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A systematic review of the socio-demographic, environmental and macroeconomic factors associated with opioid use disorder in Europe

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Abstract

Content : The United States (US) has been experiencing for several years an epidemic of overdoses directly correlated to the abuse of opioid substances. This phenomenon is called the "opioid crisis" and refers to the significant increase in the use and misuse of prescribed opioids since the late 1990s. While some studies state that Europe does not face an opioid crisis similar to the US, an increase in the use of opioids is observed in Europe. The purpose of this review is to identify systematically the socio-demographic, environmental and macroeconomic factors leading to disorders associated with the use of prescription opioid in the European context.

Methods : A literature search was conducted between February and March 2023 on four different databases. Three of them are specialized health databases : Pubmed, Medline, Academic Search premier (the last two being gathered on EBSCOhost) ; and one is a specialized economics database : Econlit.

Results : In total, 13 articles were included in the review. Unlike in the US, there is no "typical" profile of opioid user that emerges from the synthesis of studies included in this review. However, certain risk factors appear to be unanimous, and are both found in studies carried out in Europe and in the USA (like mental disorders, chronic pain, a low level of education or unemployment). The biggest differences between Europe and the US lie in environmental and macro-economic risk factors.

Conclusion : Due to the lack of information on the profiles of opioid users in Europe and the lack of research into consumption trends, it is not yet possible to determine whether Europe faces an opioid crisis. Although some factors appear to be quite similar, the analysis of environmental and macro-economic factors highlights the many differences between Europe and the US.

Key words [MeSH] : Opioid epidemic ; Analgesics, opioid ; Opioid-related disorders ; Risk factors ; Europe

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List of acronyms

- CNCP : Chronic Non-Cancer Pain
- EMCDDA : European Monitoring Centre for Drugs and Drug Addiction
- GP : General Practicioner
- ICU : Intensive Care Unit
- OUD : Opioid Use Disorder
- OTC : On-The-Counter
- PO : Prescription-Only
- UK : United Kingdom
- US : United States
- WHO : World Health Organization

Introduction

The United States (US) has been experiencing for several years an epidemic of overdoses directly correlated to the abuse of opioid substances. Of the 47,055 overdose deaths reported in 2014 in the US, 60.9% were related to opioids, which is almost three times higher than in 1999 (Vadivelu *et al*., 2018). In 2017, death by drug overdose became the number one cause of death in the US for those under 50, ahead of car accidents and firearms (Hernandez *et al*., 2020). This phenomenon is called the "opioid crisis" and refers to the significant increase in the use and misuse of opioids. The opioid crisis emerged during the late 1990s in the US and evolved essentially because of three driving forces : (1) the recognition of pain treatment as a basic human right, (2) the investment of pharmaceutical lobbies in prescribing opioids in a setting other than cancer pain, and (3) an "aggressive" management of pain after a period when pain was under-treated and under-valued (Vadivelu *et al*., 2018; Chrisholm-Burns *et al*., 2019). While illicit Fentanyl and synthetic drug usage contributes to this figure, prescribed opioids account for the major source of comsumed opioids (Han *et al*., 2017). We can also link the emergence of the opioid crisis to social and economic determinants such as poverty, unemployment, and limited economic mobility that have created a breeding ground for drug abuse within some communities (Case & Deaton, 2020; Kaufman & Hersh, 2020). In their book "Deaths of Despair and the Future of the Capitalism" published in 2020, Anne Case and Angus Deaton explored many facets of what they call the "deaths of despair". The concept refers to a "death category" that includes overdoses, suicides, and alcohol-related deaths. Their work show that the opioid overdose epidemic had a particularly devastating impact on white middle class in the US. While there are a lot of studies on the Opioid Use Disorder (OUD) in the US, there is fewer scientific evidence on this matter in Europe. Some studies state that Europe does not face an opioid crisis similar to the US, however an increase in the use of opioids is observed in Europe (Pierce *et al*.,

2021). According to the European Drug Report of 2022 from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), it is estimated that there were 1 million high-risk opioid users in the European Union, and opioids were found in 74% of fatal overdoses. In France in February 2019, the ANSM (*Agence nationale du médicament et des produits de santé*) published a report which stated that disorders associated with the use of opioid painkillers being reported to the addicto-vigilance network have more than doubled between 2006 and 2015. However, the prevalence of opioid-related disorders and overdoses in Europe varies between countries. For example, the United Kingdom (UK) has the largest increasing trend in opioid consumption (216% within the last decade), resulting in the highest consumption of opioids compared to the rest of Europe in 2018 (Pierce *et al.*, 2021). This upward trend calls for increased attention from a public health perspective.

The opioid crisis is a significant public health concern for several reasons. One major reason is the high number of overdose deaths associated with opioids as we have seen.

Furthermore, opioids are highly addictive substances, and people who use them for extended periods of time may develop a physical and psychological dependence (Savage, 1996). The use of opioids could thus lead to a cycle of addictions, where people sustain their use despite the negative consequences on their health and well-being.

Finally, opioids abuse presents economic and social consequences on the users as well as society. The costs associated with an increased mortality rate, increased emergency department visits, pharmaceuticals use, addiction treatment, overall healthcare and neonatal abstinence syndrome are substantial : several economic studies estimated that the opioid crisis cost the US $504 billion in 2015, $1 trillion in 2017 and $179 billion in 2018 (Maclean *et al*., 2022).

The purpose of this review is to identify systematically the socio-demographic, environmental and macroeconomic factors leading to disorders associated with the use of prescription opioid in the European context. In particular, we aim to answer the following questions: is Europe at risk of an opioid crisis? Are the sociodemographic, environmental and macroeconomic factors associated with opioid use in Europe similar to the factors identified in the US context?

Conceptual background

Opioids are one of the options available for the treatment of pain. However, they are not always appropriate. Given the high addictive potential of opioids, prescribing guidelines have been established by the

Centers for Disease Control and Prevention and updated in 2022. These guidelines do not include the treatment of cancer pain or palliative care.

According to these guidelines, for acute, subacute and chronic pain, non-opioid therapies are at least as effective and have fewer side effects than opioid therapies in many cases. The prescriber should consider opioids only if the estimated benefits outweigh the risks (Dowell *et al*., 2022).

If opioid therapy is initiated, the prescriber should prefer immediate-release opioids instead of extended-release and long-acting opioids. When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, the treatment should be initiated at the lowest effective dosage. When opioids are needed for acute pain, physicians should prescribe no greater quantity than needed for the expected duration of pain (Dowell *et al*., 2022). In most cases, the duration of opioid use in acute pain is between 3 and 7 days (Chou *et al*., 2020).

Finally, prescribers should re-evaluate the risks and benefits between 1 and 4 weeks after the start of treatment and then regularly throughout the course of treatment to ensure the appropriateness of opioid use in each individual case. In any case, physicians should take the time to discuss the risks of opioids with their patients before treatment (Dowell *et al*., 2022).

Although their use can induce a feeling of relaxation and euphoria in addition to pain relief, opioids also have a number of undesirable effects such as constipation, drowsiness, nausea, respiratory depression[1], and physical and mental dependence (Coudert & Decrozant, 2020).

With regular opioid use, individuals develop tolerance and physical dependence; both are predictable, physiological responses to repeated opioid exposure. However, a substantial number of individuals who misuse opioids will develop OUD, which is a complex, primary, chronic, neurobiological disease rooted in genetic, environmental and psychosocial factors (Strang *et al*., 2020). A list of criteria is set out in the fifth edition of the "Diagnostic and Statistical Manual of Mental Disorders" (DSM-5) to help health professionals detect the presence of OUD. The severity of the disorder is judged by the number of symptoms present. In the DSM-5, OUD is defined as "a problematic pattern of opioid use leading to clinically significant impairment or distress". This disorder includes both opioid abuse and opioid dependence, formerly separated into two separate disorders in the DSM-4. The

[1] Respiratory depression is a "slow and shallow breathing that can be induced by opioids and other sedatives" (American Psychological Association, n.d.)

