily life activities and reduced participation in social roles). Chronic primary pain is multifactorial, since biological, psychological, and social factors contribute to the pain syndrome.

The 6 categories for chronic secondary pain considered in the ICD-11 are:

(1) Chronic cancer-related pain, i.e., all chronic pain that arises in the context of cancer or its treatment.

(2) Chronic postsurgical or post-traumatic pain, i.e., all chronic pain from surgery or accidental trauma.

(3) Chronic neuropathic pain.

(4) Chronic secondary headache or orofacial pain.

(5) Chronic secondary visceral pain, i.e., chronic pain arising from causes such as persistent visceral inflammation or vascular or mechanic causes.

6) Chronic secondary musculoskeletal pain, i.e., rheumatoid arthritis.

1.2 Epidemiology of chronic pain

Pain is a multivalent, dynamic, and ambiguous phenomenon that is notoriously difficult to quantify. Yet, even with such limitations, CP is undoubtedly a health problem that has reached worldwide epidemic proportions. Globally, 1 in 5 adults has been estimated to suffer from pain, and another 1 in 10 adults are diagnosed with chronic pain each year [6]. In Europe, CP affects 19% of the population, with important differences among countries, ranging from 13% in the United Kingdom and Ireland to 30% in Norway [7]. In Spain, the prevalence is 16.6%, and there is at least one adult with pain in 1 out of every 4 homes [10].

In the United States, it is estimated that 20.4% of adults has suffered CP [8]. Among Asian adults, CP ranges from 7.1% (Malaysia) to 61% (Cambodia and Northern Iraq) [9]. In Niger, Africa, the population suffering pain is younger than in Asia, the average age of the sufferers being 48.28 years and predominant in the male sex [10]. Therefore, CP affects all populations and all groups around the world, regardless of age, sex, race or ethnicity, although it is not equally distributed in all societies. The wide variation in prevalence reflects, in turn, differences in the sociodemographic, economic or climatological characteristics of the populations. A high prevalence of CP may reflect, for example, the aging of the population, adverse weather conditions or precarious working conditions. Likewise, this variety may also depend on how CP is defined and the evaluation methods used in epidemiological studies [11].

The duration of CP ranges from 2 to 15 years, the median in European countries being 7.0 years [7]. Spain, Finland and Portugal have the longest duration (around 10 years), the majority of the sufferers reporting moderate or severe pain [7,12,13]. The most common location of pain is in the back. More than 40% had joint pain, most frequently knee-pain. One in five had head or neck pain, and the same proportion had hand or leg pain [14].

It has been shown that the combination of osteoarthritis and rheumatoid arthritis is the most common cause of pain (42%) [15]. The annual prevalence of chronic low back pain has been reported to range from 15% to 45%. Disorders of the musculoskeletal system, such as low back pain, neck pain, other musculoskeletal pain, and osteoarthritis of the knee are also major health problems in many countries [16,17]. Trauma or surgery caused chronic pain in 15% of the cases. Rheumatoid arthritis and migraine headaches occurred in less than 10% [15].

1.3 Social and demographic determinants of chronic pain

In addition to the well-defined biological factors, there are a variety of factors that can influence an individual's pain. CP has been defined as a changing experience that may depend on culture, history and individual conscience. Likewise, social and demographic factors, including sex/gender, age, marital status, family relations, or socioeconomic status are all important elements of the context for pain experience [18,19].

Regarding sex/gender, the prevalence of CP is known to be higher among women [20]. However, despite a large volume of experimental research in this area, a consistent pattern of sex differences in pain sensitivity, expression and impact has not yet emerged. What is known from clinical studies is that women use more analgesic medication and are more sensitive to both the dosage and type of medication. Yet, experimental research has not successfully solved the key of the differences between sexes [21]. The increased incidence of CP conditions observed in females could result from greater susceptibility to such conditions or them being more likely than men to report pain [22].

Thus, to analyse the differences between men and women, it is also interesting to analyse them from a gender perspective, implying considerations of cultural contingencies and how the status of the sexes in different societies influences embodiment, expressions, and social cognition. Women's descriptions of symptoms, their explanations and consequences are shown to be dependent on social interaction with family members, friends, neighbours, work-mates, and doctors [23].

Regarding age, CP is also highly prevalent among older adults. In aging populations, the prevalence of multiple chronic medical conditions is increasing worldwide, with a growing impact on healthcare systems [10]. In addition, these aging problems are expected to increase [11] because of the increase in life expectancy and aging trends in the workforce, among other reasons [24]. CP is also a risk factor for accelerated cognitive deterioration, suggesting potential shared mechanisms between persistent pain (or its treatment) and dementia. Since older adults

are underrepresented in clinical trials testing treatments for chronic pain, the potential impacts of polypharmacy and frailty on reported outcomes and side effect profiles are largely unknown [25].

Socioeconomic factors have been identified as a predictor of the development of certain chronic diseases [26,27]. Furthermore, the co-occurrence of two or more chronic medical conditions has been proven to be more prevalent in deprived patients [28,29]. Deprivation is defined as a manifest material or social disadvantage relative to the local community or the broader society. A lower socioeconomic status is linked with poor access to products and services which, directly or indirectly, influence health, such as healthy food, housing conditions or medical care. The socioeconomic gradient in health can be further explained on the basis of psychosocial factors and stress associated with living in an environment of relative socioeconomic disadvantage. These psychosocial factors could be either direct (e.g. allostatic load) or indirect (e.g. unhealthy behaviours due to stress, such as excess drinking and smoking) [30]. Thus, deprivation should be defined not only as a manifest material or social disadvantage but also as a predictor of certain chronic diseases, it therefore being important that health services take it into consideration.

Interesting relationships between CP and family structure have been observed. Many serious and chronic illnesses require family and friends to take on the role of informal caregiver. Informal caregiving refers to activities involved in providing assistance to relatives or friends who are unable to provide for themselves [31]. In this vein, previous studies [32] have reported that individuals living alone or who are divorced have a higher prevalence of CP.

It is worth mentioning that, although these risk factors are sometimes difficult or impossible to modify, and therefore difficult to manage from a medical perspective, it is essential to recognize them, since they determine the susceptibility of a population to suffer from CP, and must be carefully evaluated.

1.4 Impact of chronic pain

- **Comorbidities**

CP is frequently associated with other pathologies. The presence of illnesses favours the appearance of pain and, in turn, pain determines the presence of other pathologies, but the nature of this relationships and the degree of contribution to the risk of suffering pain is not well established. However, patients with comorbidities are known to suffer more intensity of pain than those with CP alone [33]. The illnesses coexisting with pain can be physical and mental.

Depression and anxiety are among the most common mental problems frequently encountered in daily clinical practice. Like other illnesses/pathological conditions, the associations between pain and depression and/or anxiety seem to be reciprocal, although the evidence that pain predisposes depression and/or anxiety is more consistent than vice versa [34]. It has been observed that 50% of CP patients report depression, in contrast to 2% to 9% of the general population [33]. Rates of anxiety among pain patients (50%) are also markedly higher compared to reported rates within the general population using similar assessment tools [35]. The associated symptoms of depression and anxiety such as inability to concentrate, disturbed sleep, pessimistic mood, fatigue and loss of motivation may weaken patients' motivation to participate in rehabilitation and adhere to treatments [36,37].

- **Individual impact**

Apart from depression and anxiety, evidence suggests that sleep disturbances are also correlated with the intensity of pain [36,38,39]. Strong negative moods may increase or perpetuate the impact of sleep disturbances on patients' pain. In addition, it is not difficult to see how negative mood, sleep disturbances and pain might each act to accentuate one another if there is no intervening action to disrupt such a self-perpetuating cycle. Addressing negative mood is likely to have a beneficial effect on patients with pain or their perception of their ability to cope with pain [40].

Another important problem to consider is the effect of pain on everyday activities and participation in social roles. The negative emotions and irritability that frequently affect these patients have an impact on their interpersonal relationships and social functioning. Pain intensity is also significantly associated with engagement in social activities, individuals reporting more intense pain being more likely to report difficulties engaging in these activities [41]. Thus, the deterioration of physical functioning and pain-related mental health are the aspects that contribute most to hindering social integration capacities.

It has been argued that no other health problem causes as much disability as CP [14]. The physical limitations experienced by patients produce greater reliance on care and assistance, which is mostly provided by the family. Hence, family members usually have to carry out new duties, such as monitoring pain, giving medication and dealing with side effects of the sufferer. The uncertainty about performing these new tasks adequately could lead to both physical and psychological deterioration in the family environment [42], which can also perpetuate the problems associated with pain, since patients are concerned about the impact of their illness on others, resulting in guilt, distress and feelings of having become a burden to others [43].

Furthermore, it is notable that the individuals whose CP produces greater physical limitations are more likely to request sick leave [44]. Some authors [45] have shown that there is a significant relationship between CP and the individual's capacity to work. Almost a third of the individuals suffering CP needed to take sick leave and over 10% lost their jobs as a result of their CP. This problem also increases employer costs through reduced productivity, high turnover rates, absenteeism and health care expenses.

Therefore, the evaluation of patients should be multifactorial, involving emotional aspects, attitudes to facing pain, cognition, coping strategies and, additionally, the impact of the pain on their daily lives.

- **Social impact**

As already been mentioned, the impact of CP extends beyond the individual and has deep and reciprocal consequences for social networks involving family, friends and work. Hence, for a better understanding of the burden of CP, it is important to study it as a whole [46].

CP is a medical and a public health issue with an important socio-economic burden. In Europe, the total costs of CP represent 3–10% of the gross domestic product (GDP) [47], including direct and indirect costs. Direct costs are associated with analgesic drugs and nonpharmacological treatments, medical visits, hospitalizations, and complementary tests [48]. Indirect costs are associated with sick leave and presenteeism, and the intangible costs related to quality of life [49].

Hospitalization is the largest single component of direct costs, while social benefits (e.g. disability allowance and unemployment benefits) comprise the biggest single component of indirect costs. In Sweden in 2008, for example, the indirect costs of sick leave longer than 15 days and early retirement accounted for 59% of the total costs in patients with diagnoses related to CP, followed by outpatient and inpatient care [47]

Indeed, it is estimated that the annual economic cost of CP in Spain is over €3000 million (2.5% of the GDP). Likewise, people with CP are absent from the workplace 40% more than individuals who do not suffer from pain, in addition to being a 30% less productive [50].

1.5 Chronic pain and its pharmacological management

As mentioned above, pain is a complex phenomenon that is influenced by biological, psychological and social factors. Therefore, a multidisciplinary approach is recommended in the treatment of pain [51]. Taking into account the manifestations of the disease, the characteristics of pain, psychological coping skills and factors related to lifestyle, the treatment can include pharmacological and non-pharmacological interventions.

Some studies [12,52] have shown that around 70% of CP patients receive pharmacological treatment for their pain and that the initial pain assessment of a CP patient involves obtaining information about the location, duration, and characteristics of the pain, as well as the impact of persisting pain on various aspects of the person's life such as sleep, emotional state, relationships, development and physical function. The health-care provider should try to investigate the associations of the pain with any triggers by asking about any known aggravating and relieving factors. The health professional should also ask which pain management treatments have previously been used and their efficacy.

To establish pharmacological treatments, many doctors are governed by the therapeutic scale of the World Health Organization (WHO), basing their decisions mainly on the intensity of pain.

The therapeutic scale states three steps for the use of analgesics, starting with simple non-opioid analgesics (acetaminophen and prostaglandin synthesis inhibitors-NSAIDs-). The second step involves weak opioids, and in a third step, if the pain increases or is persistent, strong opioids are prescribed. Each step involves more analgesic power than the previous one and treatment always starts with non-opioid analgesics, constituting the basis of pain management in combination with adjuvant therapy with medications (e.g. anticonvulsants, antidepressants, etc.).

Adjuvant drugs, such as anticonvulsants and/or antidepressants may also be prescribed. In addition, once the third step of analgesia has been applied without adequate pain control, patients should be referred to Pain Clinic, where different therapeutic options will be proposed based on the predominant type of pain.

2. OPIOIDS

2. 1 A brief history of opioids

Figure 1. Papaver somniferum

The term opioids originally referred to the alkaloid compounds found in opium *(derived from the Greek word «opos»: juice*), obtained from the sap of the *Papaver somniferum poppy* (Figure 1), and has been used for thousands of years for recreational and medicinal purposes.

Records exist that the Sumerians first grew poppies in around 3400 BC. The use of opium spread through all the important civilizations of Eurasia, where it was used for medical purposes, including the treatment of pain [53]. At the beginning of the 19th Century, the German pharmacist Friedrich Wilhelm Sertürner became the first person to extract the active ingredient from poppy seeds and named the new compound morphine in honor of Morpheus, the Greek god of dreams. During the 19th Century, the consumption of opium, especially for recreational purposes, extended through the west, dependence on it increasing too. During the American Civil War (1861-1865), soldiers were given a hypodermic syringe and a supply of morphine, which they could inject as a painkiller if they suffered war injuries. When the war was over, American society was faced with a new epidemic, none other than addiction to the opioids that had been provided to the soldiers with a complete lack of control [54].

Due to the large number of morphine addicts, it was necessary to find a new substance with similar painkilling properties but without the addiction problems. In 1874, heroin, the first semi-synthetic opioid was created and given the brand name HeroinTM, from the word “hero”, who in Greek mythology was a person with special strength and ability. It was marketed by the company Bayer for the treatment of respiratory illnesses, and was advertised as being more effective and less addictive than morphine [55]. Sales of heroin quickly soared as its use extended around the whole world. However, the fact that it was highly addictive was not observed until 1913, when the manufacturer halted its production. Years later, with the help of technological advances, opioids and their derivatives were found to result in powerful addiction.

Consequently, the beginning of the 20th Century saw the first regulations for substances and their control. Progressive restrictions were imposed on the sales of heroin and other opioids. The 1914 Narcotics Tax Act in the United States made it illegal for doctors to prescribe opioids to treat addiction, and in 1925, the League of Nations completely prohibited the sale of heroin,

which resulted in increases in the underground trafficking of the raw materials for producing this opioid.

During the second half of the 20th century, most physicians prescribed opioids for acute and cancer pain. Opioids have improved the quality of life of millions of patients with oncological pain. In contrast, they were rarely prescribed to patients with CP. Some authors indicated [56] that a lack of knowledge about the use of opiates by health professionals (physicians) and users (patients) led to a negative image of opioids in general. Opioids were often associated with advanced disease, imminent death, illicit drug addiction, euthanasia, potential risks of abuse, excessive sedation, and fear [57]. This set of beliefs and inappropriate attitudes concerning the deleterious effects of opioid administration for pain relief were defined as opiophobia [58]. This has been related to the reduced prescription of these drugs by health professionals and lower consumption by patients [59].

2.2 Recent history of opioids

In the late 1990s, healthcare systems in the United States recognized pain as a ‘‘5th vital sign’’. Some years later, in 2001, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) established the mandatory early recognition and management of pain as a standard of care [60]. It is also noteworthy that Purdue Pharma, a pharmaceutical company which had developed OxyContin, an extended-release formulation of oxycodone, was involved in funding and providing educational videos and materials regarding the need for better pain management [61].

In the recent history of opioids, it is important to mention the fundamental role of OxyContin. OxyContin is a semisynthetic opioid that was first marketed as a less addictive alternative to “narcotic” drugs, such as morphine and heroin, being aggressively marketed in USA for the opioid-based management of moderate-to-severe cancer and non-cancer pain. More than half of the total number of OxyContin prescriptions were written by primary care physicians rather than pain specialists, and prescribed for all types of pain syndromes. As a result, the sales of opioid analgesics quadrupled in the US during 1999-2010. More specifically, from 2002-2009, the number of prescriptions for extended-release opioids rose from 9.3-22.9 million, an increase of 146% [62].

It is no coincidence that, in the same period, the number of opioid overdoses in America quadrupled according to the CDC. This massive increase in prescribing has occurred despite no overall change in the amount of pain Americans having been reported in that time period [63]. As

access to prescription opioids tightens, consumers increasingly are turning to dangerous street opioids, heroin, or fentanyl, either in isolation combined with cocaine or other drugs.

Apart from the wide use of oxycodone, the United States had the highest consumption of morphine worldwide, twice that of the European Union as a whole. Morphine use is well controlled in Europe and has declined in recent decades in many European countries, with the main exceptions of Austria and Switzerland [64], even though the WHO indicated that morphine, the oldest known opioid, is the gold standard for the treatment of moderate to severe pain [65].

Although the consumption of opioids between 2000 and 2008 increased in Europe, the use of oral morphine has decreased. Some authors concluded that this is because the behavior of physicians is still largely contrary to guidelines, suggesting that cultural rather than legal factors are mainly responsible for morphinophobia [57]. Reasons for the limited consumption of morphine in other countries may include stigma, the shift from oral to other formulations, its possible side effects, as well as its low costs, that leave small profit margins for the manufacturers [64].

The most frequently used opioid in Europe is fentanyl. Its increased use has largely contributed to the rise in total opioid consumption, particularly since the early 2000s. Its easy administration and patient compliance, along with strong marketing of its transdermal use, may explain such an increase. Spain is the only country in Southern Europe in which fentanyl consumption is at the level of Western and Northern European countries. This could be due to the regulation adopted in 1995 and several informative campaigns promoted since the early 2000s to facilitate the use of opioids [61]. In contrast to the United States, oxycodone consumption has increased modestly in Europe, and is still much lower than that of fentanyl.

Many factors have contributed to the unprecedented increase in opioid use and abuse in recent years in the United States. One is the inadequate training received by physicians in pain management; another is the heightened awareness of undertreated pain among the general public and the media, leading to an increasing demand for opioids from patients, in particular those with mental health or substance abuse disorders[66].

2.3 The global burden of opioids

As mention above, opioid prescription has become more common in the general population in the last two decades [67]. This trend has occurred in several countries. However, in some of them, such as the USA and Canada, it has been accompanied by an increase in reported opioid abuse and deaths [68]. Several authors [69] have underlined the consequences of opioid over-prescription in the USA, estimating that 1 in 65 deaths was opioid related in 2016, representing an enormous burden in years of life lost (YLL). Indeed, the YLL from opioid-related deaths exceed those

attributable to hypertension, HIV/AIDS, and pneumonia. Loss of life due to opioid overdose poses a considerable societal burden, especially among adults aged 25 to 34 years, where this burden is highest. In this age group, 1 in 5 deaths is opioid related in the USA. Moreover, the recreational use of opioids among adolescents is increasing, with approximately one in seven high school seniors and university students reporting past non-medical use of these drugs [70].

In addition, prescription opioid overdose, abuse, and dependence implies high costs. In the USA, it was estimated that the societal costs attributable to the abuse of opioid prescription rose from $55.7 billion in 2007 [71] to $78.5 billion in 2013 [63]. This cost is attributable to direct healthcare costs, costs related to losses of productivity, and costs to the criminal justice system. However, many of them are inestimable, including the social impact on opioid-dependent people, and the suffering of family members as witnesses to addiction or to fatal overdose [63].

By early 2017, there were daily reports of the diversion and misuse of prescription opioids within a number of states and counties across the USA. In fact, the crisis in opioid overdose deaths exceeded all other drug-related deaths or traffic fatalities [63]. Thus, in October of 2017, President Donald Trump called for the ongoing opioid epidemic to be declared a nationwide public-health emergency [72].

3. CHRONIC PAIN AND OPIOIDS

Pain is the leading cause of disability and work absence throughout most of the industrialized world, especially when it becomes chronic [73]. Population growth and aging are strongly related to this fact. As life expectancy increases, people are living a greater number of years with impaired health and more disability [17]. Additionally, the percentage of people with pain has grown worldwide due to the adoption of lifestyle behaviors that are known to increase cancer risk and pain as a consequence, such as smoking, poor diet, physical inactivity, and reproductive changes [74].

Clinical evidence has long supported the use of opioids as a first-line treatment for moderate to severe pain, particularly for pain related to cancer [75]. This has been reflected in increased opioid consumption since the late 1980s, partly a result of the efforts made by the WHO and other organizations to assert the essential need of opioid analgesics for the treatment of chronic cancer and non-cancer pain in particular [64].

However, despite the WHO recommendations, opioid use in the context of CNCP has sparked controversy since patients with CP have reported a high incidence of adverse effects of opioid therapy, including dependence, overdose, and withdrawal [76].

The concerns of patients regarding possible adverse effects, the limited knowledge of physicians about pain management and the lack of a proper evaluation of pain at the diagnostic stage may explain why the use of opioids to treat CP remains limited in comparison with cancer pain [64]. In addition, some authors [77] have highlighted that the media has focused on the negative effects of opioid use for pain, such as stigma and misuse, rather than the positive benefits of increased pain relief and improved quality of life.

In some countries, apart from social, cultural, and educational factors, there are regulatory and governmental restrictions which negatively affect prescribing by physicians and occasionally lead to undertreatment. Even though the regulation of controlled drugs is not intended to impede legitimate prescribing for appropriate medical purposes, the impact of controlled substance therapy, specifically with chronic non-malignant pain, continues to be a contentious issue for pain specialists [78].

In addition, treatment with opioids also provokes controversy regarding the benefits it provides in CP patients since some studies [79,80] show that most people who use opioids continue to report moderate or severe pain and that functional improvements are often scarce. On the contrary, some professionals have reported that patients treated with opioids seem to experience significant functional benefits in addition to reductions in pain intensity, which reflects the variability of response to treatment depending on the patient [76].

JUSTIFICATION

Considering the foregoing, it is justified to review the prevalence of opioid use in patients with chronic non-oncological pain in the scientific literature, as well as to explore the factors associated to their use, since the prevalence of their use varies widely according to the country and the circumstances of the patients.

In countries where the prescription of opioids has increased considerably in recent years, it has been observed that people frequently misuse these drugs, this becoming the first cause of death in some countries. Hence, due to the need for the safe and rational use these drugs, we consider it of interest to investigate the evolution of opioid-related mortality and potential years of life lost in the general population in Spain from 2008 to 2017 and to determine the differences between Spain and the USA.

It is also noteworthy that the prescription of opioids has increased or decreased throughout history depending on the beliefs of health professionals and patients about these drugs, leading to undertreatment of the pain in some cases and misuse/overuse of these drugs in others. Therefore, we considered it necessary to know the perspective of the general Spanish population towards opioids in the treatment of pain to know in which point we are located.

Furthermore, there are certain controversies regarding the benefits and the consequences provided by opioid treatment. Therefore, we considered that it is important to know the experience of the patients who are under treatment with this type of medication.

THE STORY LINE OF THE THESIS

The initial situation that provided the motivation for this thesis was the low opioid prescription rates observed in Spain compared with other countries. When the doctoral project started in 2016, we deliberated if CP could be somehow undertreated due to perceptions and negative beliefs associated with opioids. However, at the beginning of the following year, a report was released by the "Spanish Drug Agency" commenting on the rise of opioid use in Spain [81]. For this reason, we decided that the first step would be to investigate the prevalence of the use of opioids through a systematic review of the literature.

Later that year (2017), a public health crisis and a state of alert associated with an increase in opioid-related morbidity and mortality were declared in the United States. We decided it was crucial to know if Spain was following the same tendency regarding the evolution of opioid-related mortality and potential years of life lost. That was, therefore, the aim of the second paper.

After the literature review, and taking into account the importance of the attitude, knowledge and beliefs of the population about opioids, the aim of the third paper was to know the perspective of the Spanish population related to the use of this analgesic.

Then, the next natural step was to know the experiences of CP patients under long-term treatment with opioids. To this end, in the fourth (and last) manuscript, we gave voice to the protagonists of this situation through the methodology of qualitative research.

OBJETIVES

GLOBAL AIM

The main aim of this thesis was to study the situation of the opioid treatments for chronic non-oncological pain.

SPECIFIC OBJETIVES

- ***Study 1***. *Prevalence of therapeutic use of opioids in chronic non-cancer pain patients and associated factors: a systematic review and meta-analysis.*

To determine the prevalence of the therapeutic use of opioids in patients with CNCP and to analyze the factors associated with their use through a systematic review of the literature.

To provide a summary measure of the information obtained through a meta-analysis.

- ***Study 2.*** *The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017. Differences between Spain and the United States.*

To investigate the evolution of opioid-related mortality and potential years of life lost in the general Spanish population from 2008 to 2017 and to compare them by gender and age.

To know the differences between Spain and the USA.

- ***Study 3.*** *Opioids in the Treatment of Pain. Beliefs, Knowledge, and Attitudes of the General Spanish Population. Identification of Subgroups Through Cluster Analysis.*

To describe the current beliefs, opinions, and attitudes of the Spanish population toward opioid use in the treatment of pain.

To identify groups of individuals based on their point of view regarding these drugs and to analyze the factors that influence this perspective in each of the identified groups.

- ***Study 4.*** *Living with opioids: A qualitative study with patients with chronic low back pain.*

To explore the experiences of patients with chronic low back pain in Spain undergoing long-term treatment with opioids.

HYPOTHESIS AND RESEARCH QUESTION

Based on the previous literature, specific hypotheses have been stated for each study.

- *Study 1. Prevalence of therapeutic use of opioids in chronic non-cancer pain patients and associated factors: a systematic review and meta-analysis.*

1.1 The prevalence of opioid use found in the studies of health records or medical surveys will be higher than the prevalence found in studies carried out in the general population.

1.2 The prevalence of short-term opioid treatments will be higher than long-term opioid treatments.

1.3 Patients with musculoskeletal pain will be more likely to receive opioid treatment than patients with other pathologies.

1.4 Patients with more types of drugs prescribed will be more likely to receive opioid treatment.

- *Study 2. The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017. Differences between Spain and the United States.*

2.1 The crude rate of opioid-related mortality will be higher in 2017 than in 2008 in Spain.

2.2 The number of opioid-related years of life lost will have increased in this period.

2.3 The group most affected by opioid-related mortality will be middle-aged men.

2.4 The standardized rates in the US population will be higher compared to standardized rates in Spain.

- *Study 3. Opioids in the Treatment of Pain. Beliefs, knowledge, and attitudes of the General Spanish population. Identification of subgroups through cluster analysis.*

3.1 The general Spanish population will refer beliefs about opioids similar to those described in other countries when relating them to concepts such as pain, illegal drugs or cancer.

3.2 Morphine will be the best known and correctly identified as an opioid by the population.

3.3 The prevalence of the Spanish population taking an opioid treatment will be similar to other southern European countries, such as Portugal.

3.4 The opinions, fears and attitude of the Spanish general population towards opioids will be determined by sex, age and previous contact with the treatment.

3.5 People that reject opioid treatment will do so for fear of side effects.

3.6 Taking into account the perspective of the Spanish population, we can differentiate at least 3 groups of people according to their point of view towards opiates.

- *Study 4. Living with opioids: A qualitative study with patients with chronic low back pain.*

4.1 What are the experiences of people with non-oncological chronic low back pain under long-term treatment with opioids in Spain?

METHODS

Study 1. *Prevalence of therapeutic use of opioids in chronic non-cancer pain patients and associated factors: a systematic review and meta-analysis.*

Study design

A systematic review of the current literature and meta-analysis.

Search strategy

The search was performed in the PubMed and SCOPUS databases. Original cross-sectional studies published from 2009 to 2019 in English or Spanish were included. The terms/keywords of interest were “opioid”, “analgesics”, and “pain”. The terms were combined with the tag for searching in the title, abstract and keywords. The search terms and search strategies were adapted to each database. Once the search strategies for both databases were executed, we imported all the references found into the Covidence online tool[82]. The process of duplicate removal, screening, data extraction and risk of bias analysis were performed by this web-based systematic review tool.

Eligibility criteria

According to the predefined inclusion criteria, an article was selected when its main aim was to determine the prevalence of the use of opioids in CNCP humans (all ages), provided these data were shown within the paper or it was possible to calculate them from it. Articles related to CNCP located in specific body regions (e.g. musculoskeletal CP) were also included. Thus, the term “chronic non-cancer pain” was not included in the search strategy in order not to limit the searches to studies presenting only data from general CNCP.

Studies including patients with cancer pain, focusing on the opinions or attitudes of physicians about opioid prescription or on the disorders derived from their consumption were excluded.

Study selection

The study selection was performed by two authors who independently screened the title and abstract of all of the papers. Shortlisted studies were then analyzed in depth according to the inclusion criteria and their reference lists were also screened to identify studies that could be included in the review. The quality of the studies were assessed following the Critical Appraisal

Checklist for Analytical Cross-sectional studies from the Joanna Briggs Institute [83]. This checklist consists of 8 items.

Extraction of data

From the selected papers, information was extracted about the primary aim of the study, characteristics of the population studied, sample source, sample size, method for data retrieval, and response rate. Likewise, the definition of CP considered in each article, prevalence of CP in the population studied, prevalence of opioid use, the method for obtaining this prevalence data, and the factors associated with opioid use were collected.

Statistical analysis

A descriptive analysis of the characteristics of all the studies included in the systematic review was carried out, and a meta-analysis was subsequently performed. The articles that were included in the meta-analysis were stratified in two groups according to the source of the sample: data from the general population or from health registries/medical surveys. In turn, articles from the general population were stratified depending on the duration of opioid treatment: long-term (commonly defined as over 3 months [84]) or short-term (less than 3 months) and depending on the type of pain: general CNCP or chronic low back pain (CLBP). The articles with data from health registries/medical surveys were stratified depending also on the type of pain: general CNCP, fibromyalgia or musculoskeletal conditions (which include musculoskeletal pain, osteoarthritis and CLBP, following The International Classification of Diseases [85]. Studies performed in populations older than 65 years [86], those that could not be compared with any other study, such as those focused on a specific type of pain [87,88] or from specific sample source [89,90], or those focused on visits rather than the patients (with the potential overlapping of the records of the patients) [91,92] were excluded from the meta-analysis.

From the studies included, the summary measure (prevalence of opioid use, defined as the number of subjects who take opioids divided by the number of individuals with CNCP) was calculated with 95% confidence intervals (CI). Studies were weighted according to the prevalence effect size and the inverse of the study variance.

The heterogeneity between the studies was determined by the DerSimonian and Laird method with Cochran's Q statistic. As heterogeneity was observed in all the study subgroups, random effects models were performed, which considers the variability of the results due to the differences between the studies. The proportion of total variability due to the heterogeneity of

the studies was estimated using the I^2 values. The results of the meta-analysis are presented in forest plots. To assess the potential publication bias in groups with three or more studies, a funnel plot, along with Begg's rank correlation and Egger's weighted regression methods, were used. A two-tailed $p<0.05$ was considered indicative of a statistically significant publication bias.

Finally, a sensitivity analysis was carried out in the groups with three or more studies to determine the influence of each of the studies on the overall estimate of the effect, and therefore the robustness or stability of the final measurement obtained, through influence graphs. The data were analyzed using Comprehensive Meta-Analysis Software Version 3.0 (Biostat, Englewood, NJ, USA).

Study 2. ***The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017. Differences between Spain and the United States.***

Study design and population

A descriptive study using the retrospective annual data from 2008 to 2017 in the Spanish and US general populations. It is based on the methodology previously used by Gomes et al [69] in the USA to compare populations.

Procedure and Instruments

Information on the population and Opioid Related Death (ORD) stratified by age and sex was obtained from the Centers for Disease Control and Prevention (CDC) WONDER Multiple Cause of Death Database for the USA [93], and the Spanish National Statistics Institute (INE) [94]. The INE keeps the "statistics of deaths according to the cause of death" [95] following the criteria established by the WHO in the International Classification of Diseases (ICD-10) [96]. This statistic provides information on mortality according to the basic cause of death and its distribution by sex and age, among other factors. A similar methodology is used by the CDC.

From these data, and according to the ICD-10 codes [96], we retrieved information on ORD specifically due to accidental poisoning (X40–X44), intentional self-inflicted poisoning (X60–X64), aggression (X85), and poisoning of undetermined intent (Y10–Y14).

Statistical Analysis

For each year (from 2008 to 2017), we report stratified (by sex and age) data on the number of ORD, crude and standardized rates of ORD per 10^5 inhabitants, years of life lost (YLL), YLL per 10^4 inhabitants, and the number of deaths by type of opioid-related death. The crude rate of ORD is defined as the quotient between the number of ORD and the total population, expressed

in terms of number of deaths per 10^5 inhabitants. YLL are defined as the sum of the remaining years that a person who has prematurely died due to opioids has not lived; that is, the sum of the difference of life expectancy and the age of death of each person who has prematurely died due to opioids. Type of opioid-related death is a qualitative variable classifying the deaths by accidental poisoning, intentional self-inflicted poisoning, aggression, and poisoning of undetermined intent. The data presented are tabulated in absolute terms and crude rates. We report the number of deaths by type of death and year in Spain in bar plots, for the total population, and for men and women separately.

The evolution over time of the standardized rates of ORD among the total population, men and women is presented in a line chart for both Spain and the USA. For this comparison, we standardized the data taking into account the different distribution of the two populations by ages. For this standardization, the direct method was used: the rate of each stratum in each population was applied to the world standard population provided by the WHO [97] to obtain data on the expected deaths, which were subsequently added and divided by the total standard population to obtain the standardized rates per 10^5 inhabitants. We report these standardized rates in a line chart. All the analyses and figures were performed using the Excel 2016 software.

Study 3. *Opioids in the Treatment of Pain. Beliefs, Knowledge, and Attitudes of the General Spanish Population. Identification of Subgroups Through Cluster Analysis*

Study design and participants.

A cross-sectional study carried out on a representative sample of the general adult population in Spain.

Sampling Method

The eligible population was obtained using a multistage stratified sampling method. The Spanish territory was divided into eight strata or areas based on geographical and historical boundaries. For each stratum, 20 municipalities were randomly selected, taking into account the Spanish rural/urban ratio of 25:75, and considering municipalities with <10,000 inhabitants as rural and those with >10,000 inhabitants as urban areas. The total number of subjects required for the study was distributed in proportion to the size of each municipality and according to the sex and age distribution of the population (18 to 44, 45 to 64 and 65 or over). The exclusion criteria were individuals younger than 18 years, lack of a landline telephone at home, or the inability to respond to the questionnaire.

Sample Size

The sample size was determined based on the study of Schiller et al. [98], in which it was estimated that 50% of subjects were afraid of taking morphine. A confidence level of 95% and a precision level of 5% were set. The required sample size was established at 1,155 subjects. The amount of randomly-selected telephone numbers was three times that of the required sample size, in anticipation of non-response.

Procedure and Instruments

Data were collected via a computer-assisted telephone interview using the Skype and the SurveyMonkey platforms, whereby the interviewers recorded the data while the interview was being conducted.

Survey Structure and Topic

The survey was structured in six blocks of questions:

The first block was designed to obtain personal information; the second block was related to the respondents' beliefs about opioids, and in this case the information was collected from an open-ended question in which the interviewees were asked what was the first thing that came to mind when they heard the word opioid; the third block revealed the level of the respondent's contact with opioids and their knowledge of them; the fourth explored the fears (side effects, death, becoming an addict, not achieving the desired results, and death) related to the intake of opioids; the fifth block collected the opinions of the responder regarding this type of treatment (tolerance, dependence, and severity of the disease); and the sixth addressed the responders' attitude toward these drugs. This attitude was obtained by means of a question that asked whether the respondent would agree to treatment with this medication if their doctor prescribed it. The questions that set out to collect information about beliefs, fears, and opinions were assessed using a five-point Likert scale (not at all, a little, some, quite a lot, and a lot).

Statistical Analysis

A descriptive analysis was performed of the variables studied, showing the frequency, central tendency, and dispersion. In addition, a hierarchical cluster analysis was performed to establish groups of individuals or patterns according to the subjects' opinions, fears, knowledge, level of contact, and attitudes toward opioids. The Euclidean distance between the groups and cluster formation criteria were used. Subsequently, the differences between the groups were analyzed

using Chi-squared tests. In addition, a multinomial logistic regression model was established to determine the factors associated with each of the groups previously identified in the cluster analysis. The covariates included in this model were the significant variables identified in the bivariate analysis.

Study 4*. Living with opioids: A qualitative study with patients with chronic low back pain.*

Study design

A qualitative study in which data were collected through 15 semi-structured interviews. Individual interviews were analyzed by qualitative content analysis as applied in health sciences research [99].

Participants and Data collection

Recruitment and data collection were conducted from April to October 2018. The participants were recruited from the Pain Clinic in Hospital Puerta del Mar. Inclusion criteria for the study were: adults suffering from chronic non-malignant low back pain and receiving long-term treatment (over three months) with opioids. Patients taking opioids for less than three months or with a pain origin other than chronic non-cancer low back pain were not included.

All the patients were recruited after a routine physical evaluation in their medical visit to the Pain Clinic. Previously, their medical data, including information on prescribed medications from the records, were evaluated and discussed by the clinician and interviewer. If the person met the inclusion criteria after an analysis of their medical records and their medical visit and physical evaluation, the practitioner explained to him or her the aim of the study. All eligible patients were approached by the physician. After this initial approach by the physician, the interviewer met the potential participant and they went to a quieter place in a clinical setting for the interview, before which the participant was shown a letter with more comprehensive information about the study and its aim. The participants were left alone to read and think carefully before giving their written informed consent. When they finished reading it, they had the opportunity to ask questions about the study, after which the interview took place. Individual, semi-structured, qualitative interviews following a guide were conducted in Spanish. The guide was based on open-ended questions developed with guidance from the literature regarding chronic pain experiences and factors associated with the use of opioids. Aspects related to the origin of their pain, opioid belief, information received about treatment, opioid experience, their family and social support were also of particular interest. If a specific topic that was not included in the first version of the interview guide came to light spontaneously in a

specific interview, it was added and asked in the subsequent interviews. Interviews were audio-recorded, transcribed verbatim and anonymized. All names used are pseudonyms. We conducted interviews until experiences were described that were very similar experiences those in earlier interviews.

Analysis

We adopted a constructionist perspective. We analyzed all the interview transcripts following qualitative content analysis as described by Graneheim and Lundman [99]. The data analysis was inductive, and thus the category construction was data-driven; no initial hypothesis guided the preliminary coding and subsequent development of categories. However, in the analysis of the results presented in the Discussion section of this paper, we followed the biomedicalization framework.

Interview transcripts were entered into Atlas.ti 1.0.16 to support the coding process. At the beginning of each interview transcript, a brief log of the interview was written, including information about the time, duration, and the feelings and perceptions of the interviewer during the conversation in order to help with the analysis process. The researcher who conducted the interviews transcribed them verbatim.

To carry out the qualitative content analysis, two researchers read the transcripts independently and assigned codes line-by-line to meaningful pieces of the interview transcripts. Then, the researchers met to compare and refine codes, which were then grouped into categories. The material was grouped into three key categories, which were further validated after re-analysis of all the interviews. Coding maps were used to help with the code grouping and the analysis of relationships between the emerging categories and codes. In the last step, an overarching theme involving these three categories was identified. The analysis was conducted in Spanish and quotes were chosen from this material to be translated into English. All the authors understand both languages and, thus, were able to participate in the whole analysis process.

Our positions as researchers have continuously been discussed in relation to ethical considerations and questions about responsibility. In line with Graneheim and Lundman (2004) [99], we argue that, in qualitative content analysis, interpretation involves a balancing act of providing interpretation while at the same time making sure that our interpretations remain always grounded on the data. By providing a thorough explanation of the analytical process, our intention is to allow the reader to assess the usefulness and transferability of the study.

RESULTS

STUDY 1

Prevalence of therapeutic use of opioids in chronic non-cancer pain patients and associated factors: a systematic review and meta-analysis.

Helena De Sola*; María Dueñas; Alejandro Salazar; Patricia Ortega-Jiménez; Inmaculada Failde*

*The author of this thesis contributed to this work by performing the search strategy, studies selection, analysing the data, and was mainly responsible for writing the manuscript.

ABSTRACT

Purpose: To determine the prevalence and factors associated with the use of opioids among patients with Chronic Non-Cancer Pain (CNCP).

Methods: A systematic review and meta-analysis. Comprehensive literature searches in PubMed and SCOPUS databases. Original papers published between 2009 and 2019 with a cross-sectional design were included. Protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO) with reference number: CRD42019137990

Results: Out of the 1062 potential articles found, 23 studies fulfilled the inclusion criteria. In the general population, the prevalence of long-term opioid use was 2.3% (95%CI:1.5%-3.6%), the prevalence of short-term opioid use was 7.3% (95%CI:4.3%-11.9%), and among people with chronic low back pain was 5.8% (95% CI:0.5% - 45.5%). The prevalence of opioid use among patients from the health records or medical surveys was 41% (95%CI:23.3%-61.3%). Finally, in patients with musculoskeletal pain, the prevalence was 20.5% (95%CI:12.9%-30.9%) and in patients with fibromyalgia, 24.5% (95%CI:22.9%-26.2%). A higher prevalence of opioid use was observed among men; younger people; patients receiving prescriptions of different type of drugs; smokers and patients without insurance or with noncommercial insurance. In addition, non-white and Asian patients were less likely to receive opioids than non-Hispanic white patients.

Conclusions: The prevalence of opioid use among patients with CNCP varies depending on the duration of treatment and the population analyzed, with higher prevalence in clinical studies based on health registries and occasional users. Age, race, and the access to and the characteristics of the health service delivery system are the factors most related to opioids use.

Keywords: Chronic pain, Meta-analysis, Opioids, Prevalence, Systematic review.

INTRODUCTION

Chronic pain (CP) is a major public health concern [1] that is associated with disability, distress, and a decrease in the quality of life of affected individuals [2]. The prevalence of moderate to severe CP in the general adult population ranges from 2% to 55% in different countries [3–5], with an estimated global annual cost over US$245 billion [6].

It has been recognized that the physiopathology of CP involves complex interactions between physical, psychological, and social factors, and that its adequate management needs a multidisciplinary approach [7]. However, pharmacological therapy remains a mainstay for treating these patients [8], opioids being one class of pharmacotherapies highly prescribed to modulate pain [9].

Opioid therapy in CP has recently received a growing interest related to the increased use observed in these patients [10–12]. This situation is of particular concern in patients with chronic non-cancer pain (CNCP), where the evidence of its benefits may be less robust than that observed in patients with acute or cancer pain [13–15]. The length of opioid therapy is also important to patients' benefits, since prescription opioids may be appropriate for short-term pain relief, but long-term opioid therapy (LTOT) cannot be associated with improvements in pain or function [16].

Furthermore, it has been shown that the introduction of high-dose and extended-release oral tablet formulations of opioids has increased the total prescriptions among CNCP patients [10,14,17], becoming an important social problem in some countries such as the United States [18,19]. The differences in opioid prescribing patterns have been related to age, gender, ethnicity, pain diagnosis, number of total medications, payment type, physician specialty, and patient relationship with provider [20]. Thus, it is necessary to collect and summaries the information published with valid and reliable results about the therapeutic use of opioids for CNCP in different countries. Additionally, it is necessary to take into account the length of the treatment and factors associated with it in order to produce international estimates. To this end, we carried out a systematic review of the literature to know the prevalence of the therapeutic use of opioids among patients with CNCP and, as a second aim, the analysis of the factors associated with their use. We also performed a meta-analysis of the prevalence of the therapeutic use of opioids to summarize the information obtained.

METHODS

Protocol and registration

The present systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [21]. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with reference number: CRD42019137990.

Design of the study

Systematic review of the current literature and meta-analysis.

Search strategy

A systematic search strategy was performed in the PubMed and SCOPUS databases. Original cross-sectional studies published from 2009 to 2019 in English or Spanish were included. The terms/keywords of interest were “opioid”, “analgesic”, and “pain”. The terms were combined with the tag for searching in the title, abstract and keywords. The search terms and search strategies were adapted to each database (Supplemental material, S1).

Once the search strategies for both databases were executed, we imported all the references found into the Covidence online tool [22]. The process of duplicate removal, screening, data extraction and risk of bias analysis were performed by this web-based systematic review tool.

Eligibility criteria

According to the predefined inclusion criteria, an article was selected when its main aim was to determine the prevalence of the use of opioids in CNCP humans (all ages), provided these data were shown within the paper or it was possible to calculate them from it. Articles related to CNCP located in specific body regions (e.g. musculoskeletal CP) were also included. Thus, the term “chronic non-cancer pain” was not included in the search strategy in order not to limit the searches to studies presenting only data from general CNCP. The criterion to define CNCP and the specific body regions where each article is focused on are specified in table 2.

Studies including patients with cancer pain, focusing on the opinions or attitudes of physicians about opioid prescription or on the disorders derived from their consumption were excluded (Supplementary material S2).

Study selection

Two authors (MD and HDS) independently screened the title and abstract of all of papers. Shortlisted studies were then analyzed in depth according to the inclusion criteria and their reference lists were also revised to identify studies that could be included in the review. The quality of the studies was assessed following the Critical Appraisal Checklist for Analytical Cross-sectional studies from the Joanna Briggs Institute [23]. This checklist consists of 8 items regarding inclusion criteria, study sample and setting, exposure measured, standard criteria for measurement, confounding factors, strategies to deal with confounders, outcomes measured and statistical analysis (Supplementary material S3). Each item was assessed as "yes", "no", "unclear" or "not applicable". For standardization, we considered "yes" as low risk of bias, and "no" and "unclear" as high risk of bias. Overall, low risk of bias (i.e., high quality study) was considered when a study accumulated at least 5 items answered as "yes". Studies assessed as 'yes' in <5 items were categorized as high risk of bias (i.e., low quality study). Any disagreements regarding the suitability of a study were resolved after appraisal by a third author (AS).

