Long-term opioid treatment of chronic nonmalignant pain: unproven efficacy and neglected safety?

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Long-term opioid treatment of chronic nonmalignant pain: unproven efficacy and neglected safety?

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Background: For the past 30 years, opioids have been used to treat chronic nonmalignant pain. This study tests the following hypotheses: (1) there is no strong evidence-based foundation for the conclusion that long-term opioid treatment of chronic nonmalignant pain is effective; and (2) the main problem associated with the safety of such treatment – assessment of the risk of addiction – has been neglected.

Methods: Scientometric analysis of the articles representing clinical research in this area was performed to assess (1) the quality of presented evidence (type of study); and (2) the duration of the treatment phase. The sufficiency of representation of addiction was assessed by counting the number of articles that represent (1) editorials; (2) articles in the top specialty journals; and (3) articles with titles clearly indicating that the addiction-related safety is involved (topic-in-title articles).

Results: Not a single randomized controlled trial with opioid treatment lasting >3 months was found. All studies with a duration of opioid treatment ≥6 months (n = 16) were conducted without a proper control group. Such studies cannot provide the consistent good-quality evidence necessary for a strong clinical recommendation. There were profound differences in the number of addiction articles related specifically to chronic nonmalignant pain patients and to opioid addiction in general. An inadequate number of chronic pain-related publications were observed with all three types of counted articles: editorials, articles in the top specialty journals, and topic-in-title articles.

Conclusion: There is no strong evidence-based foundation for the conclusion that long-term opioid treatment of chronic nonmalignant pain is effective. The above identified signs indicating neglect of addiction associated with the opioid treatment of chronic nonmalignant pain were present.

Keywords: addiction, chronic pain, neuropathic pain, opioids, overdose death, quality of evidence, treatment efficacy

Introduction

Only relatively recently in the history of medicine, was there a need to demonstrate quality of evidence and strength of recommendations to validate treatment effectiveness.[1–3] Such support has been provided for various treatments of acute pain with opioids.[4] Opiates have been used for treatment of acute and persistent pain for centuries, before the current standards of evidence quality became the norm. Compared to this, the treatment of chronic nonmalignant pain with opioids is a relatively new development. For the period 1983–2012, PubMed has more than 2,000 articles on the opioid treatment of chronic nonmalignant pain, but almost no articles on this topic

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before then. In regards to the Bonica pain clinic treatment practices from 1960–1980, Loeser wrote that

> "it did not enter our minds that there could be a significant number of chronic pain patients who were successfully managed with opioids, because if there were any, we almost never saw them."[5]

This explains the almost complete absence of publications on the opioid treatment of chronic pain before 1983. The value of opioids in the treatment of chronic pain attributable to cancer was well recognized before the 1980s. As far as nonmalignant chronic pain is concerned, several initial publications were collected and summarized in the mid-1980s.[12] The use of opioids for chronic pain management was introduced when the new standards of evidence-based medicine were already in the final stages of their establishment. Despite this, the opioid treatment of chronic pain came into practice without convincing proof of effectiveness. Since then, doubts about the effectiveness and safety of long-term treatment of chronic nonmalignant pain with opioids have been expressed in several reviews.[6–9]

The goal of the present study was to test the following hypotheses: (1) there is no strong evidence-based foundation for the conclusion that long-term opioid treatment of chronic nonmalignant pain is effective; and (2) the risk of addiction – the main problem associated with the safety of such treatment – has been neglected. The available information pertinent to these hypotheses was analyzed using scientometric approaches.

Methods

The articles were collected mainly using the National Library of Medicine's PubMed website (http://www.ncbi.nlm.nih.gov/PubMed). Articles published in English over the 30-year period of 1983–2012 were included. Keywords related to chronic pain ("chronic pain" OR "neuropathic pain") were added to the terms related to opioids ("opioids" OR "narcotic analgesics" OR "morphine"). In addition, cancer pain and terminal illness were excluded from the search by placing in the search box the following: NOT ("cancer pain" OR "terminal illness"). Boolean operations were used, in which the following variables were selected: keywords, years of publications, and type of publications. In addition to the electronic search of articles, related publications were also searched manually in the reference lists of reports and reviews.

Efficacy hypothesis

Articles found in the searches were reviewed to make sure that they fit the definition of chronic pain. Articles with titles that lacked certain indication of pain duration, such as "persistent," "persisting," or "long-term" were checked and included in the database only if the duration of pain was ≥3 months. Criteria for excluding articles were: (1) inclusions of cases with malignant pain; (2) inclusions of treatments combining opioids with local anesthetics or antidepressants; (3) duration of treatment of 1 day (or <24 hours); and (4) having fewer than ten patients.[4] To assess the quality of evidence for the efficacy for the treatment, the following factors were taken into consideration: the type of the study (randomized controlled trial [RCT] or not), the duration of opioid treatment (≥6 months or not), and the study conclusion on the treatment efficacy.