DSM-5 Criteria for Diagnosis of Opioid Use Disorder is available in appendix 1.

Methods

Literature search

A literature search was conducted between February and March 2023 on three specialized health databases : Pubmed, Medline, Academic Search premier (the last two being gathered on EBSCOhost) ; and one specialized economics database : Econlit.

The keywords used for the search equation included those related to opioid use (*opioid use disorder* or *opioid related disorder* or *opioid dependence* or *opioid addiction* or *opioid misuse* or *opioid prescription misuse* or *opioid abuse*), those related to the variable of interest (*risk factors* or *contributing factors* or *predisposing factors* or *diagnosis* or *prevention*), and those related to the geographical area of interest (*Europe*). Due to the different settings of the literature databases, the search equations were adapted to each database and are provided in appendix 2.

Inclusion and exclusion criteria

To be included in the systematic review, articles had to meet the following conditions.

- The scope of the search was restricted to articles published between 2000 (when the opioid crisis "exploded" and the phenomenon came to light) and March 2023 (when the literature search was completed).
- The language of the article had to be English or French.
- The geographical area presented by the article had to be in Europe (geographical definition)[2].
- The opioids of interest in the article could be either opioids in general with no distinction between licit and illicit opioids, but with no clear evidence that only illicit opioids are considered; or prescribed opioids. This criterion was established as a logical continuation of the American situation, where the "opioid crisis" phenomenon was in its early stages strongly characterized by the source of the opioids consumed being from prescription (Han *et al*., 2017).

[2] This definition includes : Albania, Andorra, Armenia, Austria, Azerbaijan, Belgium, Belarus, Bosnia-Herzegovina, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Luxembourg, Netherlands, Portugal, Spain, Sweden and Switzerland, Hungary, Iceland, Ireland, Italy, Kosovo, Latvia, Liechtenstein, Lithuania, Luxembourg, Northern Macedonia, Malta, Moldova, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Czech Republic, Romania, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Ukraine, United Kingdom, and the Vatican. Despite the inclusion of Russia and Turkey in the geographical definition of Europe to which we have chosen to refer, the choice was made to exclude them for this review (as Russia is mostly included in the Asian continent and Turkey is mostly included in the Middle East).

- The problematic opioid use investigated by the article could take the following forms : chronic use; abuse/overuse; misuse (use without a real need, use for a reason other than pain relief, use outside the recommendations); dependence. This criterion includes the various characteristics listed under the heading “opioid use disorder”.
- The population of interest was adolescents from 10 years to 19 years as per the current World Health Organization definition (WHO) to adults (19 years and older). This criterion allows us to focus on the population that is likely to be using opioids “consciously” and allows us to exclude newborns and children with opioid dependence as a result of maternal use during pregnancy and/or breastfeeding.
- Studies clearly identified or discussed risk factors for developing an OUD. Our risk factors of interest were :
  - Socio-demographic factors: age, gender, ethnicity, religion, education level, etc.
  - Environmental factors: life events, behaviors of the person, behaviors of health professionals, etc.
  - Macroeconomic factors: economic context, configuration and influence of the health care system, etc.
- The type of study could be quantitative observational descriptive, quantitative observational analytical, qualitative, or synthesis (systematic review, meta-analysis).
- The availability of an abstract as well as the full text was required to be included in the review.
- Studies prior to 01/01/2000 or after 31/03/2023 were excluded.
- Studies written in a language other than English or French were excluded.
- Studies dealing with a population or a phenomenon located outside the geographical territory of Europe as defined in the inclusion criteria were excluded.
- Studies focusing on any opioids other than those defined in the inclusion criteria, such as illicit opioids (including heroin or opioid-based drugs combined with another substance like desomorphine and “krokodil”), or medications that do not belong to the opioid family were excluded.
- Studies about opioid use for cancer pain management or palliative care were excluded.
- Studies focusing on a non-adolescent or non-adult population, i.e., neonates (children 28 days or younger according to WHO) or children up to 10 years of age were excluded.
- Studies that did not clearly identify or discuss risk factors, or that addressed risk factors other than those listed in the inclusion criteria were excluded.
- Practice guidelines and quantitative interventional studies (clinical trials, cost-

effectiveness analyses of a treatment, measurement tool or health intervention) were excluded.

- Studies without abstract, full text, or either were excluded.

Screening processus

The results of the literature search were sorted into three phases using Rayyan software. Three independent reviewers (MH, TB, MM) including two reviewers who were not involved in the present work (TB, MM) participated to the screening of a random sample of 50 titles and abstracts using the protocol. Setting the maximum acceptable margin of disagreement to 10% (i.e a maximum of 5 disagreements between reviewers), an initial test exhibited a disagreement on eight articles, this led to clarify and amend the protocol. The second phase of testing with another random sample led to 3 disagreements, which validated the protocol.

Data extraction

The data from the articles included in this systematic review were compiled in Excel. Two tables were created to include the general data concerning the article on the one hand (table 1) and to include their results on the other hand (table 2).

Results

Literature search

The literature search on the four databases generated 1355 potentially relevant results. Of these, 37 articles were deleted as duplicates and 19 were automatically deleted by the Rayyan software. Of the 1299 articles, 1215 articles were excluded either because no abstract was available or because they did not meet the inclusion criteria. 84 articles were eligible for full-text reading. After full-text, 71 articles were eliminated. The reasons for exclusion of articles included the following : the article is not about prescribed opioids (n=29), the studied country was not included in the list of included countries (n=9), the full-text was unavailable (n=10), the article concerned an adequate drug use (n=9), the analyses performed in the article did not identify risk factors (n=6), the type of study was not among the included criteria (n=4), the study concerned risks factors different from the included risk factors (n=2), the article was written in a language other than English or French (n=2). In total, 13 articles were included in the review. Figure 1 presents the PRISMA chart showing the different stages of the screening process.

