Addiction

REVIEW

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Development of dependence following treatment with opioid analgesics for pain relief: a systematic review

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ABSTRACT

Aims To assess the incidence or prevalence of opioid dependence syndrome in adults (with and without previous history of substance abuse) following treatment with opioid analgesics for pain relief. **Methods** Medline, Embase, CINHAL and the Cochrane Library were searched up to January 2011. Systematic reviews and primary studies were included if they reported data about incidence or prevalence of opioid dependence syndrome (as defined by DSM-IV or ICD-10) in patients receiving strong opioids (or opioid-type analgesics) for treatment of acute or chronic pain due to any physical condition. The data were abstracted, and the methodological quality was assessed using validated checklists. **Results** Data were extracted from 17 studies involving a total of 88 235 participants. The studies included three systematic reviews, one randomized controlled trial, eight cross-sectional studies and four uncontrolled case series. Most studies included adult patients with chronic non-malignant pain; two also included patients with cancer pain; only one included patients with a previous history of dependence. Incidence ranged from 0 to 24% (median 0.5%); prevalence ranged from 0 to 31% (median 4.5%). **Conclusions** The available evidence suggests that opioid analgesics for chronic pain conditions are not associated with a major risk for developing dependence.

Keywords Incidence, opioid analgesics, opioid dependence, pain relief, prevalence, systematic review.

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INTRODUCTION

Many patients world-wide do not receive adequate pain relief because of excessive regulatory restrictions on the availability and accessibility of opioid analgesics.

The problem of opioid over-regulation has been highlighted in reports from the International Narcotics Control Board (INCB) [1–4], the World Health Organization (WHO) [5], the WHO Collaborating Centre Pain and Policy Study Group [6,7], the Council of Europe [8] and by non-governmental organizations such as the Open Society Institute and Human Rights Watch [9]. A survey was conducted recently in all European countries to assess opioid formularies, including topics concerning regulations relating to dose limits, prescribing, dispensing and emergency situations [10].

A recent systematic review on the prevalence of undertreatment in cancer pain included 26 studies published from 1994 to 2007, and found that approximately 50% of patients are undertreated [11]. Another recent study reports that an estimated 83% of the world's population live in countries with low to non-existent access to medication for pain treatment, 4% have moderate access and only 7% have adequate access; only the populations of some industrialized countries have good access [12].

One reason for undertreatment is the reluctance of physicians to prescribe opioids at adequate dosages, due to concerns linked to possible opioid-induced hyperalgesia and the potential adverse effects, including fatal opioid overdose, development of tolerance and dependence syndrome, harmful use of opioid and diversion [13,14]. According to the DSM [15], dependence is a cluster of cognitive, behavioural and psychological symptoms indicating that the individual continues to use the substance despite significant substance-related problems. The fear that patients will develop dependence syndrome is particularly acute when prescribing opioids to treat a chronic non-cancer condition, as both the course of treatment and the patient's life expectancy of patients are often expected to be long.

A systematic review of four international studies found prevalence rates of pain of any type and severity level ranging from 10.5 to 55.2% [16]. A WHO survey of primary care patients seeking care in 14 countries worldwide found that 22% of primary care patients reported pain lasting more than 6 months [17]. Among chronic non-cancer pain, back pain is the most prevalent [18]. A systematic review aimed to assess the prevalence of opioid treatment in patients with chronic back pain, and found the proportion to vary substantially by treatment setting, ranging from 3 to 66% [19]. Other conditions for which opioids are prescribed include long-term post-trauma pain, osteoarthritis, rheumatoid arthritis, osteoporosis and neuropathic pain that may result from central or peripheral mechanisms. Self-reported rates of pain among HIV-infected patients range from 28 to 97%, varying with the method of assessing pain (verbal report versus pain scales) and with setting (clinics versus hospice facilities) [20]. The prevalence of pain in cancer patients has been estimated at approximately 64% in advanced or terminal phase cancer patients; at 59% in patients on anticancer treatment; and at 33% in patients after curative treatment [21]. In a European survey on 5084 adult cancer patients, 56% suffered moderate to severe pain at least monthly [22].