Data extraction

From the selected papers, information was extracted about the primary aim of the study, characteristics of the population studied, the sample source, sample size, method for data retrieval, and response rate (Table 1). Likewise, the definition of CNCP considered in each article, prevalence of CNCP in the population studied, prevalence of opioid use, the method for obtaining this prevalence data, and the factors associated with opioid use were collected (Table 2).

Statistical analysis

A descriptive analysis of the characteristics of all the studies included in the systematic review was carried out, and a meta-analysis was subsequently performed. The articles that were included in the meta-analysis were stratified in two groups according to the source of the sample: data from the general population or from health registries/medical surveys. In turn, articles from the general population were stratified depending on the duration of opioid treatment: long-term (commonly defined as over 3 months [16]) or short-term (less than 3 months) and depending on the type of pain: general CNCP or chronic low back pain (CLBP). The articles with data from health registries/medical surveys were stratified depending also on the type of pain: general CNCP, fibromyalgia or musculoskeletal conditions (which include musculoskeletal pain, osteoarthritis and CLBP, following The International Classification of

Diseases [24]) (Table 3). Studies performed in populations older than 65 years [25], those that could not be compared with any other study, such as those focused on a specific type of pain [26,27] or from specific sample source [28,29], or those focused on visits rather than the patients (with the potential overlapping of the records of the patients) [30,31] were excluded from the meta-analysis.

From the studies included, the summary measure (prevalence of opioid use, defined as the number of subjects who take opioids divided by the number of individuals with CNCP) was calculated with 95% confidence intervals (CI). Studies were weighted according to the prevalence effect size and the inverse of the study variance.

The heterogeneity between the studies was determined by the DerSimonian and Laird method with Cochran's Q statistic. As heterogeneity was observed in all the study subgroups, random effects models were performed, which considers the variability of the results due to the differences between the studies. The proportion of total variability due to the heterogeneity of the studies was estimated using the I^2 value. The results of the meta-analysis are presented in forest plots. To assess the potential publication bias in groups with three or more studies, a funnel plot, along with Begg's rank correlation and Egger's weighted regression methods, were used. A two-tailed $p<0.05$ was considered indicative of a statistically significant publication bias.

Finally, a sensitivity analysis was carried out in the groups with three or more studies to determine the influence of each of the studies on the overall estimate of the effect, and therefore the robustness or stability of the final measurement obtained, through influence graphs.

The data were analyzed using Comprehensive Meta-Analysis Software Version 3.0 (Biostat, Englewood, NJ, USA).

RESULTS

The search identified 1062 potential articles. After the selection process (Figure 1), 24 suitable articles were identified. Three more studies obtained by the additional search strategies (citation search) were added. Results of the risk of bias, measured with the Critical Appraisal Checklist for Analytical Cross-sectional studies, are shown in Supplementary Material S3. It shows that 23 articles had low risk of bias (i.e., high quality study). Out of these 23 articles, eight had been performed in the general population [27,30,32–37], and fifteen in patients with CNCP from medical surveys or medical records [25,26,43–47,28,29,31,38–42] (Table 1). The data were gathered from thirteen countries. Most studies (n=15) were restricted to adult populations (18 years or older), whereas one study also included adolescents (≥16 years) [32], three included children (all ages) [30,35,39], and one included only people over 65 [25]. In three studies, the age was not specified.

Thirteen articles were performed in patients suffering from a chronic painful process of specific cause (e.g., musculoskeletal pain) [27,29,44,46,47,30,31,36,37,40–43]. The reported participation rates in the studies ranged from 37% [43] to 84.8% [35], but in some instances, the information given by the authors was missing or unclear (Table 1). Chronic pain was defined as pain lasting at least 6 months in four of the included articles [28,32,33,35], while in the rest, it was considered as pain lasting more than 3 months. The prevalence of CNCP in the studies performed in the general population ranged between 6.8% [38] and 35.7% [34] (Table 2).

Prevalence of opioid use

Out of the eight articles set in the general population, two distinguished between short-term or occasional opioid users and long-term or persistent opioid users. The prevalence was higher in those in which the use was short or occasional (3.9% to 12.3% vs. 1.8% to 2.9%) [32,33]. Three articles (out of eight carried out in the general population) were focused on CLBP, and the prevalence ranged from 1.6% [36] to 18.8% [37]. Another article retrieving data from five countries was focused on osteoarthritis, being the total opioid prevalence 16.7% [27]

In the articles analyzing the population from medical registries or medical surveys, the prescription of opioids was variable, being 32.7% in patients that were attended to General Practices [39] or 64.4% in patients attended in a pain center [28]. In the studies in patients suffering a specific pain condition, the use of opioids ranged from 13.1% to 20.8% in the case of musculoskeletal pain [31,40], from 12% [41] to 22% in osteoarthritis [44] and from 8.4% [47] to 22.4% in fibromyalgia [42]. The highest opioid use prevalence was 81.1%, in a study performed in a nursing home with people ≥ 65 years [25] (Table 2).

Factors associated with the use of opioids

Seven of the articles included in the review analyzed the factors associated with the use of opioids, observing a greater use of these drugs in men [33,38], in young people [31,33,38], in patients receiving prescriptions of different kind of drugs [33], in smokers [43], and in patients without insurance or with noncommercial insurance, especially Medicaid and Medicare, versus those with private insurance [31,38,45] (Table 2).

The use of opioid was also related with the physician. Patients who had been followed by a physician, had higher odds of being prescribed an opioid than naive patients [45]. Moreover, if the primary care physician was trained in complementary medicine, he/she was significantly less likely to prescribe opioids [43].

Additionally, the use was greater in patients with a pain-related disability [34] and in those with more CP conditions [38]. However, patients with a higher score on the Charlson Comorbidity Index (2-3 vs. 0) had lower odds of receiving an opioid [38] (Table 2).

Race was related to the use of opioids in two studies, which showed that non-white patients [31] and Asian patients [38] were less likely to receive opioids than non-Hispanic white patients (Table 2).

Results of the meta-analysis

Out of the 23 articles included in the review, 16 were included in the meta-analysis, stratified into six subgroups. Group A [32,33] included two studies carried out in the general population, with patients with general CNCP, where the duration of the use of opioids was long-term or persistent. Group B [32–35] included four studies, also performed in the general population and with patients with general CNCP, but in which the duration of the use of opioids was short-term. Group C [36,37] included two studies in the general population which analyze patients with CLBP who had been prescribed opioids. Group D [38,39,45] consisted of three studies that included patients with general CNCP from health registries who had been prescribed opioids. Group E [40,41,43,44,46] included five studies with patients from medical surveys, with musculoskeletal conditions (including musculoskeletal pain, osteoarthritis and CLBP) and who had been prescribed opioids at the moment of the study. Finally, group F [42,47] included two studies of fibromyalgia patients from medical surveys who had been prescribed opioids (Table 3).

The characteristics and results of the meta-analysis (heterogeneity tests, estimated prevalences with 95% CI, relative weights and tests for publication bias) of the studies included in each of the six subgroups are shown in Table 3 and Figure 2, respectively.

As shown in Table 3, we found heterogeneity between the groups, demonstrating a marked variability among the estimates ($I^2 > 77$, $p < 0.05$, in all cases). Therefore, the model used for the estimations of the summary prevalence was the random effects model.

Among the results obtained, it is noteworthy that in the general population, the prevalence of long-term opioid use among patients with general CNCP was 2.3% (95% CI: 1.5% - 3.6%), the prevalence of short-term opioid use was 7.3% (95% CI: 4.3% - 11.9%), and the prevalence in CLBP was 5.8% (95% CI: 0.5% - 45.5%). The prevalence among patients from health registries or medical surveys was 41% (95% CI: 23.3% - 61.3%) in patients with general CNCP. The prevalence in patients with musculoskeletal conditions was 20.5% (95% CI: 12.9% - 30.9%) and in patients with fibromyalgia was 24.5% (95% CI: 22.9% - 26.2%) (Table 3 and Figure 2).

Figure 3 shows the funnel plot for meta-analysis of subgroups B, D and E, suggesting no evidence of publication bias. Neither Egger's test nor Begg's test were statistically significant for the publication bias (Table 3).

Finally, Figure 4 shows the result of the sensitivity analysis for subgroups B, D and E, indicating in the three cases that none of the studies included would substantially change the overall result of the study summary prevalence if the studies were eliminated from the meta-analysis. This finding indicates that the results are robust, since none of the studies exerted a great influence on the final result.

DISCUSSION

This paper analyzes the information published about the prevalence of the use of opioids in patients with CNCP and examines the factors associated with their use.

The results reveal that there were differences in the prevalence of the use of these drugs depending on the length of the treatment (2.3% in long duration or 7.3% in occasional use) [32,33]. It was also observed that when the information comes from health registries, the prevalence is much higher than in the general population, and more variable depending on the specialty of the health center.

The lower prevalence found in patients with longer treatments seems reasonable if we take into account, on the one hand, the prescribers' concern about the risk of addiction and the improper use of these drugs by some patients [48] and, on the other hand, the treatment dropout, possibly due to the appearance of analgesic tolerance, induced hyperalgesia, and side effects frequently associated with these drugs [49,50].

Likewise, the results observed in the studies based on health registries could be explained because these patients are usually treated in specialized pain units by physicians with expertise in pain management, who are more likely to prescribe more opioids than doctors in other specialties [39,51]. Regarding the specific pathologies, the prevalence in patients with musculoskeletal conditions was 20.5% and in patients with fibromyalgia 24.5%[38,52]. Musculoskeletal conditions are one of the most common causes of pain [53,54], and the use of weak opioids is recommend, since there is strong evidence that weak opioids relieve pain and disability in the short-term in these patients [55]. However, in the case of Fibromyalgia, current treatment guidelines do not recommend opioids for its symptom management [56]. Our findings suggest that, despite a lack of scientific support of opioid treatment in people with fibromyalgia, possibly because of an inability of opioids to target the pathophysiological processes involved in

this central sensitization syndrome [57], clinicians are nevertheless prescribing them for symptom management in this patient population.

In the analysis of the factors associated with the use of opioids, it was observed that younger individuals showed greater use. One explanation could be that opioids are not always recommended for the elderly population, due to a higher probability of liver or kidney dysfunction, greater risk of respiratory depression, drug interactions, organ dysfunction, co-morbidity and side effects, such as constipation, drowsiness or sedation, that can have more serious consequences in this population [38]. Likewise, it has been shown that medical personnel sometimes underestimate pain in the elderly, which leads to a lower prescription of opioids in these patients [58,59].

Regarding the race, different studies have shown that the pain experience is different according to the ethnic group. This finding has been attributed to different responses to painful stimuli and the different coping strategies for managing pain observed in these patients [31,38,60,61]. Additionally, according to Anderson et al. [62], there are other factors that could influence these differences, such as selective care and differences in the process of evaluation and allocation of treatment according to the ethnic group of the patient.

Another factor to consider is the type of care received by the patient. The type of medical insurance can influence the manner of approaching the pain and consequently determine the use of opioids. It has been shown [63] that patients with private insurance obtain better results than patients with public coverage since, in addition to the fact that the care is more immediate, the multidisciplinary approach is more common and produce better results decreasing the use of analgesic treatment [64]. In this vein, Rodondi et al [43] highlighted that the training of the physician in complementary medicine also influences on prescribing less opioid treatments, since specialized in integrative and complementary medicine could help inform and guide patients about the most effective treatment options, their potential interactions with conventional therapies, and their side effects.

Finally, it would be reasonable to think that in those studies where the prevalence of CP is higher, the use of opioids would also be greater [65]. However, when we compare the results from different countries, this hypothesis is not confirmed, as the factors that seem most important are the method of data collection and the characteristics of the population included in the studies [35,66].

Some limitations of this review should be noted. It is worth mentioning that three of the subgroups in the meta-analysis included only 2 studies. The minimum number of studies to

include in a meta-analysis has been previously discussed in the literature, without clear agreement [67–69]. Some researchers consider that a minimum of 5 studies are desirable, or even required. Others argue that, as long as the studies meet the quality criteria and statistical requirements, the meta-analysis can be carried out, as it is just a statistical combination of the results. The number of studies in the literature on a topic do not depend on us, and the lack of studies on these topics (in our case, studies carried out in general population focused on the prevalence of the use of opioid in long-term; in general population focused on the prevalence of the use of opioid in CLBP; and from health records or medical surveys focused on the use of opioid in fibromyalgia) is itself a relevant result, and it shows the need for further research on the topics. Of course, the number of studies has a direct impact on the statistical power and precision, but if those few studies are relevant and their quality is high, we believe that it is worth drawing conclusions from them. At this vein, Terri D. Pigott [67], argued that the quick answer for the minimum number of studies is two, but recommend to compute the statistical power a priori, "using assumptions about the size of an important effect in a given context, and the typical sample sizes used in a given field". Finally, Valentine et al. [69] state that a meta-analysis is always the best option to synthesize information (even if we have few studies), as other alternatives "are likely to be based on less defensible assumptions and on less transparent processes". Consequently, we decided to perform these three meta-analyses which, however, need to be interpreted with caution, given the limited statistical power.

As a strength of the study, we would like to highlight its novelty since, to the best of our knowledge, no systematic review and meta-analysis on the prevalence of the therapeutic use of opioids has been published previously.

CONCLUSIONS

This study shows that the prevalence of opioid use in patients with CNCP varies depending on the duration of treatment and the population analyzed, with higher prevalence in clinical studies based on health registries and occasional users. Likewise, age, race, and the access to and the characteristics of the health service delivery system are the factors most related to the use of opioids.

REFERENCES

1. Vos T, Flaxman AD, Naghavi M, *et al.* Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2163–2196. doi:10.1016/S0140-6736(12)61729-2.

2. de Sola H, Salazar A, Dueñas M, Ojeda B, Failde I. A nationwide cross-sectional study of the impact of chronic pain on an individual´s employment. Relationship with the family and the social support. *BMJ Open* 2016; **6**: e012246. doi:10.1136/bmjopen-2016-012246.

3. Azevedo LLFL, Costa-Pereira A, Mendonça L, Dias CCCC, Castro-Lopes JMJ. Epidemiology of Chronic Pain: A Population-Based Nationwide Study on Its Prevalence, Characteristics and Associated Disability in Portugal. *J Pain* 2012; **13**: 773–783. doi:10.1016/j.jpain.2012.05.012.

4. Mohamed Zaki LR, Hairi NN. A Systematic Review ofthe Prevalence and Measurement of Chronic Pain in Asian Adults. *Pain Manag Nurs* 2015; **16**: 440–452. doi:10.1016/j.pmn.2014.08.012.

5. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. *Br J Anaesth* 2019; **123**: e273–e283. doi:10.1016/j.bja.2019.03.023.

6. GSK. Global Pain Index 2017 Research Report. *Glob Rep Find* 2017: 1–49.

7. Broekmans S, Dobbels F, Milisen K. Pharmacologic Pain Treatment in a Multidisciplinary Pain Center. *Clin J Pain* 2010; **26**: 81–86. doi:10.1097/AJP.0b013e3181b91b22.

8. Timmerman L, Stronks DL, Groeneweg JG, Huygen FJ. Prevalence and determinants of medication non-adherence in chronic pain patients: A systematic review. *Acta Anaesthesiol Scand* 2016; **60**: 416–431. doi:10.1111/aas.12697.

9. Parsells Kelly J, Cook SF, Kaufman DW, Anderson T, Rosenberg L, Mitchell AA. Prevalence and characteristics of opioid use in the US adult population. *Pain* 2008; **138**: 507–513. doi:10.1016/j.pain.2008.01.027.

10. Alam A, Juurlink DN. The prescription opioid epidemic: an overview for

anesthesiologists. *Can J Anesth Can D Anesth* 2015; **63**: 61–68. doi:10.1007/s12630-015-0520-y.

11. Webster F, Bremner S, Oosenbrug E, Durant S, McCartney CJ, Katz J. From Opiophobia to Overprescribing: A Critical Scoping Review of Medical Education Training for Chronic Pain. *Pain Med* 2017; **18**: 1467–75. doi:10.1093/pm/pnw352.

12. Cheung CW, Qiu Q, Choi S-W, Moore B, Goucke R, Irwin M. Chronic opioid therapy for chronic non-cancer pain: a review and comparison of treatment guidelines. *Pain Physician* 2014; **17**: 401–14.

13. Campbell G, Nielsen S, Larance B, *et al.* Pharmaceutical opioid use and dependence among people living with chronic pain: associations observed within the pain and opioids in treatment (POINT) cohort. *Pain Med* 2015; **16**: 1745–1758. doi:10.1111/pme.12773.

14. Von Korff M, Kolodny A, Deyo RA, Chou R. Long-term opioid therapy reconsidered. *Ann Emerg Med* 2011; **155**: 325–328. doi:10.1059/0003-4819-155-5-201109060-00011.Long-Term.

15. Scholten W. *Access to opioid analgesics: Essential for quality cancer care. Cancer Pain.*, 2013. doi:10.1007/978-0-85729-230-19.

16. Karmali RN, Bush C, Raman SR, Campbell CI, Skinner AC, Roberts AW. Long-term opioid therapy definitions and predictors: A systematic review. *Pharmacoepidemiol Drug Saf* 2020; **29**: 252–269. doi:10.1002/pds.4929.

17. Severino AL, Shadfar A, Hakimian JK, *et al.* Pain Therapy Guided by Purpose and Perspective in Light of the Opioid Epidemic. *Front Psychiatry* 2018; **9**: 119. doi:10.3389/fpsyt.2018.00119.

18. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Physician* 2012; **15**: ES67-92.

19. Salazar A, Moreno S, De Sola H, Moral-Munoz JA, Dueñas M, Failde I. The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017. Differences between Spain and the United States. *Curr Med Res Opin* 2019; **35**: 000. doi:10.1016/j.neulet.2008.12.049.

20. Rasu RS, Knell ME. Determinants of opioid prescribing for nonmalignant chronic pain in

US outpatient settings. *Pain Med (United States)* 2018; **19**: 524–532. doi:10.1093/pm/pnx025.

21. Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. *BMJ* 2015; **349**: 1–25. doi:10.1136/bmj.g7647.

22. Veritas Health Innovation Ltd. Covidence. 2019. Available at: www.covidence.org.

23. Moola S, Munn Z, Tufanaru C, *et al.* Checklist for Analytical Cross Sectional Studies. *Joanna Briggs Inst Rev Man* 2017: 6. doi:10.17221/96/2009-CJGPB.

24. Ministerio De Sanidad Consumo y Bienestar Social. Clasificación Internacional Enfermedades (CIE-10-ES). 2020. Available at: https://eciemaps.mscbs.gob.es/ecieMaps/browser/metabuscador.html. Accessed January 2, 2020.

25. Fain KM, Alexander GC, Dore DD, Segal JB, Zullo AR, Castillo-Salgado C. Frequency and Predictors of Analgesic Prescribing in U.S. Nursing Home Residents with Persistent Pain. *J Am Geriatr Soc* 2017; **65**: 286–293. doi:10.1111/jgs.14512.

26. Marschall U, L'hoest H, Radbruch L, Häuser W. Long-term opioid therapy for chronic non-cancer pain in Germany. *Eur J Pain* 2015; **20**: 767–76. doi:10.1002/ejp.802.

27. Kingsbury SR, Gross HJ, Isherwood G, Conaghan PG. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. *Rheumatology (Oxford)* 2014; **53**: 937–947. doi:10.1093/rheumatology/ket463.

28. Scala E, Decosterd I, Faouzi M, Burnand B, Rodondi P-Y. Level of readiness of chronic pain patients to practise active self-care. *Eur J Pain (United Kingdom)* 2018; **22**: 1800–1812. doi:10.1002/ejp.1276.

29. Wand BM, Catley MJ, Rabey MI, O'Sullivan PB, O'Connell NE, Smith AJ. Disrupted Self-Perception in People With Chronic Low Back Pain. Further Evaluation of the Fremantle Back Awareness Questionnaire. *J Pain* 2016; **17**: 1001–1012. doi:10.1016/j.jpain.2016.06.003.

30. Ahn Y-JY-J, Shin J-SJ-S, Lee J-HJJ-H, *et al.* Evaluation of use and cost of medical care of common lumbar disorders in Korea: cross-sectional study of Korean Health Insurance Review and Assessment Service National Patient Sample data. *BMJ Open* 2016; **6**:

e012432. doi:10.1136/bmjopen-2016-012432.

31. Larochelle MR, Zhang F, Ross-Degnan D, *et al.* Trends in opioid prescribing and co-prescribing of sedative hypnotics for acute and chronic musculoskeletal pain: 2001–2010. *Pharmacoepidemiol Drug Saf* 2015; **24**: 885–892. doi:10.1002/pds.

32. Birke H, Kurita GP, Sjøgren P, *et al.* Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: Trends from 2000 to 2013. *Acta Anaesthesiol Scand* 2016; **60**: 623–633. doi:10.1111/aas.12700.

33. Fredheim OMS, Mahic M, Skurtveit S, Dale O, Romundstad PPP, Borchgrevink PC. Chronic pain and use of opioids: a population-based pharmacoepidemiological study from the Norwegian prescription database and the Nord-Trondelag health study. *Pain* 2014; **155**: 1213–1221. doi:10.1016/j.pain.2014.03.009.

34. Azevedo LF, Costa-Pereira A, Mendonça L, Dias CC, Castro-Lopes JM. A population-based study on chronic pain and the use of opioids in Portugal. *Pain* 2013; **154**: 2844–2852. doi:10.1016/j.pain.2013.08.022.

35. Miller A, Sanderson K, Bruno R, Breslin M, Neil AL. The prevalence of pain and analgesia use in the Australian population: Findings from the 2011 to 2012 Australian National Health Survey. *Pharmacoepidemiol Drug Saf* 2017; **26**: 1403–1410. doi:10.1002/pds.4301.

36. Gouveia N, Rodrigues A, Ramiro S, *et al.* The Use of Analgesic and Other Pain-Relief Drugs to Manage Chronic Low Back Pain: Results from a National Survey. *Pain Pract* 2017; **17**: 353–365. doi:10.1111/papr.12455.

37. Shmagel A, Ngo L, Ensrud K, Foley R. Prescription medication use among community-based US adults with chronic low back pain: a cross-sectional population based study. *J Pain* 2018; **19**: 1104–1112. doi:10.1016/j.jpain.2018.04.004.

38. Romanelli RJ, Ikeda LI, Lynch B, *et al.* Opioid Prescribing for Chronic Pain in a Community- -Based Healthcare System. *Am J Manag Care* 2017; **23**: e138–e145. Available at: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85020087701&partnerID=40&md5=0f1f91b798fc9f88b0165be777e560a3. Accessed June 4, 2019.

39. Henderson J V, Hons BBB, Harrison CM, *et al.* Prevalence, Causes, Severity, Impact, and Management of Chronic Pain in Australian General Practice Patients. *Pain Med* 2013;

14: 1346–1361. doi:10.1111/pme.12195.

40. Sites BD, Harrison J, Herrick MD, Masaracchia MM, Beach ML, Davis MA. Prescription Opioid Use and Satisfaction With Care Among Adults With Musculoskeletal Conditions. *Ann Fam Med* 2018; **16**: 6–13. doi:10.1370/afm.2148.

41. Knoop J, van Tunen J, van der Esch M, *et al.* Analgesic use in patients with knee and/or hip osteoarthritis referred to an outpatient center: a cross-sectional study within the Amsterdam Osteoarthritis Cohort. *Rheumatol Int* 2017; **37**: 1747–1755. doi:10.1007/s00296-017-3785-3.

42. Vincent A, Whipple MO, McAllister SJ, Aleman KM, St Sauver JL. A cross-sectional assessment of the prevalence of multiple chronic conditions and medication use in a sample of community-dwelling adults with fibromyalgia in Olmsted County, Minnesota. *BMJ Open* 2015; **5**: 1–5. doi:10.1136/bmjopen-2014-006681.

43. Rodondi P-YPY, Bill ASA-S, Danon N, *et al.* Primary care patients' use of conventional and complementary medicine for chronic low back pain. *J Pain Res* 2019; **12**: 2101–2112. doi:10.2147/JPR.S200375.

44. Callhoff J, Albrecht K, Redeker I, *et al.* Disease Burden of Patients With Osteoarthritis: Results of a Cross-Sectional Survey Linked to Claims Data. *Arthritis Care Res (Hoboken)* 2020; **72**: 193–200. doi:10.1002/acr.24058.

45. Lin H-CH-C, Wang Z, Simoni-Wastila L, Boyd C, Buu A. Interstate data sharing of prescription drug monitoring programs and associated opioid prescriptions among patients with non-cancer chronic pain. *Prev Med (Baltim)* 2019; **118**: 59–65. doi:10.1016/j.ypmed.2018.10.011.

46. Van Den Driest JJ, Pijnenburg P, Bindels PJEE, Bierma-Zeinstra SMAA, Schiphof D. Analgesic Use in Dutch Patients with Osteoarthritis: Frequent but Low Doses. *J Clin Rheumatol* 2019; **25**: 297–303. doi:10.1097/RHU.0000000000000853.

47. Häuser W, Jung E, Erbslöh-Möller B, *et al.* The German fibromyalgia consumer reports - A cross-sectional survey. *BMC Musculoskelet Disord* 2012; **13**: 2–7. doi:10.1186/1471-2474-13-74.

48. Allen MJM, Asbridge MM, Macdougall PC, Furlan AD, Tugalev O. Self-reported practices in opioid management of chronic noncancer pain: A survey of canadian family physicians. *Pain Res Manag* 2013; **18**: 177–184. doi:10.1155/2013/528645.

49. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain* 2004; **112**: 372–380. doi:10.1016/j.pain.2004.09.019.

50. Sehgal N, Colson J, Smith HS. Chronic pain treatment with opioid analgesics: Benefits versus harms of long-term therapy. *Expert Rev Neurother* 2013. doi:10.1586/14737175.2013.846517.

51. Pérez C, Margarit CCC, Serrano M, *et al.* Survey of European patients assessing their own noncancer chronic pain: results from Spain. *Curr Med Res Opin* 2013; **29**: 643–651. doi:10.1185/03007995.2013.787978.

52. Luo X, Pietrobon R, Hey L. Patterns and Trends in Opioid Use among Individuals with Back Pain in the United States. *Spine (Phila Pa 1976)* 2004; **29**: 884–890. doi:10.1097/00007632-200404150-00012.

53. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006; **10**: 287–333. doi:10.1016/j.ejpain.2005.06.009.

54. Pierce DPR, Pierce B, Cheng C-I, Perzhinsky J. Assessing treatment and monitoring of musculoskeletal conditions using opioid versus nonopioid therapy: A cross-sectional study. *Medicine (Baltimore)* 2019; **98**: e15128. doi:10.1097/MD.0000000000015128.

55. Airaksinen O, Brox JI, Cedraschi C, *et al.* Chapter 4: European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006; **15**: 192–300. doi:10.1007/s00586-006-1072-1.

56. Peng X, Robinson RL, Mease P, *et al.* Long-term evaluation of opioid treatment in fibromyalgia. *Clin J Pain* 2015; **31**: 7–13. doi:10.1097/AJP.0000000000000079.

57. Menzies V, Thacker LR, Mayer SD, Young AM, Evans S, Barstow L. Polypharmacy, Opioid Use, and Fibromyalgia. *Biol Res Nurs* 2017; **19**: 97–105. doi:10.1177/1099800416657636.

58. Raymond C T, John T C. Pain in older subacute care patients: associations with clinical status and treatment. *Pain Med* 2002; **3**: 231-239 9p.

59. Seers T, Derry S, Seers K, Moore RA. Professionals underestimate patients' pain. *Pain* 2018; **159**: 1. doi:10.1097/j.pain.0000000000001165.

60. Campbell CM, Edwards RR. Ethnic differences in pain and pain management. *Pain Manag* 2012; **2**: 219–230. doi:10.2217/pmt.12.7.

61. Ringwalt C, Roberts AW, Gugelmann H, Skinner AC. Racial Disparities Across Provider Specialties in Opioid Prescriptions Dispensed to Medicaid Beneficiaries with Chronic Noncancer Pain. *Pain Med (United States)* 2015; **16**: 633–640. doi:10.1111/pme.12555.

62. Anderson KO, Green CR, Payne R. Racial and Ethnic Disparities in Pain: Causes and Consequences of Unequal Care. *J Pain* 2009; **10**: 1187–1204. doi:10.1016/j.jpain.2009.10.002.

63. Meineche-Schmidt V, Jensen NH, Sjøgren P. Long-term outcome of multidisciplinary intervention of chronic non-cancer pain patients in a private setting. *Scand J Pain* 2012; **3**: 99–105. doi:10.1016/j.sjpain.2011.10.002.

64. Becker N, Sjogren P, Bech P, *et al.* Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain centre compared to general practice: a randomised controlled trial. *Pain* 2000; **84**: 203–211. doi:10.1016/s0304-3959(99)00209-2.

65. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet* 2012; **380**: 37–43. doi:10.1016/S0140-6736(12)60240-2.

66. Steingrímsdóttir ÓA, Landmark T, Macfarlane GJ, Nielsen CS. Defining chronic pain in epidemiological studies – a systematic review and meta-analysis. *Pain* 2017; **158**: 2092–2107. doi:10.1097/j.pain.0000000000001009.

67. Pigott TD. *Advances in meta-analysis*. New York: Springer US, 2012. doi:10.1007/978-1-4614-2278-5.

68. Cooper H, Hedges L, Valentine J. *The Handbook of Research Synthesis and Meta-Analysis*. New York: Russell Sage Foundation, 2009.

69. Valentine JC, Pigott TD, Rothstein HR. How Many Studies Do You Need? A Primer on Statistical Power for Meta-Analysis. *J Educ Behav Stat* 2010; **35**: 215–247. doi:10.3102/1076998609346961.

Table 1. Characteristics of the studies included in the systematic review.

First author, Year	Primary aim	Population	Sample source and timeframe	Method for data retrieval	N	Response Rate
Rodondi P. et al. 2019	To investigate among primary care patients and their physicians in western Switzerland the prevalence of use, perceived usefulness, and communication about treatments for chronic or recurrent low back pain (CLBP) including complementary medicine.	Patients with CLBP recruited during regular medical appointment. (≥18 years)	Primary care physician in western French-speaking area of Switzerland from November 1, 2015, to May 31, 2016	Self-reported questionnaires	499	37%
Callhof J. et al. 2019	To analyze factors associated with the burden of osteoarthritis (OA), taking the pattern of joint involvement into account.	Patients with OA of the knee or hip or with polyarthritis (30–79 years)	German statutory health insurance database (BARMER). Year 2016	Survey and claims data	8,995	42%
Lin H-C et al. 2019	To examine how prescription drug monitoring programs interstate data sharing with bordering states was associated with patients being prescribed opioids for non-cancer Chronic Pain (CP) treatment.	Adult patients with non-cancer CP (≥18 years).	National Ambulatory Medical Care Survey (NAMCS) 2014	The NAMCS	Weighted N=66,198,751; unweighted N=2846	

van den Driest J. J et al. 2019	To examine the analgesic used by patients with OA related pain and how the analgesics are used in the preceding month	Patients with rheumatic diseases (Age not specified)	The panel of the Dutch Arthritis Foundation	Online questionnaire	842	56%
Shmagel A. et al. 2018	To examine patterns of drugs prescription among Americans with CLBP in a nationally representative, community-based sample.	A representative sample of US adult population (aged 20–69)	The National Health and Nutrition Examination Survey (NHANES). 2009–2010.	Home-based interviews with pill bottle verification to capture prescribed medications for CP.	5,103	
Scala E. et al. 2018	To evaluate the level of readiness to practice different types of active self-care among chronic pain patients.	Patients with CP. (≥18 years).	Patients seeking care at the Pain Center University Hospital, Switzerland between June 2013 and March 2015	Self- administered questionnaire.	639	41.9%
Sites B D. et al. 2018	To understand the relationship between prescription opioid use and satisfaction with care among adults who have musculoskeletal conditions	Patients with musculoskeletal conditions (≥18 years).	Nationally representative data from the 2008-2014 Medical Expenditure Panel Survey (MEPS)	5 rounds of telephone interviews over a 30-month period and questionnaires.	19,566	
Knoop J. et al. 2017	To describe the use of analgesics; and to determine factors that are related to analgesic use in patients with knee and/or hip OA referred to an outpatient center	Patients referred to an outpatient center with knee and/or hip OA diagnosed (Age not specified)	Amsterdam Osteoarthritis (AMS-OA) cohort in an outpatient center (Reade, center for rehabilitation and rheumatology, the Netherlands) from	Questionnaires	656	

			December 2009 to July 2016			
Miller A. et al. *2017*	To estimate the prevalence of CP and analgesia use in the Australian population by age and sex; the severity of pain in the population with CP by sex; and the distribution of recent pain severity in those using analgesia by age and sex.	Representative sample of Australian population. (All ages).	The Australian Bureau of Statistics (ABS)	Face-to-face interviews conducted by trained ABS interviewers in participants' homes	n=20,426 participants from 15,565 private residences. 1 adult and 1 child aged 0 to 17 years (if applicable) in each participating household.	84.8%
Romanelli R J. et al. *2017*	To evaluate opioid prescribing in an ambulatory setting among patients with chronic non cancer pain (CNCP)	Adult patients with CP with a medical record in the Electronic Health Record system (EHR) (≥18 years).	Using Sutter EHR (Community-based open-network healthcare system in northern California)	The EHR	1,784,114	
Fain K M. et al. *2017*	To quantify prescription analgesic use of elderly nursing home residents with persistent non-cancer pain and to identify individual and facility traits associated with no treatment.	Elderly nursing home residents with persistent noncancer pain. (≥65 years)	Individuals residing in a Nursing Home in U.S. at any time between December 2007, and November 2008	The Minimum Data Set; the Online Survey, Certification, and Reporting (OSCAR) database; and Medicare Part D	2.99 million individuals	
Gouveia N. et al. *2017*	To analyze and characterize the intake profile of pain-relief drugs in a population-based study of adults with chronic low back pain (CLBP).	Adult Portuguese population with self-reported active CLBP (>18 years)	Households selected by random route methodology	Face-to-face interview.	10,661	

Ahn Y-J. et al. 2016	To assess medical care and costs of the 3 highest prevalence lumbar disorders -non-specific low back pain (nLBP), intervertebral disc disorder (IDD) and spinal stenosis (SS)- to provide basic information for standards of appropriate management.	Patients included in 2011 Korean Health Insurance Review and Assessment Service (HIRA) (All ages)	National Health Insurance National Patient Sample data provided by HIRA. Year 2011	2011 HIRA National Patient Sample (NPS)	1,375,842	
Birke H. et al. *2016*	To examine the trends regarding the prevalence of CNCP, dispensed opioids, and concurrent use of benzodiazepine (BZD)/ BZD-related drugs in the Danish population	Participants with chronic pain. (≥16 years)	The Danish National Cohort Study (DANCOS). Years 2000, 2005, 2010 and 2013.	In 2000 and 2005, face-to-face interviews and self-administered questionnaire. In 2010 and 2013, postal or web questionnaire	16,684 in 2000 10,916 in 2005 25,000 in 2010 25,000 in 2013	63% in 2000 51% in 2005 61% in 2010 57% in 2013
Wand B. M. et al. 2016	To present the outcomes of a comprehensive evaluation of the psychometric properties of the Fremantle Back Awareness Questionnaire (FreBAQ) and explore the potential relationships between body perception, nociceptive sensitivity, distress, and beliefs about back pain and the contribution these factors	People with axial CLBP (between 18 and 70 years)	From 2 metropolitan hospitals in Western Australia, private metropolitan physiotherapy clinics, pain management and general practice clinics. Also, via multimedia advertisements circulated throughout the general community Western Australia	Self- administered questionnaire and a combination of clinical bedside tests and laboratory tests	251	

	might play in explaining pain and disability				
Vincent A. et al. 2015	To evaluate the problem of multiple chronic conditions and polypharmacy in patients with fibromyalgia.	Patients with fibromyalgia. (≥21 years)	Patients identified via the Rochester Epidemiology Project (REP) in Olmsted County, Minnesota. Between January 2005 and December 2009		1,111
Larochelle M. R. et al. *2015*	To characterize trends in opioid prescribing and co-prescribing of sedative hypnotics at acute and chronic musculoskeletal pain visits from 2001 to 2010.	Patients with musculoskeletal pain. (≥18 years)	Combining the National Ambulatory Medical Care Survey & National Hospital Ambulatory Medical Care Survey.	Data collection was carried out by physicians, hospital staff, or Census field representatives.	35,302
Marschall, U. et al. 2015	To determine the prevalence and the demographic and medical predictors of Long-Term Opioid Therapy (LTOT), of high dose of LTOT and of abuse/addiction of prescribed opioids in a cohort of insureds with CNCP of a large German statutory health insurance.	Persons insured by the German statutory medical health insurance. (Age not specified).	From the records of outpatient (Association of Statutory Health Insurance Physicians bills) and inpatient care (hospital bills) of persons insured by the German statutory medical health insurance plan Barmer GEK January 2012 and December 2012.	The Barmer GEK.	870,000

Kingsbury S. R et al. 2014	To examine the impact of peripheral joint OA across five large European countries and how people with OA use pharmacotherapies.	The general population using the Internet panel maintained by Lightspeed Research. (≥18 years)	Data were derived from the 2011 five European countries (5EU) National Health and Wellness Survey (NHWS)	Respondents were emailed a link to the survey to complete on their own. ≥65-year-old population were recruited by telephone and they had the choice to complete the interview on the phone.	57, 512: France: n=15000 Germany:n=15001 Italy: n=7500 Spain: n=5011 UK: n=15000	
Fredheim O. M. S. et al. *2014*	To know the prevalence of persistent opioid use among people in the general population with self-reported CNCP	All inhabitants in the county of Nord-Trondelag in Norway (≥20 years).	Linkage of the National Norwegian prescription database and the Nord-Trøndelag health study 3 2006 to 2008	2 Postal questionnaires and a physical examination.	45,837	
Azevedo L.F. et al. *2013*	To describe the prevalence and factors associated with opioid use in subjects with CP in Portugal and to evaluate satisfaction and self-assessed treatment effectiveness.	A representative sample of the adult Portuguese population (≥18 years)	Random digit dialing.	A structured questionnaire conducted by computer-assisted telephone interviews (CATI).	5,094	76% among responding households and 51% among all identified households.
Henderson, J. V et al. *2013*	To determine the prevalence of CP, its causes, severity, management, impact on sleep, mood and activity levels, and general practitioner (GP) and patient	Patients attending to General Practice. (All ages)	The BEACH (Bettering the Evaluation And Care of Health), an Australian General Practice program.	Questionnaires were completed by the GP in discussion with the patient, using the combined knowledge of both.	5,793	79%

	satisfaction with pain management.				
Häuser W. et al. 2012	To conduct the first European fibromyalgia syndrome (FMS) consumer reports on the effectiveness and side effects of FMS-therapies in routine clinical care.	Members of the self-help organisations with diagnosis of FMS (Age not specified).	From the two largest German FMS-self help organisations and nine clinical institutions. 2010 to 2011	Self-reported questionnaires	1,661

Table 2. Prevalence of opioids' use and factors associated to opioid us in chronic pain population.

Author	Pain definition	Prevalence of CP	Method for obtaining the opioids prevalence	Prevalence of opioid use	Factors associated to opioid use in CP patients
Rodondi P. et al. 2019	Chronic Low Back Pain (CLBP) defined as pain lasting or recurring for 3 months or more.	The whole sample had CLBP (N=499)	Self-reported use of assessed therapies	52.5% of the CLBP patients	- Current smoking was associated with using opioids (OR=1.8; 95% CI,1.1–3.1) - Patients from primary care physician who were trained in complementary medicine were significantly less likely to use opioids (OR=0.5; 95% CI,0.3–0.9)
Callhof J. et al. 2019	Persons with ICD-10- GM (German Modification) diagnoses of Osteoarthritis (OA) in 2014	The whole sample had OA (N=3,564) - 758 polyarthritis (POA) - 959 hip OA. - 399 hip and knee OA - 1,448 knee OA	Analgesics were identified using ATC codes, counting patients as users if they had ≥1 prescription of the drug in that year.	14.9% of the total OA patients - 14% POA. - 14% hip OA. - 22% hip and knee OA - 14% knee OA.	
Lin H-C et al. 2019	The ICD-9-CM diagnosis codes provided by the NAMCS	The whole sample had non-cancer CP (N=2846)	The electronic health records, including information on prescribed medications	33.1% of the study sample.	- Patients aged 25–49 vs. 18–25 years (OR=2.78; 95% CI, 0.93-8.33) - Patients with Medicare (OR=1.56; 95%CI, 1.03-2.38) or Medicaid coverage (OR=2.08; 95%CI, 1.15-3.85) vs. who had private insurance coverage. - Patients being followed by the physician versus naïve patients.(OR=2.33; 95% CI, 1.49-3.57)
van den Driest J. J et al. 2019	Generalized OA was defined as self-reported OA in 3 or more groups of joints	The whole sample had OA (N=842)	Self-reported analgesics used in the preceding month	22% of the patients with OA-related pain	
Shmagel A. et al. 2018	CLBP was defined as self-reported pain in the area between the lower posterior margin of the	13.7% had CLBP (N=700)	Self-reported prescription medications used within the past 30 days	18.8% of working-age Americans with CLBP	- Low levels of education: For less than high school (OR=3.07; 95% CI, 1.12–8.39) and for high school or associates' degree (OR=4.17; 95% CI, 1.73 – 10.03) compared with college education

	ribcage and the horizontal gluteal fold on most days for at least 3 months.				- <35,000 of annual household income (OR=1.92; 95% CI, 1.19–3.11) vs >65,000 - 2 or more medical comorbidities (OR=3.32; 95%CI, 1.74–6.35) vs none or one
Scala E. et al. 2018	Pain lasting 6 months or more.	The whole sample had CP (N=639). The locations were back (71.4%), lower limb (68.4%), cervical spine (25.8%), an upper limb (25.2%) or a shoulder (23.0%).	Patients were asked whether they used non-opioid painkillers, opioids or dietary supplements 'against pain' during the last six months.	64.6% of the study sample.	
Sites B D. et al. 2018	A combination of (ICD-9-CM) codes and patient self-reported data	The whole sample had musculoskeletal pain (N=19,566)	Participant were ask to report prescription medication use and pharmacies were contacted to validate these prescriptions	13.1% opioid users. - 29.2% as low-level users (2 to 4 opioid prescriptions) - 28.9% as moderate users (5 to 9) - 41.9% as heavy users. (10 or more)	
Knoop J. et al. 2017	Clinical knee and/or hip OA diagnosed, according to the American College of Rheumatology criteria.	The whole sample had OA (N=656)	Patients were asked to list all medication used at that moment	12% use of opioids - 6% Tramadol - 3% Codeine - 1%Prednisone - 3% Other	
Miller, A. et al. 2017	Self-reported pain which persisted over a 6-month period.	- 12.7% of all ages (N=2.8 million) - 15.4% (aged ≥15 years). -14.6% males -16.1% females.	Opioid analgesia use included the use of any type of opioid analgesia over the previous 2-week.	12% males vs. 13.4% females (aged ≥15 years). - 15-24 years 17.0%. - ≥85 years and female 29.0%.	