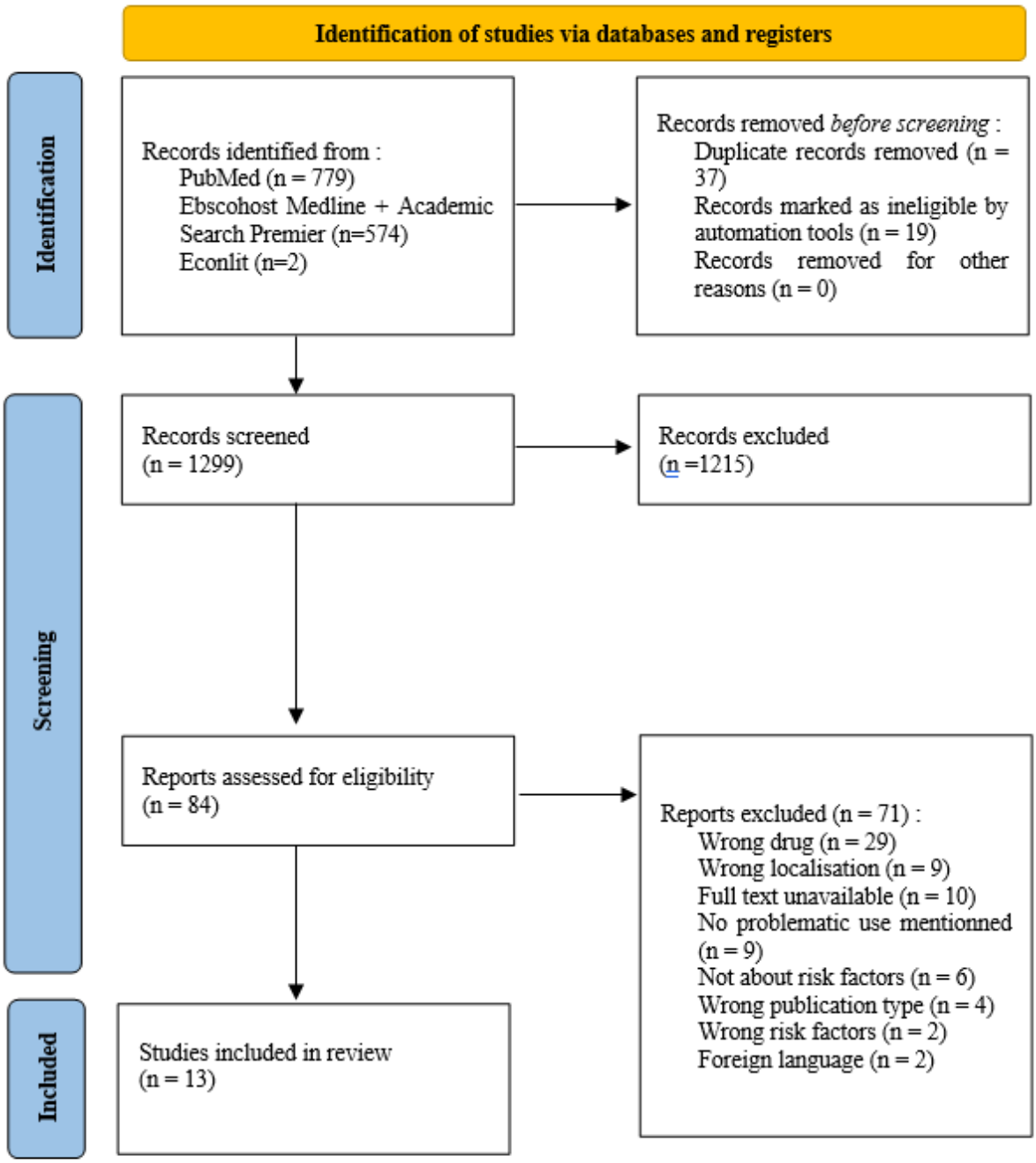

Figure 1: Flow diagram of included and excluded studies in the review

Sociodemographic risk factors

Age

While the literature in the US is quite unanimous regarding the significant association between age and OUD, there seems to be a greater divergence in Europe. Authors are divided regarding the age group being at highest risk of developing problematic opioid use : some articles identify the 40-50 as the most at risk (Kimergård *et al*., 2017; Tjäderborn *et al*., 2009), while others estimate it is under 40 years old (Chenaf *et al*., 2016; Chenaf *et al*., 2019), or over 75 (Jani *et al*., 2020; von Oelrich *et al*., 2020). Furthermore, 4 articles do not consider an "age" factor in their analyses (Ahammer & Halla, 2022; Åström *et al*., 2019; Guillou-Landreat *et al*., 2021; Kinnaird *et al*., 2019) while two studies show no significant correlation between age and problematic opioid use (Just *et al*., 2018; Just *et al*., 2020). The disorders associated to opioid misuse vary with age groups. The under-40 age group appears to be at greater risk for doctor shopping behaviors[3] and opioid-related deaths. In Chenaf *et al*. (2016), patients under 40 have a 7-fold higher risk of developing codeine shopping behavior than other patients and almost 3-fold higher adjusted-risk of all-cause mortality (Chenaf *et al*., 2019). Shopping' behaviors for prescribed and over-the-counter (OTC) codeine are significantly associated with codeine dependence (Kimergård *et al*., 2017). However, when looking at dependence without considering the adjacent "doctor shopping" behavior, the middle-aged appear to be at greater risk than other age groups. Tjäderborn *et al*. (2009) focus on tramadol addiction and Kimergård *et al*. (2017) on codeine addiction, and both find that 40-50 year olds are at greater risk of developing addiction than other age groups with a peak of cases around age 45. The authors explain that this is probably due to the high prevalence of pain disorders from this age. Articles identifying the elderly as the most at-risk age group concern chronic opioid use (Jani *et al*., 2020; Steen *et al*., 2020; von Oelreich *et al*., 2020). Over 75 are 4.6 times more likely to become long-term opioid users than those under 35 (Jani *et al*., 2020). It therefore seems complicated to determine which age group is most at risk of developing an OUD in its general definition, but certain age groups are more likely to engage in one or another problematic behavior.

[3] "Doctor shopping" is the act of consulting different clinicians to multiply prescriptions, either for a persistent illness or to obtain prescription drugs illicitly. It can also mean frequenting different pharmacies to avoid drawing the attention of pharmacists to the quantity and frequency of certain medication purchases (Sansone & Sansone, 2012).

Gender

The association between gender and the development of OUD in Europe is not clear. Most articles incorporated gender into their analyses and concluded that there was no significant correlation between gender and problematic opioid use (Chenaf *et al*., 2016; Jani *et al*., 2020; Just *et al*., 2018; Just *et al*., 2020; Kimergård *et al*., 2017; Tjäderborn *et al*., 2009). Only two studies found male at greater risk than female (Chenaf *et al*., 2019; Steen *et al*., 2020) while one study considered women at greater risk (von Oelrich *et al*., 2020).

Level of education

Educational level is found associated with the development of problematic opioid use in three articles (Ahammer & Halla, 2022; Just *et al*., 2018; von Oelreich *et al*., 2020). Having dropped out of school after high school (Just *et al*., 2018) or after elementary school (von Oelreich *et al*., 2020) represents a risk factor in OUD. In the study by Ahammer and Halla (2022), the authors concluded that having parents who have been to university (and thus a higher family education level) is a protective factor while conversely having working class parents (and thus lower education level) is associated with an increased risk of using opioids in children.

Income

Two studies included income in their analyses (Chenaf *et al*., 2016; Chenaf *et al*., 2019). The phenomenon investigated in both studies was doctor shopping behaviors being associated with low income status. The authors state that this status is determined according to the allocation of the "*Couverture Maladie Universelle Complémentaire*" (CMUC). This allocation is made in case of low income or unemployment in France. The authors therefore do not consider income as such, but the CMUC allowance, which is an indicator of income.

Comorbidities

The majority of articles agree that a psychiatric history or an active mental disorder are strong predictors of the development of opioid use disorder (Åström *et al*., 2019; Chenaf *et al*., 2016; Chenaf *et al*., 2019; Guillou-Landreat *et al*., 2021; Jani *et al*., 2020; Just *et al*., 2018; Just *et al*., 2020; Kimergård *et al*., 2017; von Oelreich *et al*., 2020). Some of them do not specify which types of mental disorder or psychiatric diagnosis present the highest risk in the development of problematic opioid use, but highlight the existence of an association between the use of other medications and increased risks of developing an OUD. Benzodiazepines (Chenaf *et al*., 2016; Chenaf *et al*., 2019; Jani *et al*., 2020; Steen *et al*., 2020),

antidepressants (Guillou-landreat *et al*., 2021; Jani *et al*., 2020; Steen *et al*., 2020), and antipsychotics (Guillou-Landreat *et al*., 2021; Jani *et al*., 2020) were the most implicated medications. These results are consistent with the rest of the studies included in the review. Indeed, four articles identify depression (whether prior to or active at the time of opioid analgesic use) or depressive symptoms as a significant risk factor in the development of OUD (Jani *et al*., 2020; Just *et al*., 2018; Just *et al*., 2020; Kimergård *et al*., 2017). Anxiety also appears to have an important role as detailed by Chenaf *et al*. (2016) who explain that higher levels of anxiety are found in opioid abusers. Kimergård *et al*. (2017) also investigated the reasons for using opioid medications in an online survey, they found that codeine non-dependent users mostly use opioids for pain management while codeine addicts report less likely this reason for their use and more likely report using opioid to help relax, decrease their worries about their problems and decrease withdrawal symptoms from other opioids.