The primary objectives of the present review are to assess the incidence or prevalence of dependence syndrome in adults with and without previous history of substance abuse following treatment with opioid analgesics for pain relief. Secondary objectives are to assess any differences in the prevalence and severity of dependence syndrome with different types of opioid analgesics, different routes of administration and durations of treatment. This review was commissioned by the WHO, within the development of the WHO guidelines for pain treatment in adults.

METHODS

The following electronic databases were searched with combinations of free text keywords as well as controlled vocabulary terms without language restrictions: the Cochrane Library, issue 1 2011; PubMed (1966–January 2011); CINAHL (1982–January 2011); Embase (1980–January 2011 (Appendix S1; online supporting information: see details given at the end). References of all included papers and narrative reviews, conference proceedings and the following websites were also searched: http://www.who.int/ictrp/en/, International Clinical Trials Registry Platform (ICTRP), Current Controlled Trials (http://www.controlled-trials.com/), Clinical Trials.gov and Trialsjournal.com.

Studies were included if they reported data about incidence or prevalence of 'dependence syndrome' as defined by DSM-IV [15] or ICD-10 [23] in people with acute and chronic pain due to any physical condition. Dependence is a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three or more of the following symptoms occurring any time in the same 12-month period: tolerance, withdrawal syndrome, substance taken in a larger amount or a longer period than intended, unsuccessful effort to control or cut down use, great deal of time spent to obtain the substance, reduction of important social, occupational or recreational activities, continued use despite knowledge of having persistent or recurrent psychological or physical problem due to substance use. Dependence could be only psychological if no signs of tolerance and withdrawal syndrome are present, or also physiological if these signs are present [15]. Patients should receive any of the following strong opioid analgesics (by any route of administration): morphine, methadone, buprenorphine, oxycodone, fentanyl, hydromorphone, levorphanol or pethidine. Studies also had to be one of the following: randomized controlled trials (RCTs), controlled clinical trials (CCTs), prospective or retrospective controlled cohort studies and their systematic reviews; cross-sectional surveys; or uncontrolled case series with at least 10 patients enrolled. Two authors inspected the search hits independently, assessed each potentially relevant study for inclusion, and extracted data. Doubts were solved by discussion between all authors.

The following checklists were used to assess the methodological quality of the included studies: AMSTAR checklist [24] for systematic reviews, the Cochrane criteria [25] for RCTs and CCTs, and the Newcastle–Ottawa Quality Assessment Scale [26] for cohort and case–control studies. For case series, the following criteria were used: number of recruited subjects, consecutive versus non-consecutive recruitment and prospective versus retrospective recruitment. We also assessed the quality of the evidence in included studies according to the GRADE methodology [27].

Results are reported as the number (and percentages) of subjects who were diagnosed as dependents over the total number of subjects exposed to treatment. In order to realize a high-quality review, we followed the methodology recommended by the Cochrane Handbook [25] and we assessed our review with the AMSTAR checklist [24].

RESULTS

After removing duplicates, 2871 potentially relevant studies were retrieved with the search. After eliminating 2736 of these studies based on their titles and abstracts, 135 studies were acquired in full text for closer inspection. We further excluded 114 studies (Appendix S2; online supporting information: see details given at the