			Participants were asked for the name or brand of all medication, and they were requested to provide the packages to the interviewer.		
Romanelli, R. J et al. 2017	Patients with 2 records of ICD-9 CM, diagnoses for a Chronic Non Cancer Pain (CNCP) condition (pain lasts longer 3 month) at least 30 days apart	6.8% (N=120,481)	The electronic health records, including information on prescribed medications.	Received any opioids among all CP Patients: - 58.1% Short-acting (immediate-release) opioids: -57.4%. Long-acting opioid: -7%	CP Conditions per Patient by CP Category: -Arthritis/joint pain (OR=1.39; 95% CI, 1.36-1.42) -Back/cervical pain (OR=1.07; 95% CI, 1.05-1.09) -Neuropathies/neuralgias (OR=1.65; 95% CI, 1.61-1.69) -Headaches/migraines (OR=1.51; 95% CI, 1.47-1.56), unclassified pain (OR, 1.48; 95% CI, 1.44-1.53). Patient demographic characteristics - Older patients (≥66 years vs 18-45 years) (OR=0.55; 95% CI, 0.52-0.58) - Those with moderate chronic disease burden (CCI score = 2-3 vs 0) (OR=0.92; 95% CI, 0.88-0.96) - Asians (vs. NonHispanicWhite)(OR=0.37; 95%; CI,0.33-0.40) Patients with higher odds of receiving an opioid were: - Men (over women). - Patients with noncommercial insurance, especially Medicaid (OR=2.77; 95% CI, 2.56-3.01) - Patients with more CP conditions (OR=3.27; 95%; CI,3.15-3.40).
Fain, K M., et al. 2017	Moderate to severe daily pain lasting at least 3 months	3.8% (N=18,526) of eligible nursing home residents had persistent pain	An opioid prescription dated within 30 days before or after persistent pain onset.	- 81.1% received an opioid drug (alone or in combination with	

				acetaminophen or prescription NSAID). -16.2% had only opioids prescription.
Gouveia N. et al. 2017	Low Back Pain lasting at least 90 days	10.4% (CI 9.56%; 11.9%) (N=1,487)	According to the national drug agency (INFARMED) classification.	- 1.6% (95% CI 0.9-2.2) among population with Active CLBP
Ahn Y-J. et al. 2016	Patients with a lumbar disorder coded by the Korean Classification of Diseases, adapted from the ICD-10	27% (Patient visiting medical institution with lumbar/spinal diagnostic codes N=371,858)	The use of medications documented in the medical record	2.3% of the total patients with lumbar disorder included for analyses (n=135,561)
Birke H., et al. 2016	Pain lasting 6 months or more.	-18.9% in 2000 - 20.2% in 2005 - 26.2% in 2010 - 26.8% in 2013.	The Danish National Prescription Registry using ATC codes. Long-term, having used at least one prescription/month for 6 months. Short- term having used at least one prescription in the previous year.	Opioid users among individuals with CP <u>Long-term</u> - 1.3% in 2000. - 1.3% in 2005 - 1.7% in 2010. - 1.8% in 2013. <u>Short-term</u> - 2.8% in 2000. - 3.1% in 2005 - 3.8% in 2010. - 3.9% in 2013.
Wand B. M. et al. 2016	To have experienced LBP for >3 months, scored ≥2 on a numeric rating scale, and ≥5 on the Roland Morris Disability Questionnaire	The whole sample had experienced LBP	Self-reported questionnaire about current pain medications	15.9% of the 251 people with CLB

Vincent A. et al. 2015	Patients with a diagnosis of fibromyalgia (HICDA or ICD-9)	The whole sample had Fibromyalgia	The use of medications documented in the medical record	22.4% among the 1,111 patients with fibromyalgia	
Larochelle, M R. et al. 2015	Pain lasting at least 3 months	53% of the visits were for CP.	The primary outcome was prescription or continuation of an opioid medication during the visit.	Combining all years, opioids were prescribed to 20.8% (95%CI 18.9–22.6%) of CP visits. 12.9% (95%CI 9.7–16.0%) in 2001. 28.2% (95%CI 21.4–34.9%) in 2007. 23.1% (95%CI 18.3–27.9%) in 2010.	Patients aged 35–49 years vs. 50–64 years (OR=1.32 (95% CI 1.11–1.56)). Hispanic vs. non-Hispanic whites (OR=0.54 (95%CI 0.39–0.74)). Patients with Medicaid (OR= 1.46 (95%CI 1.16–1.85)), Medicare patients under age 65 years (OR=2.34 (95%CI 1.77–3.10)), and patients without insurance (OR=1.54 (95%CI 1.21–1.96)) vs. private insurance. Patients visiting their assigned primary care provider (OR= 1.39 (95%CI 1.15–1.68)) and patients previously seen in that office (OR=1.94 (95%CI 1.52–2.49)).
Marschall, U. et al. 2015	According to the International Classification of Diseases (ICD-10-GM)	The whole sample had CP.	The insurance organization long-term opioid therapy (LTOT) prescriptions: defined by at least one opioid prescription per quarter for at least three consecutive quarters (one quarter = 3 months) over the last 12-month. High-dose opioid therapy (defined by ≥100 mg MEQ/day)	LTOT prescription all insureds with CNCP 1.3% (range 1.2%; 1.4%). High-dose opioid therapy among LTOT users 15.5% (range 14.2%; 16.5%)	
Kingsbury S. R et al. 2014	Respondents who self-reported a	OA prevalence 6.5% - UK 10.9% - France 6.4%	Respondents were asked whether they currently use prescription to treat	16.7% - 19.3% in the UK - 27.7% in France	

	physician diagnosis of OA	- Germany 3.8% - Spain 6.3% - Italy 3.6%	their arthritis; if so, they were asked to indicate what they were currently using	-3.5% in Germany - 6.9% in Spain - 0.7% in Italy	
Fredheim, O. M. S. et al. 2014	Pain lasting 6 months or more and pain of at least moderate intensity during the last week before participation in HUNT 3.	31.6%	The National Norwegian prescription. Two different definitions of persistent opioid use included: -<u>The wide definition</u> clinically corresponds to using opioids most days of the week (>180 DDD or 4500 OMEQ) -<u>The strict definition</u> to using opioids around the clock all days (>730 DDD or 18,000 OMEQ). Data on dispensed opioid prescriptions during the 6 months immediately before participation in HUNT 3.	Opioid users among individuals with CP <u>Persistent opioid use</u> 2.9% <u>Occasional opioid use</u> 12.3%	- Being younger than 56 years old (OR=2.22, CI 95%: 1.65;2.99) - Male (OR=1.49, CI 95%: 2;1.11) - A current smoker (OR=2, CI 95%: 1.36;2.94) - Using more than 100 DDD of benzodiazepines per year (OR=5.55, CI 95%: 3.74;8.23) - Receiving prescriptions of drugs from several ATC classes (OR=4.98, CI 95%: 3.31;7.48)
Azevedo L. F, et al. 2013	Pain lasting at least 3 months	35.7% (95% CI, 34.38–37.02)	Respondents were asked if they were using any pain medicine. If so, they were asked for the drugs and the frequency	4.24% (95%CI: 3.31–5.41) among participants who responded if they were using any pain medicine (N=1786)	-Pain-related disability PDI (per increase in 10 units) OR=1.23 CI 95% 1.02–1.50)
Henderson, J. V et al. 2013	Pain experienced every day for three months in the six months prior to this consultation	18.8% (95% CI: 17.8–19.8)	Respondents were asked if their pain was being managed and how. If the answer was “with medication”, they were	32.7% among respondents with CP (N=1,088)	

			asked to specify which medication.	
Häuser W. et al. 2012	Fibromyalgia Syndrome (FMS)- diagnosis >1 month's duration	The whole sample had FMS	Participants were asked to "indicate whether they currently use any interventions for FMS". The interventions, including drugs, were listed in different sections.	- 17.6% Weak opioids - 8.4% Strong opioids

Table 3. Characteristics of the subgroups and results of the meta-analysis.

Subgroup	Source	Type of pain	Treatment duration	Heterogeneity test	Model	Study	Events	Sample Size	Prevalence (CI95%)	Publication Bias
A	General Population Surveys	General Chronic pain	Long-term use	Q=12.44; df=1; p<0,001 I^2=91.96 There is heterogeneity	Random effects	Birke, 2016	63	3501	1.8 (1.4-2.3)	
						Fredheim, 2014	417	14477	2.9 (2.6-3.2)	
						Summary Prevalence			**2.3 (1.5-3.6)**	
B	General Population Surveys	General Chronic pain	Short-term use	Q=271.64; df=3; p<0,001 I^2=98.89 There is heterogeneity	Random effects	Miller, 2017	393	3146	12.5 (11.4-13.7)	Egg`s test: p=0.1457 Begg's test: p=0.3082
						Birke, 2016	137	3501	3.9 (3.3-4.6)	
						Fredheim, 2014	1787	14477	12.3 (11.8-12.9)	
						Azevedo, 2013	76	1786	4.3 (3.4-5.3)	
						Summary Prevalence			**7.3 (4.3-11.9)**	
C	General Population Surveys	Chronic Low Back Pain	Unspecified	Q=135.96; df=1; p<0,001 I^2=99.26 There is heterogeneity	Random effects	Shmagel. 2018	132	700	18.9(16.1-21.9)	
						Gouveia, 2017	24	1487	1.6(1.1-2.4)	
						Summary Prevalence			**5.8(0.5-45.5)**	
D		General Chronic pain	Unspecified	Q=901.59; df=2; p<0,001	Random effects	Lin, 2019	942	2846	33.1(31.4-34.9)	Egg`s test:

	Health records or Medical Surveys			I^2=99.78 There is heterogeneity		Henderson, 2013	356	1088	32.7 (30.0-35.6)	p=0.1662 Begg's test: p=0.6015
						Romanelli, 2017	69935	120481	58.0 (57.8-58.3)	
						Summary Prevalence			**41.0 (23.3-61.3)**	
E	Health records or Medical Surveys	Musculoskeletal Conditions	Unspecified	Q=509.24; df=4; p<0,001 I^2=99.22 There is heterogeneity	Random effects	Callhof, 2019	531	3564	14.9(13.8-16.1)	Egg`s test: p=0.2391 Begg's test: p=0.3272
						Rodoni, 2019	262	499	52.5(48.1-56.9)	
						Van Den Driest, 2019	186	842	22.1(19.4-25.0)	
						Sites, 2018	2564	19566	13.1(12.6-13.6)	
						Knoop, 2017	79	656	12.0(9.8-14.8)	
						Summary Prevalence			**20.5 (12.9-30.9)**	
F	Health records or Medical Surveys	Fibromyalgia	Unspecified	Q=4.412; df=1; p=0.036 I^2=77.34 There is heterogeneity	Random effects	Vincent, 2015	249	1111	22.4(20.1-25.0)	
						Häuser, 2012	381	1465	26.0(23.8-28.3)	
						Summary Prevalence			**24.5(22.9-26.2)**	

Figure legends

Figure 1. Flowchart.

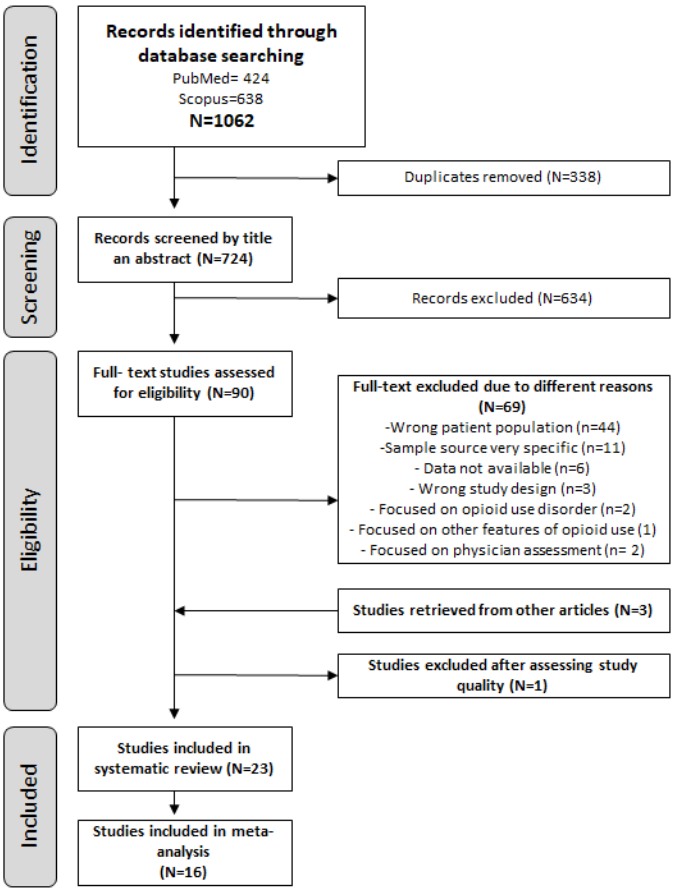


Figure 2. Results of the meta-analysis and ForestPlot.

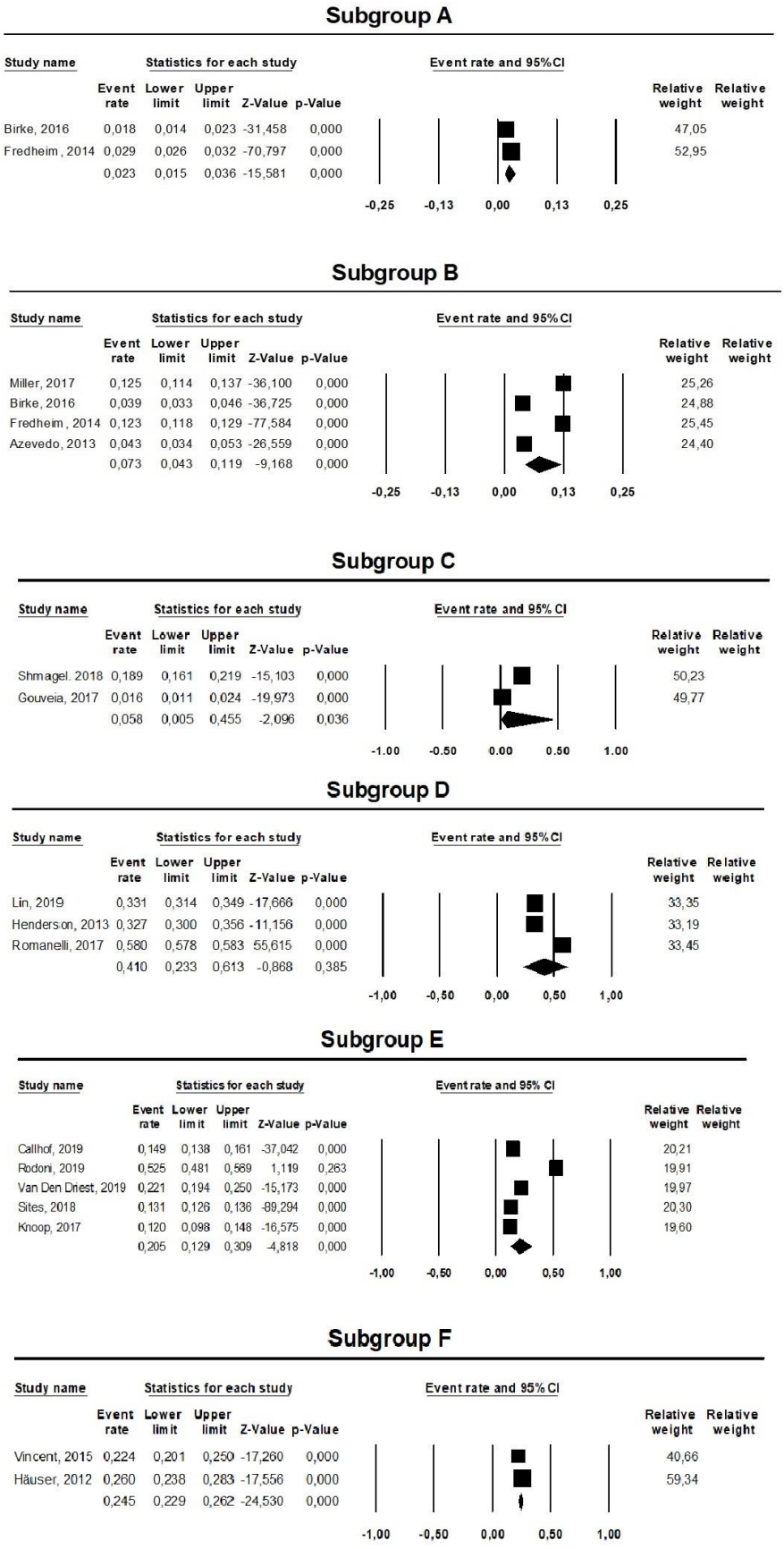


Figure 3. Publication Bias. Funnel Plots.

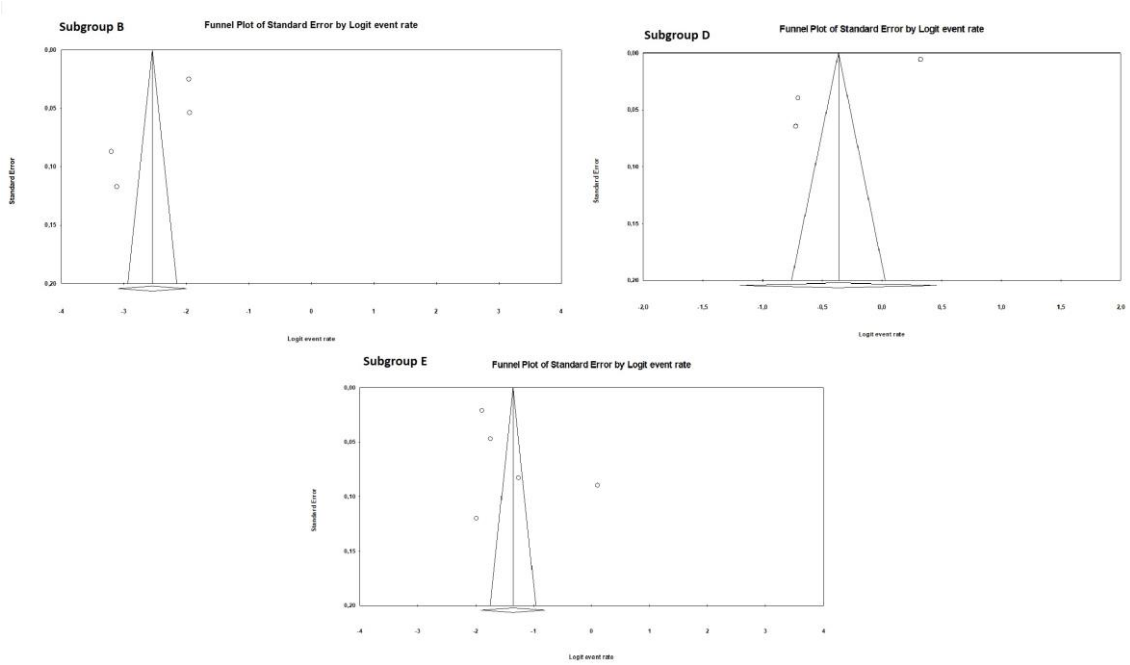
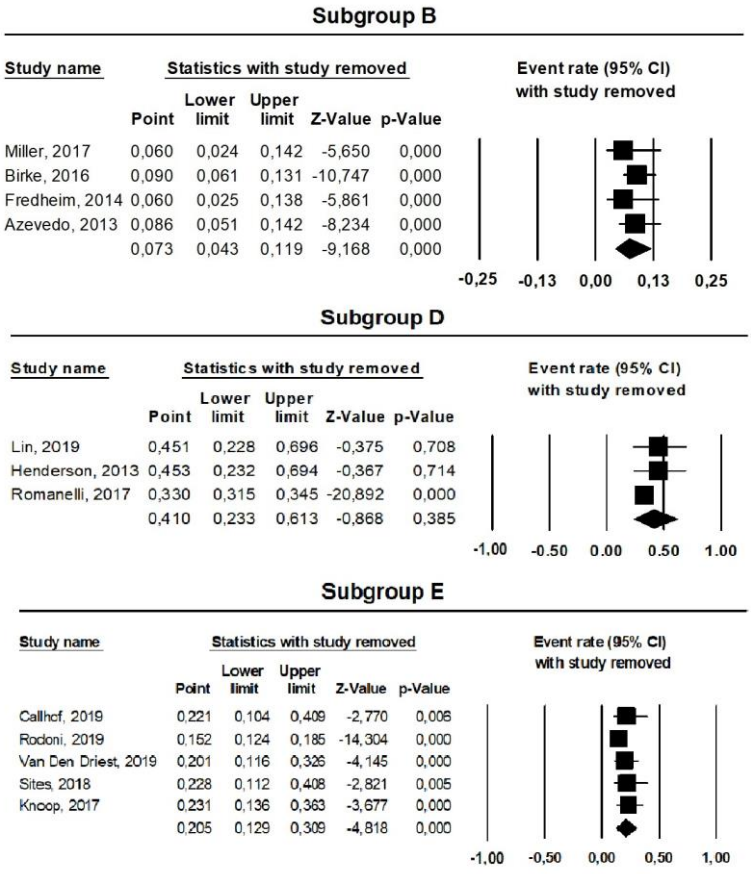


Figure 4. Influence graphics for sensibility analysis.



Subgroup B

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Miller, 2017	0,060	0,024	0,142	-5,650	0,000
Birke, 2016	0,090	0,061	0,131	-10,747	0,000
Fredheim, 2014	0,060	0,025	0,138	-5,861	0,000
Azevedo, 2013	0,086	0,051	0,142	-8,234	0,000
	0,073	0,043	0,119	-9,168	0,000

Statistics with study removed

Event rate (95% CI) with study removed

-0,25 -0,13 0,00 0,13 0,25

Subgroup D

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Lin, 2019	0,451	0,228	0,696	-0,375	0,708
Henderson, 2013	0,453	0,232	0,694	-0,367	0,714
Romanelli, 2017	0,330	0,315	0,345	-20,892	0,000
	0,410	0,233	0,613	-0,868	0,385

Statistics with study removed

Event rate (95% CI) with study removed

-1,00 -0.50 0.00 0.50 1.00

Subgroup E

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Callhof, 2019	0,221	0,104	0,409	-2,770	0,006
Rodoni, 2019	0,152	0,124	0,185	-14,304	0,000
Van Den Driest, 2019	0,201	0,116	0,326	-4,145	0,000
Sites, 2018	0,228	0,112	0,408	-2,821	0,005
Knoop, 2017	0,231	0,136	0,363	-3,677	0,000
	0,205	0,129	0,309	-4,818	0,000

Statistics with study removed

Event rate (95% CI) with study removed

-1,00 -0,50 0,00 0,50 1,00

Supplementary material

Table S1. Combined search terms used for this systematic review in each database, number of studies found, and search term used for the purpose of Figure 1.

Systematic review-PubMed (N=424)
opioid*[Title/Abstract] AND analgesic* AND pain[Title/Abstract] AND "cross-sectional" AND ("last 10 years"[PDat] AND Humans[Mesh])
Systematic review-Web of science (N=638)
(((TITLE-ABS-KEY (*opioid**) AND ALL (*analgesic**) AND TITLE-ABS-KEY (*pain*) AND TITLE-ABS-KEY (*"Cross-Sectional"*)))) AND (LIMIT-TO (DOCTYPE , *"ar"*)) AND (LIMIT-TO (PUBYEAR , *2019*) OR LIMIT-TO (PUBYEAR , *2018*) OR LIMIT-TO (PUBYEAR , *2017*) OR LIMIT-TO (PUBYEAR , *2016*) OR LIMIT-TO (PUBYEAR , *2015*) OR LIMIT-TO (PUBYEAR , *2014*) OR LIMIT-TO (PUBYEAR , *2013*) OR LIMIT-TO (PUBYEAR , *2012*) OR LIMIT-TO (PUBYEAR , *2011*) OR LIMIT-TO (PUBYEAR , *2010*) OR LIMIT-TO (PUBYEAR , *2009*)) AND (LIMIT-TO (LANGUAGE , *"English"*) OR LIMIT-TO (LANGUAGE , *"Spanish"*)) AND (LIMIT-TO (EXACTKEYWORD , *"Human"*))

Table S2. Reasons for the exclusion of the studies not included in the systematic review and meta-analysis (N=69).

Author, year	**Reason for exclusion**
Austin et al, 2017	Wrong patient population
Bastian et al, 2017	Wrong patient population
Boehnke et al, 2016	Sample source very specific
Buse et al, 2012	Wrong patient population
Carriere et al, 2017	Focused on other features of opioid use
Carriere et al, 2018	Wrong patient population
Challa et al. 2017	Sample source very specific
Chan et al, 2018	Sample source very specific
Chang et al, 2014	Wrong patient population
Civardi et al, 2018	Wrong study design
Darnall et al, 2011	Sample source very specific
Daubresse et al, 2013	Wrong patient population
Desai et al, 2019	Wrong patient population
Deyo et al, 2013	Sample source very specific
Elsesser et al, 2017	Wrong patient population
Enthoven et al, 2014	Wrong study design
Erdeljić et al, 2011	Sample source very specific
Feinberg et al, 2018	Sample source very specific
Fischer et al, 2010	Focused on opioid use disorder
Fleckenstein et al, 2010	Focused on physician assessment

Fredheim et al, 2011	Focused on opioid use disorder
Gadzhanova et al, 2015	Sample source very specific
Gomes et al, 2011	Wrong patient population
Guite et al, 2018	Wrong patient population
Hansen et al, 2015	Wrong patient population
Harle et al, 2014	Wrong patient population
Hauser et al, 2018	Wrong patient population
Healey et al, 2018	Data not available
Hemmingsson et al, 2018	Wrong patient population
Holliday et al, 2013	Focused on physician assessment
Hoppe et al, 2015	Wrong patient population
Jobski et al, 2017	Wrong patient population
Kozma et al, 2014	Wrong patient population
Kurita et al, 2012	Wrong patient population
Lin et al, 2017	Wrong patient population
Lin et al, 2018	Wrong patient population
Mailis-Gagnon et al, 2011	Wrong patient population
Marcum et al, 2011	Wrong patient population
Martel et al, 2019	Sample source very specific
Miller et al, 2018	Sample source very specific
Montero Matamala et al, 2011	Wrong patient population
Narayana et al, 2015	Wrong patient population
O'Gara et al, 2016	Wrong patient population
Pérez et al, 2009	Wrong patient population
Pérez et al, 2013	Data not available
Pierce et al, 2019	Wrong patient population
Pitkala et al, 2015	Wrong patient population
Pokela et al, 2010	Wrong patient population
Rasu et al, 2016	Data not available
Rasu et al, 2018	Wrong patient population
Rasu et al, 2013	Wrong patient population
Rivera et al, 2016	Wrong study design
Roxburgh et al, 2011	Wrong patient population
Ruscitto et al, 2015	Wrong patient population
Samison et al, 2017	Wrong patient population
Samuelsen et al, 2016	Data not available
Sawyer et al, 2010	Wrong patient population
Sites et al, 2014	Wrong patient population
Steinman et al, 2015	Wrong patient population
Stompór et al, 2019	Sample source very specific
Taylor-Stokes 2011	Data not available
Thomas et al, 2015	Wrong patient population
Todd et al, 2018	Wrong patient population
Veal et al, 2015	Wrong patient population

Westergaard et al, 2015	Wrong patient population
Yackey et al, 2018	Wrong patient population
Zheng et al, 2017	Data not available
Zin et al, 2014	Wrong patient population
Zin et al, 2017	Wrong patient population

Table S3. Risk of bias of cross-sectional studies included (N=24).

Tool used to assess the study quality and risk of bias of cross-sectional studies.

Checklist for analytical cross-sectional studies from The Joanna Briggs Institute:

1. Were the criteria for inclusion in the sample clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way?
4. Were objective, standard criteria used for measurement of the condition?
5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

Table S3. Risk of bias of cross-sectional studies included (N=24).

	Inclusion	Setting	Exposure valid and reliable	Objective	Confounding	Confounding strategies	Outcomes valid and reliable	Appropriate statistical analysis	Number of 'yes'
Ahn et al, 2016	1	1	1	1	1	1	1	1	8
Azevedo et al, 2013	1	1	1	1	1	1	1	1	8
Birke et al, 2016	1	1	1	1	1	1	1	1	8
Blanco et al, 2011	0	0	1	1	0	0	1	1	4
Callhof et al, 2019	1	1	1	1	1	0	1	1	7
Fain et al, 2017	1	1	1	1	1	1	1	1	8
Fredheim et al, 2014	1	1	1	1	1	1	1	1	8
Gouveia et al, 2017	1	1	1	1	0	0	1	1	6
Häuser et al, 2012	1	1	1	1	1	0	1	1	7
Henderson et al, 2013	1	1	1	1	1	1	1	1	8
Kingsbury et al, 2014	1	1	1	1	0	0	1	1	6
Knoop et al, 2017	1	1	1	1	1	1	1	1	8
Larochelle et al, 2015	1	1	1	1	1	1	1	1	8
Lin et al, 2019	1	1	1	1	1	0	1	1	7
Marschall et al, 2015	1	1	1	1	1	1	1	1	8

Miller et al, 2017	1	0	1	1	1	1	1	1	7
Rodondi et al, 2019	1	1	1	1	1	0	1	1	7
Romanelli et al, 2017	1	1	1	1	1	1	1	1	8
Scala et al, 2018	1	1	1	1	1	1	1	1	8
Shmagel et al, 2018	1	1	1	1	1	0	1	1	7
Sites et al, 2018	1	1	1	1	1	1	1	1	8
Van den Driest et al, 2019	1	1	1	1	0	0	1	1	6
Vincent et al, 2015	1	1	1	1	0	0	1	1	6
Wand et al, 2016	1	1	1	1	1	1	1	1	8

STUDY 2

The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017. Differences between Spain and the United States.

Current Medical Research and Opinion

2020, VOL. 36, NO. 2, 285–291. DOI: 10.1080/03007995.2019.1684251

Impact Factor: 2.345

Alejandro Salazar; Soledad Moreno; ***Helena De Sola*;*** *Jose A. Moral-Munoz JA; María Dueñas; Inmaculada Failde.*

*The author of this thesis is the corresponding author of this article and was the mainly responsible for writing the manuscript.

ABSTRACT

Objective. To investigate the evolution of opioid-related mortality and potential years of life lost in Spanish general population from 2008 to 2017. To evaluate the differences between Spain and US.

Methods: A descriptive study using retrospective annual data from 2008 to 2017 in Spanish and US general population. Information on the population and opioid-related deaths stratified by age and sex was obtained from Spanish National Statistics Institute and the Centers for Disease Control and Prevention (CDC) WONDER Multiple Cause of Death Database, according to the ICD-10 codes. Years of life lost, crude and standardised mortality rates are reported and compared with the results in US.

Results: Crude rate of opioid-related deaths per 10^5 inhabitants has changed from 1.68 in 2008 to 2.25 in 2017 in Spain, with around 30 000 years of life lost per year. The most affected groups were middle-aged men and women over 65, and the main cause of death was accidental poisoning. The standardised rates per 10^5 inhabitants across the years were between 1.19 and 1.62 in Spain and between 11.17 and 20.68 in US population.

Conclusions: An opioid overuse crisis does not seem a likely scenario in Spain. However, it is a social problem that requires special health surveillance, particularly in middle-aged men and women over 65.

Keywords: Opioid; Mortality; Years of life lost; Spanish population; US population.

INTRODUCTION

The prescription and consumption of opioids has changed in many countries in recent years as it is becoming a serious health problem in some cases [1–6]. According to the World Drug Report 2017 [7], 29.5 million people globally suffer from drug use disorders, being opioids the most harmful. The United Nations has warned of an opioid overuse crisis in the USA in 2017, although this is not the only country in which its consumption has increased [1]. In Europe, Bosetti et al [2] reported an increase in opioids consumption, with relevant differences between countries. Particularly, these authors observed the highest consumption in Western/Northern European countries and the lowest consumption in Southern/Eastern countries. Some authors [2,3] identified an upward trend similar to the USA. Although in the country where the consumption is the highest in Europe (Germany), it is approximately half of the level in the United States [3]. Despite this, a crisis similar to the US is anticipated in other countries such as the United Kingdom in 5 or 10 years [4].

In Spain, data reported by Garcia del Pozo et al in 2008 [5] revealed a huge increase in opioids consumption at the end of the 20th century and the beginning of the 21st century. More recently, The Spanish Agency for Medicines and Health Products quantified the increase from 7.25 Defined Daily Dose (DDD) per 1000 inhabitants per day in 2008 to 13.31 in 2015 [6], which represents an increase of 83.59%. However, it is not clear if the situation has worsened in recent years, and there is currently a debate in the scientific community about whether Spain presents a similar trend to the United States, and if we are on the way to a possible overuse crisis.

The aforementioned crisis is not something to be taken lightly, as higher doses of medically prescribed opioids may lead to opioid overdose [8]. This finding challenges the traditional idea that opioid overdose is related to non-medical users [9]. In addition to overdoses, many of the problems associated with the use of opioids, such as addiction, abuse or dependence [4,9–13], greater physical and psychological comorbidities [8,14–18], an increase in opioid-related mortality and potential years of life lost [4,19], have been reported. Some authors even report that the risks of opioids outweigh the benefits [4,20], and the opioid abuse can have clinical and economic consequences in the society, including patients, health care professionals, and the government [14].

Meyer et al [14] has estimated a cost of $55.7 billion attributable to prescription opioid abuse in 2007 as well as an increase of 124% in the rate of unintentional overdose deaths. This increase has been observed by other authors, particularly in the USA and Canada [19,21], being a problem

that affects especially people aged 25 to 44 [21]. This fact aggravates the situation in terms of early loss of life. Few studies have reported the data on years of life lost (YLL), either globally [22] or in the United States specifically [10,19], where it has been estimated at 830 652 YLL among people younger than 65 years in 2008. However, to the best of our knowledge, there are no studies in Spain analysing this, even though YLL is an indicator of great importance in this context, as it quantifies the costs of opioid-related deaths (ORD).

As the situation in the USA has been described as alarming, and there is evidence that some countries could be on the same path, it is important to know the situation in a country like Spain, where an increase in opioid consumption has been observed, and a similar tendency might be plausible. Replicating in Spain the results obtained by Gomes et al [19] in the US would allow us to compare the situation and can prevent a possible overuse problem.

In view of the above, we aimed to investigate the evolution of opioid-related mortality and potential years of life lost in Spanish general population from 2008 to 2017 and to compare it by gender and age. We also aimed to know the differences between Spain and the USA.

METHODS

This is a descriptive study using the retrospective annual data from 2008 to 2017 in the Spanish general population. It is based on the methodology previously used by Gomes et al [19] in the USA to compare populations.

Information on the population and ORD stratified by age and sex was obtained from the Centers for Disease Control and Prevention (CDC) WONDER Multiple Cause of Death Database for the USA [23], and the Spanish National Statistics Institute (INE, for its acronym in Spanish) for Spain [24].

The INE carries out the "Statistics of deaths according to the cause of death" [25] following the criteria established by the WHO in the International Classification of Diseases (ICD-10) [26], which includes more than 12 000 diseases. This statistic provides information on mortality according to the basic cause of death and its distribution by sex and age, among other factors. A similar methodology is used by the CDC.

From these data, and according to the ICD-10 codes [26], we retrieved information on ORD specifically due to accidental poisoning (X40-X44), intentional self-inflicted poisoning (X60-X64), aggression (X85), and poisoning of not determined intention (Y10-Y14).

For each year (from 2008 to 2017), we report stratified (by sex and age) data on number of ORD, crude and standardised rates of ORD per 10^5 inhabitants, years of life lost (YLL), YLL per 10^4 inhabitants, number of deaths by type of opioid-related death. Crude rate of ORD is defined as the quotient between the number of ORD and the total population, expressed in terms of number of deaths per 10^5 inhabitants. YLL are defined as the sum of the remaining years that a person who has prematurely died due to opioids has not lived, that is, the sum of the difference of life expectancy and the age of death of each person who has prematurely died due to opioids. Type of opioid-related death is a qualitative variable classifying the deaths in accidental poisoning, intentional self-inflicted poisoning, aggression, and poisoning of not determined intention. The data presented are tabulated in absolute terms and crude rates. We report the number of deaths by type of death and year in Spain, for the total population, men and women separately, in bar plots.

The evolution over time of the standardised rates of ORD in total population, men and women, is presented in a line chart for both Spain and the USA. For this comparison, we standardised the data taking into account the different distribution of the two populations by ages. For this standardisation, the direct method was used: the rate of each stratum in each population was applied to the world standard population provided by the WHO [27] to obtain data on the expected deaths, which were subsequently added and divided by the total standard population to obtain the standardised rates per 10^5 inhabitants. We report these standardised rates in a line chart.

All the analyses and figures were performed using the software Excel 2016.

RESULTS

Opioid-related deaths and years of life lost in Spain due to opioids in the period 2008-2017.

Between 2008 and 2017, a total of 8506 people died due to opioids, including accidental poisoning, intentional self-inflicted poisoning, aggression, and poisoning of not determined intention (Tables 1A and 1B). The cost, in terms of YLL, was 290 093.33 years (Tables 2A and 2B).

The crude rate of ORD per 10^5 inhabitants in the whole population has fluctuated (around 2) over the years (from 1.68 in 2008 to 2.25 in 2017), showing a slight upward trend in men from 2011 to 2017, and in women in the whole period Crude rates in men are always above crude rates in women (around 1 point above) (Tables 1A and 1B).

The most affected age groups were, in almost all the cases, 35-44 and 45-54, but it is remarkable the increase of the crude rates in the group of 65 or more years (from 1.25 in 2008 to 3.8 in 2017. In this regard, we observed differences between men and women, with men most affected in the age group 35-54, and women in the age group over 65 (Tables 1A and 1B).

Regarding the YLL, we further observed a fluctuant situation, with a minimum of 24 497.35 YLL in 2011 and a maximum of 32 648.99 in 2016 in the whole population (Tables 2A and 2B). Nevertheless, it was different between men and women. In particular, men lost more years of life, even more than twice than the women in most cases. The largest amounts of YLL were observed in the age group 35-44 (Tables 2A and 2B).

Number of deaths by the type of opioid-related death and year.

Most of the deaths had a well-defined cause, with only a few cases due to poisoning of not determined intention (Y10-Y14). In addition, as the years went by, the number of indeterminate cases decreased. Aggression (X85) was the least frequent cause of all (Figures 1A and 1B).

In the total population, the main cause was accidental poisoning, followed by intentional self-inflicted poisoning. When analysing by sex, the number of deaths due to intentional self-inflicted poisoning was similar in men and women, but a substantial difference in accidental poisoning was evident. Specifically, the number of deaths was higher in men compared with women (Figures 1A and 1B).

Comparison of opioid-related mortality between US and Spanish population.

After the standardisation of the rates, we observed a better situation in Spain than the USA (Figure 2). In the total population, the standardised rates per 10^5 inhabitants across the years were between 1.19 and 1.62 in Spain and between 11.17 and 20.68 in US population. This difference was even more evident for men, and slightly lower (but still relevant) for women. A greater increase in US standardised rates in recent years was observed, compared to the slight increase in Spain after standardisation. (Figure 2).

DISCUSSION

In this study, we have analysed the ORD in terms of the evolution of opioid-related mortality and potential years of life lost in Spain in the previous years. We have performed a comparison between Spain and the USA. Generally, our results reflect a better situation in Spain than in the

USA, although we cannot ignore the upward trend in the opioid-related mortality and the years of life lost.

Specifically, we found between 691 and 1049 deaths per year. Given the data on the considerable increase in the prescription and consumption of opioids previously reported [5,6], a greater increase in associated mortality could be expected; however, the increase is not a significant reason for concern.

The worst evolution has been observed in men in the study of Gomes et al [19], and this pattern is repeated in the rest of the results. Gomes et al also point out that the burden of ORD is higher among men, and our results confirm that in Spain as well. The number of YLL is worrisome in the whole population, but especially in men. According to the Spanish Report on alcohol, tobacco and illegal drugs 2017 [28], the main psychoactive substances responsible for deaths in recent years are hypnosedatives and opioids, followed by cocaine and alcohol, the latter in a lesser proportion. In more than half of the deaths in which toxicological information was collected, opioids were involved. However, the report does not specify if it was the main cause of death. In any case, this means that we must pay special attention to the consumption of opioids, as these are involved in many deaths, and our data identify these as the main cause of death. Historically, addiction to opioids has always been higher in men. In addition, it has been shown that men are more likely to increase the dose of opioid therapy compared with women [29], which is in line with our results. However, recently, there is more controversy in this regard, with higher levels of addiction in women in some cases [30–33].

Regarding the differences by age, we observed that the most affected ages were 35-54, similar to the US population [19]. However, in the group over 55 in the USA, an increase in the rates has been observed. This was also observed in our data in Spain in some of the studied years, mostly in women. It could be argued that this is due to the greater use of these drugs in cases of terminal diseases, although it must be taken into account that the registered main cause of these deaths is not the disease, but the opioid. Besides, this would not explain the gender differences. The prevalence of chronic pain is higher in women of this age group [34], with opioids being one of the most used treatments for pain [35]. A systematic review published on sex differences in opioid effect on pain [36] has found that side effects such as emesis and respiratory depression, the latter often related to an eventual death [37], are more pronounced in women. However, there is limited information on gender differences in opioid use risk factors, and a more in-depth study is required to identify whether this could explain the observed differences in mortality in women of this age group.

The main cause of death was accidental poisoning, not intentional poisoning. Roxburgh et al [38] have reported that the increase in opioid deaths was mainly caused by accidental overdoses in the Australian population, and some authors also found an increased risk of accidental death in the case of co-prescription [37]. A previous study found that even the single prescription of opioids is associated with the risk of future ORD [29]. Therefore, it is important to emphasise education and rationalise the use of these drugs to prevent accidents, as suggested by other authors [37,38], especially in men whose death rates are higher compared with women in Spain.

The comparison of the standardised rates of opioid-related mortality between Spain and the USA is significant. Even after standardisation, the ratios are clearly different between the countries, 8 to 12 times higher in the USA compared with Spain, depending on the year (the more recent, the greater the difference), and this difference is more pronounced in men, in accordance with the results by Gomes et al [19]. In this regard, Bosetti et al have reported that the Southern and Eastern European countries (Spain included) have the lowest consumption [2], which would imply, a priori, a lower risk. Additionally, a recent study of Chen et al shows that, in Europe, the most concerning increases in drug overdose deaths from opioids have been observed in the northern countries such as Estonia, largely caused by fentanyl [39]. The previous considerations indicate that, despite the increase in mortality, the situation in Spain is far different from the situation in the United States or some other countries [2–4].

Finally, we have to point out some limitations of this study. The use of secondary data is always a potential limitation, although the data were collected exactly as we needed for the purpose of the study, with precise definitions using ICD-10 codes. In addition, the data were obtained from reliable sources. However, the reliability of the determination and coding of the cause of death depends on each professional in each of the deaths, and not on the data source itself. Because of this, we believe that there is a possibility of underestimating the number of ORD, as in some cases this information may be omitted to avoid legal or administrative issues, especially in the case of accidents. Among the strengths of our study, we highlight the comparison between countries, as it provides information whether the situation in Spain is similar to the situation in the USA. Finally, the importance of the subject addressed here is another strength of the study.

CONCLUSION

The crude rate of ORD per 10^5 inhabitants has changed from 1.68 in 2008 to 2.25 in 2017 in Spain, with around 30 000 years of life lost per year, being middle-aged men and women over 65 the most affected groups. The standardised rates in US population are 8 to 12 times higher

compared to standardised rates in Spain. An opioid overuse crisis does not seem a likely scenario in Spain. However, it is a social problem that requires special health surveillance, particularly in middle-aged men and women over 65.

Transparency section.

Declaration of financial/other relationships

This work was supported by The Grünenthal Foundation, a private non-profit making organisation that promotes the dissemination of scientific knowledge and supports research. This organisation did not have any involvement in the design of the study and collection, analysis and interpretation of data or writing the manuscript. The authors declare that they have no conflict of interest.

Author contributions

IF conceived the idea of the project. The fieldwork was performed by AS, JMM and MD. AS and SM performed the statistical analysis. AS and HDS were mainly responsible for writing the manuscript. IF and SM were involved in revising the content. All the authors approved the final version of the manuscript.

REFERENCES

[1] Ballantyne JC. Opioids for the Treatment of Chronic Pain. Anesth. Analg. 2017;125:1769–1778.

[2] Bosetti C, Santucci C, Radrezza S, et al. Trends in the consumption of opioids for the treatment of severe pain in Europe, 1990-2016. Eur. J. Pain. 2019;23:697–707.

[3] Turmina Fontanella A, Goulart Molina-Bastos C, da Silva Dal Pizzol T, et al. Too much or too little opioid use? A comment on Bosetti et al. Eur. J. Pain. 2019;23:639–640.

[4] Dhalla I, Persaud N, Juurlink D. Facing up to the prescription opioid crisis. Br. Med. J. 2011;343:d5142.

[5] Garcia del Pozo J, Carvajal A, Viloria JM, et al. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. Eur. J. Clin. Pharmacol. 2008;64:411–415.

[6] Agencia Española de Medicamentos y Productos Sanitarios. Utilización de medicamentos opioides en España durante el periodo 2008-2015. 2017.

[7] United Nations Office on Drugs and Crime. World Drug Report 2017. United Nations publications; 2017.

[8] Dunn KM, Saunders KW, Rutter CM, et al. Overdose and prescribed opioids: Associations among chronic non-cancer pain patients. Ann. Intern. Med. 2010;152:85–92.

[9] Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA. 2008;300:2613–2620.

[10] Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers-United States, 1999-2008. MMWR. Morb. Mortal. Wkly. Rep. 2011;60:1487–1492.

[11] Florence CS, Zhou C, Luo F, et al. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. Med. Care. 2016;54:901–906.

[12] Webster F, Bremner S, Oosenbrug E, et al. From Opiophobia to Overprescribing: A Critical Scoping Review of Medical Education Training for Chronic Pain. Pain Med.

2017;18:1467–1475.

[13] Gomes T, Mamdani MM, Dhalla IA, et al. The burden of premature opioid-related mortality. Addiction. 2014;109:1482–1488.

[14] Meyer R, Patel AM, Rattana SK, et al. Prescription opioid abuse: a literature review of the clinical and economic burden in the United States. Popul. Health Manag. 2014;17:372–387.

[15] Buse DC, Pearlman SH, Reed ML, et al. Opioid use and dependence among persons with migraine: results of the AMPP study. Headache. 2012;52:18–36.

[16] McAdam-Marx C, Roland CL, Cleveland J, et al. Costs of opioid abuse and misuse determined from a Medicaid database. J. Pain Palliat. Care Pharmacother. 2010;24:5–18.

[17] Cicero TJ, Wong G, Tian Y, et al. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: Data from an insurance claims database. Pain. 2009;144:20–27.

[18] White AG, Birnbaum HG, Mareva MN, et al. Direct costs of opioid abuse in an insured population in the United States. J. Manag. care Pharm. 2005;11:469–479.

[19] Gomes T, Tadrous M, Mamdani MM, et al. The Burden of Opioid-Related Mortality in the United States. JAMA Netw. Open. 2018;1:e180217.

[20] Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of analgesics in older adults with arthritis. Arch. Intern. Med. 2010;170:1968–1976.

[21] Rudd RA, Seth P, David F, et al. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. Morb. Mortal. Wkly. Rep. 2016;65:1445–1452.

[22] Degenhardt L, Charlson F, Mathers B, et al. The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. Addiction. 2014;109:1320–1333.

[23] United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released 2018.

[Internet]. 2018. Available from: http://wonder.cdc.gov/mcd-icd10.html.

[24] Spanish National Statistics Institute. Official website of the Spanish National Statistics Institute [Internet]. Madrid; 2018. Available from: http://www.ine.es/.