Among other comorbidities that may promote the development of an OUD, an history of addiction is present in three articles. Tjäderborn *et al*. (2009) report an increased risk of developing OUD in patients with a documented history of substance abuse. In their study, 30% of the patients suffering from tramadol dependence had a documented history of substance abuse and 39% had a documented history of drug abuse in the last 10 years. Jani *et al*. (2020) also report an increased risk of developing chronic opioid use for patients with a history of substance abuse, especially those who use alcohol in excess. Guillou-Landreat *et al*. (2021) also discuss a history of addiction as a risk factor for opioid medication misuse, but like Tjäderborn *et al.* (2009) they do not identify a particular substance as being responsible.

Three articles identified a link between chronic non-cancer pain (CNCP) and the development of OUD. Tjäderborn *et al*. (2009) suggests that the typical individual at risk is a middle-aged man or woman with chronic pain. They explain the need for opioid treatments in this population by a high prevalence of pain disorders at that age. Because of the pervasive pain they cause, Jani *et al*. (2020) specifically identify fibromyalgia, rheumatologic conditions and diabetes as the chronic conditions that most increase the risk of developing chronic opioid use. Finally, Steen *et al.* (2020) identify the existence of neurological conditions that required neuropathic pain medication prior to amputation as a risk factor for the development of chronic opioid use. This association between pre-operative use of neuropathic medication and persistent postoperative opioid usage suggests that a large portion of these

patients are already experiencing substantial pain pre-operatively, and that this pain does not improve with amputation.

Family impact

The article by Ahammer & Halla (2022) is the only study included in the review that looks at the impact of the family environment on opioid dependence.

Firstly, if parents are opioid users, their children are themselves at greater risk of developing problematic use. The authors of the study found that if either parent used prescription opioids, the probability that the child would also use them increased from 3.6% to 6.7%. The greater and longer the exposure to opioid use, the higher the estimates of intergenerational persistence.

Family composition also plays an important role: children born in wedlock are significantly less likely to use illicit opioids on the one hand, but also to take prescription opioids on the other, than children born out of wedlock. The authors estimate an 8.4% reduction in intergenerational persistence in this case. The mother's professional occupation also has an impact: the authors find a 6.7% reduction in persistence if the mother is self-employed, and 5% if she is a stay-at-home mother. Marriage maintenance and the mother's work characteristics therefore appear to be protective factors against children's opioid use.

Lastly, the child's ethnic group and religion play a role : children from a Catholic family have the lowest probability of using opioids, while children from a Muslim family have the highest probability of becoming users. The authors point out, however, that this impact may simply be correlated with other environmental characteristics that have an impact on drug use.

Environmental risk factors

Medical history

Two studies found a significant association between the experience of traumatic injury and the development of a problematic opioid use (Åström *et al*., 2019; von Oelrich *et al*., 2020). Among injured patients included in the study by von Oelrich *et al*. (2020), opioid users were more severely injured than non-users, and a significant association is present between traumatic exposure and chronic opioid use. These findings are in line with those from the study by Åström *et al*. (2019), which also found a significant association between traumatic injury and chronic opioid use, even more so in the case of severe injuries requiring extensive surgery. In both studies, most patients still had opioid prescriptions one year after the trauma. This duration is considered inappropriate as it exceeds the period of tissue damage and initial healing, when opioids have a well-established place

in the treatment of acute pain (Åström *et al*., 2019).

Wound severity therefore seems to have an impact on post-operative opioid consumption, as does wound location. Indeed, injuries located in certain areas of the body seem to cause more risk of developing OUD than others. For example, injuries to the legs, thorax and spine are more associated with chronic opioid use than injuries to the head, abdomen or arms (von Oelrich *et al*., 2020). This observation is also partly echoed in the study by Steen *et al*. (2020). The authors found that patients with lower-body amputations (between the hip and femur, or between the ankle and foot) had an increased risk of developing chronic opioid use, compared with patients with upper-limb amputations.

Another important risk factor in the development of chronic opioid use is pre-trauma opioid use (von Oelrich *et al*., 2020). To illustrate, we can cite the study by von Oelrich *et al*. (2020), where over 30% of chronic opioid users had received at least one prescription for an opioid medication in the 180 days prior to trauma. This risk factor is also demonstrated in another study, where prior use of potent opioids was associated with a higher risk of developing shopping behaviors to obtain codeine (Chenaf *et al*., 2016).

Finally, hospitalization increases patients' risk of developing OUD. A stay in Intensive Care Unit (ICU), even for a short period, is significantly associated with chronic opioid use in patients (Åström *et al*., 2019; von Oelrich *et al*., 2020). In addition to this, the longer the duration of hospitalization, the more it is associated with chronic opioid use (Åström *et al*., 2019). These findings are in line with the risk factors cited above, since a logical link can be established between an intense and complex traumatic injury and a need for hospitalization or intensive care in ICU.

Consumers' behaviors

Consumers themselves can adopt behaviours that increase their risk of developing an OUD. Some of the participants in the study from Guillou-Landreat *et al*. (2021) presented the following misuse behaviours : not following the doctor's instructions regarding their opioid prescription (16.5% of the sample), using opioids for a reason other than pain management (15.6%), taking higher doses than recommended (13.9%) and taking opioids more frequently than recommended (10.4%). Among all these behaviors, consuming more frequently than recommended was the most significantly associated with the likelihood of developing moderate-to-severe OUD (Guillou-Landreat *et al*., 2021).

The study by Kimergård *et al*. (2017) takes a closer look at the different forms of doctor shopping behavior, depending on whether

the consumer is seeking prescription-only (PO) opioids or OTC opioids. Regarding PO codeine, 14.1% of participants reported having ever exaggerated or faked symptoms to obtain a prescription. 14% of the sample also reported having obtained prescriptions from at least three different prescribers in the previous 6 months. For OTC codeine, the most frequent behavior was to buy the drug from at least 3 different pharmacies in the previous 6 months (35.8% of participants). Finally, 2.2% of the sample reported having ordered codeine over the Internet after having been refused a purchase in a pharmacy. In this study, shopping behavior is significantly associated with the development of codeine dependence (Kimergård *et al*., 2017). We also recall that “shoppers” have an adjusted risk of all-cause mortality almost three times higher than non-shoppers (Chenaf *et al.*, 2019).

Health professionals' behaviors

Various behaviors from healthcare professionals can increase their patients' risk of developing OUD. First and foremost is the lack of information given to patients. A lack of education about the addictive potential of opioids and the other risks inherent to their use was identified as a risk factor in Kinnaird *et al*. (2019). Several study participants explained that they had not fully understood the risks before starting their treatment, and expressed frustration with their general practicioner (GP), who they felt should have given them more information. Among the barriers to communication identified by the participants, they find the length of consultation (around 10 minutes), which was felt to be too short, and the feeling of not being listened to or taken seriously by medical staff. According to Chenaf *et al*. (2016), the addictive effect of codeine is underestimated because of its "weak" opioid status. In particular, the addictive potential and the overdose risk when combined with other drugs such as benzodiazepines is not well communicated to patients.