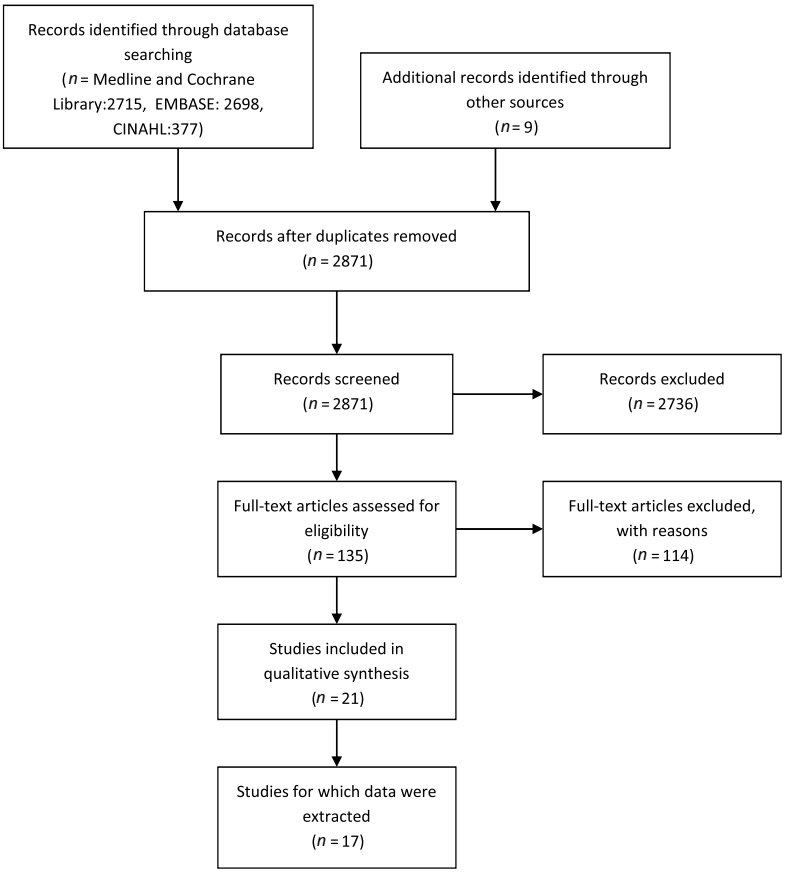

Figure 1 Flowchart showing identification of included studies

end) for the following reasons: type of outcome measures not in the inclusion criteria ($n = 85$), study design not in the inclusion criteria ($n = 28$), type of participants not in the inclusion criteria ($n = 1$). Twenty-one studies met all inclusion criteria [28–47]. In order to avoid double counting of studies that were discussed in more than one systematic review and also retrieved as a primary study, we checked our list against all references in review articles. We did not extract data from four studies because the results in one review [48] were superseded by those presented in an updated version [28], and three studies [29–31] were already discussed in two included systematic reviews [28,32]. Three primary studies were included in two reviews [29,31]; to avoid double counting of incidence data, we retrieved the full text of these articles and found that none of them reported data on incidence of dependence.

In total, we extracted data from 17 studies [28,34–47], involving a total of 88 235 participants. The studies included three systematic reviews [28,32,33], one RCT [34], eight cross-sectional studies [35–43] and four uncontrolled case series [44–47] (Fig. 1).

Two of the systematic reviews were of good methodological quality; one was a Cochrane review [28] with low risk of bias for all of the items assessed by the checklist, and the only flaws of the other review [33] were a lack of description of the characteristics of included studies and the assessment of possible publication bias. The third review [32] was of very low methodological quality, with a high risk of bias (Table 1). The RCT [34] was of moderate quality; the method of random sequence generation was adequate and subjects were not lost at follow-up, but the concealment of allocation was inadequate, and personnel, patients and outcome assessors were not blinded (Table 2). All but two [39,40] of the cross-sectional surveys were multicentre surveys recruiting a large number of patients (range 247–15 160). Only one study [41] assessing efficacy and safety of intrathecal morphine included only 19 participants. The case series were all of quite large size (range 86–904); all but one [47] used a consecutive recruitment of patents, and were retrospective (Table 3). While, for some studies, seeking actively for dependence was the primary objective of the work, for some others it was not; in those the prevalence of dependence could be underestimated.

Applying the GRADE methodology to the total results from all included studies resulted in determining a very low quality of evidence (Figs. 2 and 3).

Condition for which opioids were prescribed

All but seven studies included adult patients with chronic non-malignant pain caused by multiple clinical

Table 1 Methodological quality of systematic reviews.

Item	*Fishbain et al. 2008[34]*	*Littlejohn et al. 2004[32]*	*Noble et al. 2010[28]*
1. Was an 'a priori' design provided?	No	No	Yes
2. Was there duplicate study selection and data extraction?	Not reported	Unclear	Yes
3. Was a comprehensive literature search performed?	Yes	Unclear	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No (no selection bias)	Yes (only English language)	No (selection bias avoided)
5. Was a list of studies (included and excluded) provided?	Yes	No	Yes
6. Were the characteristics of the included studies provided?	No	No	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes	No	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	No	Yes
9. Were the methods used to combine the findings of studies appropriate?	Not applicable	Not applicable	Not applicable
10. Was the likelihood of publication bias assessed?	No	No	Yes
11. Were potential conflicts of interest included?	No	No	NO

Table 2 Methodological quality of randomized controlled trials (RCTs).