[25] Spanish National Statistics Institute. Statistics of deaths according to the cause of death. Methodology. [Internet]. 2017. Available from: https://www.ine.es/daco/daco42/sanitarias/metodologia_00.pdf.

[26] World Health Organization (WHO). ICD-10: international statistical classification of diseases and related health problems. Geneva: World Health Organization; 2004.

[27] Ahmad O, Boschi-Pinto C, Lopez A, et al. Age standardization of rates: a new WHO standard. GPE Discussion Paper Series: No.31. 2001.

[28] Observatorio Español de las Drogas y las Adicciones. Informe 2017: Alcohol, Tabaco y Drogas ilegales en España. 2017.

[29] Kaplovitch E, Gomes T, Camacho X, et al. Sex Differences in Dose Escalation and Overdose Death during Chronic Opioid Therapy: A Population-Based Cohort Study. PLoS One. 2015;10:e0134550.

[30] Chartoff EH, McHugh RK. Translational Studies of Sex Differences in Sensitivity to Opioid Addiction. Neuropsychopharmacology. 2016;41:383–384.

[31] Becker JB, Mazure CM. The federal plan for health science and technology's response to the opioid crisis: understanding sex and gender differences as part of the solution is overlooked. Biol. Sex Differ. 2019;10:3.

[32] Carew AM, Comiskey C. Treatment for opioid use and outcomes in older adults: a systematic literature review. Drug Alcohol Depend. 2018;182:48–57.

[33] Jacobs AA, Cangiano M. Medication-Assisted Treatment Considerations for Women with Opiate Addiction Disorders. Prim. Care. 2018;45:731–742.

[34] Dueñas M, Salazar A, Ojeda B, et al. A nationwide study of chronic pain prevalence in the general spanish population: identifying clinical subgroups through cluster analysis. Pain Med. 2015;16:811–822.

[35] de Sola H, Salazar A, Dueñas M, et al. Opioids in the treatment of pain. Beliefs,

knowledge, and attitudes of the general Spanish population. Identification of subgroups through cluster analysis. J. Pain Symptoms Manag. 2018;55:1095–1104.

[36] Niesters M, Dahan A, Kest B, et al. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. Pain. 2010;151:61–68.

[37] Gomes T, Juurlink DN, Antoniou T, et al. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. PLoS Med. 2017;14:e1002396.

[38] Roxburgh A, Hall WD, Dobbins T, et al. Trends in heroin and pharmaceutical opioid overdose deaths in Australia. Drug Alcohol Depend. 2017;179:291–298.

[39] Chen Y, Shiels MS, Thomas D, et al. Premature mortality from drug overdoses: A comparative analysis of 13 organisation for economic co-operation and development member countries with high-quality death certificate data, 2001 to 2015. Ann. Intern. Med. 2019;170:352–354.

Table 1A: Opioid-related deaths (ORD) in Spain in the period 2008-2012.

	2008		2009		2010		2011		2012	
	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)
Total										
0-14	0	0	0	0	1	0.01	2	0.03	0	0
15-24	42	0.82	37	0.74	23	0.47	25	0.53	30	0.64
25-34	160	0.21	146	1.92	107	1.45	96	1.36	106	1.57
35-44	295	3.87	244	3.16	248	3.17	196	2.48	231	2.91
45-54	135	2.17	131	2.04	146	2.21	152	2.24	164	2.38
55-64	44	0.89	43	0.86	45	0.89	58	1.13	51	0.97
≥65	95	1.25	95	1.23	121	1.53	186	2.31	230	2.81
Total	771	1.68	696	1.5	691	1.48	715	1.53	812	1.74
Man										
0-14	0	0	0	0	1	0.03	2	0.06	0	0
15-24	37	1.41	24	0.94	17	0.68	19	0.78	20	0.84
25-34	122	3.04	119	3.03	83	2.2	76	2.1	87	2.54
35-44	239	6.11	189	4.76	201	5.01	155	3.82	180	4.42
45-54	101	3.24	88	2.73	97	2.93	99	2.92	112	3.24
55-64	23	0.96	24	0.98	26	1.05	36	1.43	31	1.21
≥65	47	1.46	44	1.34	49	1.46	68	1.98	80	2.28
Total	569	2.5	488	2.13	474	2.06	455	1.97	510	2.21
Woman										
0-14	0	0	0	0	0	0	0	0	0	0
15-24	5	0.2	13	0.53	6	0.25	6	0.26	10	0.44
25-34	38	1.02	27	0.73	24	0.67	20	0.58	19	0.57
35-44	56	1.51	55	1.46	47	1.24	41	1.07	51	1.32
45-54	34	1.09	43	1.34	49	1.48	53	1.57	52	1.51
55-64	21	0.83	19	0.74	19	0.73	22	0.84	20	0.75
≥65	48	1.1	51	1.15	72	1.59	118	2.56	150	3.21
Total	202	0.87	208	0.89	217	0.92	260	1.1	302	1.27

ORD: Opioid-related deaths.

Table 1B: Opioid-related deaths (ORD) in Spain in the period 2013-2017.

	2013		2014		2015		2016		2017	
	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)
Total										
0-14	2	0.03	1	0.01	1	0.01	2	0.03	0	0
15-24	19	0.42	13	0.29	14	0.31	22	0.49	19	0.42
25-34	109	1.7	96	1.59	86	1.49	115	2.07	95	1.76
35-44	233	2.95	234	2.98	199	2.55	226	2.93	211	2.77
45-54	203	2.91	274	3.88	207	2.9	229	3.17	249	3.41
55-64	76	1.43	106	1.95	100	1.8	114	2	138	2.36
≥65	213	2.55	264	3.1	320	3.71	294	3.36	337	3.8
Total	855	1.84	988	2.13	927	2	1002	2.16	1049	2.25
Man										
0-14	1	0.03	0	0	1	0.03	0	0	0	0
15-24	15	0.64	11	0.48	9	0.39	14	0.61	9	0.39
25-34	78	2.42	74	2.43	68	2.35	95	3.41	69	2.55
35-44	164	4.05	177	4.41	149	3.75	173	4.41	163	4.24
45-54	144	4.11	202	5.71	138	3.86	170	4.69	188	5.12
55-64	42	1.61	61	2.3	55	2.02	69	2.47	68	2.37
≥65	89	2.49	95	2.6	125	3.36	123	3.25	140	3.64
Total	533	2.32	620	2.71	545	2.39	644	2.82	637	2.79
Woman										
0-14	1	0.03	1	0.03	0	0	2	0.06	0	0
15-24	4	0.18	2	0.09	5	0.23	8	0.37	10	0.46
25-34	31	0.98	22	0.73	18	0.62	20	0.72	26	0.96
35-44	69	1.79	57	1.48	50	1.3	53	1.39	48	1.28
45-54	59	1.69	72	2.05	69	1.94	59	1.64	61	1.68
55-64	34	1.25	45	1.62	45	1.59	45	1.54	70	2.34
≥65	124	2.6	169	3.48	195	3.97	171	3.44	197	3.91
Total	322	1.36	368	1.56	382	1.62	358	1.51	412	1.74

ORD: Opioid-related deaths.

Table 2A: Years of Live Lost (YLL) due to opioids in Spain in the period 2008-2012.

	2008		2009		2010		2011		2012	
	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants
By age group										
0-14	0.00	0.00	0.00	0.00	75.63	0.11	151.54	0.22	0.00	0.00
15-24	2603.73	5.10	2306.89	4.62	1443.50	2.97	1574.01	3.32	1889.52	4.06
25-34	8370.63	10.78	7674.06	10.08	5657.19	7.68	5088.81	7.18	5615.70	8.30
35-44	12 657.91	16.61	10 541.44	13.64	10 800.52	13.82	8568.21	10.84	10 092.01	12.71
45-54	4550.07	7.30	4447.10	6.92	5000.57	7.56	5223.96	7.71	5626.38	8.15
55-64	1089.56	2.21	1074.44	2.15	1138.70	2.25	1476.01	2.87	1294.71	2.47
≥65	1190.11	1.57	1205.92	1.56	1561.71	1.98	2414.82	3.00	2955.54	3.61
By gender										
Man	21 977.12	9.66	18 765.91	8.18	17 654.14	7.67	16 228.49	7.03	18 154.62	7.87
Woman	7407.21	3.19	7639.36	3.26	7210.96	3.06	7583.77	3.20	8564.92	3.61
Total										
Total	30 462.00	6.62	27 249.83	5.88	25 677.82	5.51	24 497.35	5.24	27 473.87	5.87

YLL: Years of Live Lost.

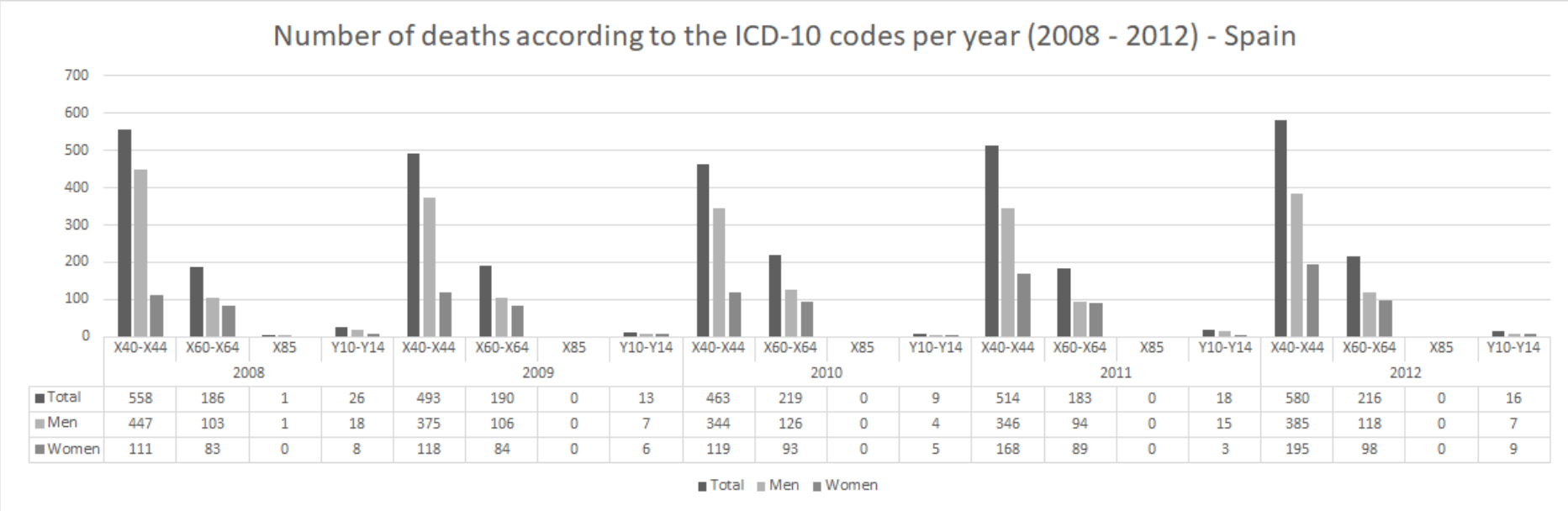
Table 2B: Years of Live Lost (YLL) due to opioids in Spain in the period 2013-2017.

	2013		2014		2015		2016		2017	
	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants
0-14	152.24	0.22	76.19	0.11	75.87	0.11	152.43	0.22	0.00	0.00
15-24	1206.36	2.65	827.88	1.84	888.62	1.99	1406.37	3.15	1214.86	2.70
25-34	5824.50	9.12	5146.52	8.5	4591.01	7.94	6191.30	11.12	5118.01	9.46
35-44	10 277.67	13.00	10 348.39	13.16	8739.63	11.20	10 006.58	12.96	9327.29	12.26
45-54	7047.15	10.09	9544.52	13.52	7149.82	10.02	7998.02	11.08	8687.54	11.88
55-64	1964.76	3.68	2756.76	5.08	2573.70	4.63	2976.85	5.21	3596.44	6.15
≥65	2817.79	3.38	3511.56	4.13	4159.42	4.82	3917.45	4.48	4459.99	5.02
Man	18 432.66	8.04	20 936.35	9.17	17 447.98	7.65	21 591.94	9.47	20 318.22	8.90
Woman	10 168.49	4.30	10 411.95	4.41	10 114.68	4.28	10 161.33	4.30	11 341.08	4.78
Total	29 289.47	6.29	32 211.82	6.93	28 178.05	6.07	32 648.99	7.03	32 404.13	6.96

YLL: Years of Live Lost.

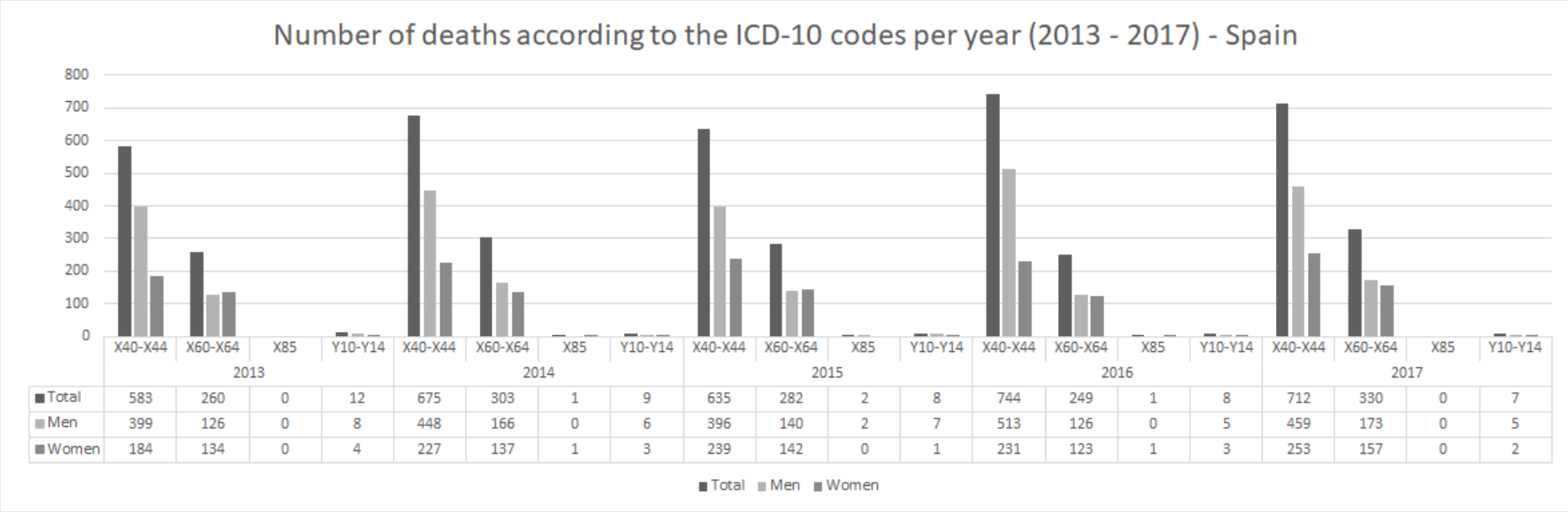
Figure legend

Figure 1A. Number of deaths according to the ICD-10 codes per year (2008 - 2012) – Spain.



ICD: International Classification of Diseases; X40-X44: Accidental poisoning; X60-X64: Intentional self-inflicted poisoning; X85: Aggression; Y10:Y14: Poisoning of not determined intention.

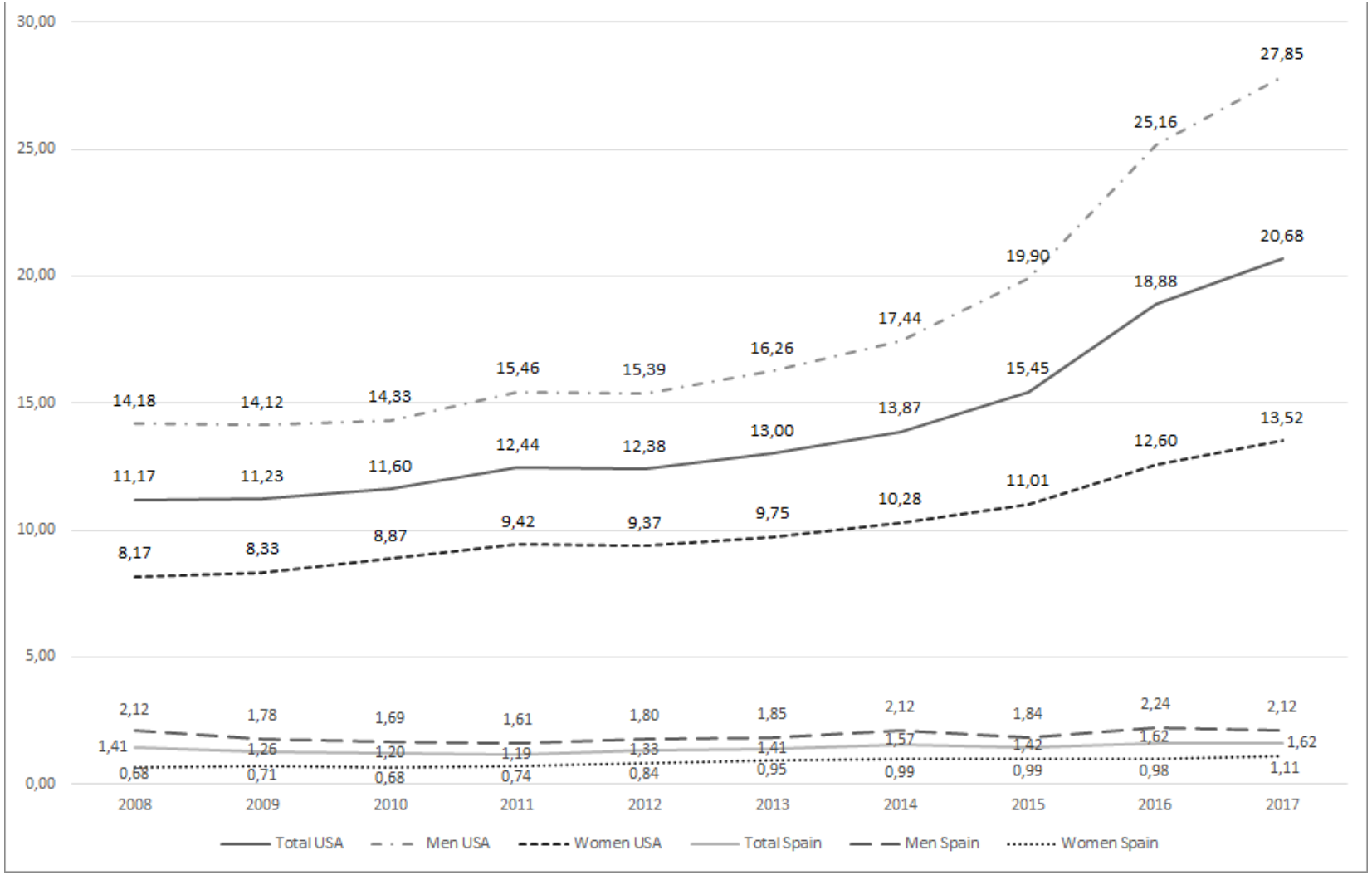
Figure 1B. Number of deaths according to the ICD-10 codes per year (2013 - 2017) – Spain



	2013				2014				2015				2016				2017			
	X40-X44	X60-X64	X85	Y10-Y14	X40-X44	X60-X64	X85	Y10-Y14	X40-X44	X60-X64	X85	Y10-Y14	X40-X44	X60-X64	X85	Y10-Y14	X40-X44	X60-X64	X85	Y10-Y14
Total	583	260	0	12	675	303	1	9	635	282	2	8	744	249	1	8	712	330	0	7
Men	399	126	0	8	448	166	0	6	396	140	2	7	513	126	0	5	459	173	0	5
Women	184	134	0	4	227	137	1	3	239	142	0	1	231	123	1	3	253	157	0	2

ICD: International Classification of Diseases; X40-X44: Accidental poisoning; X60-X64: Intentional self-inflicted poisoning; X85: Aggression; Y10:Y14: Poisoning of not determined intention.

Figure 2: Comparison of the evolution of the standardized rates of opioid related deaths (ORD per 10^5) in Spain and US by gender.



STUDY 3

Opioids in the Treatment of Pain. Beliefs, knowledge, and attitudes of the General Spanish population. Identification of subgroups through cluster analysis

Journal of Pain and Symptom Management

2018, VOL. 55, NO. 4, 285–291. DOI: 10.1016/j.jpainsymman.2017.12.474
Impact Factor: 3.378

Helena De Sola*; Alejandro Salazar; María Dueñas; Inmaculada Failde*

* The author of this thesis contributed to this work by performing the fieldwork, analysing the data, and was mainly responsible for writing the manuscript.

ABSTRACT

Context: A lack of information has been found related to patients' perception towards pain management.

Objectives: To analyze the point of view of the general Spanish population regarding the use of opioids in pain treatment. To identify groups of individuals based on this information.

Methods: Nationwide cross-sectional study on a representative sample of 1,299 Spanish adults. Data were collected on beliefs, knowledge, fears, opinions and, attitudes towards the use of opioids. A cluster analysis to identify groups of people based on these parameters, and a multinomial logistic regression model to analyze the variables related to the clusters were performed.

Results: Three groups of subjects were identified based on their perspective towards opioids: A group with a positive point of view (N=448) composed of people >65 years who would accept a treatment if prescribed and who were less fearful of these drugs; A group with a moderate point of view (N=337) formed by younger subjects with university education, better informed about opioids, afraid of these drugs (OR=2.67), and more frequently associated them with drowsiness (OR=2.58), nausea (OR=3.04), and tolerance (OR=2.16); A third group with negative point of view (N=468), with lower educational level who would more often reject treatment with opioids, more afraid of them (OR=3.95), considering that they may not be able to stop the treatment (OR=3.04) and may produce tolerance (OR=3.03).

Conclusions: The different perspectives of patients regarding the use of opioids to treat pain should be taken into consideration by the physician when designing strategies to inform patients about the treatment of pain with opioids. This should promote their correct use, specially preventing their misuse.

Keywords: Opioids, Beliefs, Knowledge, Attitudes, Opiophobia and Epidemiology.

Running Title: Vision towards the use of opioids in Spain.

INTRODUCTION

Opioids are drugs that are widely used in pain treatment worldwide, and that the World Health Organization (WHO) considers essential for the control of moderate and intense pain, particularly of oncological origin (1). For some years now, awareness has been on the rise regarding the treatment of pain in Spain because of the progressive increase in the number of pain units in hospitals and of the enhanced emphasis on pain management in the palliative care. Likewise, the prescription and use of opioids increased between 2008 and 2015 in Spain (2) but without reaching the levels observed in other European countries like Denmark (3).

Several studies have shown that some patients consider that the medical prescription of opioids is sometimes associated with terminal illness and imminent death (4). Likewise, these drugs have also been related to negative side effects, such as excessive sedation, respiratory failure, urinary retention or constipation, among others (5). This situation along with social, cultural and historical factors (6) have led to what is known as "opiophobia", a set of inappropriate attitudes and beliefs regarding the deleterious effects of opioids administration for pain relief (7). This has been related to reduced prescription of these drugs by health professionals and lower consumption by patients (8).

By contrast, in other countries where the prescription of opioids has risen considerably in recent years, it has been reported that between 24.0% and 37.1% of the patients with chronic pain may often misuse of these drugs (defined as the use of any addictive drug in a manner other than how it is indicated or prescribed) (9), which has raised some alarm among this population (10). This situation has led to the need to identify patients at risk, and to monitor their behavior more closely (11).

In view of the differences observed in studies into the viewpoints of patients regarding the use of opioids to treat pain, we conducted a population-based survey to determine the current beliefs, opinions, and attitudes of the Spanish population towards opioid use in the treatment of pain. We set out to identify groups of individuals based on their point of view regarding these drugs and to analyze the factors that influence this perspective in each of the groups identified.

METHODS

This cross-sectional study was carried out on a representative sample of the general adult population in Spain, obtained using a multistage, stratified sampling method. The eligible

population consisted of individuals aged ≥ 18 years who resided in households with a landline telephone, who agreed to participate in the study and who were able to complete the questionnaire. The exclusion criteria were individuals younger than 18 years of age, lack of a landline telephone at home, or the inability to respond to the questionnaire.

Sampling Method

The Spanish territory was divided into 8 strata or areas based on geographical and historical boundaries. For each stratum, 20 municipalities were randomly selected, taking into account the Spanish rural/urban ratio of 25:75, and considering municipalities with <10,000 inhabitants as rural and those with >10,000 inhabitants as urban areas.

The total number of subjects required for the study (see below) was distributed in proportion to the size of each municipality. In addition, the number of subjects was divided into 6 strata, according to the sex and age distribution of the population (18 to 44, 45 to 64 and 65 or over). The selected individuals were contacted through their landline telephone using the Infobel España Office v.7.1 digital telephone directory. This directory includes the telephone numbers of 90% of all Spanish households with a landline telephone and considering that 80.6% of Spanish households have a landline telephone, we had access to 72.5% of the eligible Spanish population.

Sample Size

The sample size was determined based on the study of Schiller et al.(4), in which it was estimated that 50% of subjects were afraid of taking morphine. Setting a significance level of 95% and a precision level of 5%, the required sample size was established as 1,155 subjects. In order to guarantee the number of subjects calculated and considering the response rate in a previous study involving a telephone survey (12), the amount of telephone numbers randomly selected was three times that of the required sample size.

Procedure and instruments

Data were collected via a computer assisted telephone interview (CATI) using the Skype and the SurveyMonkey platforms, whereby the interviewers recorded the data while the interview was being conducted. The interviewers received training on the purpose of the study, the working protocol and on the use of the SurveyMonkey platform. In addition, data collection was coordinated and supervised on a daily basis by a member of the research team, addressing any

problems that had arisen. Before the interview, all subjects included in the study gave their informed consent, and the study was conducted in accordance with the Helsinki Declaration, using Standard Working Procedures and Protocols.

Survey structure and topic

The survey was structured in 6 blocks of questions: the *first block* was designed to *obtain* personal information; the second block was related to the respondents' beliefs about opioids, and in this case the information was collected from an open-ended question in which the interviewees were asked what was the first thing that came to mind when they heard the word “opioid”; the third block revealed the level of the respondent’s contact with opioids and their knowledge of them; the fourth block explored the fears (side effects, death, becoming an addict, not achieving the desired results, and death) related to the opioids intake; the fifth block collected the opinions of the responder regarding this type of treatment (tolerance, dependence, severity of the disease); and the sixth block addressed the responders’ attitude towards these drugs. This attitude was obtained by means of a question that asked whether the respondent would agree to treatment with this medication or not if their doctor prescribed it. The questions that set out to collect information about beliefs, fears and opinions were assessed using a 5-point Likert scale ("not at all", "a little", "some", "quite a lot" and "a lot").

In order to facilitate the analysis and interpretation of the results, three new variables were created. The first variable was designated as the "level of contact with the treatment" and it was constructed using three questions that referred to the drugs Tramadol, Morphine, Tapentadol, Oxycodone, Fentanyl and Buprenorphine. The questions were:

1. *“Are you currently following a treatment with any of these opioids?"* If the answer was affirmative, we considered the respondent to have "maximal contact" with opioids.
2. "*Have you ever been treated with any of these opioids?* If the answer was affirmative, we considered the respondent to have "medium contact" with opioids.
3. *"Do you know anyone who is currently or has ever been treated with an opioid?"* If the answer was affirmative, we considered the respondent to have "minimal contact", while they were considered as having "no contact" if the response was negative.

A second variable, considered "level of opiophobia", was established based on four questions gathering information about the individual’s fear of: side effects, becoming an addict, not achieving the desired results, and death. The responses to these questions were categorized on a scale ranging from 0 = “not at all” to 4 = “a lot”. The final score of this new variable was the

sum of the scores given on a scale from 0 to 16, where 0 is equivalent to no opiophobia and 16 corresponded to maximal opiophobia.

In addition, to determine the respondents' knowledge about the opioids indicated above, a third variable was created that we called "correct identification of opioids" based on the responses to the questions: *"Have you heard of any of the following medications?"*; and *"Could you tell me which of the following drugs you think is an opioid?*". The answers to these questions were dichotomous ("Yes" and "No") and we considered that an individual correctly identified the drugs only if they responded affirmatively to both questions.

Statistical Analysis

A descriptive analysis of the variables studied was carried out, calculating the frequency, central tendency and dispersion. In addition, a hierarchical cluster analysis was performed to establish groups of individuals or patterns according to the subjects' opinions, fears, knowledge, level of contact and attitude toward opioids. The Euclidean distance between the groups and cluster formation criteria were used. Subsequently, the differences between the groups were analyzed using Chi-squared tests. In addition, a multinomial logistic regression model was established to determine the factors associated with each of the groups previously identified in the cluster analysis. The covariates included in this model were the significant variables identified in the bivariate analysis.

RESULTS

General characteristics of respondents

We carried out 3,844 contacts, 1,299 of which considered valid. The response rate was 33.79%. Of the total number of subjects interviewed, 50.7% were women and the global average age of the cohort was 50.48 years (SD=15.9). The majority of subjects had completed secondary education (45.9%).

Morphine was the best-known medication (99.2%) and it was correctly identified by 64.9% of respondents. However, fewer subjects correctly identified Tramadol (14.2%), and while oxycodone was recognized by 11.3% of respondents, Fentanyl, Buprenorphine or Tapentadol were only identified correctly by slightly more than 5% of them. More than 50% of participants knew someone who had taken opioid medication (minimal contact with treatment), although only 3.8% were taking any of these drugs at the time of the interview (maximum contact) (table

1). Most of the subjects with maximum contact were women (60%), over 65 years and mainly with primary education (43%).

Beliefs, fears, opinions and attitude towards opioids

Figure 1 is a Word cloud showing the beliefs of the respondents with regard to opioids, where the size of each word indicates how often the respondents related it to opioids. Although the most frequent response was "I do not know with which word to relate them", the words "pain", "illegal drugs", "medications", "opium" and "painkillers" were much repeated (figure 1).

Regarding fear of opioids (figure 2), side effects (48%) or of a failure to achieve the expected results (47%) were the fears most frequently reported by respondents, although nearly 35% of them expressed the fear of becoming addicted.

With regard the respondents' opinions on opioids, most of the interviewed agreed that these drugs may cause sleep or sedation (50.8%), that they are used when a disease is severe (42.6%), and that increasingly large doses are required (44.7%). However, almost 50% of them disagreed that opioids should only be used with terminally ill patients. Only slightly more than 30% of the respondents related these drugs with constipation (table 2).

When analyzing the attitude of the respondents towards the use of opioids, it was notable that most of respondents stated that they would agree to take them if they were prescribed medically (86.3%) as they generally placed confidence in their doctor (64.4%).

Patterns of opinions, fears and attitudes in the population surveyed, and associated factors.

From the clusters analysis, three groups of subjects were identified (table 3).

The first group (N=448), considered with the most Positive Point of View (PPV) towards opioids, was mainly composed of individuals over 65 years who would accept opioid treatment if it were prescribed by a doctor. In addition, they reported fewer fears towards these drugs, and they were more frequently of the opinion that opioids do not cause side effects and they are not associated with terminal illness, addiction or the need to increase the dose in order to achieve the desired effect (tolerance).

The second group (N=337) was characterized by having a Moderate Point of View (MPV) toward opioids and it was comprised of a larger proportion of young people with university education. The individuals in this group more often identified the opioids correctly than those in the other

2 groups and they not only thought that these drugs produced side effects (sleep, nausea, constipation), but they were also afraid of not getting the expected results if they took them. The third group (N=468), with the most Negative Point of View (NPV) towards opioids, included the subjects with the lowest educational level and with a stronger negative attitude regarding the acceptance of treatment with these drugs. These individuals had the highest level of opiophobia and they had the worse opinion of these drugs, considering them associated with terminal illness, addiction and tolerance.

Factors associated to each group identified according to their point of view toward opioids

The opinion that increasingly large doses of opioids are required (MPV:OR=2.16; NPV:OR=3.03) and a higher level of opiophobia (MPV:OR=2.67; NPV:OR=3.95) were the two variables most strongly associated to the groups with a worse vision of these drugs (MPV, NPV versus PPV). However, while respondents in the MPV group more strongly agreed that opioids produce sleepiness (OR=2.58) and nausea (OR=3.04), respondents with a more negative vision (NPV) placed more importance on not being able to stop taking them whenever they wanted to (OR=3.04) (table 4).

DISCUSSION

To our knowledge, this is the first study carried out in Spain to analyze the perspective of the general population toward opioids, based on the beliefs, knowledge, fears and opinions. This analysis enabled us to identify three groups of individuals with a clearly distinct point of view regarding these drugs, as well as specific factors associated with each of these groups.

Among the results obtained, it is noteworthy that most respondents did not have a clear idea about opioids and those who did, mostly considered them to be related with "pain", "illegal drugs" and "medication". This is consistent with the findings of a study carried out in Portugal (13) where 32.3% of the general population were unable to recognize the term “morphine”. However, when these individuals were specifically asked about this drug, 99.2% answered that they knew about it even though it was only identified as an opioid by 64.9% of them.

In our study, 3.8% of the respondents were under a treatment with opioids at the time of the survey. This is similar to the situation described in Portugal (4.37%) (14), and in Scotland, where the opioid use increased to 3.6%, mainly due to the use of Tramadol(15). According to the report of the Spanish Agency of Medicines and Sanitary Products (2), Tramadol is the opiate that has

experienced a greater increase in use in recent years, which may explain why it is the best known opioid after morphine in our study.

It is important to note that three different profiles of participants were identified in this study, including a group of better-informed young people who are more concerned about the side effects of opioids, who have a more critical attitude towards opioids and who are less willing to take them upon medical prescription (MPV). Another group of participants with a generally lower educational level (NPV) seemed to show more deep-rooted opiophobia. Finally, there was a group of older respondents who had more confidence in their physician when prescribed these drugs and they were less concerned about their adverse effects (PPV). In this vein, it is noticeable that, as other studies show, elderly patients assume pain and taking medication as part of their aging process and only 15% expect that the treatment has few side effects (16). This could explain the results found in our study regarding older people being less afraid of the adverse effects associated with opioids.

Similarly, the higher educational level of the youngest group in our study could condition their attitudes, making them more demanding with the treatment. The WHO states that, among other educational organizations, universities play a key role in establishing knowledge, behavior and attitudes towards health, promoting the "empowerment of students in health" and enabling them to better control adverse health determinants (17). This could explain why the youngest group with the highest proportion of individuals with university education is indeed more critical, not only of the most well-known aspects of these drugs like addiction and tolerance, but also, of other less common aspects that may affect their quality of life.

Studies have shown that when taking opioids, confidence in their effects and a positive attitude towards them is closely related to the improvement in the quality of life and the pain relief obtained by the patient, or that described by acquaintances and relatives (18,19). This circumstance could explain the results observed in the PPV group, which was precisely the group with the greatest level of contact with these drugs. An alternative explanation could be that a greater exposure to opioids expels the fear of their adverse effects, tipping the balance in favor of their pain-relieving effects. This hypothesis could be particularly relevant if we consider that this group included an older population that might be more concerned about pain relief and less concerned about the side effects of these drugs (18,19).

Tolerance was identified as a risk in both the MPV and NPV groups. The NPV group referred to the risk of being unable to stop taking opioids, these individuals were more reluctant to accept

them if prescribed by a doctor. One of the reasons for maintaining inappropriate beliefs and attitudes towards these drugs may be a lack of knowledge about them, leading to opiophobia, a phenomenon that includes a fear of tolerance (7). This is consistent with the characteristics of the NPV group, where the respondents attained a generally poorer level of education.

In accordance with our results, fear of addiction has previously been shown to be an important barrier to opioid use in patients suffering moderate or severe chronic pain, representing one of the reasons why this pain is often under treated (20,21). Indeed, opioid use in the United States represents 80% of the total worldwide consumption (22,23) and the misuse behavior rate is 34.1% (24), much higher than in other countries. Given the importance of controlling pain in patients with chronic moderate or severe pain and avoiding problems of the misuse of opioids, it is important to find a balance between these two extremes in the Spanish population. Thus, identifying groups with different perceptions towards opioids, such as those observed in the present study, should be useful when establishing future healthcare strategies.

Finally, some strengths and weaknesses of the present study should be noted. One strength is the clusters analysis used to identify different groups of subjects based on beliefs, fears, opinions and attitudes towards opioids, stands out as one of the strengths of this work. Other studies (12,25) have applied this analysis to cohorts of patients with chronic pain, demonstrating its usefulness. However, as far as we know, this is the first time that this type of analysis has been applied in this kind of study. Another strength is that the study was carried out on a large sample from the general population using an exhaustive sampling procedure, representing populations of different ages and sex.

Among the weaknesses of the study, we must consider that the information was gathered by telephone, which limited the duration of the interview. However, the use of telephone surveys has been considered by some to be more adequate in population studies than "face-to-face" surveys (26), particularly since they allow greater coverage of the *population* being *studied* and they permit a representative sample to be obtained by randomization of telephone numbers. Another issue that must be taken into account is the low response rate observed in this study (33.79%), which could have introduced selection bias. However, we consider that this is unlikely to affect the validity of the results since the distribution of the sample is identical to that of the target population, ensuring that the responses are representative. Furthermore, although higher response rates have been obtained (e.g., 70%) (21), rates similar to ours (33% and 42%) were also reported using the same method (27,28).

Another possible limitation is that we did not assess “opiophobia” directly and its measurement was based on four questions about the individual’s fear (side effects, becoming addicted, not achieving the desired results, and death). However, the term "opiophobia", as previously described in the introduction(7), is a definition that includes similar issues as those considered in this paper. Given that the general population was target in this study, we believe that the inclusion of the exact definitions of both tolerance and dependence in the questionnaire would have complicated the collection data.

In summary, as well as demonstrating the lack of knowledge in the Spanish population about opioids, this study shows that the side effects of these drugs are the most feared aspects associated with their use in the treatment of pain. Furthermore, this study reveals the factors related with the different perceptions and concerns among the general population regarding the use of opioid treatments, which largely depends on educational level, age and prior contact with opioids. Healthcare professionals should pay particular attention to the patient profile when designing strategies to inform patients and treat their pain using opioids. The information given should be personalized to suit the patient’s characteristics, paying special attention to the possible benefits of the treatment in the MPV and NPV groups, and to the risks and adverse effects in the group with PPV. This should improve the clinical management of opioids and promote their correct use, specially preventing their misuse.

Disclosures and Acknowledgments

This work was supported by the External Chair of Pain, a collaboration between the University of Cádiz and the Grünenthal Foundation. The Grünenthal Foundation is a private non-profit making organization that promotes the dissemination of scientific knowledge and supports research. The authors would like to acknowledge the effort of the interviewers who collected the data through the telephone interviews.

REFERENCES

1. World Health Organization. Access to Controlled Medications Programme. Ensuring balance in national policies on controlled substances: guidance for availability and accessibility of controlled medicines. 2011. p. 1–78.
2. Agencia española de medicamentos y productos sanitarios. Utilización de medicamentos opioides en España durante el periodo 2008-2015. 2017.
3. Birke H, Kurita GP, Sjøgren P, et al. Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: Trends from 2000 to 2013. Acta Anaesthesiol Scand. 2016;60(5):623–33.
4. Schiller M, Pyszora A, Graczyk M, et al. Are the patients afraid of opioids? Pilot study of the patients with chronic cancer and non-malignant pain. Adv Palliat Med. 2007;6(4):121–4.
5. Verloo H, Cohen C, Borloz C, et al. Risks associated with the use of morphine for analgesia: attitudes and perceptions amongst nursing students in French-speaking Switzerland. Nursing (Lond). 2013;3:1–8.
6. Krakauer EL, Phuong Cham NT, Husain SA, et al. Toward safe accessibility of opioid pain medicines in vietnam and other developing countries: A balanced policy method. J Pain Symptom Manage. 2015;49(5):916–22.
7. Ferreira M, Verloo H, Mabire C, et al. Psychometric evaluation of the French version of the questionnaire attitudes towards morphine use; a cross-sectional study in Valais, Switzerland. BMC Nurs. 2014;13(1):1–8.
8. Motov SM, Khan ANGA. Problems and barriers of pain management in the emergency department: Are we ever going to get better? J Pain Res. 2009;2:5–11.
9. Jamison RN, Butler SF, Budman SH, et al. Gender Differences in Risk Factors for Aberrant Prescription Opioid Use. J Pain. 2011;11(4):312–20.
10. The president's commission on combating drug addiction and the opioid crisis. [Internet]. 2017. Available from: https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Meeting Draft of Final Report - November 1%2C 2017.pdf2017.
11. McHugh RK, Weiss RD, Cornelius M, et al. Distress intolerance and prescription opioid misuse among patients with chronic pain. J Pain. 2016;17(7):806–14.
12. Dueñas M, Salazar A, Ojeda B, et al. A Nationwide Study of Chronic Pain Prevalence in the General Spanish Population : Identifying Clinical Subgroups Through Cluster Analysis. Pain Med. 2014;16(4):811–22.

13. Verloo H, Mpinga EK, Ferreira M, et al. Morphinofobia: the situation among the general population and health care professionals in. BMC Palliat Care. 2010;9(15):2–9.
14. Azevedo LF, Costa-Pereira A, Mendonça L, et al. A population-based study on chronic pain and the use of opioids in Portugal. Pain [Internet]. 2013 Dec [cited 2017 Jun 13];154(12):2844–52.
15. Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995-2010: Repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. Eur J Pain. 2015;19:59–66.
16. Pautex S, Rexach-Cano L, Van Den Noortgate N, et al. Management of chronic pain in old patients: Belgium, Spain and Switzerland. Eur Geriatr Med. 2013;4(4):281–7.
17. Muñoz M, Cabieses B. Universidades y promoción de la salud: ¿cómo alcanzar el punto de encuentro? Rev Panam Salud Pública. 2008;24(2):139–46.
18. Akiyama M, Hirai K, Takebayashi T, et al. The effects of community-wide dissemination of information on perceptions of palliative care, knowledge about opioids, and sense of security among cancer patients, their families, and the general public. Support Care Cancer. 2015;24:347–56.
19. Shinjo T, Morita T, Hirai K, et al. Why people accept opioids: role of general attitudes toward drugs, experience as a bereaved family, information from medical professionals, and personal beliefs regarding a good death. J Pain Symptom Manage. 2015;49(1):45–54.
20. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: A literature review. Eur J Pain. 2007;11(5):490–518.
21. Morley-Forster PK, Clark AJ, Speechley M, et al. Attitudes toward opioid use for chronic pain: A Canadian physician survey. Pain Res Manag. 2003;8(4):189–94.
22. Manchikanti L, Helm S, Fellows B, et al. Opioid epidemic in the United States. Pain Physician. 2012;15:ES9-38.
23. Sirohi S, Tiwari AK. Pain in the management of opioid use disorder. J Pain Res. 2016;9:963–6.
24. Wasan AD, Butler SF, Budman SH, et al. Does Report of Craving Opioid Medication Predict Aberrant Drug Behavior Among Chronic Pain Patients? Clin J Pain. 2010;25(3):193–8.
25. Wurm M, Edlund S, Tillfors M, et al. Characteristics and consequences of the co-occurrence between social anxiety and pain-related fear in chronic pain patients receiving multimodal pain rehabilitation treatment. Scand J Pain. 2016;12:45–52.

26. Klevens J, Trick WE, Kee R, et al. Concordance in the measurement of quality of life and health indicators between two methods of computer-assisted interviews: Self-administered and by telephone. Qual Life Res. 2011;20(8):1179–86.

27. Boscarino J a, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J Addict Dis. 2011;30:185–94.

28. Català E, Reig E, Artés M, et al. Prevalence of pain in the Spanish population: Telephone survey in 5000 homes. Eur J Pain. 2002;6(2):133–40.

Table 1. General characteristics of the population surveyed.

Variables	Categories	%
General characteristics of the population surveyed.		
Sex	Female	50.7
Age	18-44	44.1
	45-64	32.6
	65 or over	23.3
Educational level	No education received	5.9
	Primary studies	20.2
	Secondary studies	45.9
	University studies	28.1
Are you currently or have you ever been engaged in any profession related to healthcare?	Yes	14.4
Level of contact with opioid	No contact	36.0
	Minimal contact	51.2
	Medium contact	8.9
	Maximal contact	3.8
Correct identification of opioids	Tramadol	14.2
	Tapentadol	5.5
	Morphine	64.9
	Oxycodone	11.3
	Fentanyl	6.0
	Buprenorphine	5.7

Table 2. Respondents' opinion associated with opioid use.

Respondents' opinion on opioids		
Variables	**Categories**	**%**
Respondents' opinion on opioids tolerance		
Increasingly larger doses are required	Completely disagree	14.3
	Slightly disagree	16.3
	Moderately agree	44.7
	Strongly agree	18.2
	Undecided	6.5
Respondents' opinion on opioids dependence		
There is a risk of being unable to stop taking them	Completely disagree	22.7
	Slightly disagree	23.6
	Moderately agree	34.7
	Strongly agree	10.1
	Undecided	8.9
Respondents' opinion on opioids side effects		
They may cause somnolence	Completely disagree	4.5
	Slightly disagree	8.5
	Moderately agree	50.8
	Strongly agree	22.1
	Undecided	14.2
They may cause constipation	Completely disagree	7.2
	Slightly disagree	11.7
	Moderately agree	24.8
	Strongly agree	8.7
	Undecided	47.6
They may cause nausea	Completely disagree	6.5
	Slightly disagree	11.2
	Moderately agree	42.2
	Strongly agree	13.5
	Undecided	26.6
They may cause nervousness	Completely disagree	20.4
	Slightly disagree	15.5
	Moderately agree	31.1
	Strongly agree	9.2
	Undecided	23.8
Respondents' opinion on severity of the disease		
Opioids are only for terminally ill patients	Completely disagree	49.7
	Slightly disagree	15.5
	Moderately agree	22.1
	Strongly agree	8.2
	Undecided	4.5
Opioids use means that the illness is serious	Completely disagree	24.6
	Slightly disagree	13.1
	Moderately agree	42.6
	Strongly agree	15.7
	Undecided	4.0
Opioids should be the last treatment option	Completely disagree	22.3
	Slightly disagree	12.9
	Moderately agree	37.4
	Strongly agree	18.1
	Undecided	9.3

Table 3. Classification of the individuals into groups according to their opinions, beliefs and attitude towards opioids.