Addiction hypothesis

The following signs were used to determine whether attention to the addiction-related safety of long-term opioid treatment was insufficient: the number of journal editorials on this topic, the number of articles in the top specialty journals, and the number of journal articles with titles clearly stating that the addiction-related safety of the treatment is involved. The editorials (articles solicited by an editorial board to provide an editorial perspective on an article published in a journal) on several topics associated with the safety of long-term opioid treatment of chronic pain were selected in the following way: keywords related to chronic pain ("chronic pain" OR "neuropathic pain") and opioids ("opioids" OR "narcotic analgesics" OR "morphine") were combined with keywords associated with addiction ("addiction" OR "dependence" OR "abuse" OR "misuse") or with overdose death ("death" OR "mortality" OR "fatality"). The article type was selected by using the PubMed filtering tool "Editorial."

To quantitatively evaluate the presentation of the above topics in leading medical journals, the 20 top journals were selected with the approach used previously.[10] The journal selection was based on two factors: (1) the rank of a journal sorted by the impact factor, as indicated by Journal Citation Report for 2011 (http://science.thomsonreuter.com) and (2) the journal specialty area. They included biomedical journals in general (ten journals), pharmacology (six journals), and psychiatry or neurology (four journals). The impact factor was used for the selection of journals in each specialty area category separately. The following journals were included: *Addiction, The American Journal of Psychiatry, Annals of Internal Medicine, Annals of Neurology, Archives of General Psychiatry, BMJ, The Journal of Clinical Investigation, The Journal of Pharmacology and Experimental Therapeutics, JAMA: The Journal of the American Medical Association, Lancet,*

The New England Journal of Medicine, Nature Medicine, Nature Neuroscience, Nature Reviews Drug Discovery, Nature Reviews Neuroscience, Nature, Pharmacological Reviews, Proceedings of the National Academy of Science of the United States of America, Science (New York, NY, USA), and *Trends in Pharmacological Sciences*. All types of articles were used for this index.

To select articles with titles clearly indicating that they are devoted to specific topics (topic-in-title articles), the indicator "(Title)" was added to the selected terms placed into PubMed search boxes. All types of articles were used for this index also.

Results

Efficacy hypothesis

The electronic and manual search of the literature identified 2,356 articles. The results of this initial search were reviewed and reduced to 250 articles; see flowchart (Figure 1) and Supplementary material. Fifty-three articles were original clinical research articles on the opioid treatment of chronic nonmalignant pain (Table 1).[11–63] Analysis of these publications revealed that 25 are reports of RCT studies, the rest are studies that lack a proper control group.[64] Most of the RCT studies had a treatment duration of ≤1 month. Only one study is in the "≥3 months category" (90 days).[58] The other randomized investigation with long treatment duration (16 weeks) was an open study.[65] Table 2 presents 16 studies in which the duration of opioid treatment was ≥6 months, none of which is an RCT. Thus, there is not a single study that both fits the high quality of evidence category and has a long-term opioid treatment (duration of treatment ≥6 months). Systematic reviews on the opioid treatment of chronic nonmalignant pain have come to the same conclusion regarding long-term efficacy of the treatment, ie, there is insufficient evidence to make a definite conclusion (Table 3).[6–9]

Addiction hypothesis

The results on the editorials related to addiction in chronic nonmalignant pain patients are presented in Table 4. There were no editorials on this topic in 1983–1992, one in