Adams et al. 2006[34]	
Method of randomization (avoidance of selection bias)	Yes
Allocation concealment (avoidance of selection bias)	No
Blinding of personnel and participants (avoidance of performance bias)	No
Blinding of outcome assessor (avoidance of detection bias)	No
Incomplete outcome data (avoidance of attrition bias)	Yes

conditions. Among the remaining studies, one included only patients with headache [33], two children or adolescents with sickle cell disease [37,39] and two [40,47] also included patients with cancer pain. Two studies [35,43] did not report the condition for which opioids were prescribed (Table 4).

Types of opioids administered

Seven studies did not report the type of opioid administered. Among the other nine studies, two systematic reviews [28,32] stated that use of any opioid was included, and the other systematic review [33] included studies assessing any opioid except for tramadol. The RCT [34] compared hydrocodone with tramadol. Two cross-sectional studies [40,43] reported combined data on dependence from use of both weak and strong opioids, and no separate data were reported; another study [41] included only patients receiving intrathecal morphine. Finally, one uncontrolled case series [46] included patients receiving intravenous administration of meperidine, morphine, hydromorphone and nalbuphine.

Length of treatment

Eleven studies reported data on the length of treatment. In one study [46], opioids were given for 3 days to treat acute pain, then administration was stopped and re-started on the following day only if severe pain recurred. In the other 10 studies [28,33,34,36–42,44,47], opioids were administered for a period ranging from 3 to 81 months.

Effects of the intervention

All the included studies were uncontrolled case series or cross-sectional surveys with high heterogeneity in the results. For this reason, although we had planned originally to perform a meta-analysis, we judged it to be not appropriate. Incidence was assessed by four case series [44–47], with 1361 participants and one RCT [34] with 4000 participants; additionally, two systematic reviews [28,33] with 3304 participants included case series that assessed incidence. Incidence ranged from 0 to 27% (median 4.9%). The other studies were cross-sectional studies; prevalence ranged from 0 to 31% (median 5.9%) (Table 4).

Data from one systematic review [32] were not considered because the authors did not report the study design of included studies, therefore it was not possible to know if data were related to incidence, prevalence or both.

Chronic non-cancer pain

Incidence of dependence in adults without previous history of dependence

It was possible to extract these data from three case series [44–46] with 1188 participants: the RCT [34]

Table 3 Methodological quality of case series.

Item	*Quang-Cantagrel et al. 2000[44]*	*Fleming et al. 2008[45]*	*Morrison 1991[46]*	*Passik et al. 2006[47]*
Number of recruited subjects	86	904	198	173
Consecutive recruitment	Yes	Yes	Yes	No
Prospective recruitment	No	No	No	Yes

GRADE Evidence Profile

Author(s): Amato
Date: 24/06/2011
Question: Should opioid treatment be used in patients with acute or cronic pain ?
Patient or population: People with acute and chronic pain due to any physical condition for which opioid analgesics have been prescribed.
Settings: inpatient or outpatient
Systematic review:

Quality assessment						Summary of findings				
						No of patients	Effect		Quality	Importance
No of studies	Design	Limitations	Consistency	Directness	Other considerations	opioid treatment	Relative (95% CI)	Absolute (95% CI)		
dependence (objective Follow up:)										
17	Any other evidence[1]	Serious limitations (-1)[1],	Important inconsistency (-1)[2]	No uncertainty	None	3186/77806 (4,1%)	RR (to)	/1 000 (to)	⊕◯◯◯ Very low	9

Footnotes:

1. 3 systematic reviews, two of good quality, one was a Cochrane review with low risk of bias and for the other review the only flaws were a lack of description of the characteristics of included studies and the assessment of possible publication bias. The third review was at high risk of bias for all the item assessed by the checklist 1 RCT of moderate quality, the concealment of allocation was inadequate and personnel, patients and outcome assessors were not blinded 9 Cross sectional studies, all were multicentre surveys recruiting a large number of patients (range 247 – 15160 patients). 4 Uncontrolled Case series, all of quite big size (range 86 to 904); all but one used a consecutive recruitment of patents, and were retrospective 7 Cross sectional studies, all were multicentre surveys recruiting a large number of patients (range 247 – 15160 patients). 3 Uncontrolled Case series, all of quite big size (range 86 to 904); all but one used a consecutive recruitment of patents, and were retrospective
2. Wide heterogeneity in the results