	Group 1-PPV N=448(35.8%)	Group 2- MPV N=337(26.9%)	Group 3- NPV N=468(37.4%)	p-value
Sociodemographic variables				
Age:				
- 18-44	155(34.6%)	**180(53.4%)**	216(46.2%)	
- 45-64	171(38.2%)	103(30.6%)	139(29.7%)	<0.001[a]
- 65 or over	**122(27.2%)**	54(16%)	113(24.1%)	
Sex:				
- Male	159(47.3%)	236(52.7%)	220(47.2%)	0.184
- Female	177(52.7%)	212(47.3%)	246(52.8%)	
Educational level:				
- No education received	25(5.6%)	14(4.2%)	**35(7.5%)**	
- Primary studies	90(20.1%)	49(14.6%)	**111(23.8%)**	0.001[a]
- Secondary studies	202(45.2%)	156(34.6%)	214(45.8%)	
- University studies	130(29.1%)	**116(34.6%)**	107(22.9%)	
Correct identification of any opioid				
- No	167(37.3%)	86(25.5%)	162(34.6%)	0.002[a]
- Yes	281(62.7%)	**251(74.5%)**	306(65.4%)	
Level of contact				
- No contact	162(36.2%)	**115(34.1%)**	172(36.8%)	
- Minimal contact	194(43.3%)	187(55.5%)	261(55.8%)	
- Medium contact	60(13.4%)	29(8.6%)	25(5.3%)	<0.001[a]
- Maximal contact	**32(7.1%)**	6(1.8%)	10(2.1%)	
Fears associated with opioids use				
Fear of death				
- Not at all or a little	**391(87.3%)**	230(68.2%)	187(40%)	
- Some	28(6.3%)	26(7.7%)	52(11.1%)	<0.001[a]
- Quite a lot or a lot	29(6.5%)	81(24%)	**229(48.9%)**	
Fear of becoming an addict				
- Not at all or a little	**396(88.4%)**	284(84.3%)	7(1.5%)	
- Some	35(7.8%)	52(15.4%)	43(9.2%)	<0.001[a]
- Quite a lot or a lot	17(3.8%)	1(0.3%)	**418(89.3%)**	
Fear of side effects				
- Not at all or a little	**365(81.5%)**	85(25.2%)	42(9%)	
- Some	69(15.4%)	58(17.2%)	45(9.6%)	<0.001[a]
- Quite a lot or a lot	14(3.1%)	194(57.6%)	**381(81.4%)**	
Fear of not getting the desired results				
- Not at all or a little	**370(82.6%)**	44(13.1%)	106(22.6%)	<0.001[a]
- Some	50(11.2%)	56(16.6%)	42(9%)	
- Quite a lot or a lot	28(6.3%)	**237(70.3%)**	320(68.4%)	
Respondents' opinion on opioids				
Opinion on opioids tolerance				
Increasingly larger doses are required				
- Completely disagree or slightly agree	176(39.3%)	102(30.3%)	107(22.9%)	<0.001[a]
- Moderately or strongly agree	228(50.9%)	230(68.2%)	**330(70.5%)**	
- Undecided	44(9.8%)	5(1.5%)	31(6.6%)	
Opinion on opioids dependence				
There is a risk of being unable to stop taking them				<0.001[a]

- Completely disagree or slightly agree	**266(59.4%)**	176(52.2%)	135(28.8%)	
- Moderately or strongly agree	123(27.5%)	147(43.6%)	**293(62.6%)**	
- Undecided	59(13.2%)	14(4.2%)	40(8.5%)	
Opinion on opioids side effects				
They may cause somnolence				
- Completely disagree or slightly agree	**84(18.8%)**	31(9.2%)	47(10.0%)	<0.001[a]
- Moderately or strongly agree	277(61.8%)	**283(84.0%)**	354(75.6%)	
- Undecided	87(19.4%)	23(6.8%)	67(14.3%)	
They may cause constipation				
- Completely disagree or slightly agree	**96(21.4%)**	55(16.3%)	88(18.8%)	<0.001[a]
- Moderately or strongly agree	113(25.2%)	**151(44.8%)**	159(34%)	
- Undecided	239(53.3%)	131(38.9%)	221(47.2%)	
They may cause nausea				
- Completely disagree or slightly agree	**119(26.6%)**	40(11.9%)	63(13.5%)	<0.001[a]
- Moderately or strongly agree	174(38.8%)	**248(73.6%)**	277(59.2%)	
- Undecided	155(34.6%)	49(14.5%)	128(27.4%)	
They may cause nervousness				
- Completely disagree or slightly agree	**188(42%)**	139(41.2%)	127(27.1%)	<0.001[a]
- Moderately or strongly agree	104(23.2%)	161(47.8%)	**234(50%)**	
- Undecided	156(34.8%)	37(11%)	107(22.9%)	
Opinion on severity of the disease				
Opioids are only for terminally ill patients				
- Completely disagree or slightly agree	**324(72.3%)**	234(69.4%)	259(55.3%)	<0.001[a]
- Moderately or strongly agree	92(20.5%)	92(27.3%)	**196(41.9%)**	
- Undecided	32(7.1%)	11(3.3%)	13(2.8%)	
Opioids use means that the illness is serious				
- Completely disagree or slightly agree	**222(49.6%)**	134(39.8%)	121(25.9%)	<0.001[a]
- Moderately or strongly agree	199(44.4%)	193(57.3%)	**335(71.6%)**	
- Undecided	27(6%)	10(35%)	12(2.6%)	
Opioids should be the last treatment option				
- Completely disagree or slightly agree	**196(43.8%)**	137(40.7%)	110(23.5%)	<0.001[a]
- Moderately or strongly agree	199(44.4%)	178(52.8%)	**319(68.2%)**	
- Undecided	53(11.8%)	22(6.5%)	39(8.3%)	
Attitude towards opioid				
Supposing that you suffer from severe pain. would you take opioids?				<0.001[a]
No	34(7.6%)	50(14.8%)	**101(21.6%)**	
Yes	**414(92.4%)**	287(85.2%)	367(78.4%)	
[a] Pearson Chi-squared test				

Table 4. Factors associated with the groups with the worst vision on opioids vs the group with a positive vision.

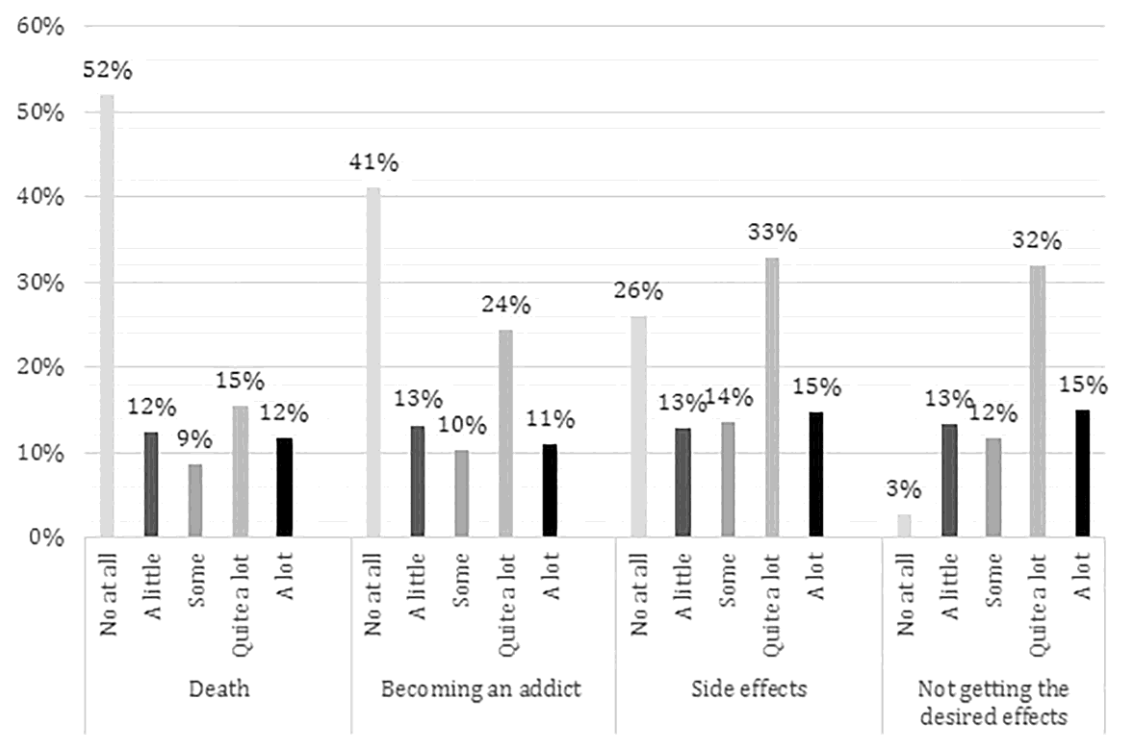
Variables	Cluster MPV (N = 336)				Cluster NPV (N = 466)			
	Wald Statistic	OR	CI 95%	p-value	Wald Statistic	OR	CI 95%	p-value
Sex:								
- Female*								
- Male					4.60	1.80	(1.05;3.07)	0.032
Level of contact:								
- Maximal contact*								
- Medium contact	3.62	4.38	(0.96;20.08)	0.057				
- Minimal contact	4.48	4.57	(1.12;18.64)	0.034				
- No contact	4.55	4.75	(1.13;19.90)	0.033				
Increasingly larger doses are required:								
- Completely disagree or slightly agree*								
- Moderately or strongly agree	9.70	2.16	(1.33;3.51)	0.002	12.89	3.03	(1.65;5.55)	<0.001
- Undecided	0.70	0.56	(0.14;2.17)	0.403	3.57	3.62	(0.95;13.73)	0.059
There is a risk of being unable to stop taking them:								
- Completely disagree or slightly agree*								
- Moderately or strongly agree					13.97	3.04	(1.70;5.45)	<0.001
- Undecided					0.10	0.84	(0.29;2.44)	0.746
They may cause somnolence:								
- Completely disagree or slightly agree*								
- Moderately or strongly agree	6.92	2.58	(1.27;5.23)	0.009				
- Undecided	0.02	1.07	(0.40;2.89)	0.898				
They may cause nausea:								
- Completely disagree or slightly agree*								
- Moderately or strongly agree	11.48	3.04	(1.60;5.78)	0.001				
- Undecided	0.68	0.72	(0.33;1.57)	0.411				
Degree of opiophobia (0 no opiophobia-16 maximal opiophobia)	184.41	2.67	(2.01;2.55)	<0.001	350.92	3.95	(3.42;4.56)	<0.001

Goodness of fit to the model: χ2 = 1482.7; gl = 20; P value <0.001.
Reference group of the dependent variable: Group with a Positive Vision of opioids (PPV).
MPV: Group with a Moderate Vision of opioids. NPV: Group with a Negative Vision of opioids.
OR = odds ratio; CI = confidence interval. *Reference category.

Figure legend

Figure 1. A word cloud showing the beliefs of the respondents with regard to opioids, where the size of each word indicates how often the respondents related it to opioids

Figure 2. Summary of respondents' fears associated with opioid usage.



STUDY 4

Living with opioids: A qualitative study with patients with chronic low back pain.

Health Expectations

2020, In press.

Impact Factor: 2.847

Helena De Sola*; *Amaia Maquibar; Inmaculada Failde; Alejandro Salazar; Isabel Goicolea.*

* The author of this thesis contributed to this work by performing the fieldwork, analysing the data, and was mainly responsible for writing the manuscript.

ABSTRACT

Background: opioids are one of the most prescribed treatments for chronic pain (CP). However, their long-term use (>3 months) has been surrounded by controversy, due to loss of beneficial effects.

Objective: to explore the experiences of people with chronic non-malignant low back pain in Spain undergoing long-term treatment with opioids.

Design: qualitative study

Setting and participants: we conducted 15 semi-structured interviews at the Pain Clinic with persons taking opioids treatment.

Methods: The interviews were analyzed by qualitative content analysis as described by Graneheim and Lundman, and developed categories and themes discussed in light of a biomedicalization framework.

Main results: we developed one overarching theme - *Living with opioids: dependence and autonomy while seeking relief* - and three categories: *The long pathway to opioids due to the invisibility of pain; Opioids: from blind date to a long-term relationship;* and *What opioids cannot fix.*

Discussion: The long and difficult road to find effective treatments was a fundamental part of coping with pain, involving long-term relationships with the health system. This study reflects the benefits, and drawbacks of opioids, along with struggles to maintain autonomy and make decisions while undergoing long-term treatment with opioids. The paper also highlights the consequences of pain in the economy, family and social life of patients.

Conclusions: patients' experiences should be considered to a greater extent by healthcare professionals when giving information about opioids and setting treatment goals. Greater consideration of the social determinants of health that affect CP experiences might lead to more effective solutions to CP.

Keywords

Chronic Pain; Low Back Pain; Opioid; Treatment; Biomedicalization; Experience

INTRODUCTION

Chronic pain (CP), defined as pain that persists beyond the normal tissue healing time (3 months as a convenient cut-off point), is a health problem that has reached epidemic proportions worldwide. The average CP prevalence is 27% in European countries, consistent with international estimates [1]. In Spain, around 17% of the population suffer from this illness, making it a major healthcare problem [2].

Opioids are one of the most prescribed analgesic pharmacological treatments for CP [3]. Prescriptions for opioids have increased dramatically in the last few decades, numbers being far higher in countries such as the United States or Canada [4]. According to the National American Survey on Drug Use and Health (NSDUH) report in 2016, more than one-third of American adults were prescribed opioids[5]. Although to a lesser extent, an increase has also been observed in some European countries[6–8], including Spain (83.59% from 2008 to 2015) [9].

Opioid therapy has been found to be associated with the alleviation of pain in the short term [10]. However, their prescription for long-term use sometimes presents a dilemma [11], since it has been accompanied by a great increase in overdoses, abuse, addiction, and recreational use in some countries such as the United States [12]. Clinicians therefore face the potentially conflicting duties of relieving pain on the one hand, viewed worldwide as an ethical medical obligation [13], and preventing the potential harm to the patient of long-term opioid consumption on the other [14]. Dispelling the myriad myths associated with pain and fears associated with opioid prescription is no easy matter. Part of the solution depends on educating and training health care professionals in pain management [15].

Patients who experience CP could also face this quandary since opioids have been related to negative side effects, such as excessive sedation, respiratory failure, urinary retention, or constipation [16]. These side effects, along with social, cultural, and historical factors, have given rise to a set of attitudes and beliefs regarding the deleterious effects of opioid administration for pain relief [17]. The main reasons for this inappropriate set of attitudes and beliefs are the lack of knowledge regarding opioids and the stigmatization that some patients felt when prescribed opioids [18].

The benefits of opioids have also been surrounded by controversy [19]. Some studies [20,21] have shown that most people using opioids continue to report moderate or severe pain, and that functional improvements are often limited. Other authors [22] have shown that increases in the intensity of pain are connected with skipping doses, since patients reduce or stop taking their

opioid therapy to avoid side effects. Despite the existence of clinical guidelines that regulate the correct use of opioids in the treatment of pain [23,24], in Spain, CP management still remains weak [25]. Fear of addiction might be an important reason why CP is often undertreated [16].

Recent literature [18,26–28] has explored the experience of adults using prescription opioids to manage CNCP, concluding that there were many negative aspects to using opioids daily, in most cases these were outweighed by the positive effects and most of the negative aspects were socio-culturally induced rather than caused by the drug itself. However, these studies have been carried out in countries such as the United States or Canada, where the trend of opioid use has been accompanied by an increase in reported opioid abuse and opioid-related death [29] which is a different situation compared to Spain [30–33] .

Considering the potential worries and difficulties associated with the use of opioids, it is very important that patients communicate and relate to healthcare providers their experience with opioids in an open and effective manner. However, although the number of individuals living with CP and taking opioids is increasing, to the best of our knowledge, no study has been performed to explore the experiences of patients taking opioid medications in Spain. Thus, this study aims to fill this gap in knowledge by exploring the experiences of patients with CP receiving long-term treatment (more than three months) with opioids in Spain.

Spanish healthcare system

The Spanish healthcare system has universal coverage, is almost entirely funded by taxes and is free of charge at the point of delivery, except for pharmaceutical products for people under 65, which require a co-payment of 40% of their price. Provision of care is predominantly within the public network of healthcare facilities. Primary healthcare is the first point of contact for individuals with the healthcare system, and thus professionals working there as GPs, nurses and midwifes act as gatekeepers of the system. The primary healthcare network is an integrated part of the public systems through mutually supportive referral systems with secondary and tertiary healthcare facilities. In the case of patients who experience CP, after visiting their GP they are referred to a specialist, usually a rheumatologist or traumatologist, and then to the Pain Clinic if the pain does not remit.

The Pain Clinic is a unit specialized in the management and treatment of all complex types of pain conditions, especially in those patients who do not respond to conventional treatment and those who require special drugs or treatment techniques, such as local infiltration of anesthetics and/or steroids or radiofrequency neurolysis.

Opioid treatments can be prescribed by GPs or specialist doctors. All official opioid prescriptions must include the denomination "Official Narcotics Prescription", with the exception of those that are issued in electronic format. In each Official Narcotics Prescription only one type of opioid treatment must be prescribed, with a maximum treatment length of three months and without exceeding a total of four containers.

Theoretical Framework

CP is considered to be a complex biopsychosocial event [34]. Besides the physical experience of pain, individuals suffering from CP often experience mental and emotional disturbances and their family environment might also be severely affected [35]. Given its complexity, healthcare services should address CP following a multidisciplinary approach, although pharmacological therapy is still considered the cornerstone (and sometimes the only approach) of the control of pain [36]. Moreover, as we have previously described, long-term treatment with opioids might help to relieve pain in some cases, but result in other issues related not only with adverse effects, but also with communication, negotiation and power relationship problems between patients and providers, stigma and the role of family and support networks. Following an emergent design, a biomedicalization framework was chosen, meaning that the analysis of the interviews guided the choice of theory. Thus, the theoretical framework was mainly used in the discussion section to contrast the results of this study with previous evidence and to frame participants' experiences in the wider context of healthcare. Biomedicalization was described by Clarke et al. (2003) as the "increasingly complex, multi-sited, multidirectional processes of medicalization, both extended and reconstituted through the new social forms of highly technoscientific biomedicine". Biomedicalization is driven by and at the same time fosters five key overlapping processes: major shifts in health and healthcare policies and funding; the focus on health itself and elaboration of risk and surveillance biomedicines; technoscientization of biomedicine; major changes in the production and consumption of biomedical knowledge; and transformation of bodies and new individual and collective identities. The results of this study are better understood and explained in the light of this framework as we will explain in the discussion section.

MATERIAL AND METHODS

Study design

This is a qualitative study in which data were collected through 15 semi-structured interviews to explore the experiences of chronic low back pain (CLBP) patients taking opioids to treat their

pain. Individual interviews were analyzed by qualitative content analysis as applied in health sciences research [37].

Participants and Data collection

The study protocol was approved by the Clinical Research Ethics Committee of the "Puerta del Mar" University Hospital (Cádiz, Spain), ensuring compliance with the standards of good clinical practice.

Recruitment and data collection were conducted from April to October 2018. The participants were recruited from the Pain Clinic in Hospital Puerta del Mar. Inclusion criteria for the study were: adults suffering from chronic non-malignant low back pain and receiving long-term treatment (over three months) with opioids. Patients taking opioids for less than three months or with another pain origin than chronic non-cancer low back pain were not included.

All the patients were recruited after a routine physical evaluation in their medical visit to the Pain Clinic. Previously, their medical data, including information on prescribed medications from the records, were evaluated and discussed by the clinician and interviewer. If the person met the inclusion criteria after an analysis of their medical records and their medical visit and physical evaluation, the clinician explained to him or her the aim of the study. All seventeen eligible patients were approached by the clinician. After this initial approach by the clinician, the interviewer met the potential participant and they went to a quieter place in a clinical setting for the interview, before with the participant was shown a letter with more comprehensive information about the study and its aim. The participants were left alone to read and think carefully before giving their written informed consent. When they finished reading it, they had the opportunity to ask questions about the study, after which the interview took place. At this stage, two people rejected the participation, alluding to lack of time. Individual, semi-structured, qualitative interviews following a guide were conducted in Spanish. The guide was based on open-ended questions developed with guidance from the literature regarding chronic pain experiences and factors associated with the use of opioids (Table 2). Aspects related to the origin of their pain, opioid belief, information received about treatment, opioid experience, their family and social support were also of particular interest. If a specific topic that was not included in the first version of the interview guide came to light spontaneously in a specific interview, it was added and asked in the subsequent interviews. Interviews were audio-recorded, transcribed verbatim and anonymized. All names used here are pseudonyms. We conducted

interviews until very similar experiences were described in the last interviews as in the previous interviews.

Analysis

We adopted a constructionist perspective. We analyzed all the interview transcripts following qualitative content analysis as described by Graneheim and Lundman [37]. The data analysis was inductive, and thus the category construction was data-driven; no initial hypothesis guided the preliminary coding and subsequent development of categories. However, in the analysis of the results presented in the Discussion section, we followed the biomedicalization framework described above.

Interview transcripts were entered into Atlas.ti 1.0.16 to support the coding process. At the beginning of each interview transcript, a brief log of the interview was written, including information about the time, duration, and the feelings and perceptions of the interviewer during the conversation in order to help with the analysis process. The researcher who conducted the interviews transcribed them verbatim.

To carry out the qualitative content analysis, two researchers read the transcripts independently and assigned codes line-by-line to meaningful pieces of the interview transcripts. Then, the researchers met to compare and refine codes, which were then grouped into categories. The material was grouped into three key categories, which were further validated after re-analysis of all the interviews. Coding maps were used to help with the code grouping and the analysis of relationships between the emerging categories and codes. In the last step, an overarching theme involving these three categories was identified. The analysis was conducted in Spanish and quotes were chosen from this material to be translated into English. All the authors understand both languages and, thus, were able to participate in the whole analysis process.

Our positions as researchers have continuously been discussed in relation to ethical considerations and questions about responsibility. In line with Graneheim and Lundman (2004) [37], we argue that, in qualitative content analysis, interpretation involves a balancing act of providing interpretation while at the same time making sure that our interpretations remain always grounded on the data. By providing a thorough explanation of the analytical process, our intention is to allow the reader to assess the study's usefulness and transferability.

RESULTS

Fifteen people aged from 40 to 88 were interviewed (9 women and 6 men). One participant had completed higher education and the rest elementary education. Four had a declaration of total disability to work, two were on sick leave and nine were retired or unemployed. Thirteen were prescribed a treatment with a strong opioid, one of the two who were taking weak opioids had a PRN order (Table 1 near here).

From the analysis, one overarching theme was developed: "Living with opioids: dependence and autonomy while seeking relief", which crosscut three categories: "The long pathway to opioids due to the invisibility of pain"; "opioids: from blind date to a long-term relationship"; and "what opioids cannot fix".

The quest for effective treatment was a fundamental part of the participants' struggle to cope with the pain, and it involved long-term relationships with the health system. In relation with this, the theme "living with opioids: dependence and autonomy while seeking relief" refers to how navigating the health system meant that the study participants were dependent on healthcare professionals exercising their power to refer them to specialized care to get access to a diagnosis and treatment, including opioids. At the same time, it also meant having, to a certain extent, room to make decisions, to exercise autonomy, despite having little information and meeting professionals that hardly coordinated/communicated with each other.

The two first categories "the long pathway to opioids due to the invisibility of pain" and "opioids: from blind date to a long-term relationship" refer to the journey participants made to get a diagnosis and treatment with opioids, and their experiences during this long and difficult process, which was quite unique for each person. The third category, "what opioids cannot fix", describes the circumstances and situations experienced by the patients before and after the painful episode started, and how they have influenced the whole process. In this case, opioids do not have any effect since they are not enough to remedy the deficiencies derived from these situations.

The long pathway to opioids due to the invisibility of pain

This first category describes the long and difficult pathway that participants followed from the onset of their pain until getting treatment with opioids. This journey could start as soon as early adolescence (Table 3).

For the participants, the fact that pain "cannot be seen" explained such a lengthy journey to obtain diagnosis and prescriptions. They mentioned numerous consequences of this invisibility of pain in individual and social spheres, as well as in their encounters with the health care system. At the individual level, the invisibility of pain meant that it could be ignored or minimized by those suffering from it. As Alejandro (51 years old, 4 years taking morphine) said, *"mine [pain] was caused by work, by lifting weight, my back started hurting, and… I was walking and limping, and I thought it was…well, nothing. I thought it will go away. By the time I realized and went to the doctor, I was using crutches".*

In the social arena, the long history of pain, together with the lack of physical signs, could lead, in the view of participants, to indifference or a lack of empathy. As Hugo (52 years old, 5 years taking morphine) claimed, *"my family say that I'm exaggerating"*. Relatives and friends were described as having got used to seeing participants in pain and therefore minimized its importance. Participants described the difficulty in lending credibility to the severity of the problem when there were no physical signs. As Rafael (52 years old, 5 years taking tapentadol) put it: *"They've seen me in pain for so long… I think 'if they could know how much pain I feel' but they see me every day in the same situation and they've become used to seeing me in pain".*

In relation to the healthcare services, participants described how they had to struggle with healthcare professionals to be believed and have their pain taken seriously, as Laura referred (Table 3). Similar to what happened in the individual sphere, referrals from primary and emergency care to specialized pain services did not begin until the patient's mobility was severely affected, until the pain manifested itself through physical signs or until they visited the same facility several times without improvement. That led to long waiting times and delays in receiving an appropriate diagnosis and treatment.

Entering the referral system was the beginning of a tortuous journey of hopes and disappointments, a trial/error process that involved trying different treatments with the dream of a pain-free life, as the quote from Lola portrays (Table 3)

The Pain Clinic was commonly the place where the long-term treatment with opioids was established, although in some cases treatment with opioids had started before reaching such specialized services, i.e. in primary healthcare facilities. This relationship with opioids, frequently initiated at the Pain Clinic, is the focus of the next category.

Opioids: from blind date to a long-term relationship

This category portrays beliefs and perceptions of the benefits and drawbacks of treatment with opioids, in addition to struggles to keep autonomy and make decisions while being a long-term patient within the health system.

It was difficult for participants to recall their first contact with opioids, since the common experience of the interviewees was that they had been given little or no information about the new medication they were prescribed. Consequently, it was difficult for participants to distinguish between medications that were in fact opioids and other drugs (Table 3).

When the participants realized that they were being prescribed opioids, they seemed to accept the treatment due to the intensity of pain suffered, despite having the perception that opioids were for terminal diseases or relating them with drugs and addiction (Table 3, Sofia and Lola quotations). Yet, the perception of opioids as a "serious" prescription was maintained over time and the fact that their acquisition is regulated and controlled was mentioned repeatedly in the interviews. There is also a paradox since although some of the participants noticed adverse effects of their medication and they reflected on the difficulty involved in quitting this long-term treatment they weighed in favor of relief. As Sofia (46 years old, 2 years taking oxycodone) said: *"The truth is that they benefited me, I mean, I experienced no strange reactions… well, drowsiness, I am like an animal in hibernation, sleeping the whole day"*. This understating of the effects - drowsiness, in that case - could also be related to the lack of information received from healthcare professionals. As we see in the next quote, Rafael explained commonly experienced adverse effects with opioids like tolerance and dependence without naming them specifically:

"The point is that coincidentally my illness has become worse, and thus, they go parallelly, the increase in medication dosage and the increase in pain, and consequently they are increasing the dosage because my pain is getting worse. The pain I had six months ago is now worse. What's happening is it's like my body got used to the treatment."

As time passed, the participants appeared to start taking a more active attitude towards coping with pain. They described how they had learned ways to relieve the pain, including resting, losing some weight, exercising (e.g. swimming, Pilates, walking) and taking other medication as needed (e.g. muscle relaxants, nonsteroidal anti-inflammatory drugs). As a reaction to the adverse effects experienced, they seemed to become progressively more active in decision-making related to pain management, and less likely to rely exclusively on opioids. In this sense, medication-related decisions were frequently made without consulting the healthcare professionals.

"It was the bad sweating that I suffered... I read the information pamphlet and read sweating was an adverse effect and then I wondered, 'what if I reduce a little bit the dose? Let's do an experiment!' I thought 'maybe the doctor will get angry with me, but I am going to experiment', without quitting totally. I thought 'I am going to take less than what I was told, and I'll see if I can continue without pain and avoid that unpleasant sweating' and, right now, indeed, I am taking half of the pill". Pilar (56 years old, 8 years taking tapentadol)

But these more active coping strategies to reduce pain did not mean total skepticism of opioids. Although the participants complained that opioids had not totally eliminated the pain, there was a common feeling that they contributed to pain reduction. Sofía said: *"I was unable to take a step, and thanks to starting to take morphine, I can now stand up. If I was not taking it, I wouldn't be doing what I am; I do minimal things but I at least do them."*

The interviews unveiled that their experience with opioids was strongly intertwined with many other life circumstances that lie far beyond the scope of action of any medication, as explained in the next category.

What opioids cannot fix

This category describes different spheres of the participants' lives where pain has an impact on a range of economic, familiar and/or social issues that cannot be addressed through opioids (alone). Moreover, these issues may not only be the consequence of pain, but what caused it in the first place.

Besides physical limitations and problems, the emotional sphere was one of the most strongly affected areas, one that opioids could not improve and could even affect negatively. Although in some cases reductions in pain led to a better mood, in others, sadness due to physical limitations and fear of pain was constant. The next quote reflects how pain (and the opioid medication to treat it) had disrupted a participant's life and hindered them from doing basic daily activities.

"I have noticed changes in my mood, you know? I have …. a strong personality. I don't know whether it's the pill or whether it's the…. Not being able to move as I wish, not being able to do things the way I would like to. I often feel useless, even with my partner… I cannot even have sex as a normal person would, I'm limited!" Laura (55 years old, 1 year taking tramadol).

In certain cases, these decreases in mood caused by pain resulted in mental health comorbidities among the participants. Sometimes this was exacerbated when participants were told about the chronicity of their illness (Table 3).

To navigate life suffering pain, family support was regarded as essential by the participants. However, at the same time, being dependent on their help because of their physical limitations raised perceptions of being a burden. Moreover, as described in the first category, participants related sometimes feeling neglected, as if their families had got used to seeing them in pain. Roberto (*72 years old, 2 years taking tapentadol)* explained: *"They help me, everything that needs to be done now it's done by my sons-in-law, poor them, because I can´t. But you often feel useless; it bothers you that someone is working hard on your behalf, but they are very nice".*

The women participating in the study, regardless of whether they were on sick leave or retired, did not identify housework and childcare as work, and they mentioned still being the only person responsible for housework despite their disabling pain. In addition, as the Pilar quote shows in Table 3, women refer to the "little things" that their partners do at home as their "help", showing that housework is not a shared responsibility from the start.

The participants were aware of the importance of maintaining an active social life, and consequently appeared to make an effort to do so. This was easier with people who shared the same pathology, problems and treatment. Lola (41 *years old, 8 years taking tapentadol)* said: *"I'm part of a Facebook group of people with the same surgery as I had. You can hear some people encouraging others; at night you know that half of them have been awake like you, and you are there… and that cheers you up a little bit. Now, I'm surprised to see how many people are taking opioids; indeed, we all take them as if it was water. It's much more common than I had ever imagined".* Outside "pain friends" circles, the experience was different and participants related having felt judged by other people when they disclosed they were taking opioids.

Narratives of hard lives where pain was 'just' another added difficulty were a constant in the interviews. Having performed manual labor from a young age was common among these patients, and sometimes the cause of the illness and the pain. Sofía stated: *"I was a cleaner, and they told me 'throw this in the garbage' and I pulled the trolley and that was it… because my back creaked and afterwards my back was destroyed from my job as a cleaning woman".* Likewise, poor working conditions and living with economic difficulties appeared intertwined as a cause and consequence of pain. As Rafael mentioned: *"At home the only income is my salary.*

I have to pay the mortgage, for my children's studies… well, our income is reduced as I'm on sick leave…so I cannot stop working and this situation has led me to a state of anxiety." As is the case with family support, there were also differences between men and women related to economic difficulties. For two men who participated in the study, the pressure of being the breadwinner had negative emotional consequences. For three of the women, being economically dependent on their partners led to them having feelings of helplessness. Ana (41 years old, 5 years taking tramadol) said: *"The point is that I get on well with my husband, but if I did not get on well with him… what could I do? I'm unemployed, I don't have anything, (she gets emotional) "my God".*

DISCUSSION

The findings of this study show how the experience of relieving pain is a constant struggle among people who suffer from it. Opioids become a way of reducing pain, facilitating physical and social functioning and making a more independent lifestyle possible. However, these feelings of independence about physical or social functioning are in conflict with concerns of dependence on the medication.

Our results described how the participants' experiences were severely influenced by the invisibility of their pain, in the same line as findings from previous research [38–40] . In this sense, the absence of a uniform classification and a validated diagnostic tool in this type of pathology hinders the standardization of treatments that biomedicalization has brought to other diseases, leading to uncertainty in the treatment and diagnosis of the patient, and making it very much dependent on the individual perception of the treating physician [40,41]. Thus, as we have seen in our results, the choice of where to refer patients and how to treat them is a lengthy trial and error process, which is certainly not ideal, and opens the door to disparate access to health care.

In this study, the overwhelming majority of participants eventually treated in the Pain Clinic after lengthy periods navigating through the healthcare system were employed in unskilled jobs and reported having a basic level of education. We argue, based on the discourse of biomedicalization [42], that this overrepresentation of patients from lower socio-economic backgrounds in our study is because the quest for a diagnosis and treatment could presumably be "easier" and "shorter" for those who can afford private medical care and can skip the mutual referral system between the GPs and specialists of the public health system. The increase in stratifying fee-for-service options, which is another characteristic of biomedicalization, enables

the more wealthy to address their illness, circumventing waiting times for medical procedures and obtaining access to multidisciplinary intervention in the biological, psychological and social aspects of their chronic pain condition [43].

In relation to experiences with opioids, our findings show that opioids were insufficient to relieve all the pain, as examples of limitations to daily life because of pain were an important part of the participants' narratives. However, the participants' perception was also that their physical functioning and quality of life had improved thanks to opioids. These contradictions between perceived improvement and narratives of severe limitations were recurrent in the participants' accounts. As other authors have shown [18], due to a lack of information or misinformation, patient expectations regarding the results they can expect from this treatment may be unrealistic. In line with this, the difficulties the participants found to identify side effects, tolerance or dependence were also noteworthy. Exemplifying the heterogeneity in the production, distribution and access to biomedical knowledge that is part of biomedicalization, the majority of the participants stated that they had looked on the internet to be informed about opioids and their consequences, and in many cases developed individual strategies to deal with the side effects they experienced. Having to look oneself for information about the treatment prescribed reflects a shift in responsibility for care practices, which is put increasingly on healthcare-users, this change being another essential component of biomedicalization [42]. Even if access to medical knowledge is improved thanks to new technologies, the ability to benefit from that information depends strongly on individual health literacy levels. According to a report published by the WHO in 2013 [44], more than half of the Spanish population have inadequate or problematic health literacy levels [44]. Furthermore, the population with a lower social status have much higher proportions of limited health literacy levels [45,46]. In addition, increased responsibility for their own healthcare driven by biomedicalization processes leads to self-blame for any health problems that arise. As seen in some of the quotations of the participants, they blamed their pain on things they have done, like pulling too much weight or waiting too long to seek medical care instead of placing the blame on their working conditions when evidence shows that unskilled workers have the highest prevalence of musculoskeletal disorders, a large proportion of which can certainly be attributed to working conditions [47].

Finally, another basic process of biomedicalization is the production of new identities and reframing of old ones by technoscientific means. In this sense, the social role and identity of chronic patients for whom no cure is available despite all the technoscientific advances remain a challenge due to the invisibility of pain. In the social arena, the participants of our study felt

stigmatized in several ways. They felt neglected due to the invisibility of pain. Many patients with CP do not present any visible symptoms and remain stoic when they feel pain, resulting in a lack of empathy from friends [48]. In addition, the participants felt stigmatized because of the treatment with opioids. Ljungvall et al [26] described how participants experienced being stigmatized because of their repeated contacts with medical care workers, who see them as drug-seeking behaviors. However, in our study, the participants experienced this stigmatization by relatives and friends who expressed many concerns and prejudices about opioids. The negative consequences of "double" or "layered" stigmatized conditions - "CP sufferer" and "drug addict" – have also been described by Dassieu et al. [31], who suggest that being doubly stigmatized reinforces people's isolation as well as their experience of loss of dignity. Interestingly, in our study, the participants referred to sharing their experience of CP and opioid treatments with 'pain friends', among whom treatment with opioids was common. Peer support has been shown [49] to reduce social isolation, encourage shared experiential learning and foster psychosocial well-being. Thus, "taking charge" of their health, understood in biomedicalization as responsibility for care practices, by means of active coping strategies such as maintaining an active social life with "pain friends" was crucial for the health of the participants, as reported in the literature [18].

As previously described [28,50], family support was also very important for the participants with regard to the management of their pain. Some, however, considered themselves to be a burden due to their physical disability. This feeling could result from a sense of inequity or imbalance if they perceive that what they receive outweighs what they provide [51]. In addition, some participants described feelings of depression and uncertainty, as well as a decreased sense of autonomy and/or self-confidence because of both physical and economic dependence. These worries emerge strongly in this study. As a result, physicians often find themselves trying to bridge the gap between the chronic pain patient's expectations for effective pain relief and the harsh biomedical reality [52]. However, medication, opioids in these cases, is not enough to solve problems of another nature that in some cases predated the pain.

Clinical implications

Greater awareness should be raised among health care professionals about the experiences of patients with CP to counterbalance the negative effects of the invisibility of pain such as the lack of credibility given to symptoms expressed by patients and delays in access to diagnosis and treatment. This would shorten and improve patients' relationship with health care services.

Regarding information about long-term treatment with opioids, there is a need to improve the quantity and quality of information provided to patients. Furthermore, health care professionals should be aware of the extended use of alternative information sources like internet or peers among patients who experience CP, to ensure they are able to assess the credibility of the information they access and are able to understand and make use of this information, i.e. to ensure they have sufficient health literacy levels.

Finally, an interdisciplinary approach and health care team that includes social workers and psychologists is essential to address all those spheres of life affected by and affecting CP experiences and where opioids have little or no effect.

Methodological considerations

As previously described, several steps were taken to strengthen the trustworthiness of the findings. These do, however, need to be interpreted with some limitations in mind. Concerning transferability, it is important to consider the context where this study was conducted: a group of individuals with chronic pain, treated in a Pain Clinic of the Spanish healthcare system. With this in mind, we consider that the results from this study could be relevant for understanding the experiences of people with CP who are taking long-term treatment with opioids in other countries with similar socio-cultural aspects and health care systems, since the consequences they face and concerns they have about opioids may be the same.

Regarding credibility, we chose participants with different sex/gender, ages, and experiences to increase the likelihood of shedding light on the research question. What is more, the open-ended questions made it possible to share both positive and negative experiences. However, people who were at the beginning of the illness process may not have been reached, since we recruited participants via the Pain Clinic. Nonetheless, as we discuss in this study, CP is an illness that implies a long and difficult process before being be diagnosed and treated. Thus, opioids as a treatment are usually prescribed to those who have been suffering pain for a long-term period.

Another limitation of this study is that, although the results suggested gender differences in the patients' experiences with both CP and its treatment with opioids, the data were not rich enough to support a deep analysis and the elaboration of conclusions. Further research with this aim is required.

CONCLUSIONS

The participants' experiences were strongly shaped by the invisibility of pain, which led to a long-term relationship with the health care system and different forms of stigmatization. The participants made up for the limited information received from health care professionals by surfing the internet or asking peers. Yet, they showed limited knowledge about side effects and the long-term consequences of the treatment.

The burden of social determinants of health was increased by CP and at the same time a source of complications in CP experiences.

REFERENCES

1. Lin J, Scott W, Carpenter L, et al. Acceptance and commitment therapy for chronic pain: Protocol of a systematic review and individual participant data meta-Analysis. *Syst Rev*. 2019;8(1):1-10. doi:10.1186/s13643-019-1044-2

2. Dueñas M, Salazar A, Ojeda B, et al. A nationwide study of chronic pain prevalence in the general spanish population: identifying clinical subgroups through cluster analysis. *Pain Med*. 2015;16(4):811-822. doi:10.1111/pme.12640

3. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *Jama*. 2016;315(15):1624-1645. doi:10.1001/jama.2016.1464

4. Fischer B, Jones W, Rehm J. Trends and changes in prescription opioid analgesic dispensing in Canada 2005-2012: An update with a focus on recent interventions. *BMC Health Serv Res*. 2014;14:1-8. doi:10.1186/1472-6963-14-90

5. Walker G. The opioid crisis: A 21st century pain. *Drugs of Today*. 2018;54(4):283-286. doi:10.1358/dot.2018.54.4.2812620

6. Birke H, Kurita GP, Sjøgren P, et al. Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: Trends from 2000 to 2013. *Acta Anaesthesiol Scand*. 2016;60(5):623-633. doi:10.1111/aas.12700

7. Werber A, Marschall U, Helmut L, Hauser W, Moradi B, Schiltenwolf M. Opioid therapy in the treatment of chronic pain conditions in Germany. *Pain Physician*. 2015;(18):E323-E332.

8. Todd A, Akhter N, Cairns J-MM, et al. The Pain Divide: A cross-sectional analysis of chronic pain prevalence, pain intensity and opioid utilisation in England. *BMJ Open*. 2018;8(7):1-9. doi:10.1136/bmjopen-2018-023391

9. Agencia Española de Medicamentos y Productos Sanitarios. *Utilización de Medicamentos Opioides En España Durante El Periodo 2008-2015*.; 2017.

10. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain*. 2004;112(3):372-380. doi:10.1016/j.pain.2004.09.019

11. Carrico JA, Mahoney K, Raymond KM, et al. The Association of Patient Satisfaction-Based Incentives with Primary Care Physician Opioid Prescribing. *J Am Board Fam Med*. 2018;31(6):941-943. doi:10.3122/jabfm.2018.06.180067

12. Meyer R, Patel AM, Rattana SK, Quock TP, Mody SH. Prescription Opioid Abuse: A Literature Review of the Clinical and Economic Burden in the United States. *Popul Health Manag*. 2014;17(6):372-387. doi:10.1089/pop.2013.0098

13. Brennan F, Carr DB, Cousins M. Pain management: A fundamental human right. *Anesth Analg*. 2007;105(1):205-221. doi:10.1213/01.ane.0000268145.52345.55

14. Buchman DZ, Ho A, Illes J. You Present like a Drug Addict : Patient and Clinician Perspectives on Trust and Trustworthiness in Chronic Pain Management. *Pain Med*. 2016;17:1394-1406. doi:10.1093/pm/pnv083

15. Carvalho AS, Pereira SM, Jácomo A, et al. Ethical decision making in pain management: A conceptual framework. *J Pain Res*. 2018;11:967-976. doi:10.2147/JPR.S162926

16. de Sola H, Salazar A, Dueñas M, Failde I. Opioids in the treatment of pain. Beliefs, knowledge, and attitudes of the general Spanish population. Identification of subgroups through cluster analysis. *J Pain Symptom Manage*. 2018;55(4):1095-1104. doi:10.1016/j.jpainsymman.2017.12.474

17. Ferreira M, Verloo H, Mabire C, Vieira MMS, Marques-Vidal P. Psychometric evaluation of the French version of the questionnaire attitudes towards morphine use; a cross-sectional study in Valais, Switzerland. *BMC Nurs*. 2014;13(1):1-8. doi:10.1186/1472-6955-13-1

18. Brooks EA, Unruh A, Lynch ME. Exploring the lived experience of adults using prescription opioids to manage chronic noncancer pain. *Pain Res Manag*. 2015;20(1):15-22. doi:dx.doi.org/16497

19. Von Korff M, Kolodny A, Deyo RA, Chou R. Long-term opioid therapy reconsidered. *Ann Emerg Med*. 2011;155(5):325-328. doi:10.1059/0003-4819-155-5-201109060-00011.Long-Term

20. Sullivan MD, Von Korff M, Banta-Green C, Merrill JO, Saunders K. Problems and concerns of patients receiving chronic opioid therapy for chronic non-cancer pain. *Pain*. 2010;149(2):345-353. doi:10.1016/j.pain.2010.02.037.Problems

21. Rosenblum A, Marsch L, Herman J, Russell KP. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Exp Clin Psychopharmacol*. 2008;16(5):405-416. doi:10.1037/a0013628.Opioids

22. Nordahl Christensen H, Olsson U, From J, et al. Opioid-induced constipation, use of laxatives, and health-related quality of life. *Scand J Pain*. 2016;11:104-110. doi:10.1016/j.sjpain.2015.12.007

23. Jiménez JS, Tejedor Varillas A, García CRG, et al. *LA ATENCIÓN AL PACIENTE CON DOLOR CRÓNICO NO ONCOLÓGICO (DCNO) EN ATENCIÓN PRIMARIA (AP)*.; 2015. https://www.semfyc.es/wp-content/uploads/2016/06/DOCUMENTO-CONSENSO-DOLOR-17-04-A.pdf.