Secondly, a lack of monitoring and follow-up of patients undergoing opioid treatment increases the risk of developing OUD. Kinnaird *et al*. (2019) show that repeating prescriptions with few or no restrictions increases both the quantities taken and the risk of using codeine for a reason other than that of the initial consultation. This behavior is further encouraged by the fact that treatment is minimally supervised by professionals. Jani *et al*. (2020) also explain that chronic opioid use is facilitated by prescribers providing repeated prescriptions without regularly reviewing the efficacy and appropriateness of the treatment.

The choice of prescribed opioid also plays an important role in the development of OUD. Jani *et al*. (2020) show that starting

directly with potent opioids (dosage above 120 MME[4]/day) increases the risk of continuing with increasingly potent dosages during the year following initiation of treatment in patients with chronic pain. Guillou-Landreat *et al*. (2021) reach the same conclusion in the same population: people starting on more potent opioids, and oxycodone in particular, are more likely to develop a moderate to severe form of opioid use disorder (4 symptoms or more according to DSM-5). Finally, according to Kinnaird *et al*. (2019), doctors who prescribe codeine as a first-line pain medication increase their patients' risk of developing dependence.

Physicians therefore seem to bear a significant share of the responsibility for the development of problematic opioid drug use. The qualitative study of Kinnaird *et al*. (2019) adds another reasoning concerning the role of the pharmacist. This study suggests that problematic codeine use was also facilitated by minimal interaction with the pharmacist. Thus, most OTC codeine users in the study reported that they were rarely questioned by pharmacists about whether codeine was a safe choice, even when they regularly visited the same pharmacy and obtained large quantities of codeine (Kinnaird *et al*., 2019). This seems to be linked to the fact that patients do not develop a relationship of trust with their pharmacist. Interactions with the pharmacist are perceived as "less important" and therefore health education is not provided by the pharmacist. In addition, consumers feel less guilty about lying to their pharmacist to obtain codeine than they do about lying to their GP. Finally, participants also noted that the ease and speed of access to obtain codeine at the pharmacy deterred them from waiting and consulting their doctor about their codeine use (Kinnaird *et al*., 2019).

Macroeconomic risk factors

Employment

Guillout-Landreat *et al*. (2021) refer to psycho-social difficulties. According to them, financial difficulties and difficulties in maintaining or taking on employment can contribute to a person's vulnerability to develop OUD. This observation is shared as well by Ahammer & Halla (2022). In their study, they observed that the higher the employment rate in the community, the lower the risk of using opioids (Ahammer & Halla, 2022).

In the study by Jani *et al*. (2019), three regions of England are associated with the highest levels of long-term opioid use. These regions are : North-West, Yorkshire and the Humber, and South West. These regions are also associated with

[4] Morphine Milligram Equivalent

intermediate (in the case of South-West) to high (in the case of North-West and Yorkshire and the Humber) levels of deprivation. However, the authors did not find such high proportions in the North-East region, which is also one of the most deprived (appendix 3).

Healthcare characteristcs

The way medication is delivered seems to have an impact on people's opioid consumption. In Kimergård *et al*. (2017), 43.7% of participants had OTC products sold in pharmacies as their main source of codeine, 43.4% consumed mainly PO codeine and 3.2% of the sample obtained most of their codeine by ordering freely on Internet. Some patients report having been able to "feed" their codeine addiction due to the easy access in pharmacies, without having to consult their doctor and without being questioned by pharmacists about their consumption (Kinnaird *et al*., 2019). OTC codeine is associated with a higher risk of dependence when the regulations supposed to be enforced by pharmacists (control and limitations on quantities purchased) are absent (Kinnaird *et al*., 2019), while a ban on direct marketing to consumers seems to be a protective factor against the development of OUD (Just *et al*., 2020 ; Kimergård *et al*., 2017).

A lack of scientific research and the absence of precise guidelines concerning opioid-based pain treatments could have increased opioid consumption in the population. Overuse of codeine is observed in primary care, where its status as a "weak" opioid leads to an underestimation of the dependence risks (Chenaf *et al*., 2016 ; Kinnaird *et al*., 2019). Lack of knowledge about pain management and the various possible therapies (including non-pharmacological interventions) leads to overconfidence in opioid treatments, which are then overprescribed by some prescribers (Jani *et al*., 2020) or given as first-line treatment without assessing other, less risky possibilities (Kinnaird *et al*., 2019).

Furthermore, the lack of psychological, social and community resources, as well as the lack of pain specialists and social workers, prevent the development of effective prevention and rehabilitation strategies for people using opioids (Kinnaird *et al*., 2019). For some patients, the disengagement of healthcare professionals, the lack of access to appropriate resources and patient responsibility to self-manage their addiction encourages patients to use the internet to get more information about codeine and how to manage addiction (Kinnaird *et al*., 2019). We also see this in the study by Kimergård *et al*. (2017), in which 12% of the sample report seeking advice on the internet, only 5.4% prefer to consult a doctor and less than 1% seek advice from the pharmacist. Others prefer to seek advice from family or friends

for information. These means can be beneficial, as they increase patients' autonomy and confidence in their own ability to manage their treatment. However, these sources also lead to potentially inaccurate information that can delay or prevent patients from seeking help from healthcare professionals (Kinnaird *et al*., 2019).

Finally, of the total sample included in Kimergård *et al*. (2017), only 2.5% received specialized treatment for their codeine dependence. This fact further illustrates the lack of accessible specialized resources, or at least the lack of knowledge about them.

Tackling all these risk factors will undoubtedly require a change in the economic environment that governs resource availability (Kinnaird *et al*., 2019).

Table 1: Presentation and methodological characteristics of included articles						
Authors and year of publication	**Title**	**Localisation**	**Type of article**	**Sample size**	**Data source**	**Data collection period**
von Oelreich, E. *et al*. (2020)	Risk factors and outcomes of chronic opioid use following trauma	Sweden	Cohort Study	n=83.930 -Injured patients : n=13.309 -Control group : n=70.621	Trauma register from the Karolinska University Hospital	January 2006-December 2015
Guillou-Landreat, M. *et al.* (2021)	Analgesic Opioid Misuse and Opioid Use Disorder among Patients with Chronic Non-Cancer Pain and Prescribed Opioids in a Pain Centre in France	France	Cross-sectional study	n=115	Self-administered questionnaires from patients of the pain centre of Brest University Hospital.	June 2016 - September 2016
Chenaf, C. *et al.* (2016)	Codeine Shopping Behavior in a Retrospective Cohort of Chronic Noncancer Pain Patients: Incidence and Risk Factors	France	Retrospective cohort study	n=1958 -Nonshoppers : n=1893 -Shoppers : n=65	"*Echantillon Généraliste des Bénéficiaires*" database from the French national health insurance system	January 2004 - September 2013

Tjäderborn, M. *et al*. (2009)	Tramadol dependence: a survey of spontaneously reported cases in Sweden	Sweden	Case-control study	n=104	"Swedish Drug Information System" database	January 1995 - December 2006
Just, M. *et al.* (2018)	Risk of opioid misuse in chronic non-cancer pain in primary care patients - a crosssectional study	Germany	Cross-sectional study	n=93	Self-report questionnaires from patients of 15 GPs located in the Bonn Area	No information
Kimergård, A. *et al.* (2017)	Codeine use, dependence and help-seeking behaviour in the UK and Ireland: an online cross-sectional survey	UK + Ireland	Cross-sectional study	n=316	Self-report online questionnaire	July 2015 - March 2016
Chenaf, C. *et al*. (2019)	Prescription opioid analgesic use in France: trends and impact on morbidity-mortality	France	Cross-sectional study	n=98.122	"*Echantillon Généraliste des Bénéficiaires*" database from the French national health insurance system	January 2004 - December 2017
Kinnaird, E. *et al.* (2019)	From pain treatment to opioid dependence: a qualitative study of the environmental influence on codeine use in UK adults	UK	Qualitative study	n=16	Semistructured interviews on patients recruited online	May 2015 -April 2016