Figure 2 GRADE profile for cancer and non-cancer pain, outcome dependence following opioid treatment

GRADE Evidence Profile

Author(s): Amato
Date: 24/06/2011
Question: Should opioid treatment be used in patients with acute or cronic non cancer pain ?
Patient or population: People with acute and chronic pain due to any physical condition for which opioid analgesics have been prescribed.
Settings: inpatient or outpatient
Systematic review:

Quality assessment						Summary of findings				
						No of patients	Effect		Quality	Importance
No of studies	Design	Limitations	Consistency	Directness	Other considerations	opioid treatment	Relative (95% CI)	Absolute (95% CI)		
dependence (objective Follow up:)										
13	Any other evidence[1]	Serious limitations (-1)[2]	No important inconsistency	No uncertainty	None	2321/69333 (3,3%)	RR (to)	/1 000 (to)	⊕◯◯◯ Very low	9

Footnotes:

1. 3 systematic reviews, two of good quality, one was a Cochrane review with low risk of bias for all the items considered and for the other, the only flows were a lack of description of the characteristics of included studies and the assessment of possible pubblication biasand; the third review was at high risk of bias for all the item assessed by the checklist. 7 Cross sectional studies, all were multicentre surveys recruiting a large number of patients (range 247 – 15160 patients). 3 Uncontrolled Case series, all of quite big size (range 86 to 904); all but one used a consecutive recruitment of patents, and were retrospective 7 Cross sectional studies, all were multicentre surveys recruiting a large number of patients (range 247 – 15160 patients). 3 Uncontrolled Case series, all of quite big size (range 86 to 904); all but one used a consecutive recruitment of patents, and were retrospective
2. Wide heterogeneity in the results

Figure 3 GRADE profile for non-cancer pain, outcome dependence following opioid treatment

with 4000 participants, and two systematic reviews [28,33] with 3304 participants. The study by Quang-Cantagrel *et al.* [44] included 86 patients with chronic non-cancer pain treated with time-release morphine, time-release oxycodone, methadone or transdermal fentanyl patch for a mean time of 8.8 months. Only one patient (1%) developed dependence. The study by Fleming *et al.* [45] included 904 patients with chronic non-cancer pain who received daily or intermittent therapy in the previous 6 months; the type of opioid was not reported. Ninety-nine patients (11%) developed dependence. The study by Morrison [46] included 198 children and adolescents with sickle cell disease who received meperidine, morphine, hydromorphone or nalbuphine intravenously for 3 days to treat acute pain; treatment was re-started if acute pain recurred. Only one patient (0.5%) developed dependence. Adams *et al.* [34] studied 4000 patients with non-cancer pain treated with hydrocodone for 12 months, and reported a 4.9% incidence of dependence.

Table 4 Characteristics of included studies.