24. Cátedra Extraordinaria del Dolor FUNDACIÓN GRÜNENTHAL UNIVERSIDAD SALAMANCA. *"DOLOR CRÓNICO ENFERMEDAD EN SÍ MISMA" XIII REUNIÓN DE EXPERTOS*.; 2013.

25. Dueñas M, Salazar A, Sánchez M, De Sola H, Ojeda B, Failde I. Relationship Between Using Clinical Practice Guidelines for Pain Treatment and Physicians' Training and Attitudes Toward Patients and the Effects on Patient Care. *Pain Pract*. 2017;18(1):38-47. doi:10.1111/papr.12579

26. Ljungvall H, Rhodin A, Wagner S, Zetterberg H, Åsenlöf P. "my life is under control with these medications": An interpretative phenomenological analysis of managing chronic pain with opioids. *BMC Musculoskelet Disord*. 2020;21(1):1-14. doi:10.1186/s12891-020-3055-5

27. St. Marie B. Primary care experiences of people who live with chronic pain and receive opioids to manage pain: A qualitative methodology. *J Am Assoc Nurse Pract*. 2016;28(8):429-435. doi:10.1002/2327-6924.12342

28. Frank JW, Levy C, Matlock DD, et al. Patients' perspectives on tapering of chronic opioid therapy: A qualitative study. *Pain Med (United States)*. 2016;17(10):1838-1847. doi:10.1093/pm/pnw078

29. Allen MJM, Asbridge MM, MacDougall PC, Furlan AD, Tugalev O. Self-reported practices in opioid management of chronic noncancer pain: A survey of Canadian family physicians. *Pain Res Manag*. 2013;18(4):177-184. doi:10.1155/2013/528645

30. Antoniou T, Ala-Leppilampi K, Shearer D, Parsons JA, Tadrous M, Gomes T. "Like being put on an ice floe and shoved away": A qualitative study of the impacts of opioid-related policy changes on people who take opioids. *Int J Drug Policy*. 2019;66:15-22. doi:10.1016/j.drugpo.2019.01.015

31. Dassieu L, Kaboré JL, Choinière M, Arruda N, Roy É. Painful lives: Chronic pain experience among people who use illicit drugs in Montreal (Canada). *Soc Sci Med*. 2020;246(July 2019):112734. doi:10.1016/j.socscimed.2019.112734

32. United Nations Office on Drugs and Crime. *Global Overview on Drug Demand and Supply: Latest Trends, Cross-Cutting Issues*.; 2017.

33. Salazar A, Moreno S, De Sola H, Moral-Munoz JA, Dueñas M, Failde I. The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017. Differences between Spain and the United States. *Curr Med Res Opin*. 2019;35(11):000. doi:10.1016/j.neulet.2008.12.049

34. Ache dos Santos FA, Barcellos de Souza J, Ledur Antes D, D'Orsi E. Prevalence of chronic pain and its association with the sociodemographic situation and physical activity in leisure of elderly in Florianópolis, Santa Catarina: population-based study. *REV BRAS EPIDEMIOL*. 2015;18(1):234-247. doi:10.1590/1980-5497201500010018

35. Dueñas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. *J Pain Res*. 2016;9:457-467. doi:10.2147/JPR.S105892

36. Timmerman L, Stronks DL, Groeneweg JG, Huygen FJ. Prevalence and determinants of medication non-adherence in chronic pain patients: A systematic review. *Acta Anaesthesiol Scand*. 2016;60(4):416-431. doi:10.1111/aas.12697

37. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: Concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today*. 2004;24(2):105-112. doi:10.1016/j.nedt.2003.10.001

38. Slater H, Jordan JE, Chua J, Schütze R, Wark JD, Briggs AM. Young people's experiences of persistent musculoskeletal pain, needs, gaps and perceptions about the role of digital technologies to support their co-care: A qualitative study. *BMJ Open*. 2016;6(12):1-11. doi:10.1136/bmjopen-2016-014007

39. Ojala T, Häkkinen A, Karppinen J, Sipilä K, Suutama T, Piirainen A. Although unseen, chronic pain is real-A phenomenological study. *Scand J Pain*. 2014;6:33-40. doi:10.1016/j.sjpain.2014.04.004

40. Kempner J. Invisible people with invisible pain: A commentary on “Even my sister says I’m acting like a crazy to get a check”: Race, gender, and moral boundary-work in women’s claims of disabling chronic pain. *Soc Sci Med*. 2017;189:152-154. doi:10.1016/j.socscimed.2017.06.009

41. Itz C, Huygen F, Kleef M van. A proposal for the organization of the referral of patients with chronicnon-specific low back pain. *Curr Med Res Opin*. 2016;32(11):1903-1909. doi:10.1080/03007995.2016.1220933

42. Clarke AE, Shim JK, Mamo L, Fosket JR, Fishman JR. Biomedicalization: Technoscientific Transformations of Health, Illness, and U.S. Biomedicine. *Am Sociol Rev*. 2003;68(4):161-194.

43. Meineche-Schmidt V, Jensen NH, Sjøgren P. Long-term outcome of multidisciplinary intervention of chronic non-cancer pain patients in a private setting. *Scand J Pain*. 2012;3(2):99-105. doi:10.1016/j.sjpain.2011.10.002

44. World Health Organization (WHO). Health literacy The solid facts. In: *The Solid Facts*. Copenhagen; 2013:1-68. doi:10.1002/rcm.3390

45. Linander I, Alm E, Hammarström A, Harryson L. Negotiating the (bio)medical gaze – Experiences of trans-specific healthcare in Sweden. *Soc Sci Med*. 2017;174:9-16. doi:10.1016/j.socscimed.2016.11.030

46. Washington TA, Fanciullo GJ, Sorensen JA, Baird JC. Quality of chronic pain websites. *Pain Med*. 2008;9(8):994-1000. doi:10.1111/j.1526-4637.2008.00419.x

47. Olaya-Contreras P, Styf J. Biopsychosocial function analyses changes the assessment of the ability to work in patients on long-term sick-leave due to chronic musculoskeletal pain: the role of undiagnosed mental health comorbidity. *Scand J Public Health*. 2013;41(3):247-255. doi:10.1177/1403494812473380

48. Monsivais DB. Decreasing the stigma burden of chronic pain. *J Am Assoc Nurse Pract*. 2013;25(10):551-556. doi:10.1111/1745-7599.12010

49. Finlay KA, Elander J. Reflecting the transition from pain management services to chronic pain support group attendance: An interpretative phenomenological analysis. *Br J Health Psychol*. 2016;21(3):660-676. doi:10.1111/bjhp.12194

50. Jamison RN, Virts KL. The influence of family support on chronic pain. *Behav Res Ther*. 1990;28(1):283-287. doi:10.1016/0005-7967(90)90079-X

51. Kowal J, Wilson KG, McWilliams L a., Péloquin K, Duong D. Self-perceived burden in chronic pain: Relevance, prevalence, and predictors. *Pain*. 2012;153(8):1735-1741. doi:10.1016/j.pain.2012.05.009

52. Bäckryd E. “Professional helper” or “helping professional?” the patient–physician relationship in the chronic pain setting, with special reference to the current opioid debate. *J Contin Educ Health Prof*. 2016;36(2):133-137. doi:10.1097/CEH.0000000000000062

Table 1. Characteristics of the sample

	Gender	Age	Income/Occupation	Years with pain	Under opioids' treatment	Opioid currently prescribed
Julia	Female	88	Retirement (Housewife)	15	1 year	Tapentadol
María	Female	40	Total permanent disability (Administrative assistant)	22	8 years	Tapentadol
Laura	Female	55	Sick leave (Administrative assistant)	14	1 year	Tramadol (PRN)
Juan	Male	72	Retirement (accountant)	4	4 years	Tapentadol
Pilar	Female	56	Unemployed (Housewife)	13	13 years	Tapentadol
Lola	Female	41	Total permanent disability (Administrative assistant)	8	8 years	Tapentadol
Carlos	Male	66	Retirement (bricklayer)	2	6 months	Tapentadol
Rafael	Male	52	Sick leave (watchman)	5	5 years	Tapentadol
Ana	Female	41	Unemployed (Housewife)	7	5 years	Tramadol
Leticia	Female	72	Retirement (hairdresser)	48	4 years	Tramadol y Tapentadol
Sofia	Female	46	Total permanent disability (Cleaner)	2	2 years	Oxycodone
Alejandro	Male	51	Total permanent disability (bricklayer)	9	4 years	Morphine
Roberto	Male	72	Retirement (mechanic)	"Long time ago"	2 years	Tapentadol
Carmen	Female	80	Retirement (cleaner)	30	"many years."	Tramadol
Hugo	Male	52	Unemployed (carpenter)	5	5 years	Morphine

Table 2. Interview guide used for the semi-structured interviews.

Exploring pain How did the pain start? *Exploring prescription of opioids and information* Can you tell me about how you started taking opioids? How did your doctor suggest taking these medications? How did you react when your doctor told you that you will be taking an opioid treatment? What was your opinion about opioid medications before taking it? And now? Has your opinion changed? Were other alternatives considered? Which ones? What type of information about opioids have you received? What is your opinion about the information that your doctor gave you about the treatment? Have you sought information through other means? Which ones? *Daily life and opioids* Can you describe a usual day in your life? Since you started this treatment with opioids, have you changed your daily activities? Since you started this treatment with opioids, could you describe how your health is? Could you describe your mood since you started this treatment with opioids? Do you think that opioids cause side effects? How? *Taking opioids* Have you ever tried to stop or decrease the opioid dose? Why? How was the experience? Since you started this treatment, have you needed to increase the dose? Do you think you would have needed to increase the doses? Why? What is the best way to relieve your pain? *Social relationships and work* How is your social life since you are under an opioid treatment? Can you describe the relationship with your family? Has this relationship changed since you are under treatment? Can you describe your working life? *Final questions* How is your experience with opioid treatments In general? Would you like to add anything else?

Table 3. Quotations illustrating categories and theme.

Theme: "Living with opioids: dependence and autonomy while seeking relief"
Category: "The long pathway to opioids due to the invisibility of pain" **Ana, 41 years old, 5 years taking tramadol:** *"since I was a kid, I've always had back pain. I had to come frequently to the hospital, always with "lumbago", mainly "lumbago".* **Carlos, 66 years old, 6 months tapentadol***: I have had this problem for at least 2 years, and it has been getting worse and worse... I wanted the doctors to see me, but there was a long waiting list for the specialist. I had to go to the emergency room because I couldn't take it anymore. Over and over again to the emergency room... and again a dropper, only a dropper... until finally the neurosurgeon saw me and said: something must be done here, and he sent me here to the Pain Clinic.* **Rafael, 52 years old, 5 years taking tapentadol:** *(talking about a previous health problem in the eye) "well, it was more visible, the eye was really red, red, red, and people asked me "What happened? Did you hit something or what did you do?" […] You could see the surprised and shocked faces. But now (with Chronic Pain (CP))... they see me so fine, so healthy, and in my inside, I am dying with pain".* **Lola, 41 years old, 8 years taking tapentadol:** *"My parents took me first to the emergency room, and they injected me with morphine, and sent me home in an ambulance […] The following day it was the same. Another injection and go home. Then, they told me that I needed surgery because all my lumbar area was calcified. Then I could feel something strange… and they prescribed (small pause) morphine, and each time the dosage was increased more, and more… and there was no pain relief. They told me there were two possible big issues with my type of surgery: instability remaining in the backbone or leaving residues of spinal discs, and I had both".*
Category: "Opioids: from blind date to a long-term relationship" **Laura, 55 years old, 1 year taking tramadol:** *"The doctor told me: 'I'm going to prescribe you this medication that I think is going to help you'. I found out later that tramadol was an opioid, when I searched it on the internet, and people told me: 'uh, that medicine has this and that…' and I said, 'that much?' 'yes, yes, it's like morphine, a derivative'. After this, I saw what it was. But my doctor didn't tell me anything."* **Sofia, 46 years old, 2 years taking oxycodone:** *"I didn't know what morphine was. I had heard that it was for drug addicts, that's the truth... I didn't know... That's what I have always heard in my house. I knew there were patches and all that stuff, but I didn't know for what exactly.* **Lola, 41 years old, 8 years taking tapentadol:** *"I was very wrong […] I remember that morphine was used with my grandfather before dying to relieve his pain and all that stuff, so I never thought I would have to take it as they say "as an outpatient treatment, at home." I didn't think it would be like that".*

María, 8 years old, 8 years taking tapentadol: *"The morphine has caused me... I sleep with a CPAP because of the dryness that morphine left me. It caused me sleep apnea. It's left many side-effects apart from my illness because all the medication that I have been taken.*

Ana, 41 years old, 5 years taking tramadol*: "It's true that opioids must have some effect, because I remember that once I ran out of them ... and I do not know if it was a day or two without taking them, and look, I was a physical wreck. I had to lie in bed […] When I bought and took them, it made me "Boom!". I rush out to the shops! My husband was shocked! I said: "the pill, look what the pill has done to me".*

Category: "What opioids cannot fix"

Ana, 41 years old, 5 years taking tramadol: *"For some time I had to take anxiolytics. The doctor said that my problem had no solution, that I was going to be in pain forever, and I fell apart. But it's true that I had no other option. I always try to say to myself: 'no, come on, I'm not going to cry'. This is what I have and that's all there is to it. Your mind is the one that has to say: 'hey, we stop here, I will not cry'.*

Pilar, 56 years old, 8 years taking tapentadol: *"I have little help to be honest. I often get angry with him [her husband] because of that. All the work is for me. Well, if I'm cleaning, of course he helps me, but the housework… he doesn't… he hangs out the washing, he helps me with little things like that, he helps me making the bed and that's all.*

María, 8 years old, 8 years taking tapentadol: *"I speak to my very close friends and I have to explain that it's morphine and that this is what I need for my chronic pain. The society is not… not well informed; it's seen like… phew… so bad, she's dying or it must be bad if she is taking morphine, and it's not like that".*

Lola,* 41 years old, 8 years taking tapentadol: "My family has been my lifesaver. Without my father and my mother… look, I am giving more importance to them than to my partner. During the day, my partner is not with me. He cannot stop working to stay with me… it is understandable with just one salary for both of us. If he stops working, we cannot live."*

GENERAL DISCUSSION

Throughout the 4 studies that compose it, this doctoral thesis addresses diverse aspects and consequences of the use of opioid treatment in recent years. To this end, we first analyzed the prevalence of the use of an opioid treatment in chronic pain patients. Secondly, taking into account the consequences of the use of opioids, we studied the mortality related to their use. Then, we further investigated the point of view of the general Spanish population about the treatment of CP with opioids. Finally, we took a deeper look at the experiences of people that are taking opioids to treat their pain. The conclusion can be drawn that the appropriate use of opioids is a way of reducing pain. However, it presents a constant struggle with concerns related to dependence and addiction to the medication, sometimes related with the death of the patients.

In the first paper, we present a systematic review following a rigorous methodology that analyzed the information published about the prevalence of opioid use in patients with CNCP and the main factors related to the use of opioids. The results obtained reveal important differences in the prevalence that are related with the length of the treatment, the occasional use of opioids being more prevalent than their long-term use.

The lower prevalence found in patients with longer-term treatments seems reasonable if we take into account the prescribers' concern about the risk of addiction and the improper use of these drugs by some patients [100]. The results are consistent with those found in the third study of the thesis about the perspective of the Spanish population regarding opioids. These results highlight the concerns about the risk of addiction, with the notable existence of a group of people that had taken opioids in the past, but would refuse to take them again, arguing the difficulty in stopping taking this drug. Another reason that would justify the lower prevalence of the long-term use of opioids is the active attitude of the patient coping with pain [101]. As our fourth study about the experiences with opioids of the patients shows, as time went by, the participants became progressively more active in decision-making related to pain management and less likely to rely exclusively on opioids, since they had learned other ways to relieve the pain, such as losing weight, exercising and taking other medication as needed.

We could think that the prevalence of the use of opioids is greater when the prevalence of CP is higher [29]. However, comparing the results from different countries, this hypothesis was not

confirmed, since there are different cultural, social, political, and historical factors, as well as others related to advertising and marketing [4,62] that could influence the use of opioids for pain relief. In this regard, Bosetti et al. [64] have reported that Southern and Eastern European countries have the lowest consumption, which would imply, a priori, a lower risk. These results are consistent with those presented in the second paper of the thesis where, even after standardization, the rates of opioid-related mortality between Spain and the USA are clearly different, these being 8–12 times higher in the USA than in Spain, depending on the year.

Regarding factors associated with the use of opioids, we found that patients without insurance or those who had non-commercial insurance presented greater use of opioids. The type of medical insurance can influence the way pain is approached and consequently determine the use of opioids. Some studies have shown [102,103] that patients with private insurance receive more immediate attention with a multidisciplinary approach, leading to better results and a decrease in the use of analgesic treatment. In line with this, in our fourth study, carried out in the public Pain Clinic, we found that the vast majority of participants had unskilled jobs and a basic level of education, and they reported obtaining a diagnosis only after lengthy experiences of navigating through the healthcare public system. We argued that the difficulty in obtaining a diagnosis and treatment could presumably be exacerbated for those with a lower educational and economic level who cannot afford private medical care and can avoid the mutual referral system between the GPs and specialists of the public health system.

Gender is another factor related to opioid use. The results of our systematic review showed that opioid use was more prevalent among young men. Additionally, this group also showed the worst evolution of opioid-related death in the second paper. According to the Spanish Report on alcohol, tobacco and illegal drugs of 2017 [104], the main psychoactive substances involved in the deaths in recent years in Spain are hypnosedatives and opioids, reported in over half of the deaths. However, the report does not specify if opioids were the main cause of death, a causal relationship between their use and the main cause of death being difficult to establish. Nevertheless, historically, it has been shown that addiction to opioids has always been higher in men [105].

As we have seen in the group containing young men, an increase in opioid-related death has also been observed in the group of women over 55. We argued that they have more risk of suffering side effects such as respiratory depression often related to eventual death [106], since

chronic conditions are more prevalent in women of these ages [107], opioids being one of the most common treatments [108]. Although there is limited information about gender differences in the risk factors related to opioid use [109], what is known from clinical studies is that women are more sensitive to both dosage and type of medication [21].

The willingness to accept treatment with opioids was analyzed in the third paper, identifying three different profiles. One group had a positive vision of opioids, had more confidence in their physician when prescribing these drugs, and were less concerned about their adverse effects. The other two groups were more worried about the side effects of the opioids and less willing to take them upon medical prescription. One of these groups showed more deep-rooted opiophobia. In spite of this, many patients who see opioids as a last resource, say they would eventually be willing to start treatment if the pain became severe [110]. In this vein, when we analyze the experiences of people taking opioid treatments in the fourth study, the participants admitted to having accepted their treatment due to the intensity of pain suffered, even though they had previously related opioids to terminal diseases or to drugs and addiction. In this sense the pain-relieving effects tipped the balance in favor of patients accepting the treatment with opioids despite their concerns.

Taking a more in-depth look at the experiences of people taking an opioid treatment, the fourth study of the thesis shows that relieving pain is a constant struggle for people who suffer from it. These experiences were severely influenced by the invisibility of their pain and the long and difficult process to get a diagnosis. Participants were dependent on healthcare professionals exercising their power to refer them to specialized care to get access to a diagnosis and treatment, including opioids. At the same time, to a certain extent, they had room to make decisions and exercise autonomy, despite the lack of information available to them. Other authors have shown [77] that this lack of information or misinformation can also lead to unrealistic patient expectations regarding the results of this treatment. In this vein, concerns regarding adverse effects and unrealistic expectations of the treatment goals can be considered the most important consequences of the lack of information received.

The support of relatives and friends is essential for CP patients, as shown in the fourth paper. However, interestingly, the participants preferred to share their experience of opioids with ‘pain friends’, who were usually receiving the same kind of treatment. The stigmatization of CP people is revealed in the literature, which sought to identify the ‘pain-prone personality’ [111]. In this

sense, the patients in our study stated feeling stigmatized for taking opioids too, since relatives and friends showed concerns and prejudices about this treatment. In this vein, in the third paper, we saw how the general population related opioids to "illegal drugs" such as heroin or cocaine and drug abuse. These types of beliefs could result in a lack of empathy and stigmatization for CP patients consuming opioids, as reflected in the patients' discourse.

Family support was very important for helping the participants with the management of their pain. Some patients, however, may consider themselves to be a burden for their family due to their physical disability [43]. In addition, some participants described feelings of depression and helplessness, as well as a decreased sense of autonomy and/or self-confidence because of both physical and economic dependence. As a result, physicians often find themselves trying to bridge the gap between the chronic pain patient's expectations for effective pain relief and the harsh biomedical reality [112]. However, medication, opioids in these cases, is not enough to solve problems of another nature that in some cases predate the pain.

To sum up, as shown throughout the thesis, CP and its treatment are intertwined with different spheres of the patients' daily life. Each patient suffering pain has to go through a hard process of legitimating their pain in their social context [113], which could result in feelings of sadness and uncertainty [46]. Thus, pain has an impact that cannot be addressed through opioids alone; rather, a more comprehensive approach to the illness is required.

Finally, it is worth remembering here some limitations found throughout the thesis. The specific limitations of each study have already been mentioned in each manuscript. However, some general limitations of the thesis are worth discussing in a bit more depth. The combination of aims and methods made it impossible to work with the same population. We have argued that this can also be seen as a strength, since that let us carry out a thesis with a broad vision. Another limitation is that the third study about the perspective of the general Spanish population was conducted before the United States epidemiological alert was pronounced, which could have had an impact on the results. This study was conducted in the context of Spain and thus the transferability to other populations should be done with caution. However, it showed similar results to other nearby countries. Furthermore, the description of the methodology is transparent enough so that other authors are able to determine the transferability and applicability to other countries.

CONCLUSIONS

In view of the results obtained in the different studies, the following conclusions can be drawn:

From paper 1:

1. The prevalence of opioid use in patients with CNCP varies depending on the duration of treatment and the population analyzed, the prevalence being much higher when opioids are prescribed for occasional rather than long-term use and when the analysis is based on clinical studies or health registries rather than on the general population.

2. A greater use of opioids was observed in men, younger individuals, patients receiving prescriptions of different kinds of drugs, patients with a pain-related disability and in those who suffering more CP conditions.

3. The prescription of opioids was higher in patients without insurance or with non-commercial insurance compared with those with private insurance.

4. Race was also related to the use of opioids, non-white and Asian patients being less likely to receive opioids than non-Hispanic white patients.

From paper 2:

5. The crude rate of ORD per 10^5 inhabitants has changed from 1.68 in 2008 to 2.25 in 2017 in Spain, with around 30,000 years of life lost per year, middle-aged men and women over 65 the most affected groups.

6. The standardized rates of ORD in the US population are 8–12 times higher than those in Spain.

7. An opioid overuse crisis does not seem a likely scenario in Spain. However, it is a social problem that requires special health surveillance, particularly in middle-aged men, and women over 65.

From paper 3:

8. There is a lack of knowledge of opioids in the general Spanish population. The side effects of these drugs are the most feared aspects associated with their use in the treatment of pain.
9. There are three different profiles of people regarding their point of view towards opioids, which largely depends on educational level, age, and previous contact with opioids.

10. The different perspectives regarding the use of opioids to treat pain should be taken into consideration by physicians when informing patients in order to promote their correct use, and to prevent their misuse in particular.

From paper 4:

11. The participants' experiences were strongly shaped by the invisibility of pain, which led to a long-term relationship with the health care system and different forms of stigmatization. The participants made up for the limited information received from health care professionals by surfing the internet or asking peers. Yet, they showed limited knowledge about side effects and the long-term consequences of the treatment.

12. The burden of social determinants of health was increased by CP and at the same time was a source of complications in CP experiences.

BIBLIOGRAPHY

1. Declaration of Montreal. International Society for the Study of Pain. IASP. Declaration that access to pain management is a fundamental human right. http://www.iasp-pain.org/. Published 2010. Accessed May 18, 2019.

2. Julien N, Lacasse A, Labra O, Asselin H. Review of chronic non-cancer pain research among Aboriginal people in Canada. *Int J Qual Heal Care*. 2018;30(3):178-185. doi:10.1093/intqhc/mzx195

3. Treede R-D. The International Association for the Study of Pain definition of pain: as valid in 2018 as in 1979, but in need of regularly updated footnotes. *Pain reports*. 2018;3(2):e643. doi:10.1097/PR9.0000000000000643

4. Steingrímsdóttir ÓA, Landmark T, Macfarlane GJ, Nielsen CS. Defining chronic pain in epidemiological studies – a systematic review and meta-analysis. *Pain*. 2017;158:2092-2107. doi:10.1097/j.pain.0000000000001009

5. Smith BH, Fors EA, Korwisi B, et al. The IASP classification of chronic pain for ICD-11. *Pain*. 2018;160(1):45-52. doi:10.1097/j.pain.0000000000001413

6. International Association for the Study of Pain. *Unrelieved Pain Is a Major Global Healthcare Problem*. Washington DC.; 2004.

7. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10(4):287-333. doi:10.1016/j.ejpain.2005.06.009

8. Dahlhamer J, Lucas J, Zelaya C. Pain Awareness Month — September 2018 Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States , 2016. *Morb Mortal Wkly Rep*. 2018;67(36). doi:10.15585/mmwr.mm6736a2

9. Mohamed Zaki LR, Hairi NN. A Systematic Review ofthe Prevalence and Measurement of Chronic Pain in Asian Adults. *Pain Manag Nurs*. 2015;16(3):440-452. doi:10.1016/j.pmn.2014.08.012

10. Assadeck H, Toudou M, Hassane F, Douma D, Adehossi E. Prevalence and characteristics

of chronic pain: Experience of Niger. *Scand J Pain*. 2017;17:252-255. doi:10.1016/J.SJPAIN.2017.07.008

11. Cheung CW, Choi SW, Wong SSC, Lee Y, Irwin MG. Changes in Prevalence, Outcomes, and Help-seeking Behavior of Chronic Pain in an Aging Population Over the Last Decade. *Pain Pract*. 2017;17(5):643-654. doi:10.1111/papr.12496

12. Dueñas M, Salazar A, Ojeda B, et al. A nationwide study of chronic pain prevalence in the general spanish population: identifying clinical subgroups through cluster analysis. *Pain Med*. 2015;16(4):811-822. doi:10.1111/pme.12640

13. Azevedo L, Costa-Pereira A, Mendonça L, Dias C, Castro-Lopes J. Epidemiology of Chronic Pain: A Population-Based Nationwide Study on Its Prevalence, Characteristics and Associated Disability in Portugal. *J Pain*. 2012;13(8):773-783. doi:10.1016/j.jpain.2012.05.012

14. Azevedo LLFL, Costa-Pereira A, Mendonça L, Dias CCCC, Castro-Lopes JMJ. Epidemiology of Chronic Pain: A Population-Based Nationwide Study on Its Prevalence, Characteristics and Associated Disability in Portugal. *J Pain*. 2012;13(8):773-783. doi:10.1016/j.jpain.2012.05.012

15. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10(4):287-333. doi:10.1016/j.ejpain.2005.06.009

16. Bergman S, Petersson IF, Svensson B, Jacobsson LT. Chronic musculoskeletal pain, prevalence rates, and sociodemographic associations in a Swedish population study. *J Rheumatol*. 2001;28(6).

17. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163-2196. doi:10.1016/S0140-6736(12)61729-2

18. Borsook D, Youssef AM, Simons L, Elman I, Eccleston C. When pain gets stuck: the evolution of pain chronification and treatment resistance. *Pain*. 2018;159(12):2421-2436. doi:10.1097/j.pain.0000000000001401

19. Larsson B, Dragioti E, Grimby-Ekman A, Gerdle B, Björk J. Predictors of chronic pain intensity, spread, and sensitivity in the general population: A two-year follow-up study from the SWEPAIN cohort. *J Rehabil Med*. 2019;51(3):183-192. doi:10.2340/16501977-2519

20. Van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. *Br J Anaesth*. 2013;111(1):13-18. doi:10.1093/bja/aet123

21. Rovner GS, Sunnerhagen KS, Björkdahl A, et al. Chronic pain and sex-differences; Women accept and move, while men feel blue. *PLoS One*. 2017;12(4):1-12. doi:10.1371/journal.pone.0175737

22. Fullerton EF, Doyle HH, Murphy AZ. Impact of sex on pain and opioid analgesia: a review. *Curr Opin Behav Sci*. 2018;23:183-190. doi:10.1016/j.cobeha.2018.08.001

23. Johansson EE, Hamberg K, Westman G, Lindgren G. The meanings of pain: An exploration of women's descriptions of symptoms. *Soc Sci Med*. 1999;48(12):1791-1802. doi:10.1016/S0277-9536(99)00080-5

24. Shaw WS, Besen E, Pransky G, et al. Manage at work: A randomized, controlled trial of a self-management group intervention to overcome workplace challenges associated with chronic physical health conditions. *BMC Public Health*. 2014;14:515. doi:10.1186/1471-2458-14-515

25. Domenichiello AF, Ramsden CE. The silent epidemic of chronic pain in older adults. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2019. doi:10.1016/j.pnpbp.2019.04.006

26. Cassell A, Edwards D, Harshfield A, et al. The epidemiology of multimorbidity in primary care. *Br J Gen Pract*. 2018;(April):1-7.

27. Jay MA, Bendayan R, Cooper R, Muthuri SG. Lifetime socioeconomic circumstances and chronic pain in later adulthood: Findings from a British birth cohort study. *BMJ Open*. 2019;9(3):1-10. doi:10.1136/bmjopen-2018-024250

28. Leiser S, Déruaz-Luyet A, N'Goran AA, et al. Determinants associated with deprivation in multimorbid patients in primary care — A cross-sectional study in Switzerland. *PLoS One*. 2017;12(7):1-12. doi:10.1371/journal.pone.0181534

29. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet*. 2012;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2

30. Briesacher BA, Gurwitz JH, Soumerai SB. Patients at-risk for cost-related medication nonadherence: A review of the literature. *J Gen Intern Med*. 2007;22(6):864-871. doi:10.1007/s11606-007-0180-x

31. Jones SL, Hadjistavropoulos HD, Janzen JA, Hadjistavropoulos T. The Relation of Pain and Caregiver Burden in Informal Older Adult Caregivers. *Pain Med*. 2011;12:51-58.

32. Inoue S, Kobayashi F, Nishihara M, et al. Chronic Pain in the Japanese Community--Prevalence, Characteristics and Impact on Quality of Life. *PLoS One*. 2015;10(6):e0129262. doi:10.1371/journal.pone.0129262

33. Fuss I, Angst F, Lehmann S, Michel B a, Aeschlimann A. Prognostic factors for pain relief and functional improvement in chronic pain after inpatient rehabilitation. *Clin J Pain*. 2014;30(4):279-285. doi:10.1097/AJP.0b013e31829a4d11

34. Hanssen DJC, Naarding P, Collard RM, Comijs HC, Oude Voshaar RC. Physical, lifestyle, psychological, and social determinants of pain intensity, pain disability, and the number of pain locations in depressed older adults. *Pain*. 2014;155(10):2088-2096. doi:10.1016/j.pain.2014.07.019

35. Feingold D, Brill S, Goor-Aryeh I, Delayahu Y, Lev-Ran S. Misuse of prescription opioids among chronic pain patients suffering from anxiety: A cross-sectional analysis. *Gen Hosp Psychiatry*. 2017;47:36-42. doi:10.1016/j.genhosppsych.2017.04.006

36. Hong JH, Kim HD, Shin HH, Huh B. Assessment of depression, anxiety, sleep disturbance, and quality of life in patients with chronic low back pain in Korea. *Korean J Anesthesiol*. 2014;66(6):444-450. doi:10.4097/kjae.2014.66.6.444

37. Lerman SF, Rudich Z, Brill S, Shalev H, Shahar G. Longitudinal Associations Between Depression, Anxiety, Pain, and Pain-Related Disability in Chronic Pain Patients. *Psychosom Med*. 2015;77(3):333-341. doi:10.1097/PSY.0000000000000158

38. Yamada K, Kubota Y, Shimizu Y, Shibata M, Morotomi N. Association of sleep sufficiency and duration with chronic pain prevalence: A population-based cross-sectional study. *J Psychosom Res*. 2019;120(March):74-80. doi:10.1016/j.jpsychores.2019.03.005

39. Ando H, Ikegami K, Sugano R, Nozawa H, Michii S, Shirasaka T. Relationships Between Chronic Musculoskeletal Pain and Working Hours and Sleeping Hours : A Cross-sectional Study. *J UOEH*. 2019;41(1):25-33.

40. Ojeda B, Salazar A, Calahorro M, et al. Understanding the different relationships between mood and sleep disorders in several groups of non-oncological patients with chronic pain. *Curr Med Res Opin*. 2018;34(4):669–676. doi:10.1080/03007995.2017.1384372

41. Andrews NE, Strong J, Meredith PJ. The Relationship between Approach to Activity Engagement, Specific Aspects of Physical Function, and Pain Duration in Chronic Pain. *Clin J Pain*. 2016;32(1):20-31. doi:10.1097/AJP.0000000000000226

42. Ojeda B, Salazar A, Dueñas M, Torres LLM, Mico JJA, Failde I. The Impact of Chronic Pain : The Perspective of Patients, Relatives, and Caregivers. *Fam Syst Heal*. 2014;32(4):399-407. doi:10.1037/fsh0000069

43. Kowal J, Wilson KG, McWilliams L a., Péloquin K, Duong D. Self-perceived burden in chronic pain: Relevance, prevalence, and predictors. *Pain*. 2012;153(8):1735-1741. doi:10.1016/j.pain.2012.05.009

44. Mayer S, Spickschen J, Stein KV, Crevenna R, Dorner TE, Simon J. The societal costs of chronic pain and its determinants: The case of Austria. *PLoS One*. 2019;14(3):e0213889. doi:10.1371/journal.pone.0213889

45. de Sola H, Salazar A, Dueñas M, Ojeda B, Failde I. Nationwide cross-sectional study of the impact of chronic pain on an individual´s employment. Relationship with the family and the social support. *BMJ Open*. 2016;6(12):e012246. doi:10.1136/bmjopen-2016-012246

46. Reid KJ, Harker J, Bala MM, et al. Epidemiology of chronic non-cancer pain in Europe: narrative review of prevalence, pain treatments and pain impact. *Curr Med Res Opin*. 2011;27(2):449-462. doi:10.1185/03007995.2010.545813

47. Breivik H, Eisenberg E, O'Brien T. The individual and societal burden of chronic pain in

Europe: The case for strategic prioritisation and action to improve knowledge and availability of appropriate care. *BMC Public Health*. 2013;13(1). doi:10.1186/1471-2458-13-1229

48. Pérez C, Navarro A, Saldaña MT, Wilson K, Rejas J. Modelling the Predictive Value of Pain Intensity on Costs and Resources Utilization in Patients with Peripheral Neuropathic Pain. *Clin J Pain*. 2015;31(3):273-279. doi:10.1097/AJP.0000000000000110

49. North RB, Shipley J, Wang H, Mekhail N. A Review of Economic Factors Related to the Delivery of Health Care for Chronic Low Back Pain. *Neuromodulation Technol Neural Interface*. 2014;17:69-76. doi:10.1111/ner.12057

50. de Sola H, Salazar A, Dueñas M, Ojeda B, Failde I. A nationwide cross-sectional study of the impact of chronic pain on an individual´s employment. Relationship with the family and the social support. *BMJ Open*. 2016;6(12):e012246. doi:10.1136/bmjopen-2016-012246

51. Hooten WM. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. *Mayo Clin Proc*. 2016;91(7):955-970. doi:10.1016/j.mayocp.2016.04.029

52. Dureja G, Jain P, Shetty N. Prevalence of Chronic Pain, Impact on Daily Life, and Treatment Practices in India. *Pain*. 2014;14(2):E51–E62.

53. Alam A, Juurlink DN. The prescription opioid epidemic: an overview for anesthesiologists. *Can J Anesth Can D Anesth*. 2015;63(1):61-68. doi:10.1007/s12630-015-0520-y

54. Serrano MD, González E, Antequera R, López-Muñoz F, Alamo C. Una visión histórica de las drogas de abuso desde la perspectiva criminológica (Parte II). *Cuad Med Forense*. 2011;17(2):21-33. doi:10.4321/s1135-76062011000200003

55. ESCOHOTADO A. *HISTORIA GENERAL DE LAS DROGAS*.; 1989.

56. Dhalla I, Persaud N, Juurlink D. Facing up to the prescription opioid crisis. *Br Med J*. 2011;343(d5142 doi:):d5142. doi:10.1136/bmj.d5142

57. Verloo H, Mpinga EK, Ferreira M, Rapin C, Chastonay P. Morphinofobia: the situation

among the general population and health care professionals in. *BMC Palliat Care*. 2010;9(15):2-9. doi:10.1186/1472-684X-9-15

58. Ferreira M, Verloo H, Mabire C, Vieira MMS, Marques-Vidal P. Psychometric evaluation of the French version of the questionnaire attitudes towards morphine use; a cross-sectional study in Valais, Switzerland. *BMC Nurs*. 2014;13(1):1-8. doi:10.1186/1472-6955-13-1

59. Motov SM, Khan ANGA. Problems and barriers of pain management in the emergency department: Are we ever going to get better? *J Pain Res*. 2009;2:5-11. doi:10.2147/JPR.S4324

60. Manchikanti L, Helm S, Fellows B, et al. Opioid epidemic in the United States. *Pain Physician*. 2012;15:ES9-38. doi:10.1007/s11606-012

61. Garcia del Pozo J, Carvajal A, Viloria JM, Velasco A, Garcia del Pozo V. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. *Eur J Clin Pharmacol*. 2008;64(4):411-415. doi:10.1007/s00228-007-0419-9

62. Severino AL, Shadfar A, Hakimian JK, et al. Pain Therapy Guided by Purpose and Perspective in Light of the Opioid Epidemic. *Front Psychiatry*. 2018;9(April):119. doi:10.3389/fpsyt.2018.00119

63. *The President's Commission on Combating Drug Addiction and the Opioid Crisis*.; 2017.

64. Bosetti C, Santucci C, Radrezza S, Erthal J, Berterame S, Corli O. Trends in the consumption of opioids for the treatment of severe pain in Europe, 1990–2016. *Eur J Pain*. 2019;23(4):697-707. doi:10.1002/ejp.1337

65. Scholten W. *Access to Opioid Analgesics: Essential for Quality Cancer Care. Cancer Pain.*; 2013. doi:10.1007/978-0-85729-230-19.

66. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Physician*. 2012;15(3 Suppl):ES67-92.

67. Merlin J, Tamhane A, Starrels JL, Kertesz S, Saag M, Cropsey K. Factors Associated with

Prescription of Opioids and Co- prescription of Sedating Medications in Individuals with HIV. *AIDS Behav*. 2016;20(3):687-698. doi:10.1007/s00210-015-1172-8.The

68. Allen MJM, Asbridge MM, MacDougall PC, Furlan AD, Tugalev O. Self-reported practices in opioid management of chronic noncancer pain: A survey of Canadian family physicians. *Pain Res Manag*. 2013;18(4):177-184. doi:10.1155/2013/528645

69. Gomes T, Tadrous M, Mamdani MM, Paterson JM, Juurlink DN. The Burden of Opioid-Related Mortality in the United States. *JAMA Netw Open*. 2018;1(2):e180217. doi:10.1001/jamanetworkopen.2018.0217

70. Gomes T, Mamdani MM, Dhalla IA, Cornish S, Paterson JM, Juurlink DN. The burden of premature opioid-related mortality. *Addiction*. 2014;109(9):1482-1488. doi:10.1111/add.12598

71. Meyer R, Patel AM, Rattana SK, Quock TP, Mody SH. Prescription Opioid Abuse: A Literature Review of the Clinical and Economic Burden in the United States. *Popul Health Manag*. 2014;17(6):372-387. doi:10.1089/pop.2013.0098

72. The Lancet. The opioid crisis in the USA: a public health emergency. *Lancet*. 2017;390(10107):2016. doi:10.1016/S0140-6736(17)32808-8

73. Gouveia N, Rodrigues A, Eusébio M, et al. Prevalence and social burden of active chronic low back pain in the adult Portuguese population: results from a national survey. *Rheumatol Int*. 2015;36(2):1-15. doi:10.1007/s00296-015-3398-7

74. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108. doi:10.3322/caac.21262

75. Hastie BA, Gilson AM, Maurer MA, Cleary JF. An Examination of Global and Regional Opioid Consumption Trends 1980 – 2011. *J Pain Palliat Care Pharmacother*. 2014;28(3):259-275. doi:10.3109/15360288.2014.941132

76. Warner EA. Opioids for the treatment of chronic noncancer pain. *Am J Med*. 2012;125(12):1155-1161. doi:10.1016/j.amjmed.2012.04.032

77. Brooks EA, Unruh A, Lynch ME. Exploring the lived experience of adults using prescription

opioids to manage chronic noncancer pain. *Pain Res Manag*. 2015;20(1):15-22. doi:dx.doi.org/16497

78. Manchikanti L, Pampati V, Damron KS, Fellows B, Barnhill RC, Beyer CD. Prevalence of opioid abuse in interventional pain medicine practice settings: a randomized clinical evaluation. *Pain Physician*. 2001;4(4):358-365.

79. Sullivan MD, Von Korff M, Banta-Green C, Merrill JO, Saunders K. Problems and concerns of patients receiving chronic opioid therapy for chronic non-cancer pain. *Pain*. 2010;149(2):345-353. doi:10.1016/j.pain.2010.02.037.Problems

80. Rosenblum A, Marsch L, Herman J, Russell KP. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Exp Clin Psychopharmacol*. 2008;16(5):405-416. doi:10.1037/a0013628.Opioids

81. Agencia Española de Medicamentos y Productos Sanitarios. *Utilización de Medicamentos Opioides En España Durante El Periodo 2008-2015*.; 2017.

82. Veritas Health Innovation Ltd. Covidence. 2019. www.covidence.org.

83. Moola S, Munn Z, Tufanaru C, et al. Checklist for Analytical Cross Sectional Studies. *Joanna Briggs Inst Rev Man*. 2017:6. doi:10.17221/96/2009-CJGPB

84. Karmali RN, Bush C, Raman SR, Campbell CI, Skinner AC, Roberts AW. Long-term opioid therapy definitions and predictors: A systematic review. *Pharmacoepidemiol Drug Saf*. 2020;29(3):252-269. doi:10.1002/pds.4929

85. Ministerio De Sanidad Consumo y Bienestar Social. Clasificación Internacional Enfermedades (CIE-10-ES). https://eciemaps.mscbs.gob.es/ecieMaps/browser/metabuscador.html. Published 2020. Accessed January 2, 2020.

86. Fain KM, Alexander GC, Dore DD, Segal JB, Zullo AR, Castillo-Salgado C. Frequency and Predictors of Analgesic Prescribing in U.S. Nursing Home Residents with Persistent Pain. *J Am Geriatr Soc*. 2017;65(2):286-293. doi:10.1111/jgs.14512

87. Marschall U, L'hoest H, Radbruch L, Häuser W. Long-term opioid therapy for chronic non-

cancer pain in Germany. *Eur J Pain*. 2015;20(5):767-776. doi:10.1002/ejp.802

88. Kingsbury SR, Gross HJ, Isherwood G, Conaghan PG. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. *Rheumatology (Oxford)*. 2014;53(5):937-947. doi:10.1093/rheumatology/ket463

89. Scala E, Decosterd I, Faouzi M, Burnand B, Rodondi P-Y. Level of readiness of chronic pain patients to practise active self-care. *Eur J Pain (United Kingdom)*. 2018;22(10):1800-1812. doi:10.1002/ejp.1276

90. Wand BM, Catley MJ, Rabey MI, O'Sullivan PB, O'Connell NE, Smith AJ. Disrupted Self-Perception in People With Chronic Low Back Pain. Further Evaluation of the Fremantle Back Awareness Questionnaire. *J Pain*. 2016;17(9):1001-1012. doi:10.1016/j.jpain.2016.06.003

91. Ahn Y-JY-J, Shin J-SJ-S, Lee J-HJJ-H, et al. Evaluation of use and cost of medical care of common lumbar disorders in Korea: cross-sectional study of Korean Health Insurance Review and Assessment Service National Patient Sample data. *BMJ Open*. 2016;6(9):e012432. doi:10.1136/bmjopen-2016-012432

92. Larochelle MR, Zhang F, Ross-Degnan D, et al. Trends in opioid prescribing and co-prescribing of sedative hypnotics for acute and chronic musculoskeletal pain: 2001–2010. *Pharmacoepidemiol Drug Saf*. 2015;24(8):885-892. doi:10.1002/pds

93. Centers for Disease Control and Prevention (CDC) NC for HS (NCHS). United States Department of Health and Human Services (US DHHS). Multiple cause of death 1999–2017. CDC WONDER Online Database. http://wonder.cdc.gov/mcd-icd10.html. Published 2018. Accessed September 15, 2019.