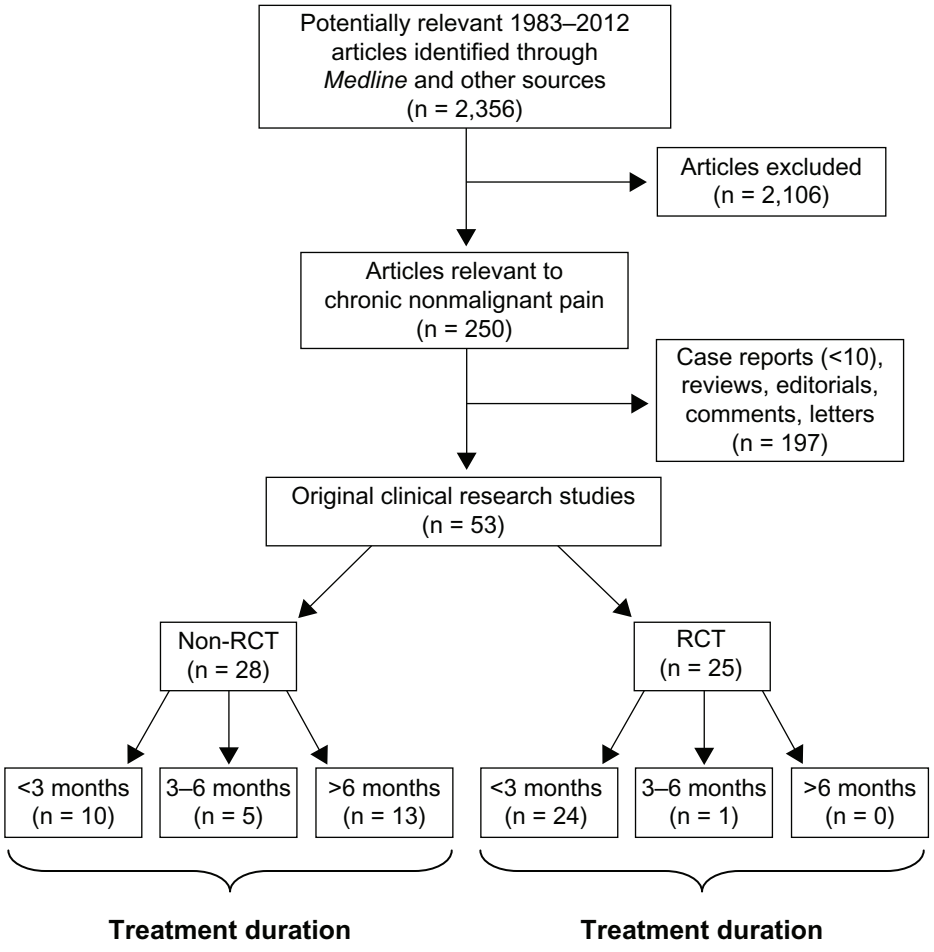

Figure 1 Flow chart of screened, excluded, and included articles on chronic nonmalignant pain from 1983–2012.
Abbreviation: RCT, randomized controlled trial.

Table 1 Duration of opioid treatment in studies on chronic nonmalignant pain

Duration of treatment	Number of studies without a proper control group*,[11–38]				Number of randomized controlled trials[39–63]			
	≤1 m	>1 m–<3 m	≥3 m	≥1 y	≤1 m	>1 m–<3 m	≥3 m	≤1 y
Years								
1983–1992	1	0	0	3	1	0	0	0
1993–2002	4	1	2	6	10	2	0	0
2003–2012	4	0	3	4	5	6	1	0
Total	9	1	5	13	16	8	1	0

Note: *Studies without a proper control group (see Grimes and Schulz).[64]
Abbreviations: m, month; y, year.

1993–2002, and four in 2003–2012. For the same period, editorials on opioid addiction in general (the right side of Table 4) were numerous (171 from 2003–2012). As far as editorials on death associated with opioid treatment of chronic nonmalignant pain are concerned, only two were found – both recent – in 2010–2011.[67,69]

Representation of opioid addiction in the top 20 journals is shown in Table 5 (left side – opioid addiction in patients with chronic pain; right side – opioid addiction in general). Once again, the problem of opioid addiction in chronic pain patients was discussed in only six articles (five of which appeared in 2003–2012). The problem of death associated with opioid treatment of chronic pain was discussed only in three articles from the top journals.[71,72,77]

The topic-in-title articles (articles clearly announcing that they are devoted to opioid addiction, dependence, abuse, or misuse) are presented in Table 6. The right side of the table presents the articles on addiction-related problems in general, and the left side presents those specifically in chronic pain patients. It indicates that in 1983–1992 only two topic-in-title articles related to opioid addiction in chronic pain patients were published; in the next 10-year period, this number increased to 13; and was 51 for 2003–2012. It is of interest that in the 15 years following 1983, the word "addiction" in titles appeared only once; the word "abuse" was used in the rest of the article titles. On the other hand, topic-in-title articles on addiction-related problems in general (the right side of Table 6) were numerous (1,404 in 2003–2012). It is of interest that during 1983–2002 when opioids were introduced for the treatment of chronic nonmalignant pain, there was a clear decrease in the number of articles devoted to the problem of opioid addiction in general (from 893 in 1973–1982 to 536 and 628 in 1983–1992 and 1993–2002, respectively).

Topic-in-title articles on death associated with opioid addiction in chronic pain patients are presented in Table 7. This table indicates only four such articles, all in 2003–2012. Topic-in-title articles on death associated with opioid addiction in general (the right side of Table 7) were also very rare (two to four articles per decade).