Author, year	*Study design*	*Condition (n patients)*	*Type of opioid administered*	*Length of treatment*	*Frequency of dependence (%)*
Fishbain 2008[33]	Systematic review, study design of included studies not reported	Chronic non-cancer pain ($n = 2507$)	Any opioid apart from tramadol	Mean: 27.2 months	82/2507 (3.27%)
Littlejohn *et al.* 2004[32]	SR which included 1 RCT and 3 case series; 1 study design not clear	Non-cancer pain	Any	Not reported	0/46(0%) 52/414 (12.6%), 6/87 (6.9%), 35/144 (24%), 27%
Noble *et al.* 2010[28]	SR of case series	Chronic non-cancer pain (n 4884)	Any opioid	At least 6 months	7/2613 (0.27%) only studies which reported this outcomes 7/4884 (0.14%) (all studies)
Adams *et al.* 2006[34]	RCT	Chronic non-cancer pain ($n = 4000$)	Hydrocodone Tramadol	12 months	208/4000 (4.9%) for hydrocodone
Becker *et al.* 2008[35]	Cross-sectional survey	Not reported ($n = 6879$)	Not reported	Not reported	602/6879 (8.75%)
Boscarino *et al.* 2010[37]	Cross-sectional survey	Non-malignant pain ($n = 705$)	Not reported	At least 12 months	182/705 (25.8%).
Edlund *et al.* 2007[37]	Cross-sectional survey	Chronic non-cancer pain ($n = 15\,160$)	Not reported	At least 91 days of continuous use of opioids within a 6-month period	326/15 160 (2%)
Edlund *et al.* 2010[38]	Cross-sectional survey	Chronic non-cancer pain ($n = 36\,605$ with full medical coverage and $n = 9651$ disadvantaged and vulnerable people)	Not reported	At least 30 days of continuous use of opioids within a 6-month period	1188/36 605 (3.2%) 277/9651 (2.9%)
Elander *et al.* 2003[39]	Cross-sectional survey	Sickle cell disease ($n = 51$)	Not reported	Not reported	16/51 (31%)
Hojsted *et al.* 2010[40]	Cross-sectional survey	Chronic non-cancer pain $n = 253$ Cancer pain $n = 18$	Weak opioid 27% (tramadol, codeine) Strong opioid 71% (morphine, oxycodone, methadone, fentanyl, ketobemidone)	Mean: 6.8 years	27/187 (14.4%)
Njee 2004[41]	Cross-sectional survey	Chronic non-cancer pain (n 19)	Intrathecal morphine	More than 1 year	0/19
Radat *et al.* 2008[43]	Cross-sectional survey	Chronic headache (n 247)	Not reported	At least 10 days in a month for at least 3 months	4/247 (0.8%)
Wu 2008[43]	Cross-sectional survey	Not reported (n 2 675)	Darvocet, Darvon, Tylenol with codeine, Percocet, Percodan, Tylox, Vicodin, Lortab, Lorcet, Lorcet plus, codeine, Demerol, Dilaudid, Fioricet, Fiorinal, hydrocodone, methadone, morphine, Oxycontin, Phenaphen with codeine, propoxyphene, SK 65, Stadol, Talacen, Talwin, Talwin NX, tramadol, Ultram	Not reported	214/2 675 (9%)
Quang-Cantagrel *et al.* 2000[44]	Case series	Chronic non-cancer pain ($n = 86$)	Time release morphine, time release oxycodone, methadone, transdermal fentanyl patch	Mean: 8.8 ± 6.3 months	1/86 (1.1%)
Fleming *et al.* 2008[45]	Case series	Chronic non-cancer pain ($n = 904$)	Not reported	Not reported	99/904 (11%)
Morrison 1991[46]	Case series	Sickle cell disease (n 198)	Meperidine, morphine, hydromorphone; nalbuphine	3 days	1/198 (0.5%)
Passik 2006[47]	Case series	AIDS pain with SUD (n 73) Cancer pain, without SUD (n 100)	Not reported	Not reported	Cancer pain: 0/100 (0%) AIDS: results not informative

RCT: randomized controlled trial; SR: systematic review; SUD: substance use disorder.

In the three case series and one RCT described in the systematic review by Littlejohn *et al.* [32], the reported incidences of dependence were 12.6, 6.9, 24 and 0%, respectively. Among the 26 case series included in the Cochrane systematic review by Noble *et al.* [28], 18 studies did not report whether addiction was observed. Among the studies where dependence was reported, the total incidence was 0.27%. The authors reported that if we assume that there were no cases of dependence among the studies that did not report specific information (as it seems likely that such an important adverse event would be reported if observed), the incidence falls to 0.14%.

It was not possible to assess incidence of dependence for subgroups of patients by conditions, because the vast majority of studies did not specify the conditions for which opioids were prescribed. Only two studies specify the condition: Morrison [46] found a 0.5% incidence in 198 children and adolescents with sickle cell disease, while the cross-sectional survey by Radat *et al.* [42] included 247 patients with chronic headache and reported a 0.8% prevalence.

Incidence of dependence in adults with previous history of dependence

Only one study reported separate data for this subgroup of patients [47]; this study included AIDS patients with previous or current substance use disorders (SUD), and the majority of them (89%) had current SUD. Therefore, the results from this subgroup of patients are not informative, because it is impossible to attribute the observed behaviours to dependence on the prescribed opioid and not, as seems more likely, to the current dependence on other drugs.