94. Spanish National Statistics Institute. Official website of the Spanish National Statistics Institute.

95. Spanish National Statistics Institute. *Statistics of Deaths According to the Cause of Death. Methodology.*; 2017.

96. World Health Organization (WHO). *ICD-10: International Statistical Classification of*

Diseases and Related Health Problems. Geneva: World Health Organization; 2004.

97. Ahmad O, C B-P, A L. Age standardization of rates: a new WHO standard. GPE Discussion Paper Series: No.31. 2001.

98. Schiller M, Pyszora A, Graczyk M, Gajewska A, Krajnik M. Are the patients afraid of opioids? Pilot study of the patients with chronic cancer and non-malignant pain. *Adv Palliat Med*. 2007;6(4):121-124.

99. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: Concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today*. 2004;24(2):105-112. doi:10.1016/j.nedt.2003.10.001

100. Allen MJM, Asbridge MM, Macdougall PC, Furlan AD, Tugalev O. Self-reported practices in opioid management of chronic noncancer pain: A survey of canadian family physicians. *Pain Res Manag*. 2013;18(4):177-184. doi:10.1155/2013/528645

101. Timmerman L, Stronks DL, Groeneweg JG, Huygen FJ. Prevalence and determinants of medication non-adherence in chronic pain patients: A systematic review. *Acta Anaesthesiol Scand*. 2016;60(4):416-431. doi:10.1111/aas.12697

102. Meineche-Schmidt V, Jensen NH, Sjøgren P. Long-term outcome of multidisciplinary intervention of chronic non-cancer pain patients in a private setting. *Scand J Pain*. 2012;3(2):99-105. doi:10.1016/j.sjpain.2011.10.002

103. Becker N, Sjogren P, Bech P, et al. Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain centre compared to general practice: a randomised controlled trial. *Pain*. 2000;84(2-3):203-211. doi:10.1016/s0304-3959(99)00209-2

104. Observatorio Español de las Drogas y las Adicciones. *Informe 2017: Alcohol, Tabaco y Drogas Ilegales En España.*; 2017.

105. Kaplovitch E, Gomes T, Camacho X, Dhalla IA, Mamdani MM, Juurlink DN. Sex differences in dose escalation and overdose death during chronic opioid therapy: A population-based cohort study. *PLoS One*. 2015;10(8). doi:10.1371/journal.pone.0134550

106. Niesters M, Dahan A, Kest B, et al. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. *Pain*. 2010;151(1):61-68. doi:10.1016/j.pain.2010.06.012

107. Jiménez-Trujillo I, López-de-Andrés A, del Barrio JL, Hernández-Barrera V, Valero-de-Bernabé M, Jiménez-García R. Gender Differences in the Prevalence and Characteristics of Pain in Spain: Report from a Population-Based Study. *Pain Med*. 2019;00(0):1-11. doi:10.1093/pm/pnz004

108. Miller A, Sanderson K, Bruno R, Breslin M, Neil AL. The prevalence of pain and analgesia use in the Australian population: Findings from the 2011 to 2012 Australian National Health Survey. *Pharmacoepidemiol Drug Saf*. 2017;26(11):1403-1410. doi:10.1002/pds.4301

109. Serdarevic M, Striley CW, Cottler LB, Professions H. Gender differences in prescription opioid use. *Curr Opin psychiatry J*. 2017;30(4):238-246. doi:10.1097/YCO.0000000000000337.Gender

110. Reid CM, Gooberman-Hill R, Hanks GW. Opioid analgesics for cancer pain: Symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. *Ann Oncol*. 2008;19(1):44-48. doi:10.1093/annonc/mdm462

111. Holloway I, Sofaer-Bennett B, Walker J. The stigmatisation of people with chronic back pain. *Disabil Rehabil*. 2007;29(18):1456-1464. doi:10.1080/09638280601107260

112. Bäckryd E. "Professional helper" or "helping professional?" the patient–physician relationship in the chronic pain setting, with special reference to the current opioid debate. *J Contin Educ Health Prof*. 2016;36(2):133-137. doi:10.1097/CEH.0000000000000062

113. Lehti A, Fjellman-Wiklund A, Stålnacke BM, Hammarström A, Wiklund M. Walking down 'Via Dolorosa' from primary health care to the specialty pain clinic – patient and professional perceptions of inequity in rehabilitation of chronic pain. *Scand J Caring Sci*. 2017;31(1):45-53. doi:10.1111/scs.12312

ANNEXES

Taylor & Francis
Taylor & Francis Group

Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017: differences between Spain and the United States

Alejandro Salazar, Soledad Moreno, Helena De Sola, Jose Antonio Moral-Munoz, María Dueñas & Inmaculada Failde

To cite this article: Alejandro Salazar, Soledad Moreno, Helena De Sola, Jose Antonio Moral-Munoz, María Dueñas & Inmaculada Failde (2020) The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017: differences between Spain and the United States, Current Medical Research and Opinion, 36:2, 285-291, DOI: 10.1080/03007995.2019.1684251

To link to this article: https://doi.org/10.1080/03007995.2019.1684251

Accepted author version posted online: 22 Oct 2019.
Published online: 06 Nov 2019.

Submit your article to this journal

Article views: 70

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=icmo20

CURRENT MEDICAL RESEARCH AND OPINION
2020, VOL. 36, NO. 2, 285–291
https://doi.org/10.1080/03007995.2019.1684251
Article ST-0322.R1/1684251
All rights reserved: reproduction in whole or part not permitted

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Check for updates

The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017: differences between Spain and the United States

Alejandro Salazar[a,b,c*], Soledad Moreno[d*], Helena De Sola[a,b,e], Jose Antonio Moral-Munoz[a,b,f], María Dueñas[a,b,c] and Inmaculada Failde[a,b,e]

[a]Biomedical Research and Innovation Institute of Cádiz (INiBICA), Cádiz, Spain; [b]The Observatory of Pain Department, University of Cádiz, Cádiz, Spain; [c]Department of Statistics and Operational Research, University of Cádiz, Cádiz, Spain; [d]Department of Mathematics, University of Cádiz, Cádiz, Spain; [e]Preventive Medicine and Public Health Area, University of Cádiz, Cádiz, Spain; [f]Department of Nursing and Physiotherapy, University of Cádiz, Cádiz, Spain

ABSTRACT

Objective: To investigate the evolution of opioid-related mortality and potential years of life lost in Spanish general population from 2008 to 2017. To evaluate the differences between Spain and the US.

Methods: A descriptive study using retrospective annual data from 2008 to 2017 in Spanish and US general population. Information on the population and opioid-related deaths stratified by age and sex was obtained from Spanish National Statistics Institute and the Centers for Disease Control and Prevention (CDC) WONDER Multiple Cause of Death Database, according to the ICD-10 codes. Years of life lost, crude and standardized mortality rates are reported and compared with the results in US.

Results: Crude rate of opioid-related deaths per 10^5 inhabitants has changed from 1.68 in 2008 to 2.25 in 2017 in Spain, with around 30,000 years of life lost per year. The most affected groups were middle-aged men and women over 65, and the main cause of death was accidental poisoning. The standardized rates per 10^5 inhabitants across the years were between 1.19 and 1.62 in Spain and between 11.17 and 20.68 in the US population.

Conclusions: An opioid overuse crisis does not seem a likely scenario in Spain. However, it is a social problem that requires special health surveillance, particularly in middle-aged men and women over 65.

ARTICLE HISTORY
Received 17 June 2019
Revised 21 October 2019
Accepted 21 October 2019

KEYWORDS
Opioid; mortality; years of life lost; Spanish population; US population

Introduction

The prescription and consumption of opioids have changed in many countries in recent years as it is becoming a serious health problem in some cases[1–6]. According to the World Drug Report[7] 2017, 29.5 million people globally suffer from drug use disorders, being opioids the most harmful. The United Nations has warned of an opioid overuse crisis in the USA in 2017, although this is not the only country in which its consumption has increased[1]. In Europe, Bosetti et al.[2] reported an increase in opioids consumption, with relevant differences between countries. Particularly, these authors observed the highest consumption in Western/Northern European countries and the lowest consumption in Southern/Eastern countries. Some authors[2,3] identified an upward trend similar to the USA. Although in the country where the consumption is the highest in Europe (Germany), it is approximately half of the level in the United States[3]. Despite this, a crisis similar to the US is anticipated in other countries such as the United Kingdom in 5 or 10 years[4].

In Spain, data reported by Garcia del Pozo et al.[5] in 2008 revealed a huge increase in opioids consumption at the end of the 20th century and the beginning of the 21st century. More recently, The Spanish Agency for Medicines and Health Products quantified the increase from 7.25 Defined Daily Dose (DDD) per 1,000 inhabitants[6] per day in 2008 to 13.31 in 2015, which represents an increase of 83.59%. However, it is not clear if the situation has worsened in recent years, and there is currently a debate in the scientific community about whether Spain presents a similar trend to the United States, and if we are on the way to a possible overuse crisis.

The aforementioned crisis is not something to be taken lightly, as higher doses of medically prescribed opioids may lead to opioid overdose[8]. This finding challenges the traditional idea that opioid overdose is related to non-medical users[9]. In addition to overdoses, many of the problems associated with the use of opioids, such as addiction, abuse or dependence[4,9–13], greater physical and psychological comorbidities[8,14–18], an increase in opioid-related mortality and potential years of life lost[4,19], have been reported. Some

CONTACT Helena De Sola helena.desolaperea@alum.uca.es Preventive Medicine and Public Health Area, University of Cádiz, Avenida Ana de Viya, 52, 11009, Cádiz, Spain
*Both contributed equally to the writing of the article.
This article was originally published with errors, which have now been corrected in the online version. Please see Correction (http://dx.doi.org/10.1080/03007995.2019.1705005).

© 2019 Informa UK Limited, trading as Taylor & Francis Group

authors even report that the risks of opioids outweigh the benefits[4,20], and the opioid abuse can have clinical and economic consequences in the society, including patients, health care professionals, and the government[14].

Meyer et al.[14] have estimated a cost of $55.7 billion attributable to prescription opioid abuse in 2007 as well as an increase of 124% in the rate of unintentional overdose deaths. This increase has been observed by other authors, particularly in the USA and Canada[19,21], being a problem that affects especially people aged 25–44[21]. This fact aggravates the situation in terms of early loss of life. Few studies have reported the data on years of life lost (YLL), either globally[22] or in the United States specifically[10,19], where it has been estimated at 830,652 YLL among people younger than 65 years in 2008. However, to the best of our knowledge, there are no studies in Spain analyzing this, even though YLL is an indicator of great importance in this context, as it quantifies the costs of opioid-related deaths (ORD).

As the situation in the USA has been described as alarming, and there is evidence that some countries could be on the same path, it is important to know the situation in a country like Spain, where an increase in opioid consumption has been observed, and a similar tendency might be plausible. Replicating in Spain the results obtained by Gomes et al.[19] in the US would allow us to compare the situation and can prevent a possible overuse problem.

In view of the above, we aimed to investigate the evolution of opioid-related mortality and potential years of life lost in Spanish general population from 2008 to 2017 and to compare it by gender and age. We also aimed to know the differences between Spain and the USA.

Methods

This is a descriptive study using the retrospective annual data from 2008 to 2017 in the Spanish general population. It is based on the methodology previously used by Gomes et al.[19] in the USA to compare populations.

Information on the population and ORD stratified by age and sex was obtained from the Centers for Disease Control and Prevention (CDC) WONDER Multiple Cause of Death Database for the USA[23], and the Spanish National Statistics Institute (INE, for its acronym in Spanish) for Spain[24].

The INE carries out the "Statistics of deaths according to the cause of death[25]" following the criteria established by the WHO in the International Classification of Diseases (ICD-10)[26], which includes more than 12,000 diseases. This statistic provides information on mortality according to the basic cause of death and its distribution by sex and age, among other factors. A similar methodology is used by the CDC.

From these data, and according to the ICD-10 codes[26], we retrieved information on ORD specifically due to accidental poisoning (X40–X44), intentional self-inflicted poisoning (X60–X64), aggression (X85), and poisoning of not determined intention (Y10–Y14).

For each year (from 2008 to 2017), we report stratified (by sex and age) data on number of ORD, crude and standardized rates of ORD per 10^5 inhabitants, years of life lost (YLL), YLL per 10^4 inhabitants, number of deaths by type of opioid-related death. Crude rate of ORD is defined as the quotient between the number of ORD and the total population, expressed in terms of number of deaths per 10^5 inhabitants. YLL are defined as the sum of the remaining years that a person who has prematurely died due to opioids has not lived, that is, the sum of the difference of life expectancy and the age of death of each person who has prematurely died due to opioids. Type of opioid-related death is a qualitative variable classifying the deaths in accidental poisoning, intentional self-inflicted poisoning, aggression, and poisoning of not determined intention. The data presented are tabulated in absolute terms and crude rates. We report the number of deaths by type of death and year in Spain, for the total population, men and women separately, in bar plots.

The evolution over time of the standardized rates of ORD in total population, men and women, is presented in a line chart for both Spain and the USA. For this comparison, we standardized the data taking into account the different distribution of the two populations by ages. For this standardization, the direct method was used: the rate of each stratum in each population was applied to the world standard population provided by the WHO[27] to obtain data on the expected deaths, which were subsequently added and divided by the total standard population to obtain the standardized rates per 10^5 inhabitants. We report these standardized rates in a line chart. All the analyses and figures were performed using the software Excel 2016.

Results

Opioid-related deaths and years of life lost in Spain due to opioids in the period 2013–2016

Between 2008 and 2017, a total of 8506 people died due to opioids, including accidental poisoning, intentional self-inflicted poisoning, aggression, and poisoning of not determined intention (Tables 1 and 2). The cost, in terms of YLL, was 290,093.33 years (Tables 3 and 4).

The crude rate of ORD per 10^5 inhabitants in the whole population has fluctuated (around 2) over the years (from 1.68 in 2008 to 2.25 in 2017), showing a slight upward trend in men from 2011 to 2017, and in women in the whole period Crude rates in men are always above crude rates in women (around 1 point above) (Tables 1 and 2).

The most affected age groups were, in almost all the cases, 35–44 and 45–54, but the increase of the crude rates in the group of 65 or more years (from 1.25 in 2008 to 3.8 in 2017) is remarkable. In this regard, we observed differences between men and women, with men most affected in the age group 35–54, and women in the age group over 65 (Tables 1 and 2).

Regarding the YLL, we further observed a fluctuant situation, with a minimum of 24,497.35 YLL in 2011 and a maximum of 32,648.99 in 2016 in the whole population (Tables 3 and 4). Nevertheless, it was different between men and women. In particular, men lost more years of life, even more than twice than the women in most cases. The largest amounts of YLL were observed in the age group 35–44 (Tables 3 and 4).

Table 1. Opioid-related deaths (ORD) in Spain in the period 2008–2012.

	2008		2009		2010		2011		2012	
	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)
					Total					
0–14	0	0	0	0	1	0.01	2	0.03	0	0
15–24	42	0.82	37	0.74	23	0.47	25	0.53	30	0.64
25–34	160	0.21	146	1.92	107	1.45	96	1.36	106	1.57
35–44	295	3.87	244	3.16	248	3.17	196	2.48	231	2.91
45–54	135	2.17	131	2.04	146	2.21	152	2.24	164	2.38
55–64	44	0.89	43	0.86	45	0.89	58	1.13	51	0.97
≥65	95	1.25	95	1.23	121	1.53	186	2.31	230	2.81
Total	771	1.68	696	1.5	691	1.48	715	1.53	812	1.74
					Man					
0–14	0	0	0	0	1	0.03	2	0.06	0	0
15–24	37	1.41	24	0.94	17	0.68	19	0.78	20	0.84
25–34	122	3.04	119	3.03	83	2.2	76	2.1	87	2.54
35–44	239	6.11	189	4.76	201	5.01	155	3.82	180	4.42
45–54	101	3.24	88	2.73	97	2.93	99	2.92	112	3.24
55–64	23	0.96	24	0.98	26	1.05	36	1.43	31	1.21
≥65	47	1.46	44	1.34	49	1.46	68	1.98	80	2.28
Total	569	2.5	488	2.13	474	2.06	455	1.97	510	2.21
					Woman					
0–14	0	0	0	0	0	0	0	0	0	0
15–24	5	0.2	13	0.53	6	0.25	6	0.26	10	0.44
25–34	38	1.02	27	0.73	24	0.67	20	0.58	19	0.57
35–44	56	1.51	55	1.46	47	1.24	41	1.07	51	1.32
45–54	34	1.09	43	1.34	49	1.48	53	1.57	52	1.51
55–64	21	0.83	19	0.74	19	0.73	22	0.84	20	0.75
≥65	48	1.1	51	1.15	72	1.59	118	2.56	150	3.21
Total	202	0.87	208	0.89	217	0.92	260	1.1	302	1.27

Abbreviation. ORD, Opioid-related deaths.

Table 2. Opioid-related deaths (ORD) in Spain in the period 2013–2017.

	2013		2014		2015		2016		2017	
	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)	ORD	ORD per 10^5 inhabitants (crude rates)
					Total					
0–14	2	0.03	1	0.01	1	0.01	2	0.03	0	0
15–24	19	0.42	13	0.29	14	0.31	22	0.49	19	0.42
25–34	109	1.7	96	1.59	86	1.49	115	2.07	95	1.76
35–44	233	2.95	234	2.98	199	2.55	226	2.93	211	2.77
45–54	203	2.91	274	3.88	207	2.9	229	3.17	249	3.41
55–64	76	1.43	106	1.95	100	1.8	114	2	138	2.36
≥65	213	2.55	264	3.1	320	3.71	294	3.36	337	3.8
Total	855	1.84	988	2.13	927	2	1002	2.16	1049	2.25
					Man					
0–14	1	0.03	0	0	1	0.03	0	0	0	0
15–24	15	0.64	11	0.48	9	0.39	14	0.61	9	0.39
25–34	78	2.42	74	2.43	68	2.35	95	3.41	69	2.55
35–44	164	4.05	177	4.41	149	3.75	173	4.41	163	4.24
45–54	144	4.11	202	5.71	138	3.86	170	4.69	188	5.12
55–64	42	1.61	61	2.3	55	2.02	69	2.47	68	2.37
≥65	89	2.49	95	2.6	125	3.36	123	3.25	140	3.64
Total	533	2.32	620	2.71	545	2.39	644	2.82	637	2.79
					Woman					
0–14	1	0.03	1	0.03	0	0	2	0.06	0	0
15–24	4	0.18	2	0.09	5	0.23	8	0.37	10	0.46
25–34	31	0.98	22	0.73	18	0.62	20	0.72	26	0.96
35–44	69	1.79	57	1.48	50	1.3	53	1.39	48	1.28
45–54	59	1.69	72	2.05	69	1.94	59	1.64	61	1.68
55–64	34	1.25	45	1.62	45	1.59	45	1.54	70	2.34
≥65	124	2.6	169	3.48	195	3.97	171	3.44	197	3.91
Total	322	1.36	368	1.56	382	1.62	358	1.51	412	1.74

Abbreviation. ORD, Opioid-related deaths.

Table 3. Years of Live Lost (YLL) due to opioids in Spain in the period 2008–2012.

	2008		2009		2010		2011		2012	
	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants
					By age group					
0–14	0.00	0.00	0.00	0.00	75.63	0.11	151.54	0.22	0.00	0.00
15–24	2,603.73	5.10	2,306.89	4.62	1,443.50	2.97	1,574.01	3.32	1,889.52	4.06
25–34	8,370.63	10.78	7,674.06	10.08	5,657.19	7.68	5,088.81	7.18	5,615.70	8.30
35–44	12,657.91	16.61	10,541.44	13.64	10,800.52	13.82	8,568.21	10.84	10,092.01	12.71
45–54	4,550.07	7.30	4,447.10	6.92	5,000.57	7.56	5,223.96	7.71	5,626.38	8.15
55–64	1,089.56	2.21	1,074.44	2.15	1,138.70	2.25	1,476.01	2.87	1,294.71	2.47
≥65	1,190.11	1.57	1,205.92	1.56	1,561.71	1.98	2,414.82	3.00	2,955.54	3.61
					By gender					
Man	21,977.12	9.66	18,765.91	8.18	17,654.14	7.67	16,228.49	7.03	18,154.62	7.87
Woman	7,407.21	3.19	7,639.36	3.26	7,210.96	3.06	7,583.77	3.20	8,564.92	3.61
					Total					
Total	30,462.00	6.62	27,249.83	5.88	25,677.82	5.51	24,497.35	5.24	27,473.87	5.87

Abbreviation. YLL, Years of Live Lost.

Table 4. Years of Live Lost (YLL) due to opioids in Spain in the period 2013–2017.

	2013		2014		2015		2016		2017	
	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants	YLL	YLL per 10^4 inhabitants
0–14	152.24	0.22	76.19	0.11	75.87	0.11	152.43	0.22	0.00	0.00
15–24	1,206.36	2.65	827.88	1.84	888.62	1.99	1,406.37	3.15	1,214.86	2.70
25–34	5,824.50	9.12	5,146.52	8.5	4,591.01	7.94	6,191.30	11.12	5,118.01	9.46
35–44	10,277.67	13.00	10,348.39	13.16	8,739.63	11.20	10,006.58	12.96	9,327.29	12.26
45–54	7,047.15	10.09	9,544.52	13.52	7,149.82	10.02	7,998.02	11.08	8,687.54	11.88
55–64	1,964.76	3.68	2,756.76	5.08	2,573.70	4.63	2,976.85	5.21	3,596.44	6.15
≥65	2,817.79	3.38	3,511.56	4.13	4,159.42	4.82	3,917.45	4.48	4,459.99	5.02
Man	18,432.66	8.04	20,936.35	9.17	17,447.98	7.65	21,591.94	9.47	20,318.22	8.90
Woman	10,168.49	4.30	10,411.95	4.41	10,114.68	4.28	10,161.33	4.30	11,341.08	4.78
Total	29,289.47	6.29	32,211.82	6.93	28,178.05	6.07	32,648.99	7.03	32,404.13	6.96

Abbreviation. YLL, Years of Live Lost.

Number of deaths by the type of opioid-related death and year

Most of the deaths had a well-defined cause, with only a few cases due to poisoning of not determined intention (Y10–Y14). In addition, as the years went by, the number of indeterminate cases decreased. Aggression (X85) was the least frequent cause of all (Figures 1(A,B)).

In the total population, the main cause was accidental poisoning, followed by intentional self-inflicted poisoning. When analyzing by sex, the number of deaths due to intentional self-inflicted poisoning was similar in men and women, but a substantial difference in accidental poisoning was evident. Specifically, the number of deaths was higher in men compared with women (Figures 1(A,B)).

Comparison of opioid-related mortality between US and Spanish population in 2016

After the standardization of the rates, we observed a better situation in Spain than the USA (Figure 2). In the total population, the standardized rates per 10^5 inhabitants across the years were between 1.19 and 1.62 in Spain and between 11.17 and 20.68 in US population. This difference was even more evident for men, and slightly lower (but still relevant) for women. A greater increase in US standardized rates in recent years was observed, compared to the slight increase in Spain after standardization. (Figure 2).

Discussion

In this study, we have analyzed the ORD in terms of the evolution of opioid-related mortality and potential years of life lost in Spain in the previous years. We have performed a comparison between Spain and the USA. Generally, our results reflect a better situation in Spain than in the USA, although we cannot ignore the upward trend in the opioid-related mortality and the years of life lost.

Specifically, we found between 691 and 1049 deaths per year. Given the data on the considerable increase in the prescription and consumption of opioids previously reported[5,6], a greater increase in associated mortality could be expected; however, the increase is not a significant reason for concern.

The worst evolution has been observed in men in the study of Gomes et al.[19], and this pattern is repeated in the rest of the results. Gomes et al also point out that the burden of ORD is higher among men, and our results confirm that in Spain as well. The number of YLL is worrisome in the whole population, but especially in men. According to the Spanish Report on alcohol, tobacco and illegal drugs[28] 2017, the main psychoactive substances responsible for deaths in recent years are hypnosedatives and opioids, followed by

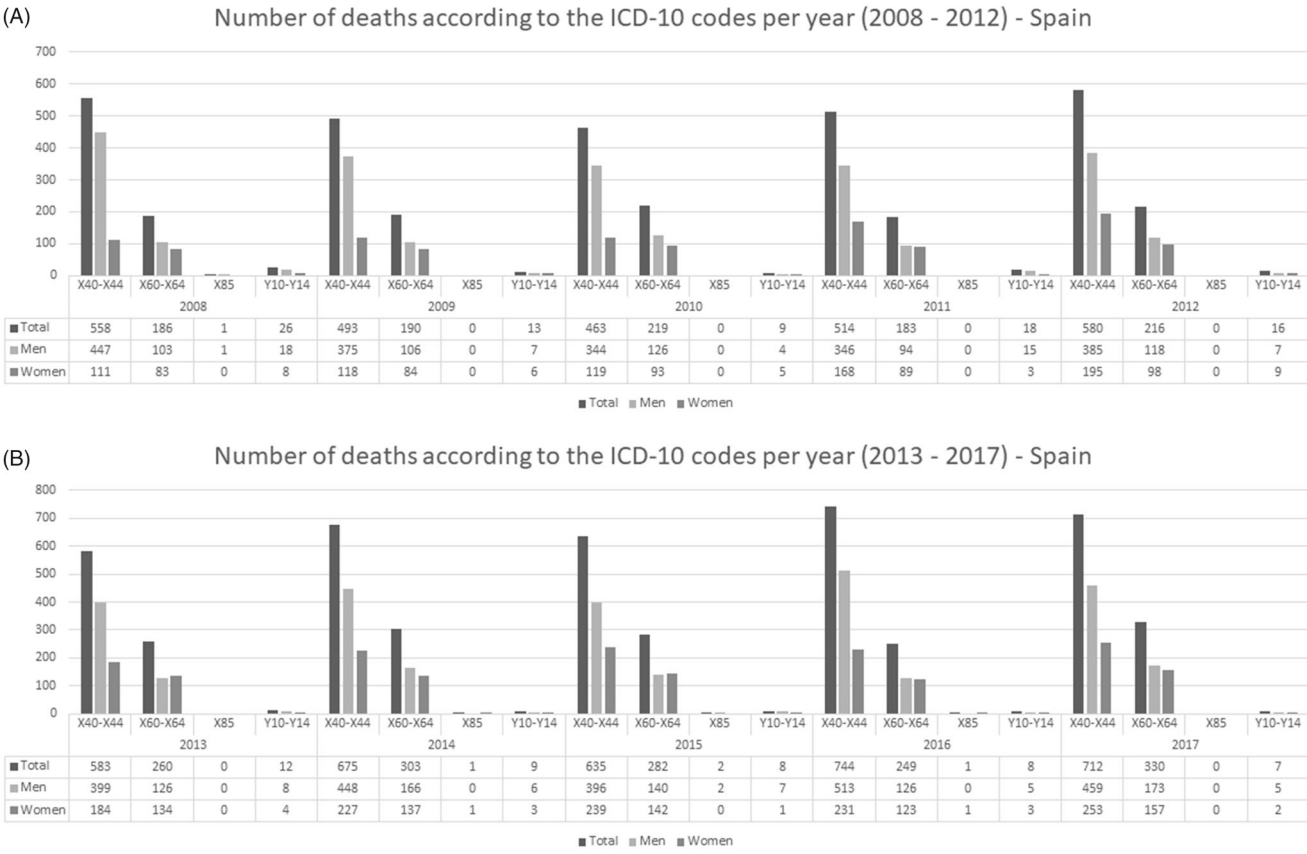


Figure 1. (A) Number of deaths according to the ICD-10 codes per year (2008–2012) – Spain. (B) Number of deaths according to the ICD-10 codes per year (2013–2017) – Spain. Abbreviations. ICD, International Classification of Diseases; X40–X44, Accidental poisoning; X60–X64, Intentional self-inflicted poisoning; X85, Aggression; Y10:Y14, Poisoning of not determined intention.

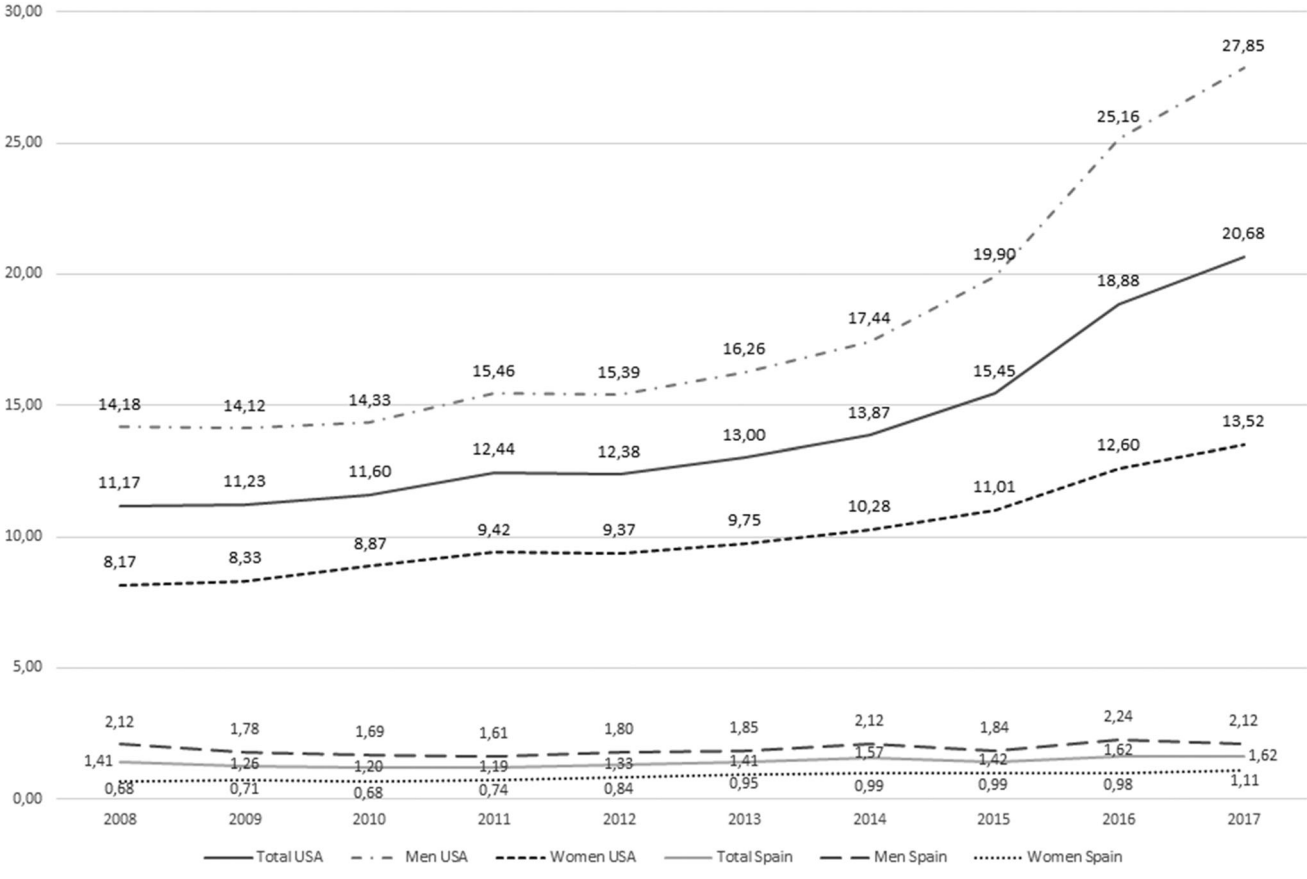


Figure 2. Comparison of the evolution of the standardized rates of opioid related deaths (ORD per 10^5) in Spain and US by gender.

cocaine and alcohol, the latter in a lesser proportion. In more than half of the deaths in which toxicological information was collected, opioids were involved. However, the report does not specify if it was the main cause of death. In any case, this means that we must pay special attention to the consumption of opioids, as these are involved in many deaths, and our data identify these as the main cause of death. Historically, addiction to opioids has always been higher in men. In addition, it has been shown that men are more likely to increase the dose of opioid therapy compared with women[29], which is in line with our results. However, recently, there is more controversy in this regard, with higher levels of addiction in women in some cases[30–33].

Regarding the differences by age, we observed that the most affected ages were 35–54, similar to the US population[19]. However, in the group over 55 in the USA, an increase in the rates has been observed. This was also observed in our data in Spain in some of the studied years, mostly in women. It could be argued that this is due to the greater use of these drugs in cases of terminal diseases, although it must be taken into account that the registered main cause of these deaths is not the disease, but the opioid. Besides, this would not explain the gender differences. The prevalence of chronic pain is higher in women of this age group[34], with opioids being one of the most used treatments for pain[35]. A systematic review published on sex differences in opioid effect on pain[36] has found that side effects such as emesis and respiratory depression, the latter often related to an eventual death[37], are more pronounced in women. However, there is limited information on gender differences in opioid use risk factors, and a more in-depth study is required to identify whether this could explain the observed differences in mortality in women of this age group.

The main cause of death was accidental poisoning, not intentional poisoning. Roxburgh et al.[38] have reported that the increase in opioid deaths was mainly caused by accidental overdoses in the Australian population, and some authors also found an increased risk of accidental death in the case of co-prescription[37]. A previous study found that even the single prescription of opioids is associated with the risk of future ORD[29]. Therefore, it is important to emphasize education and rationalize the use of these drugs to prevent accidents, as suggested by other authors[37,38], especially in men whose death rates are higher compared with women in Spain.

The comparison of the standardized rates of opioid-related mortality between Spain and the USA is significant. Even after standardization, the ratios are clearly different between the countries, 8–12 times higher in the USA compared with Spain, depending on the year (the more recent, the greater the difference), and this difference is more pronounced in men, in accordance with the results by Gomes et al.[19] In this regard, Bosetti et al. have reported that the Southern and Eastern European countries (Spain included) have the lowest consumption[2], which would imply, *a priori*, a lower risk. Additionally, a recent study of Chen et al. shows that, in Europe, the most concerning increases in drug overdose deaths from opioids have been observed in the northern countries such as Estonia, largely caused by fentanyl[39]. The previous considerations indicate that, despite the increase in mortality, the situation in Spain is far different from the situation in the United States or some other countries[2–4].

Finally, we have to point out some limitations of this study. The use of secondary data is always a potential limitation, although the data were collected exactly as we needed for the purpose of the study, with precise definitions using ICD-10 codes. In addition, the data were obtained from reliable sources. However, the reliability of the determination and coding of the cause of death depends on each professional in each of the deaths, and not on the data source itself. Because of this, we believe that there is a possibility of underestimating the number of ORD, as in some cases this information may be omitted to avoid legal or administrative issues, especially in the case of accidents. Among the strengths of our study, we highlight the comparison between countries, as it provides information whether the situation in Spain is similar to the situation in the USA. Finally, the importance of the subject addressed here is another strength of the study.

Conclusion

The crude rate of ORD per 10^5 inhabitants has changed from 1.68 in 2008 to 2.25 in 2017 in Spain, with around 30,000 years of life lost per year, being middle-aged men and women over 65 the most affected groups. The standardized rates in US population are 8–12 times higher compared to standardized rates in Spain. An opioid overuse crisis does not seem a likely scenario in Spain. However, it is a social problem that requires special health surveillance, particularly in middle-aged men and women over 65.

Transparency

Declaration of funding

This work was supported by The Grünenthal Foundation, a private non-profit making organization that promotes the dissemination of scientific knowledge and supports research. This organization did not have any involvement in the design of the study and collection, analysis and interpretation of data or writing the manuscript.

Declaration of financial/other relationships

The authors and CMRO peer reviewers declare that they have no conflicts of interest.

Author contributions

IF conceived the idea of the project. The fieldwork was performed by AS, JMM, and MD. AS and SM performed the statistical analysis. AS and HDS were mainly responsible for writing the manuscript. IF and SM were involved in revising the content. All the authors approved the final version of the manuscript.

Acknowledgements

None reported.

ORCID

Alejandro Salazar http://orcid.org/0000-0001-9567-462X
Helena De Sola http://orcid.org/0000-0003-0196-4875
Jose Antonio Moral-Munoz http://orcid.org/0000-0002-6465-982X
María Dueñas http://orcid.org/0000-0003-4822-7258
Inmaculada Failde http://orcid.org/0000-0002-6603-3054

References

[1] Ballantyne JC. Opioids for the treatment of chronic pain. Anesth Analg. 2017;125(5):1769–1778.
[2] Bosetti C, Santucci C, Radrezza S, et al. Trends in the consumption of opioids for the treatment of severe pain in Europe, 1990–2016. Eur J Pain. 2019;23(4):697–707.
[3] Turmina Fontanella A, Goulart Molina-Bastos C, da Silva Dal Pizzol T, et al. Too much or too little opioid use? Eur J Pain. 2019;23(4):639–640.
[4] Dhalla I, Persaud N, Juurlink D. Facing up to the prescription opioid crisis. Br Med J. 2011;343(1):d5142.
[5] Garcia del Pozo J, Carvajal A, Viloria JM, et al. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. Eur J Clin Pharmacol. 2008;64(4):411–415.
[6] Agencia Española de Medicamentos y Productos Sanitarios. Utilización de medicamentos opioides en España durante el periodo 2008–2015. Madrid, Spain; 2017.
[7] United Nations Office on Drugs and Crime. World drug report 2017. Vienna, Austria: United Nations publications; 2017.
[8] Dunn KM, Saunders KW, Rutter CM, et al. Overdose and prescribed opioids: Associations among chronic non-cancer pain patients. Ann Intern Med. 2010;152(2):85–92.
[9] Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA. 2008;300(22):2613–2620.
[10] Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers-United States, 1999–2008. MMWR. 2011;60:1487–1492.
[11] Florence CS, Zhou C, Luo F, et al. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med Care. 2016;54(10):901–906.
[12] Webster F, Bremner S, Oosenbrug E, et al. From opiophobia to overprescribing: a critical scoping review of medical education training for chronic pain. Pain Med. 2017;18(8):1467–1475.
[13] Gomes T, Mamdani MM, Dhalla IA, et al. The burden of premature opioid-related mortality. Addiction. 2014;109(9):1482–1488.
[14] Meyer R, Patel AM, Rattana SK, et al. Prescription opioid abuse: a literature review of the clinical and economic burden in the United States. Popul. Health Manag. 2014;17(6):372–387.
[15] Buse DC, Pearlman SH, Reed ML, et al. Opioid use and dependence among persons with migraine: results of the AMPP study. Headache. 2012;52(1):18–36.
[16] McAdam-Marx C, Roland CL, Cleveland J, et al. Costs of opioid abuse and misuse determined from a Medicaid database. J Pain Palliat Care Pharmacother. 2010;24(1):5–18.
[17] Cicero TJ, Wong G, Tian Y, et al. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: data from an insurance claims database. Pain. 2009;144(1):20–27.
[18] White AG, Birnbaum HG, Mareva MN, et al. Direct costs of opioid abuse in an insured population in the United States. J Manag Care Pharm. 2005;11(6):469–479.
[19] Gomes T, Tadrous M, Mamdani MM, et al. The burden of opioid-related mortality in the United States. JAMA Netw Open. 2018;1(2):e180217.
[20] Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med. 2010;170(22):1968–1976.
[21] Rudd RA, Seth P, David F, et al. Increases in drug and opioid-involved overdose deaths – United States, 2010–2015. MMWR Morb Mortal Wkly Rep. 2016;65(5051):1445–1452.
[22] Degenhardt L, Charlson F, Mathers B, et al. The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. Addiction. 2014;109(8):1320–1333.
[23] United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS) [Internet]. Multiple cause of death 1999–2017. CDC WONDER Online Database, released 2018. Georgia; 2018 [cited 2019 Feb. 22]. Available from: http://wonder.cdc.gov/mcd-icd10.html.
[24] Spanish National Statistics Institute. Official website of the Spanish National Statistics Institute [Internet]. Madrid; 2018 [cited 2019 Oct. 23]. Available from: http://www.ine.es/.
[25] Spanish National Statistics Institute. Statistics of deaths according to the cause of death. Methodology. [Internet]. Madrid; 2017 [cited 2019 Oct. 23]. Available from: https://www.ine.es/daco/daco42/sanitarias/metodologia_00.pdf.
[26] World Health Organization (WHO). ICD-10: International statistical classification of diseases and related health problems. Geneva: World Health Organization; 2004.
[27] Ahmad O, Boschi-Pinto C, Lopez A, et al. Age standardization of rates: a new WHO standard. GPE Discussion Paper Series: No.31. 2001.
[28] Observatorio Español de las Drogas y las Adicciones. Informe 2017: Alcohol, Tabaco y Drogas ilegales en España. 2017.
[29] Kaplovitch E, Gomes T, Camacho X, et al. Sex differences in dose escalation and overdose death during chronic opioid therapy: a population-based cohort study. PLOS One. 2015;10(8):e0134550.
[30] Chartoff EH, McHugh RK. Translational studies of sex differences in sensitivity to opioid addiction. Neuropsychopharmacol. 2016;41(1):383–384.
[31] Becker JB, Mazure CM. The federal plan for health science and technology's response to the opioid crisis: understanding sex and gender differences as part of the solution is overlooked. Biol Sex Differ. 2019;10(1):1.
[32] Carew AM, Comiskey C. Treatment for opioid use and outcomes in older adults: a systematic literature review. Drug Alcohol Depend. 2018;182:48–57.
[33] Jacobs AA, Cangiano M. Medication-assisted treatment considerations for women with opiate addiction disorders. Prim Care. 2018;45(4):731–742.
[34] Dueñas M, Salazar A, Ojeda B, et al. A nationwide study of chronic pain prevalence in the general spanish population: identifying clinical subgroups through cluster analysis. Pain Med. 2015;16(4):811–822.
[35] de Sola H, Salazar A, Dueñas M, et al. Opioids in the treatment of pain. Beliefs, knowledge, and attitudes of the general Spanish population. Identification of subgroups through cluster analysis. J Pain Symptoms Manag. 2018;55(4):1095–1104.
[36] Niesters M, Dahan A, Kest B, et al. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. Pain. 2010;151(1):61–68.
[37] Gomes T, Juurlink DN, Antoniou T, et al. Gabapentin, opioids, and the risk of opioid-related death: a population-based nested case-control study. PLOS Med. 2017;14(10):e1002396.
[38] Roxburgh A, Hall WD, Dobbins T, et al. Trends in heroin and pharmaceutical opioid overdose deaths in Australia. Drug Alcohol Depend. 2017;179:291–298.
[39] Chen Y, Shiels MS, Thomas D, et al. Premature mortality from drug overdoses: A comparative analysis of 13 organisation for economic co-operation and development member countries with high-quality death certificate data, 2001 to 2015. Ann Intern Med. 2019;170(5):352–354.

Original Article

Opioids in the Treatment of Pain. Beliefs, Knowledge, and Attitudes of the General Spanish Population. Identification of Subgroups Through Cluster Analysis

Helena de Sola, MSc, Alejandro Salazar, PhD, María Dueñas, PhD, and Inmaculada Failde, PhD

Preventive Medicine and Public Health Area (H.d.S., I.F.), University of Cádiz, Cádiz; The Observatory of Pain (External Chair of Pain) (H.d.S., A.S., M.D., I.F.), University of Cádiz, Cádiz, Grünenthal Foundation-University of Cádiz, Cádiz; Institute of Research and Innovation in Biomedical Sciences of the Province of Cádiz (INIBICA) (H.d.S., A.S., M.D., I.F.), Cádiz; and Department of Statistics and Operational Research (A.S., M.D.), University of Cádiz, Cádiz, Spain

Abstract

Context. A lack of information has been found related to patients' perception toward pain management.

Objectives. To analyze the point of view of the general Spanish population regarding the use of opioids in pain treatment. To identify groups of individuals based on this information.

Methods. Nationwide cross-sectional study on a representative sample of 1299 Spanish adults. Data were collected on beliefs, knowledge, fears, opinions, and attitudes toward the use of opioids. A cluster analysis to identify groups of people based on these parameters and a multinomial logistic regression model to analyze the variables related to the clusters were performed.

Results. Three groups of subjects were identified based on their perspective toward opioids: a first group with a positive point of view ($N = 448$) composed of people older than 65 years who would accept a treatment if prescribed and who were less fearful of these drugs; a second group with a moderate point of view ($N = 337$) formed by younger subjects with university education, better informed about opioids, afraid of these drugs (odds ratio [OR] 2.67), and more frequently associated them with drowsiness (OR 2.58), nausea (OR 3.04), and tolerance (OR 2.16); and a third group with a negative point of view ($N = 468$), with lower educational level who would more often reject treatment with opioids, more afraid of them (OR 3.95), considering that they may not be able to stop the treatment (OR 3.04) and may produce tolerance (OR 3.03).

Conclusion. The different perspectives of patients regarding the use of opioids to treat pain should be taken into consideration by the physician when designing strategies to inform patients about the treatment of pain with opioids. This should promote their correct use, specially preventing their misuse. J Pain Symptom Manage 2018;55:1095–1104. © *2017 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Opioids, beliefs, knowledge, attitudes, opiophobia, epidemiology

Introduction

Opioids are drugs that are widely used in pain treatment worldwide and that the World Health Organization considers essential for the control of moderate and intense pain, particularly of oncological origin.[1] For some years now, awareness has been on the rise regarding the treatment of pain in Spain because of the progressive increase in the number of pain units in hospitals and of the enhanced emphasis on pain management in the palliative care. Likewise, the prescription and use of opioids increased between 2008 and 2015 in Spain[2] but

Address correspondence to: Alejandro Salazar, PhD, Edificio Ciencias de la Salud, Universidad de Cádiz, Avda. Ana de Viya 52, 11009 Cádiz, Spain. E-mail: alejandro.salazar@uca.es

Accepted for publication: December 6, 2017.