Just, J. *et al.* (2020)	Rate of opioid use disorder in adults who received prescription opioid pain therapy - A secondary data analysis	Germany	Cross-sectional study	n=9204	Epidemiological Survey of Substance Abuse from 2015	March 2015-July 2015
Jani, M. *et al.* (2020)	Time trends and prescribing patterns of opioid drugs in UK primary care patients with non-cancer pain: A retrospective cohort study	UK	Retrospective cohort study	n=1.968.742	"Clinical Practice Research Datalink" database	January 2006-December 2017
Steen, T. *et al*. (2020)	The demographics of persistent opioid consumption following limb amputation	Iceland	Retrospective cohort study	N = 328	Landspitali University Hospital electronical database	December 2005-December 2015
Åström, J. *et al*. (2019)	An observational study on risk factors for prolonged opioid prescription after severe trauma	Sweden	Observational study	N = 29	"SweTrau" database and "Take Care" electronical medical records from the Stockholm region	April 2013-March 2015
Ahammer, A. & Halla, M. (2022)	The intergenerational persistence of opioid dependence: Evidence from administrative data	Austria	Empirical analysis	n=81.307	Several administrative databases, including "Upper Austrian Health Insurance Fund" database	1984-2017

Table 2: Summary of risk factors associated with the development of problematic opioid use

Authors and year of publication	Opioid type	Problematic consumption type	Socio-demographic risk factors	Environmental risk factors	Macro-economic risk factors
von Oelreich, E. *et al*. (2020)	All prescription opioids	Chronic use	▪Age : Older age (75+) ▪Sex : Female ▪Level of education : Low level (9 years or less) ▪Comorbid condition : History of psychiatric disorder	▪Traumatic injury ▪Preinjury opioid use (minimum 1 prescription in the 180 days preceding the trauma) ▪Severe thoracic/spinal/leg injury (in comparison with head/abdominal/arm injury) ▪ICU admission	No information
Guillou-Landreat, M. *et al.* (2021)	All prescription opioids	Misuse	▪Comorbid conditions : History of psychiatric disorder, history of substance abuse, history of neurological disorder	▪Strong opioids prescription (in comparison with weak and moderate opioids), particularly oxycodone ▪Taking more frequent doses than prescribed (in comparison with taking a higher dosage than prescribed)	▪Unemployment

Chenaf, C. et al. (2016)	Codeine	Shopping behaviors	▪Age : Younger age (<40 years) ▪Income : Low income ▪Comorbid condition : History of psychiatric disorder	▪Previous use of opioids ▪Lack of patient education about addictive potential of codeine ▪Lack of knowledge about effective and safe pain management	No information
Tjäderborn, M. *et al.* (2009)	Tramadol	Dependence	▪Age : Middle-age (around 45 years) ▪Comorbid condition : Chronic pain, history of substance abuse	No information	No information
Just, M. *et al*. (2018)	All prescription opioids	Misuse	▪Level of education : Low level (high school only) ▪Comorbid condition : History of depression	No information	No information
Kimergård, A. *et al*. (2017)	Codeine	Misuse and dependence	▪Age : Middle-age (around 45 years) ▪Comorbid conditions : Emotional distress (anxiety, depression)	▪Shopping behaviours ▪Daily use ▪Lack of patient education about the side effects of codeine	No information

Chenaf, C. *et al*. (2019)	All prescription opioids	Shopping behaviors	▪Age : Younger age (<45 years) ▪Sex : Male ▪Income : Low income ▪Comorbid condition : History of psychiatric disorder	No information	No information
Kinnaird, E. *et al*. (2019)	Codeine	Dependence	No information	▪Lack of information and communication between the GP and the patient resulting in a lack of patient education ▪Possibility to repeat prescription with no or little restrictions on amount and frequency ▪Minimal supervision on codeine therapy from health professionals ▪Being prescribed codeine as a first resort for pain ▪Minimal interaction with the pharmacist/no pharmacist regulation/lack of trust in the relation pharmacist-patient	▪Breakdown in structures to stop sales of codeine for use other than as indicated ▪Perceived limitations of pain therapy in primary care resulting in overreliance on codeine ▪Lack of psychological, social community and pain specialist resources ▪Inabilities to effectively monitor OTC codeine consumption and intervene to halt escalating use

Just, J. et al. (2020)	All prescription opioids	OUD	▪Comorbid condition : History of psychiatric disorder	No information	▪Protective environmental factors : compulsory health insurance, accessible primary care sector/specialized pain therapy/opioid maintenance therapy/specialized addiction therapy, regulatory restrictions for opioids
Jani, M. et al. (2020)	All prescription opioids	Chronic use	▪Age : Older age (75< years) ▪Comorbid condition : History of depression, history of substance abuse, fibromyalgia, rheumatological condition, diabetes	▪High initial dose ▪High potency ▪Prescribers with high prescribing practice ▪Prescribers providing repeat prescriptions, assuming drug effectiveness without regular review	▪High level of social deprivation ▪Unclear guidance regarding best practice in managing non-cancer pain and considerable heterogeneity in guidance internationally regarding dose thresholds that warrant caution ▪Minimal guidance based on scientific evidence on how best to reduce/discontinue opioids in chronic pain

Steen, T. et al. (2020)	All prescription opioids	Chronic use	▪Age : Older age (60< years) ▪Gender : Male ▪Comorbid conditions : History of psychiatric disorder, history of neurological disorder	▪Lower extremity amputation (compared with upper extremity amputation)	No information
Åström, J. et al. (2019)	All prescription opioids	Chronic use	▪Comorbid conditions : History of psychiatric disorder	▪High injury severity ▪Extensive surgery ▪Extended hospital stay ▪Preoperative opioid use	No information
Ahammer, A. & Halla, M. (2022)	All prescription opioids (+illicit opioids)	Dependence	▪Having at least one parent using prescription opioids ▪Religion : Muslim (in comparison with Catholic) ▪Family composition : Being born outside of wedlock (in comparison with inside of wedlock) ▪Level of education : Lower level	No information	▪Lower employment in the community

Discussion

Unlike in the US, there is no typical at-risk community that emerges from the synthesis of studies included in this review. However, certain risk factors appear to be unanimous, and are both found in studies carried out in Europe and in the US. The risk factor that recurs most frequently in this review is the existence of a mental disorder, particularly depression and anxiety. A mental disorder combined with opioid use favor the development of OUD, and the same conclusion is drawn in the US. For example, in Blanco & Volkow (2019), a history of anxiety disorder increases the risk of OUD by 50%, and a history of addiction to another substance increases the risk by 300%. History of addiction is highlighted as well in this review (Tjäderborn *et al*., 2009; Jani *et al*., 2020; Guillou-Landreat *et al*., 2021). Depression is significantly associated with opioid misuse in Grattan *et al*. (2012) and with chronic use in Haider *et al*. (2020) and Sullivan (2018). Similarly, a low level of education and difficulties relating to employment and/or income are considered risk factors for the development of OUD as much in Europe as in studies in the US (Altekruse *et al*., 2020; Haider *et al*., 2020).

The results obtained are not only consistent with those from the US, but also with each other. Indeed, the scientific literature has already shown that certain populations accumulate multiple pains : more precarious populations also have a generally lower level of education, more mental problems and suffer more from chronic pain (Cockerham *et al*., 2016; Kuruvilla & Jacob, 2007; Murali & Oyebode, 2004; Silva-Laya *et al*., 2020). In the study by Ahammer & Halla (2022), we saw that inequalities in the development of OUD can begin in childhood. Children who are exposed to their parents' problematic opioid use are more likely to evolve in an unstable living environment, encountering various obstacles such as conflict, violence and emotional difficulties (Ahammer & Halla, 2022). These experiences often lead to various difficulties and limitations in adulthood, whether social, psychological or financial, and thus create a fertile ground for the development of OUD with populations that accumulate risk factors.