Indirect information can be derived by logistic regression analysis performed in three cross-sectional surveys [35–37] (44 189 patients included) that assessed risk factors or predictors of dependence. Becker *et al.* [35] reported that, in the multivariate analysis, respondents meeting criteria for abuse/dependence were more likely to report non-medical use of another prescription drug [adjusted odds ratio (AOR): 1.7; 95% confidence interval (CI): 1.2–2.3], to have used heroin (AOR: 2.9; 95% CI: 1.2–6.9) and to have initiated substance use before the age of 13 (AOR: 4.7; 95% CI: 1.1–19.9). In the study by Boscarino *et al.* [36], logistic regression indicated that current opioid dependence was associated with history of opioid abuse (OR: 3.81; $P < 0.001$). Edlund *et al.* [37] reported that previous history of opioid abuse was a predictor of current opioid dependence/abuse based on logistic regression (OR: 5.55, 95% CI: 4.06–7.58; OR: 5.50, 95% CI: 2.94–10.30).

Cancer pain

No conclusions can be drawn about the incidence of dependence in cases of cancer pain treatment, because only two studies [40,47] with a total of 118 participants reported data on dependence for these patients. The study by Passik *et al.* [47] included 100 patients with cancer pain and did not report the type of opioid used or the length of treatment; none of the patients developed dependence (0%). The other study [40] is a cross-sectional survey, and the data regarding cancer pain were not disaggregated from data relating to non-cancer pain. Cancer pain patients accounted for only 7% of the total sample; therefore, results on this subgroup could not be considered informative.

Acute pain

Two studies [39,46] assessed the incidence or prevalence of dependence following opioid given for acute pain in patients with sickle cell disease. In one case series [46], 198 children with sickle cell disease received meperidine, morphine, hydromorphone or nalbuphine with intravenous administration for 3 days, which was re-started if acute pain recurred. Only 0.5% developed dependence. In the other cross-sectional study [39], 51 adult patients received opioids, but information on dosages, type of drugs and length of treatment was not reported. Prevalence of dependence was 31%.

Method of administration

The majority of studies did not specify the method of administration; thus, it was not possible to assess whether the administration method influenced incidence or prevalence of dependence. Only two studies limited the inclusion for administration method. One [41] included 19 patients receiving only intrathecal morphine, and the prevalence of dependence was of 0%; the other study [46] included 198 patients receiving intravenous administration of meperidine, morphine, hydromorphone or nalbuphine, and the incidence of dependence was 0.5%.

Types of opioid

Seven studies did not specify the type of opioid administered; the three systematic reviews included the use of any kind of opioid, and one study assessed both weak and strong opioids together. One study [34] included 4000 patients receiving hydrocodone for non-cancer pain and reported a 4.9% prevalence of dependence. Another study [38] specifically reported information regarding prediction of abuse/dependence based on different types of opioid administered. Logistic regression in this study revealed that use of Schedule II long-acting opioids was a predictor of abuse or dependence compared to Schedules

III or IV (results are reported separately for people with full medical and pharmacy coverage and for disadvantaged and vulnerable population): Schedule II long only: OR: 1.83 (95% CI: 1.47–2.27), OR: 2.98 (95% CI: 1.92–4.61); Schedules II or IV plus Schedule II long: OR: 1.70 (95% CI: 11.35–2.36), OR: 2.16 (95% CI: 1.88–4.25); and Schedule II short and long: OR: 1.78 (95% CI: 1.35–2.36), OR: 2.16 (95% CI: 1.21–3.87) [38]. One study [41] included 19 patients receiving intrathecal morphine for non-cancer pain and reported a 0% prevalence of dependence. A study [44] including 86 patients receiving time-release morphine, time-release oxycodone, methadone or transdermal fentanyl patch for non-cancer pain reported a 1.1% incidence of dependence. Another study [46] included patients receiving meperidine, morphine, hydromorphone or nalbuphine, and the incidence of dependence was 0.5%.

None of the included studies reported the time since the start of opioid therapy after which dependence become evident.

DISCUSSION

Few studies could be included in this review, despite a very comprehensive bibliographical search for published, unpublished and ongoing studies. Among almost 2000 titles and abstracts scrutinized, very few assessed and reported data on the development of dependence.

The results of the 17 included studies were extremely heterogeneous, with data on dependence indicating incidences ranging from 0 to 24% (median 0.5%), and prevalences from 0 to 31% (median 4.5%). All but two studies [40,47] included only patients with non-cancer pain, and all but three [39,46,47] included only adult patients with chronic pain. It was not possible to retrieve information on incidence of dependence for cancer patients, as only two studies [40,47] reported data for these patients; in one [47], none of the subjects developed dependence, while no conclusions could be drawn from the other [40], as it did not disaggregate the data relating to cancer pain from the non-cancer pain data, and cancer pain patients accounted for only 7% of the total sample. Information could not be retrieved for patients with acute pain, because only two studies included this type of patient group [39,46]. The data were inadequate to determine the risk related to specific drugs or method of administration, and it was not possible to retrieve information about the time following prescription of opioids after which dependence occurred, because none of the included studies reported this information.