© 2017 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2017.12.474

without reaching the levels observed in other European countries like Denmark.[3]

Several studies have shown that some patients consider that the medical prescription of opioids is sometimes associated with terminal illness and imminent death.[4] Likewise, these drugs have also been related to negative side effects, such as excessive sedation, respiratory failure, urinary retention, or constipation, among others.[5] This situation along with social, cultural, and historical factors[6] has led to what is known as opiophobia, a set of inappropriate attitudes and beliefs regarding the deleterious effects of opioid administration for pain relief.[7] This has been related to reduced prescription of these drugs by health professionals and lower consumption by patients.[8]

By contrast, in other countries where the prescription of opioids has risen considerably in recent years, it has been reported that between 24.0% and 37.1% of the patients with chronic pain may often misuse these drugs (defined as the use of any addictive drug in a manner other than how it is indicated or prescribed),[9] which has raised some alarm among this population.[10] This situation has led to the need to identify patients at risk and to monitor their behavior more closely.[11]

In view of the differences observed in studies into the viewpoints of patients regarding the use of opioids to treat pain, we conducted a population-based survey to determine the current beliefs, opinions, and attitudes of the Spanish population toward opioid use in the treatment of pain. We set out to identify groups of individuals based on their point of view regarding these drugs and to analyze the factors that influence this perspective in each of the identified groups.

Methods

This cross-sectional study was carried out on a representative sample of the general adult population in Spain, obtained using a multistage stratified sampling method. The eligible population consisted of individuals aged 18 years and older who resided in households with a landline telephone, who agreed to participate in the study, and who were able to complete the questionnaire. The exclusion criteria were individuals younger than 18 years, lack of a landline telephone at home, or the inability to respond to the questionnaire.

Sampling Method

The Spanish territory was divided into eight strata or areas based on geographical and historical boundaries. For each stratum, 20 municipalities were randomly selected, taking into account the Spanish rural/urban ratio of 25:75 and considering municipalities with less than 10,000 inhabitants as rural and those with more than 10,000 inhabitants as urban areas.

The total number of subjects required for the study (see the following) was distributed in proportion to the size of each municipality. In addition, the number of subjects was divided into six strata, according to the sex and age distribution of the population (18−44, 45−64, and 65 or older). The selected individuals were contacted through their landline telephone using the Infobel España Office version 7.1 digital telephone directory (Kapitol SA/NV, Brussels, Belgium). This directory includes the telephone numbers of 90% of all Spanish households with a landline telephone, and considering that 80.6% of Spanish households have a landline telephone, we had access to 72.5% of the eligible Spanish population.

Sample Size

The sample size was determined based on the study of Schiller et al.,[4] in which it was estimated that 50% of subjects were afraid of taking morphine. Setting a significance level of 95% and a precision level of 5%, the required sample size was established as 1155 subjects. To guarantee the number of subjects calculated and considering the response rate in a previous study involving a telephone survey,[12] the amount of telephone numbers randomly selected was three times that of the required sample size.

Procedure and Instruments

Data were collected via a computer-assisted telephone interview using the Skype and the SurveyMonkey platforms, whereby the interviewers recorded the data while the interview was being conducted. The interviewers received training on the purpose of the study, the working protocol, and on the use of the SurveyMonkey platform. In addition, data collection was coordinated and supervised on a daily basis by a member of the research team, addressing any problems that had arisen. Before the interview, all subjects included in the study gave their informed consent, and the study was conducted in accordance with the Declaration of Helsinki, using standard working procedures and protocols.

Survey Structure and Topic

The survey was structured in six blocks of questions: the first block was designed to obtain personal information; the second block was related to the respondents' beliefs about opioids, and in this case the information was collected from an open-ended question in which the interviewees were asked what was the first thing that came to mind when they heard the word opioid; the third block revealed the level of the respondent's contact with opioids and their knowledge of them; the fourth block explored the fears (side effects, death, becoming an addict, not

achieving the desired results, and death) related to the intake of opioids; the fifth block collected the opinions of the responder regarding this type of treatment (tolerance, dependence, and severity of the disease); and the sixth block addressed the responders' attitude toward these drugs. This attitude was obtained by means of a question that asked whether the respondent would agree to treatment with this medication or not if their doctor prescribed it. The questions that set out to collect information about beliefs, fears, and opinions were assessed using a five-point Likert scale (not at all, a little, some, quite a lot, and a lot).

To facilitate the analysis and interpretation of the results, three new variables were created. The first variable was designated as the level of contact with the treatment, and it was constructed using three questions that referred to the drugs tramadol, morphine, tapentadol, oxycodone, fentanyl, and buprenorphine. The questions were as follows:

1. "*Are you currently following a treatment with any of these opioids?*" If the answer was affirmative, we considered the respondent to have maximal contact with opioids.
2. "*Have you ever been treated with any of these opioids?*" If the answer was affirmative, we considered the respondent to have medium contact with opioids.
3. "*Do you know anyone who is currently or has ever been treated with an opioid?*" If the answer was affirmative, we considered the respondent to have minimal contact, whereas they were considered as having no contact if the response was negative.

A second variable, level of opiophobia, was established based on four questions gathering information about the individual's fear of side effects, becoming an addict, not achieving the desired results, and death. The responses to these questions were categorized on a scale ranging from 0 = not at all to 4 = a lot. The final score of this new variable was the sum of the scores given on a scale from 0 to 16, where 0 is equivalent to no opiophobia and 16 corresponded to maximal opiophobia.

In addition, to determine the respondents' knowledge about the opioids indicated previously, a third variable was created that we called correct identification of opioids based on the responses to the questions: "*Have you heard of any of the following medications?*"; and "*Could you tell me which of the following drugs you think is an opioid?*" The answers to these questions were dichotomous (yes and no), and we considered that an individual correctly identified the drugs only if they responded affirmatively to both questions.

Statistical Analysis

A descriptive analysis of the variables studied was carried out, calculating the frequency, central tendency, and dispersion. In addition, a hierarchical cluster analysis was performed to establish groups of individuals or patterns according to the subjects' opinions, fears, knowledge, level of contact, and attitudes toward opioids. The Euclidean distance between the groups and cluster formation criteria were used. Subsequently, the differences between the groups were analyzed using Chi-squared tests. In addition, a multinomial logistic regression model was established to determine the factors associated with each of the groups previously identified in the cluster analysis. The covariates included in this model were the significant variables identified in the bivariate analysis.

Results

General Characteristics of Respondents

We carried out 3844 contacts, 1299 of which were considered valid. The response rate was 33.79%. Of the total number of subjects interviewed, 50.7% were women, and the global average age of the cohort was 50.48 years (SD 15.9). Most subjects had completed secondary education (45.9%).

Morphine was the best-known medication (99.2%), and it was correctly identified by 64.9% of respondents. However, fewer subjects correctly identified tramadol (14.2%), and oxycodone was recognized by 11.3% of respondents, whereas fentanyl, buprenorphine, or tapentadol was only identified correctly by slightly more than 5% of them. More than 50% of participants knew someone who had taken opioid medication (minimal contact with treatment), although only 3.8% were taking any of these drugs at the time of the interview (maximum contact) (Table 1). Most subjects with maximum contact were women (60%), older than 65 years, and mainly with primary education (43%).

Beliefs, Fears, Opinions, and Attitudes Toward Opioids

Figure 1 shows a word cloud with the beliefs of the respondents with regard to opioids, where the size of each word indicates how often the respondents related it to opioids. Although the most frequent response was *I do not know with which word to relate them*, the words pain, illegal drugs, medications, opium, and painkillers were much repeated (Fig. 1).

With regard to fear of opioids (Fig. 2), side effects (48%) or of a failure to achieve the expected results (47%) were the fears most frequently reported by respondents, although nearly 35% of them expressed the fear of becoming addicted.

With regard to the respondents' opinions on opioids, most of the interviewed agreed that these drugs

Table 1
General Characteristics of the Population Surveyed

Variables	Categories	%
General characteristics of the population surveyed		
Sex	Female	50.7
Age	18–44	44.1
	45–64	32.6
	65 or older	23.3
Educational level	No education received	5.9
	Primary studies	20.2
	Secondary studies	45.9
	University studies	28.1
Are you currently or have you ever been engaged in any profession related to health care?	Yes	14.4
Level of contact with opioid	No contact	36.0
	Minimal contact	51.2
	Medium contact	8.9
	Maximal contact	3.8
Correct identification of opioids	Tramadol	14.2
	Tapentadol	5.5
	Morphine	64.9
	Oxycodone	11.3
	Fentanyl	6.0
	Buprenorphine	5.7

may cause sleep or sedation (50.8%), that they are used when a disease is severe (42.6%), and that increasingly large doses are required (44.7%). However, almost 50% of them disagreed that opioids should only be used with terminally ill patients. Only slightly more than 30% of the respondents related these drugs with constipation (Table 2).

When analyzing the attitude of the respondents toward the use of opioids, it was notable that most respondents stated that they would agree to take them if they were prescribed medically (86.3%) as they generally placed confidence in their doctor (64.4%).

Patterns of Opinions, Fears, and Attitudes in the Population Surveyed As Well As Associated Factors

From the cluster analysis, three groups of subjects were identified (Table 3). The first group ($N = 448$), considered with the most positive point of view (PPV) toward opioids, was mainly composed of individuals older than 65 years who would accept opioid treatment if it were prescribed by a doctor. In addition, they reported fewer fears toward these drugs, and they were more frequently of the opinion that opioids do not cause side effects, and they are not associated with terminal illness, addiction, or the need to increase the dose to achieve the desired effect (tolerance).

The second group ($N = 337$) was characterized by having a moderate point of view (MPV) toward opioids, and it comprises a larger proportion of young people with university education. The individuals in this group more often identified the opioids correctly than those in the other two groups, and they not only thought that these drugs produced side effects (sleep, nausea, and constipation) but also were afraid of not getting the expected results if they took them.

The third group ($N = 468$), with the most negative point of view (NPV) toward opioids, included the subjects with the lowest educational level and with a stronger negative attitude regarding the acceptance of treatment with these drugs. These individuals had the highest level of opiophobia, and they had the worse opinion of these drugs, considering them

Fig. 1. A word cloud showing the beliefs of the respondents with regard to opioids, where the size of each word indicates how often the respondents related it to opioids.

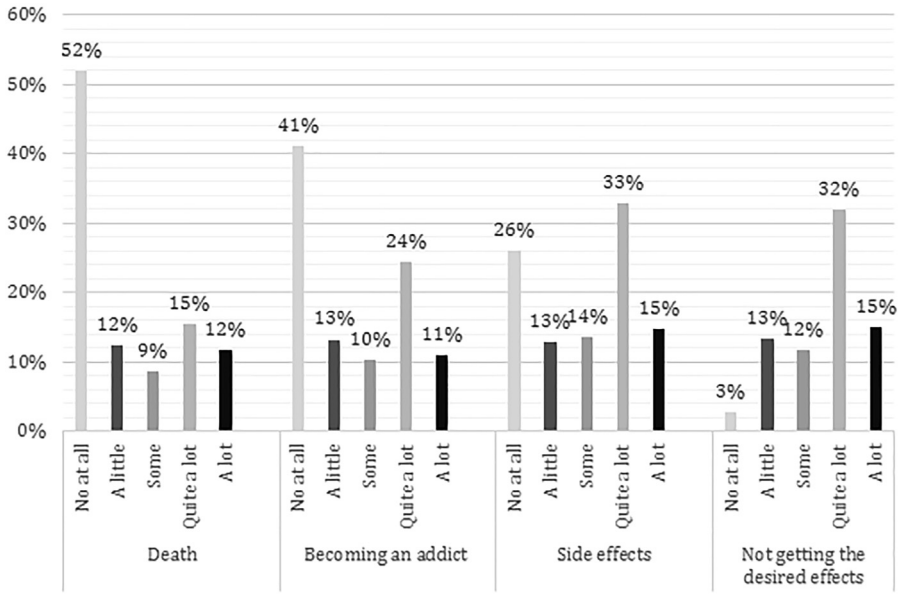


Fig. 2. Summary of respondents' fears associated with opioid usage.

associated with terminal illness, addiction, and tolerance.

Factors Associated to Each Group Identified According to Their Point of View Toward Opioids

The opinion that increasingly large doses of opioids are required (MPV: OR 2.16; NPV: OR 3.03) and a higher level of opiophobia (MPV: OR 2.67; NPV: OR 3.95) were the two variables most strongly associated with the groups with a worse vision of these drugs (MPV, NPV vs. PPV).

However, although respondents in the MPV group more strongly agreed that opioids produce sleepiness (OR 2.58) and nausea (OR 3.04), respondents with a more negative vision (NPV) placed more importance on not being able to stop taking them whenever they wanted to (OR 3.04) (Table 4).

Discussion

To our knowledge, this is the first study carried out in Spain to analyze the perspective of the general population toward opioids, based on the beliefs, knowledge, fears, and opinions. This analysis enabled us to identify three groups of individuals with a clearly distinct point of view regarding these drugs and specific factors associated with each of these groups.

Among the results obtained, it is noteworthy that most respondents did not have a clear idea about opioids and those who did mostly considered them to be related with pain, illegal drugs, and medication. This is consistent with the findings of a study carried out in Portugal,[13] where 32.3% of the general population were unable to recognize the term morphine. However, when these individuals were specifically asked about this drug, 99.2% answered that they knew about it although it was only identified as an opioid by 64.9% of them.

In our study, 3.8% of the respondents were under a treatment with opioids at the time of the survey. This is similar to the situation described in Portugal (4.37%)[14] and Scotland, where the opioid use increased to 3.6%, mainly because of the use of tramadol.[15] According to the report of the Spanish Agency of Medicines and Sanitary Products,[2] tramadol is the opiate that has experienced a greater increase in use in recent years, which may explain why it is the best-known opioid after morphine in our study.

It is important to note that three different profiles of participants were identified in this study, including a group of better-informed young people who are more concerned about the side effects of opioids, who have a more critical attitude toward opioids, and who are less willing to take them on medical prescription (MPV). Another group of participants with a generally lower educational level (NPV) seemed to show more deep-rooted opiophobia. Finally, there was a group of older respondents who had more confidence in their physician when these drugs were prescribed, and they were less concerned about their adverse effects (PPV). In this vein, it is noticeable that, as other studies show, elderly patients assume pain and taking medication as part of their aging process, and only 15% expect that the treatment has few side effects.[16] This could explain the results found in our study regarding older people being less afraid of the adverse effects associated with opioids.

Table 2
Respondents' Opinion Associated With Opioid Use

Respondents' Opinion on Opioids		
Variables	Categories	%
Respondents' opinion on opioids tolerance		
Increasingly larger doses are required	Completely disagree	14.3
	Slightly disagree	16.3
	Moderately agree	44.7
	Strongly agree	18.2
	Undecided	6.5
Respondents' opinion on opioids' dependence		
There is a risk of being unable to stop taking them	Completely disagree	22.7
	Slightly disagree	23.6
	Moderately agree	34.7
	Strongly agree	10.1
	Undecided	8.9
Respondents' opinion on opioids' side effects		
They may cause somnolence	Completely disagree	4.5
	Slightly disagree	8.5
	Moderately agree	50.8
	Strongly agree	22.1
	Undecided	14.2
They may cause constipation	Completely disagree	7.2
	Slightly disagree	11.7
	Moderately agree	24.8
	Strongly agree	8.7
	Undecided	47.6
They may cause nausea	Completely disagree	6.5
	Slightly disagree	11.2
	Moderately agree	42.2
	Strongly agree	13.5
	Undecided	26.6
They may cause nervousness	Completely disagree	20.4
	Slightly disagree	15.5
	Moderately agree	31.1
	Strongly agree	9.2
	Undecided	23.8
Respondents' opinion on severity of the disease		
Opioids are only for terminally ill patients	Completely disagree	49.7
	Slightly disagree	15.5
	Moderately agree	22.1
	Strongly agree	8.2
	Undecided	4.5
Opioids use means that the illness is serious	Completely disagree	24.6
	Slightly disagree	13.1
	Moderately agree	42.6
	Strongly agree	15.7
	Undecided	4.0
Opioids should be the last treatment option	Completely disagree	22.3
	Slightly disagree	12.9
	Moderately agree	37.4
	Strongly agree	18.1
	Undecided	9.3

Similarly, the higher educational level of the youngest group in our study could condition their attitudes, making them more demanding with the treatment. The World Health Organization states that, among other educational organizations, universities play a key role in establishing knowledge, behavior, and attitudes toward health, promoting the empowerment of students in health, and enabling them to better control adverse health determinants.[17] This could explain why the youngest group with the highest proportion of individuals with university education is indeed more critical, not only of the most well-known aspects of these drugs like addiction and tolerance but also of other less common aspects that may affect their quality of life.

Studies have shown that when taking opioids, confidence in their effects and a positive attitude toward them is closely related to the improvement in the quality of life and the pain relief obtained by the patient or that described by acquaintances and relatives.[18,19] This circumstance could explain the results observed in the PPV group, which was precisely the group with the greatest level of contact with these drugs. An alternative explanation could be that a greater exposure to opioids expels the fear of their adverse effects, tipping the balance in favor of their pain-relieving effects. This hypothesis could be particularly relevant if we consider that this group included an older population that might be more concerned about pain relief and less concerned about the side effects of these drugs.[18,19]

Tolerance was identified as a risk in both the MPV and NPV groups. The NPV group referred to the risk of being unable to stop taking opioids; these individuals were more reluctant to accept them if prescribed by a doctor. One of the reasons for maintaining inappropriate beliefs and attitudes toward these drugs may be a lack of knowledge about them, leading to opiophobia, a phenomenon that includes a fear of tolerance.[7] This is consistent with the characteristics of the NPV group, where the respondents attained a generally poorer level of education.

In accordance with our results, fear of addiction has previously been shown to be an important barrier to opioid use in patients suffering moderate or severe chronic pain, representing one of the reasons why this pain is often undertreated.[20,21] Indeed, opioid use in the U.S. represents 80% of the total worldwide consumption,[22,23] and the misuse behavior rate is 34.1%,[24] much higher than in other countries. Given the importance of controlling pain in patients with chronic moderate or severe pain and avoiding problems of the misuse of opioids, it is important to find a balance between these two extremes in the Spanish population. Thus, identifying groups with different perceptions toward opioids, such as those observed in the present study, should be useful when establishing future health care strategies.

Finally, some strengths and weaknesses of the present study should be noted. One strength that stands out in this work is the cluster analysis used to identify different groups of subjects based on beliefs, fears, opinions, and attitudes toward opioids. Other studies[12,25] have applied this analysis to cohorts of patients with chronic pain, demonstrating its usefulness. However, as far as we know, this is the first time that this type of analysis has been applied in this kind of study. Another strength is that the study was carried

Table 3

Classification of the Individuals Into Groups According to Their Opinions, Beliefs, and Attitudes Toward Opioids

Variable	Group 1—PPV $N = 448$ (35.8%)	Group 2—MPV $N = 337$ (26.9%)	Group 3—NPV $N = 468$ (37.4%)	P
Sociodemographic variables				
Age				
18–44	155 (34.6)	**180 (53.4)**	216 (46.2)	
45–64	171 (38.2)	103 (30.6)	139 (29.7)	<0.001[a]
65 or older	**122 (27.2)**	54 (16)	113 (24.1)	
Sex				
Male	159 (47.3)	236 (52.7)	220 (47.2)	0.184
Female	177 (52.7)	212 (47.3)	246 (52.8)	
Educational level				
No education received	25 (5.6)	14 (4.2)	**35 (7.5)**	
Primary studies	90 (20.1)	49 (14.6)	**111 (23.8)**	0.001[a]
Secondary studies	202 (45.2)	156 (34.6)	214 (45.8)	
University studies	130 (29.1)	**116 (34.6)**	107 (22.9)	
Correct identification of any opioid				
No	167 (37.3)	86 (25.5)	162 (34.6)	0.002[a]
Yes	281 (62.7)	**251 (74.5)**	306 (65.4)	
Level of contact				
No contact	162 (36.2)	**115 (34.1)**	172 (36.8)	
Minimal contact	194 (43.3)	187 (55.5)	261 (55.8)	
Medium contact	60 (13.4)	29 (8.6)	25 (5.3)	<0.001[a]
Maximal contact	**32 (7.1)**	6 (1.8)	10 (2.1)	
Fears associated with opioid use				
Fear of death				
Not at all or a little	**391 (87.3)**	230 (68.2)	187 (40)	
Some	28 (6.3)	26 (7.7)	52 (11.1)	<0.001[a]
Quite a lot or a lot	29 (6.5)	81 (24)	**229 (48.9)**	
Fear of becoming an addict				
Not at all or a little	**396 (88.4)**	284 (84.3)	7 (1.5)	
Some	35 (7.8)	52 (15.4)	43 (9.2)	<0.001[a]
Quite a lot or a lot	17 (3.8)	1 (0.3)	**418 (89.3)**	
Fear of side effects				
Not at all or a little	**365 (81.5)**	85 (25.2)	42 (9)	
Some	69 (15.4)	58 (17.2)	45 (9.6)	<0.001[a]
Quite a lot or a lot	14 (3.1)	194 (57.6)	**381 (81.4)**	
Fear of not getting the desired results				
Not at all or a little	**370 (82.6)**	44 (13.1)	106 (22.6)	<0.001[a]
Some	50 (11.2)	56 (16.6)	42 (9)	
Quite a lot or a lot	28 (6.3)	**237 (70.3)**	320 (68.4)	
Respondents' opinion on opioids				
Opinion on opioids' tolerance				
Increasingly larger doses are required				
Completely disagree or slightly agree	176 (39.3)	102 (30.3)	107 (22.9)	<0.001[a]
Moderately or strongly agree	228 (50.9)	230 (68.2)	**330 (70.5)**	
Undecided	44 (9.8)	5 (1.5)	31 (6.6)	
Opinion on opioids' dependence				
There is a risk of being unable to stop taking them				
Completely disagree or slightly agree	**266 (59.4)**	176 (52.2)	135 (28.8)	<0.001[a]
Moderately or strongly agree	123 (27.5)	147 (43.6)	**293 (62.6)**	
Undecided	59 (13.2)	14 (4.2)	40 (8.5)	
Opinion on opioids' side effects				
They may cause somnolence				
Completely disagree or slightly agree	**84 (18.8)**	31 (9.2)	47 (10.0)	<0.001[a]
Moderately or strongly agree	277 (61.8)	**283 (84.0)**	354 (75.6)	
Undecided	87 (19.4)	23 (6.8)	67 (14.3)	
They may cause constipation				
Completely disagree or slightly agree	**96 (21.4)**	55 (16.3)	88 (18.8)	<0.001[a]
Moderately or strongly agree	113 (25.2)	**151 (44.8)**	159 (34)	
Undecided	239 (53.3)	131 (38.9)	221 (47.2)	
They may cause nausea				
Completely disagree or slightly agree	**119 (26.6)**	40 (11.9)	63 (13.5)	<0.001[a]
Moderately or strongly agree	174 (38.8)	**248 (73.6)**	277 (59.2)	
Undecided	155 (34.6)	49 (14.5)	128 (27.4)	
They may cause nervousness				
Completely disagree or slightly agree	**188 (42)**	139 (41.2)	127 (27.1)	<0.001[a]
Moderately or strongly agree	104 (23.2)	161 (47.8)	**234 (50)**	
Undecided	156 (34.8)	37 (11)	107 (22.9)	

(*Continued*)

Table 3
Continued

Variable	Group 1—PPV $N = 448$ (35.8%)	Group 2—MPV $N = 337$ (26.9%)	Group 3—NPV $N = 468$ (37.4%)	P
Opinion on severity of the disease				
Opioids are only for terminally ill patients				
Completely disagree or slightly agree	**324 (72.3)**	234 (69.4)	259 (55.3)	<0.001[a]
Moderately or strongly agree	92 (20.5)	92 (27.3)	**196 (41.9)**	
Undecided	32 (7.1)	11 (3.3)	13 (2.8)	
Opioids use means that the illness is serious				
Completely disagree or slightly agree	**222 (49.6)**	134 (39.8)	121 (25.9)	<0.001[a]
Moderately or strongly agree	199 (44.4)	193 (57.3)	**335 (71.6)**	
Undecided	27 (6)	10 (35)	12 (2.6)	
Opioids should be the last treatment option				
Completely disagree or slightly agree	**196 (43.8)**	137 (40.7)	110 (23.5)	<0.001[a]
Moderately or strongly agree	199 (44.4)	178 (52.8)	**319 (68.2)**	
Undecided	53 (11.8)	22 (6.5)	39 (8.3)	
Attitude toward opioid				
Supposing that you suffer from severe pain. Would you take opioids?				<0.001[a]
No	34 (7.6)	50 (14.8)	**101 (21.6)**	
Yes	**414 (92.4)**	287 (85.2)	367 (78.4)	

PPV = positive point of view; MPV = moderate point of view; NPV= negative point of view.
Bold numerals highlight the most relevant information.
[a]Pearson Chi-squared test.

out on a large sample from the general population using an exhaustive sampling procedure, representing populations of different ages and sex.

Among the weaknesses of the study, we must consider that the information was gathered by telephone, which limited the duration of the interview. However, the use of telephone surveys has been considered by some to be more adequate in population studies than face-to-face surveys,[26] particularly because they allow greater coverage of the population being studied and they permit a representative sample to be obtained by randomization of telephone

Table 4
Factors Associated With the Groups With the Worst Vision on Opioids Vs. the Group With a Positive Vision

Variables	Cluster MPV ($N = 336$) Wald Statistic	OR	95% CI	P	Cluster NPV ($N = 466$) Wald Statistic	OR	95% CI	P
Sex								
Female[a]								
Male					4.60	1.80	1.05, 3.07	0.032
Level of contact								
Maximal contact[a]								
Medium contact	3.62	4.38	0.96, 20.08	0.057				
Minimal contact	4.48	4.57	1.12, 18.64	0.034				
No contact	4.55	4.75	1.13, 19.90	0.033				
Increasingly larger doses are required								
Completely disagree or slightly agree[a]								
Moderately or strongly agree	9.70	2.16	1.33, 3.51	0.002	12.89	3.03	1.65, 5.55	<0.001
Undecided	0.70	0.56	0.14, 2.17	0.403	3.57	3.62	0.95, 13.73	0.059
There is a risk of being unable to stop taking them								
Completely disagree or slightly agree[a]								
Moderately or strongly agree					13.97	3.04	1.70, 5.45	<0.001
Undecided					0.10	0.84	0.29, 2.44	0.746
They may cause somnolence								
Completely disagree or slightly agree[a]								
Moderately or strongly agree	6.92	2.58	1.27, 5.23	0.009				
Undecided	0.02	1.07	0.40, 2.89	0.898				
They may cause nausea								
Completely disagree or slightly agree[a]								
Moderately or strongly agree	11.48	3.04	1.60, 5.78	0.001				
Undecided	0.68	0.72	0.33, 1.57	0.411				
Degree of opiophobia (0: no opiophobia–16: maximal opiophobia)	184.41	2.67	2.01, 2.55	<0.001	350.92	3.95	3.42, 4.56	<0.001

MPV = moderate point of view, group with a moderate vision of opioids; NPV = negative point of view, group with a negative vision of opioids; OR = odds ratio.
Goodness of fit to the model: $\chi 2 = 1482.7$; df = 20; $P < 0.001$.
Reference group of the dependent variable: Group with a positive vision of opioids (positive point of view).
[a]Reference category.

numbers. Another issue that must be taken into account is the low response rate observed in this study (33.79%), which could have introduced selection bias. However, we consider that this is unlikely to affect the validity of the results because the distribution of the sample is identical to that of the target population, ensuring that the responses are representative. Furthermore, although higher response rates have been obtained (e.g., 70%),[21] rates similar to ours (33% and 42%) were also reported using the same method.[27,28]

Another possible limitation is that we did not assess opiophobia directly, and its measurement was based on four questions about the individual's fear (side effects, becoming addicted, not achieving the desired results, and death). However, the term opiophobia, as previously described in the introduction section,[7] is a definition that includes similar issues as those considered in this article. Given that the general population was target in this study, we believe that the inclusion of the exact definitions of both tolerance and dependence in the questionnaire would have complicated the collection data.

In summary, demonstrating the lack of knowledge in the Spanish population about opioids, this study shows that the side effects of these drugs are the most feared aspects associated with their use in the treatment of pain. Furthermore, this study reveals the factors related with the different perceptions and concerns among the general population regarding the use of opioid treatments, which largely depends on educational level, age, and prior contact with opioids. Health care professionals should pay particular attention to the patient profile when designing strategies to inform patients and treat their pain using opioids. The information given should be personalized to suit the patient's characteristics, paying special attention to the possible benefits of the treatment in the MPV and NPV groups and to the risks and adverse effects in the group with PPV. This should improve the clinical management of opioids and promote their correct use, specially preventing their misuse.

Disclosures and Acknowledgments

This work was supported by the External Chair of Pain, a collaboration between the University of Cádiz and the Grünenthal Foundation. The Grünenthal Foundation is a private nonprofit making organization that promotes the dissemination of scientific knowledge and supports research. The authors acknowledge the effort of the interviewers who collected the data through the telephone interviews.

References

1. World Health Organization. Access to Controlled Medications Programme. Ensuring balance in national policies on controlled substances: Guidance for availability and accessibility of controlled medicines. Geneva: World Health Organization, 2011:1–78.

2. Agencia española de medicamentos y productos sanitarios. Utilización de medicamentos opioides en España durante el periodo 2008-2015. [Spanish Agency of Medicines and Health Products. Use of opioid drugs in Spain during the period 2008-2015, 2017.]. Madrid: Spanish Ministry of Health, Social Services, and Equality, 2017.

3. Birke H, Kurita GP, Sjøgren P, et al. Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: trends from 2000 to 2013. Acta Anaesthesiol Scand 2016;60:623–633.

4. Schiller M, Pyszora A, Graczyk M, et al. Are the patients afraid of opioids? Pilot study of the patients with chronic cancer and non-malignant pain. Adv Palliat Med 2007;6:121–124.

5. Verloo H, Cohen C, Borloz C, et al. Risks associated with the use of morphine for analgesia: attitudes and perceptions amongst nursing students in French-speaking Switzerland. Nursing (London) 2013;3:1–8.

6. Krakauer EL, Phuong Cham NT, Husain SA, et al. Toward safe accessibility of opioid pain medicines in Vietnam and other developing countries: a balanced policy method. J Pain Symptom Manage 2015;49:916–922.

7. Ferreira M, Verloo H, Mabire C, et al. Psychometric evaluation of the French version of the questionnaire attitudes towards morphine use; a cross-sectional study in Valais, Switzerland. BMC Nurs 2014;13:1–8.

8. Motov SM, Khan ANGA. Problems and barriers of pain management in the emergency department: are we ever going to get better? J Pain Res 2009;2:5–11.

9. Jamison RN, Butler SF, Budman SH, et al. Gender differences in risk factors for aberrant prescription opioid use. J Pain 2011;11:312–320.

10. The President's Commission on Combating Drug Addiction and the Opioid Crisis. 2017. Available from https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Meeting Draft of Final Report - November 1%2C 2017.pdf. Accessed February 24, 2017.

11. McHugh RK, Weiss RD, Cornelius M, et al. Distress intolerance and prescription opioid misuse among patients with chronic pain. J Pain 2016;17:806–814.

12. Dueñas M, Salazar A, Ojeda B, et al. A nationwide study of chronic pain prevalence in the general Spanish population: identifying clinical subgroups through cluster analysis. Pain Med 2014;16:811–822.

13. Verloo H, Mpinga EK, Ferreira M, et al. Morphinofobia: the situation among the general population and health care professionals in North-Eastern Portugal. BMC Palliat Care 2010;9:15.

14. Azevedo LF, Costa-Pereira A, Mendonça L, et al. A population-based study on chronic pain and the use of opioids in Portugal. Pain 2013;154:2844–2852.

15. Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995-2010: repeated cross-sectional

analysis of dispensed prescribing for a large geographical population in Scotland. Eur J Pain 2015;19:59–66.

16. Pautex S, Rexach-Cano L, Van Den Noortgate N, et al. Management of chronic pain in old patients: Belgium, Spain and Switzerland. Eur Geriatr Med 2013;4:281–287.

17. Muñoz M, Cabieses B. Universidades y promoción de la salud: ¿cómo alcanzar el punto de encuentro? [Universities and health promotion: how to reach the meeting point?]. Rev Panam Salud Pública [Panamanian Journal of Public Health] 2008;24:139–146.

18. Akiyama M, Hirai K, Takebayashi T, et al. The effects of community-wide dissemination of information on perceptions of palliative care, knowledge about opioids, and sense of security among cancer patients, their families, and the general public. Support Care Cancer 2015;24:347–356.

19. Shinjo T, Morita T, Hirai K, et al. Why people accept opioids: role of general attitudes toward drugs, experience as a bereaved family, information from medical professionals, and personal beliefs regarding a good death. J Pain Symptom Manage 2015;49:45–54.

20. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. Eur J Pain 2007;11:490–518.

21. Morley-Forster PK, Clark AJ, Speechley M, et al. Attitudes toward opioid use for chronic pain: a Canadian physician survey. Pain Res Manag 2003;8:189–194.

22. Manchikanti L, Helm S, Fellows B, et al. Opioid epidemic in the United States. Pain Physician 2012;15:ES9–ES38.

23. Sirohi S, Tiwari AK. Pain in the management of opioid use disorder. J Pain Res 2016;9:963–966.

24. Wasan AD, Butler SF, Budman SH, et al. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? Clin J Pain 2010;25:193–198.

25. Wurm M, Edlund S, Tillfors M, et al. Characteristics and consequences of the co-occurrence between social anxiety and pain-related fear in chronic pain patients receiving multimodal pain rehabilitation treatment. Scand J Pain 2016;12:45–52.

26. Klevens J, Trick WE, Kee R, et al. Concordance in the measurement of quality of life and health indicators between two methods of computer-assisted interviews: self-administered and by telephone. Qual Life Res 2011;20:1179–1186.

27. Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J Addict Dis 2011;30:185–194.

28. Català E, Reig E, Artés M, et al. Prevalence of pain in the Spanish population: telephone survey in 5000 homes. Eur J Pain 2002;6:133–140.

UCA

Helena de Sola Perea <helena.desolaperea@alum.uca.es>

Health Expectations - Decision on Manuscript HEX-2019-3385.R2

6 mensajes

Gie Anne Sanao <onbehalfof@manuscriptcentral.com> 19 de mayo de 2020, 10:05
Responder a: HEXedoffice@wiley.com
Para: Helena.desolaperea@alum.uca.es

19/05/2020

Dear Ms De Sola,

Thank you very much for the revised version of your manuscript "Living with opioids: A qualitative study with patients with chronic low back pain." (HEX-2019-3385.R2). I am pleased to accept it for publication in Health Expectations.

The final version of your article cannot be published until the publisher has received the appropriate signed license agreement. Once your article has been received by Wiley for production the corresponding author will receive an email from Wiley's Author Services system which will ask them to log in and will present them with the appropriate license for completion.

Payment of your Open Access Article Publication Charge (APC):
All articles published in Health Expectations are fully open access: immediately and freely available to read, download and share. Health Expectations charges an article publication charge (APC).

Before we can publish your article, your payment must be completed. The corresponding author for this manuscript will have already received a quote email shortly after original submission with the estimated Article Publication Charge; please let us know if this has not been received. Once your accepted paper is in production, the corresponding author will receive an e-mail inviting them to register with or log in to Wiley Author Services (www.wileyauthors.com) where the publication fee can be paid by credit card, or an invoice or proforma can be requested. The option to pay via credit card and claim reimbursement from your institution may help to avoid delays with payment processing

You will be hearing in due course from a member of the Production Team who will send page proofs and any production queries.

Thank you again for your contribution.

Yours sincerely,

Professor Carolyn Chew-Graham
Editor, Health Expectations

A/A de la Comisión de Evaluación del Programa de Doctorado Ciencias de la Salud de la Universidad de Cádiz:

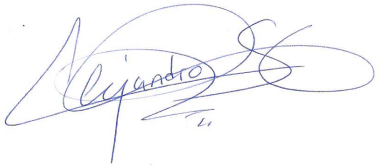
Los Doctores María Dueñas Rodríguez, Alejandro Salazar Couso, Patricia Ortega Jiménez e Inmaculada Failde Martínez, dan su consentimiento como coautores de la publicación:

1. *Prevalence of therapeutic use of opioids in chronic non-cancer pain patients and associated factors: a systematic review and meta-analysis.*

Para que este artículo sea presentado en la defensa de la Tesis de Helena De Sola Perea, renunciando a presentar estos resultados como parte de otra tesis doctoral en otra Universidad.

En Cádiz, 30 de Abril de 2020

Fdo. María Dueñas Rodríguez



Fdo. Alejandro Salazar Couso

Fdo. Patricia Ortega Jiménez

Fdo. Inmaculada Failde Martinez

A/A de la Comisión de Evaluación del Programa de Doctorado Ciencias de la Salud de la Universidad de Cádiz:

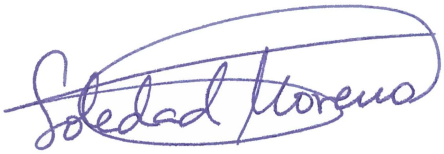
Los Doctores Alejandro Salazar Couso, Soledad Moreno Pulido, Jose A. Moral Muñoz, María Dueñas Rodríguez, e Inmaculada Failde Martínez, dan su consentimiento como coautores de la publicación:

2. *The evolution of opioid-related mortality and potential years of life lost in Spain from 2008 to 2017. Differences between Spain and the United States.*

Para que este artículo sea presentado en la defensa de la Tesis de Helena De Sola Perea, renunciando a presentar estos resultados como parte de otra tesis doctoral en otra Universidad.

En Cádiz, 30 de Abril de 2020

Fdo. Alejandro Salazar Couso



Fdo. Soledad Moreno Pulido

Fdo. Jose Antonio Moral Muñoz

Fdo. María Dueñas Rodríguez

Fdo. Inmaculada Failde Martinez

A/A de la Comisión de Evaluación del Programa de Doctorado Ciencias de la Salud de la Universidad de Cádiz:

Los Doctores Alejandro Salazar Couso, María Dueñas Rodríguez, e Inmaculada Failde Martínez, dan su consentimiento como coautores de la publicación:

3. *Opioids in the Treatment of Pain. Beliefs, Knowledge, and Attitudes of the General Spanish Population. Identification of Subgroups Through Cluster Analysis.*

Para que este artículo sea presentado en la defensa de la Tesis de Helena De Sola Perea, renunciando a presentar estos resultados como parte de otra tesis doctoral en otra Universidad.

En Cádiz, 30 de Abril de 2020

Fdo. Alejandro Salazar Couso

Fdo. María Dueñas Rodríguez

Fdo. Inmaculada Failde Martinez

A/A de la Comisión de Evaluación del Programa de Doctorado Ciencias de la Salud de la Universidad de Cádiz:

Los Doctores Amaia Maquibar Landa, Inmaculada Failde Martínez, Alejandro Salazar Couso e Isabel Goicolea Julián dan su consentimiento como coautores de la publicación:

4. *Living with opioids: A qualitative study with patients with chronic low back pain.*

Para que este artículo sea presentado en la defensa de la Tesis de Helena De Sola Perea, renunciando a presentar estos resultados como parte de otra tesis doctoral en otra Universidad.

En Cádiz, 30 de Abril de 2020

Fdo. Amaia Maquibar Landa

Fdo. Alejandro Salazar Couso

Fdo. Inmaculada Failde Martínez

Fdo. Isabel Goicolea Julián

EDUCA, Escuela de Doctorado de la Universidad de Cádiz

INFORME DE PROGRESO DE ACTIVIDADES FORMATIVAS DE DOCTORADO
(Estudios regulados por R.D. 99/2011 de 28 de Enero)

Estudiante: **44967707Q Dª. HELENA DE SOLA PEREA**
Programa de Doctorado: **8203 - Ciencias de la Salud**

Actividad formativa: 8203B01 Presentación del proyecto en el Grupo/ Equipo de Investigación

Tipo: **Obligatoria (mínimo 10.00 h.)** Horas realizadas:**25.00 h.** **Actividad superada**

Curso	Descripción	Documento justificativo	Horas
2017/18	Presentación del Plan Investigación	Defensa_Plan_InvestigaciA_n.pdf	25.00

Actividad formativa: 8203B02 Presentación de un plan de investigación

Tipo: **Obligatoria (mínimo 50.00 h.)** Horas realizadas:**75.00 h.** **Actividad superada**

Curso	Descripción	Documento justificativo	Horas
2017/18	Plan de Investigación	Plan_de_investigaciA_n_02._Helena_de_Sola.pdf	75.00

Actividad formativa: 8203B03 Presentación de resultados en el centro/ departamento

Tipo: **Obligatoria (mínimo 15.00 h.)** Horas realizadas:**50.00 h.** **Actividad superada**

Curso	Descripción	Documento justificativo	Horas
2019/20	Presentación de resultados preliminares	Presentacion_resultados_preliminares.pdf	50.00

Actividad formativa: 8203B04 Publicación científica

Tipo: **Obligatoria (mínimo 100.00 h.)** Horas realizadas:**375.00 h.** **Actividad superada**

Curso	Descripción	Documento justificativo	Horas
2017/18	Opioids in the Treatment of Pain.	Opioids_in_the_Treatment_of_Pain._Belie...pdf	200.00
2018/19	British Medical Journal Open. FACTOR DE IMPACTO: 2.562. Q1	Nationwide_cross- sectional_study_of_the...pdf	175.00

Actividad formativa: 8203B05 Asistencia a conferencias

Tipo: **Obligatoria (mínimo 10.00 h.)** Horas realizadas:**16.00 h.** **Actividad superada**

Curso	Descripción	Documento justificativo	Horas
2017/18	Escuela de Doctorado de la Universidad de Cádiz	Escuela_de_Doctorado_de_la_Universidad_...pdf	8.00
2017/18	Jornada atracción de talento	Jornadas_de_atraccion_de_talentos..pdf	8.00

Actividad formativa: 8203P01 Asistencia a congresos

Tipo: **Optativa** Horas realizadas:**10.00 h.** **Actividad superada**

Curso	Descripción	Documento justificativo	Horas
2017/18	IV Encuentro Grupo de Investigación de Salud Pública de Cádiz	Asistencia_Encuentro_Grupo_de_investiga...pdf	2.00
2017/18	Jornadas innovación docente Universidad de Cádiz 2016	Jornadas_innovacion_docente.pdf	2.00
2017/18	XIII Congreso de la Sociedad Española del Dolor	CertificadoAsistenciaPamplona.pdf	2.00
2017/18	XXV Congreso de la Asociación Andaluza del Dolor y Asistencia Co	Certificado_poster_Sancti_Petri.pdf	2.00
2017/18	XXXIV Reunión Ciéntifica de la SEE	Certificado_de_asistencia.SEE2016.pdf	2.00

Actividad formativa: 8203P02 Presentación de resultados en un congreso internacional

Tipo: **Optativa** Horas realizadas:**15.00 h.** **Actividad superada**

Curso	Descripción	Documento justificativo	Horas
2017/18	16th World Congress on Pain	Certificado_IASP_2016_poster_Helena.pdf	15.00

Actividad formativa: 8203P04 Movilidad de investigación

Tipo: **Optativa** Horas realizadas:**160.00 h.** **Actividad superada**

Curso	Descripción	Documento justificativo	Horas
2019/20	Estancia Internacional de Investigacion	Certificado_Estancia_Umea_4_meses_.pdf	160.00

Actividad formativa: 8203P12 Presentación de resultados en un congreso nacional

Tipo: **Optativa** Horas realizadas:**25.00 h.** **Actividad superada**

Curso	Descripción	Documento justificativo	Horas
2017/18	XIII Congreso de la Sociedad Española del Dolor	certificado_poster_opiaceos.pdf	5.00
2017/18	XIII Congreso de la Sociedad Española del Dolor	certificado.adeherencia_guias.pdf	5.00
2017/18	XIII Congreso de la Sociedad Española del Dolor	certificado_POSTER_bajas.pdf	5.00
2017/18	XXXIV Reunión Ciéntifica de la SEE	Comunicacion_Oral_SEE.pdf	5.00
2017/18	XXXIV Reunión Ciéntifica de la SEE	II_Comunicacion_Oral_SEE..pdf	5.00

Actividad formativa: 8203T01 Cursos de formación

Tipo: **Transversal (mínimo 100.00 h.)** Horas realizadas:**257.00 h.** **Actividad superada**

Curso	Descripción	Documento justificativo	Horas
2017/18	Análisis Multinivel	Analisis_Multinivel.pdf	15.00
2017/18	Métodos y técnicas de investigación cualitativa	Cert_Curso_Cualitativa_EASP.pdf	162.00
2017/18	Redacción en inglés de artículos científicos	Redaccion_en_ingles_de_articulos_cienti...pdf	50.00
2018/19	Deontología profesional	DeontologA_a.pdf	30.00

Total horas actividades formativas completadas: **1008.00**

Las horas especificadas corresponden a las reconocidas por la Comisión Académica del Programa en el día de la fecha.
El estudiante ha completado todos los requisitos de su plan de estudios para la superación de las actividades formativas.

Cádiz, a 20 de mayo de 2020