Although there are similarities in certain aspects, the biggest differences between Europe and the US lie in environmental and macro-economic risk factors.

Several studies in Europe have focused on a source of opioids that is absent in the US : OTC opioids, the best known being codeine. In France, codeine was the best-selling opioid analgesic in 2013 and the third best-selling drug of all drugs combined (Chenaf *et al*., 2016). In 2016, the UK was the world's second largest

consumer of codeine (Kinnaird *et al*., 2019). These countries both have OTC codeine. The accessibility of OTC codeine was identified as a risk factor for the development of dependence and misuse in this review. Indeed, the absence of pharmacist interpellation, the possibility of visiting several different pharmacies and the fact of not having to lie to the doctor to obtain several prescriptions may contribute to nurturing patients' addiction (Kinnaird *et al*., 2019). Codeine addiction could be reduced if resctrictive measures were put in place (Kimergård *et al*., 2017; Kinnaird *et al*., 2019) as in Germany or the US, where opioids are available by prescription only (Just *et al*., 2018; Just *et al*., 2020). However, there are other arguments against introducing such restrictions. The first reason given is that the demonization of opioids leads to controls and restrictions that result in difficulties in accessing pain treatments (Tjäderborn *et al*., 2009). According to the WHO, reduced access to opioid-based treatments has led to severe under-treatment of pain in over 150 countries, where a minority of patients have access according to very strict criteria (Tjäderborn *et al*., 2009). It has also been suggested that access to OTC codeine can both ease the burden on primary care (by reducing the number of GP consultations) and contribute to patient empowerment (Kinnaird *et al*., 2019). We can therefore see that there are advantages and disadvantages to each approach, and it would be ideal to be able to balance the two. It would be possible, for example, to maintain OTC sales of reduced dosages of certain opioids, but increase their control and the patient knowledge in order to oppose shopping behavior.

Strengthening controls on opioid use and preventing the development of OUD in at-risk populations can only be achieved with the involvement of healthcare profess-sionals. We have seen that the lack of information and education given to patients encourages the development of OUD (Chenaf *et al*., 2016; Kinnaird *et al*., 2019). Certain individual characteristics have been identified as risk factors in the development of OUD, so it seems adequate to recommend greater awareness of these at-risk profiles by healthcare providers (Jani *et al*., 2020). Despite physicians' central role in communicating the risks and monitoring opioid treatment, they may be limited by a series of obstacles linked to the healthcare system, such as a lack of resources and a lack of time to devote to their patients (Kinnaird *et al*., 2019). Communication could also be impaired by a lack of awareness on the part of doctors, who disempower themselves and consider that patients' addiction is mainly the result of individual behaviors and a lack of self-control (Kennedy-Hendricks *et al*., 2016).

This perception of patients' control or responsibility over the disease can lead to negative judgments and attitudes of detachment from healthcare professionals (Van Boekel *et al*., 2013), resulting in poorer care and follow-up (Kennedy-Hendricks *et al*., 2016). These various obstacles could explain why we found in our review that some patients felt insufficiently supported and preferred to seek advice on the Internet (Kimergård *et al*., 2017; Kinnaird *et al*., 2019). Over-responsibilization of patients is also a possible cause of over-prescription of opioids by some doctors, who are then responsible for an excessive number of prescriptions but also tend to prescribe for longer durations (Jani *et al*., 2020). Studies in the US show that over-prescribing opioids has been a major factor in the development of the opioid crisis (Chisholms-Burns *et al*., 2019; Jani *et al*., 2020; Vadivelu *et al*., 2018) and increase the risk of chronic use, misuse and diversion of drugs (Neuman *et al*., 2019). Finally, given that some European countries have OTC opioids, it seems important not to overlook the role of the pharmacist. In Kimergård *et al*. (2017), the hypothesis is that greater involvement of pharmacies in the identification, treatment and referral processes would be highly beneficial and would offer immediate support as close to the community to people suffering from OUD. This idea is supported in Chisholms-Burns *et al*. (2019), who argue that the pharmacist has a key role in the prevention and monitoring of OUD.

Another possible cause of over-prescribing could be the lack of uniformity in opioid treatment guidelines. In Jani *et al*. (2020), the authors explain that in the US precautions are advised at 50 MME/day and above, whereas in the UK it is suggested that treatment be re-evaluated at 120 MME/day. There is thus a lack of scientific consensus on the risk-benefit balance of opioid treatments.

Furthermore, we found that opioids were widely prescribed in Europe for CNCP despite what the guidelines say (Chenaf *et al*., 2016; Guillou-Landreat *et al*., 2021; Just *et al*., 2018). This review showed that consuming opioids in the context of CNCP increased people's risk of developing OUD. In the US opioid crisis, pharmaceutical lobbies were primarily responsible for promoting opioids to treat CNCP : in particular, they used intensive and aggressive marketing campaigns that downplayed both the risks of addiction and tolerance, and exaggerated the benefits (Chisholms-Burns *et al*., 2019; Maclean *et al*., 2022; Vadivelu *et al*., 2018). We can cite the example of Purdue Pharma, the company behind the marketing of OxyContin, which is often seen as the trigger for the opioid crisis in the US

(Maclean *et al*., 2022). In 2001, the manufacturer spent $200 million promoting OxyContin : more than 20,000 conferences encouraging healthcare professionals to prescribe OxyContin, free coupons and promotional products offered to patients, bonuses for their representatives who managed to sign up the most doctors, etc. This resulted in a 10-fold increase in prescriptions in 2002 (Vadivelu *et al*., 2018). We have not found such a phenomenon in the European literature. We can then turn to another line of thought that has been highlighted in this review : the lack of knowledge about pain management. Jani *et al*. (2020) and Kinnaird *et al*. (2019) consider that lack of knowledge about pain management has contributed to over-reliance on opioids, prescribing them in overly high doses and as a first-line treatment without considering other, less risky alternatives. A study conducted in the US reveals that doctors regularly report that medical school does not prepare them sufficiently for pain management : the number of hours devoted to this topic by 104 medical schools during the entire educational curriculum varies between 11 and 31 hours (Helmerhorst *et al*., 2017). This can also be observed in Europe, where many medical schools devote little or no time to pain management in their curriculum, and where the subject is considered "secondary" compared to the rest (Larjow *et al*., 2016).

Finally, economic risk factors have received little attention in this review. Two studies from Germany suggest that a potential opioid crisis was partially averted due to key elements of their healthcare system (Just *et al*., 2018 ; Just *et al*., 2020). The authors cite, among other things, compulsory, high-quality healthcare, a ban on direct-to-consumer marketing by the pharmaceutical industry, compulsory health insurance, a well-funded and accessible primary care sector, easy access to specialized pain and addiction therapies (Just *et al*., 2018; Just *et al*., 2020). However, these elements are not present in all European countries, so it makes sense to take a closer look at the societal and healthcare system influence on opioid use in European populations. This will have to take into account the great diversity between the different European countries.

Limitations

There are a number of limitations to this review, partly related to the content of the studies included. Several authors pointed out that, despite rising opioid consumption, there is very little data available on the profile of opioid users in Europe. Chenaf *et al*. (2019) explain that unlike the US, France has no monitoring system to identify and track trends in opioid use. Just *et al*. (2020)

explain much the same thing : they suggest that the underfunding of cause-of-death analysis in Germany and the lack of monitoring of opioids other than heroin creates a blur around opioid users.