Furthermore, it was not possible to determine directly the specific risk of dependence among patients with history of previous drug abuse, as only one study reported separate data for this subgroup [47]. This study included AIDS patients, 89% of whom had current SUD; thus, the reported data about behaviour indicative of dependence cannot be attributed to dependence developed from the prescribed opioid. Indirect information about the risk of developing dependence for patients with previous history of dependence can be drawn from the regression analysis performed in several cross-sectional surveys to individuate predictors of dependence. All these studies found obvious indications that previous opioid abuse or dependence was a strong predictor of current dependence to a prescribed opioid.

Due to these limitations, the data on incidence/prevalence of dependence in this review can be applied only to patients with chronic non-cancer pain who have used opioids for more than 3 months. Such patients are probably the most frequently studied with respect to the problem of developing dependence, because they have a long life expectancy and are expected to receive drugs for a long time. Furthermore, all the present data have been derived from studies with weak designs, e.g. uncontrolled case series and cross-sectional surveys. These studies suffer from low-quality reporting, with little information on the characteristics of patients, type of opioids administered and route of administration. Moreover, while for some studies seeking actively for dependence was the primary objective of the work, for some others it did not; in those the prevalence of dependence could be underestimated. Applying the GRADE methodology showed that the quality of evidence was very low.

However, our results are in line with the results of other published reviews. Authors of a narrative review [49] found a prevalence of dependence ranging from 0 to 50% in patients with chronic non-malignant pain and from 0 to 7.7% in patients with cancer pain. A systematic review [19] assessing the prevalence of substance use disorders among patients receiving opioid for non-cancer pain found prevalences ranging from 3 to 43%, with a life-time prevalence as high as 54%; we excluded this review because it assessed prevalences of any substance use disorders and not specifically dependence syndrome to opioid as defined by DSM-IV or ICD-10. The observed heterogeneity is due probably to many factors, including the use of different methods to assess dependence, study design, characteristics of included patients, differences in risk factors for the development of dependence and lengths of treatment and follow-up. The magnitude by which these factors differ could explain differences in incidences or prevalences, but this could not be explored further because the retrieved studies did not report enough information.

The most impressive finding of the present review is the deficiency of good-quality studies. This seems to stand in contrast to the widespread concern of doctors and authorities relating to the prescription of opioids for pain

management. Prospective observational studies of good methodological quality should be designed and conducted to assess incidence of dependence among chronic pain patients. Such studies should report detailed information on patients' characteristics, diseases for which opioid is prescribed, type of opioid prescribed, method of administration, doses and lengths of treatment and the lengths of treatment after which dependence occurs.

Moreover, there is a problem in the heterogeneity of the dependence criteria. Tolerance and withdrawal syndrome plus craving are sufficient for a dependence diagnosis in ICD-10, without requiring loss of control over use and without negative health or social consequences. This is not equivalent to a combination of loss of control and continued use despite knowledge of negative consequences, as is stated in the DSM-IV criteria. Studies should therefore report clearly which criteria are used to assess dependence.

The present data on the incidence and prevalence of dependence following the prescription of opioids to treat chronic and acute pain cannot be considered conclusive. However, due to the necessity to treat world-wide diseases involving chronic and non-chronic pain, clinicians should consider the use of opioids because of their proven effectiveness in treating pain and ameliorating quality of life of suffering patients—regardless of the fact that the published literature does not permit a conclusive statement about the risk of dependence. Clinical practice guidelines recommend that: 'Adherence monitoring is crucial to avoid abuse of the drugs and at the same time to encourage appropriate use, and involves the initiation of drug screening, pill counts, and patient care agreements, with the motto of "trust but verify" ' [50]. Moreover, guidelines recommend screening for potential comorbitities and risk factor for abuse and dependence such as anxiety, depression, psychotic disorders and current or past substance abuse [50–52].

Declarations of interest

None.

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