Such a lack of data could also be due to the difficulty of identifying an OUD. To make a diagnosis of OUD, the patient must present at least 2 of the 11 symptoms listed by the DSM-5. However, these symptoms seem difficult to assess, since they are essentially based on what the patient agrees to communicate. As we have seen, addiction is still a highly stigmatized phenomenon : patients may therefore wish to minimize or even conceal their symptoms for fear of negative judgment.

This may have led to various biases in the included studies. Indeed, the samples in some of them were created on a voluntary basis by patients, through self-report. Here again, the stigma of addiction could have led to social desirability bias or selection bias for example, possibly causing a lack of representativeness in the sample or an underestimation of the populations' consumption.

Secondly, as demonstrated in this review, OUD can take many forms : dependence and the behaviors associated with it can take the form of abuse in dosage, abuse in frequency, shopping behaviors, chronic consumption, and so on. As all the articles did not focus on the same facet of the disorder, it was complicated to draw generalities or conclusions about some risk factors.

Finally, we noted a lack of inclusion of non-individual factors in the analyses carried out by the various authors. Indeed, when we looked at environmental and macro-economic risk factors, the data rarely came from more than three of the 13 articles included.

Other limitations have to do with the choices made in producing this review. Our aim was to provide a picture of the European situation. However, we found that there were significant differences across European countries. It therefore seems inappropriate to generalize on such a large scale. We could consider “breaking down” Europe for future studies on this subject, for example by grouping countries according to the way their healthcare systems function and are structured, or according to the economic context in which they evolve. This would enable us to take better account of the responsibility and specifity of environmental and societal factors.

This will only be possible once research has been carried out in more areas. Current research is essentially focused on Scandinavia, Germany, UK and France. As a result, a large part of Europe, namely Eastern Europe and Mediterranean Europe, is not included.

Finally, much has changed since the beginning of the opioid crisis. Studies carried out in the US have highlighted that consumption has shifted from prescribed opioids to illicit opioids, notably heroin and Fentanyl, which are now considered to be the new hotspots in the opioid crisis in the US and Canada (Altekruse *et al*., 2020; Chisholms-Burns *et al*., 2019; Maclean *et al.*, 2022; Pierce *et al*., 2021). In our review, we have chosen to consider only prescribed opioids. To complete the research, we should therefore consider looking at opioid use disorder in the context of illicit opioid use.

Conclusion

Although some of the individual risk factors for the development of OUD present in the US do not stand out in the synthesis of European literature, other important factors appear to be quite similar. In particular, mental illness, chronic pain, a lower level of education and precariousness are common to both the US and Europe. However, analysis of environmental and macro-economic factors highlights the many differences between the two continents, suggesting that the risk factors identified in the US opioid crisis are not quite the same as those present in Europe. Given the lack of information on the profiles of opioid users in Europe, and the lack of research into consumption trends, it is not yet possible to determine whether Europe also faces an opioid crisis. Nonetheless, this review demonstrates the existence of a public health problem that should not be neglected nor minimized.

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Appendixes

Appendix 1 : DSM-5 Criteria for Diagnosis of Opioid Use Disorder

In order to confirm a diagnosis of OUD, at least two of the following should be observed within a 12-month period:

- Opioids are often taken in larger amounts or over a longer period of time than intended.
- There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
- A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
- Craving, or a strong desire to use opioids.
- Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
- Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
- Important social, occupational or recreational activities are given up or reduced because of opioid use.
- Recurrent opioid use in situations in which it is physically hazardous.
- Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
- Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect ; (b) markedly diminished effect with continued use of the same amount of an opioid.
- Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome ; (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms.

Severity can be :

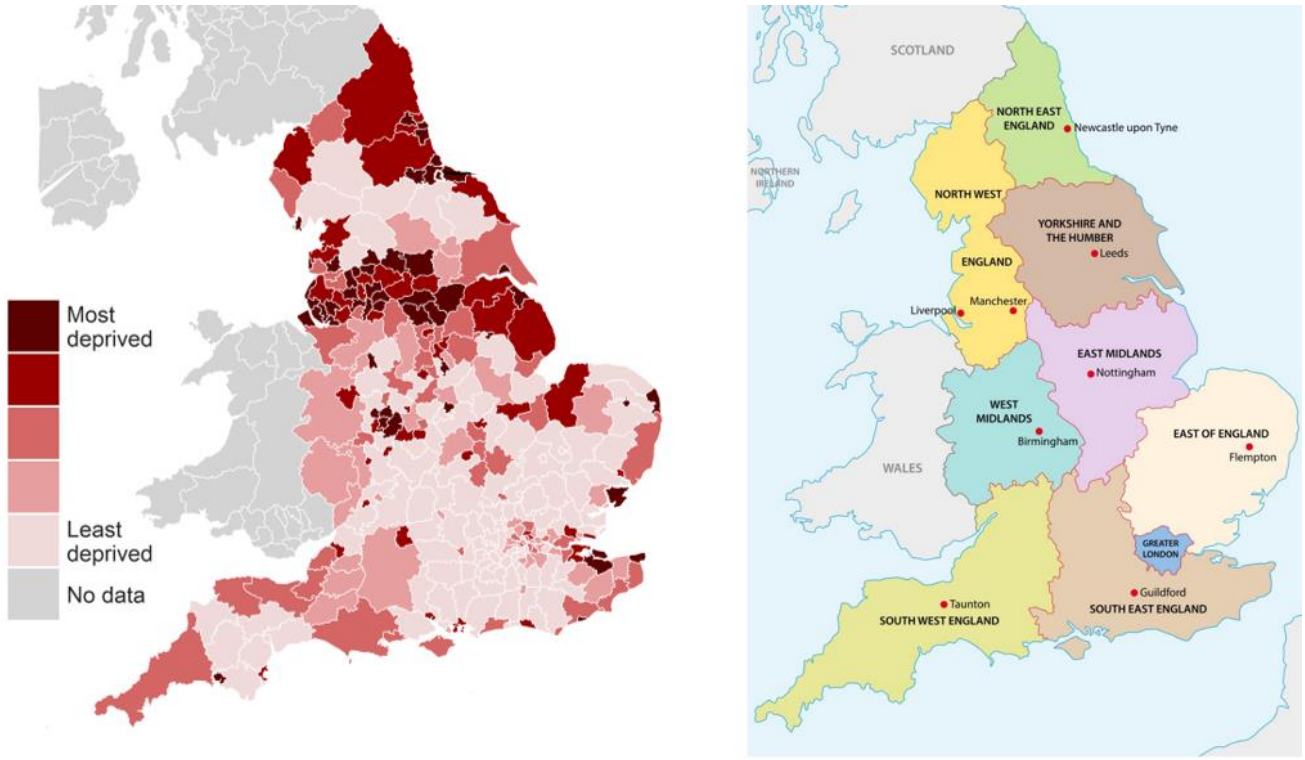
- Mild : 2-3 symptoms
- Moderate : 4-5 symptoms
- Severe : 6 or more symptoms

Appendix 2 : Search equations used for the different databases

PUBMED	"Opioid-Related Disorders"[Majr] AND (diagnosis OR prevention OR risk factors) AND Europe

EBSCOHOST (Medline + Academic Search Premier)	("opioid use disorder" or "opioid related disorder" or "opioid dependence" or "opioid addiction" or "opioid misuse" or "opioid prescription misuse" or "opioid abuse") AND ("risk factors" or "contributing factors" or "predisposing factors") AND "europe"
Econlit	("opioid use disorder" or "opioid related disorder" or "opioid dependence" or "opioid addiction" or "opioid misuse" or "opioid prescription misuse" or "opioid abuse") AND "europe"

Appendix 3 : Indices of multiple deprivation across England in 2019



(source : BBC News)

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