Discussion

Efficacy hypothesis

Simple scientometric assessment of articles on long-term opioid treatment of chronic nonmalignant pain indicates the absence of high-quality evidence on efficacy. There is not a single RCT study lasting >3 months (Table 1). The longest randomized investigation (16 weeks) was limited by being an open study.[65] All studies with opioid treatment ≥6 months (Table 2) were conducted without a proper control group;[64] therefore, they do not provide the consistent good-quality evidence to support a strong clinical recommendation.[1–3] Systematic reviews on opioid treatment of chronic nonmalignant pain have concluded that there is insufficient evidence to make a definite conclusion on the efficacy of long-term treatment.[6–9]

Addiction hypothesis

The problem of safety of opioid treatment revealed itself most dramatically in rising numbers of opioid overdose deaths. According to the 2008 National Survey on Drug Use and Health (NSDUH) sponsored by the Substance Abuse and Mental Health Service Administration (SAMHSA), there has been at least a ten-fold increase in the medical use of opioids from 1988–2007.[149] In 2007, 11,499 deaths were caused by overdoses of opioids, roughly a four-fold increase compared with 1999. Remarkably, even an increase of that size somehow did not trigger a timely response by the medical journals. This phenomenon is especially noticeable if one looks at the number of editorials on death associated with opioid treatment of chronic pain patients. Only two editorials on this topic were found (both late, in 2010–2011), as if there had been no dramatic increase in opioid-related deaths in 1999–2007.

Opioid abuse, misuse, and addiction are the main reasons leading to the opioid overdose deaths. Somehow the

Table 2 Studies with the duration of opioid treatment ≥6 months

Reference	Study design	Diagnosis	Opioid	Route of administration	Number of enrolled patients	Length of treatment
France et al[11]	Case series (uncontrolled, retrospective, selected patients)	Back pain	Codeine, oxycodone, hydromorphone	Oral	16	6–22 months
Portenoy and Foley[12]	Descriptive study (uncontrolled, retrospective, patients selected from two separate studies)	Back pain, postherpetic neuralgia, neuropathic pain	Oxycodone, methadone, levorphanol, codeine	Oral	38	6 months to 10 years
Zenz et al[13]	Descriptive study (uncontrolled, prospective)	Back pain, neuropathic pain	Sustained-release dihydrocodeine, buprenorphine, sustained-release morphine	Oral	100	≥1 year (20 patients)
Kanoff[15]	Descriptive study (uncontrolled, prospective)	Reflex sympathetic dystrophy, arachnoiditis	Morphine via implanted delivery system	Intrathecal	15	2–44 months
Hassenbusch et al[16]	Descriptive study (uncontrolled, prospective)	Neuropathic pain	Morphine, sufentanil via implanted delivery system	Intrathecal	22	12–56 months (18 patients)
Tutak and Doleys[17]	Descriptive study (uncontrolled, prospective)	Back pain	Morphine via implanted delivery system	Intrathecal	26	16–27 months
Angel et al[19]	Descriptive study (uncontrolled, prospective)	Back pain, neuropathic pain	Morphine via implanted delivery system	Intrathecal	15	3 years (11 patients)
Anderson and Burchiel[20]	Descriptive study (uncontrolled, prospective)	Neuropathic pain, nociceptive pain	Morphine via implanted delivery system	Intrathecal	40	24 months (20 patients)
Harati et al[24]	Descriptive study (uncontrolled, prospective)	Diabetic neuropathy	Tramadol	Oral	117	6 months (100 patients)
Milligan et al[25]	Descriptive study (uncontrolled, prospective)	Neuropathic pain, nociceptive pain	Fentanyl	Transdermal	532	12 months (301 patients)
Mironer and Tollison[26]	Descriptive study (uncontrolled, prospective)	Back pain, neuropathic pain	Methadone	Intrathecal	24	6 months (9 patients)
Anderson et al[28]	Uncontrolled study (prospective, randomized to morphine intrathecal infusion or its epidural injection)	Chronic nonmalignant pain	Morphine via implanted delivery system	Intrathecal	40	6 months (27 patients)
Allan et al[31]	Uncontrolled study (prospective, multicenter, randomized to oral morphine)	Back pain	Fentanyl	Transdermal	680	13 months
Chao[32]	Descriptive study (uncontrolled, retrospective)	Back pain, neuropathic pain	Sustained-release morphine	Oral	68	12 months
McIlwain and Ahdieh[33]	Descriptive study (uncontrolled, prospective, multicenter)	Osteoarthritis	Extended-release oxymorphone	Oral	153	12 months (61 patients)
Portenoy et al[36]	Uncontrolled registry study	Osteoarthritis, diabetic neuropathy, back pain	Controlled-release oxycodone	Oral	219	1–3 years (14–39 patients)

Table 3 Systematic reviews on opioid treatment of chronic pain

Study	Type of pain	Opioid	Route of administration	Duration of treatment	Conclusion on the treatment efficacy
Kalso et al[6]	Osteoarthritis, diabetic neuropathy, peripheral neuropathic pain, phantom limb pain, postherpetic neuralgia, musculoskeletal pain	Morphine, oxycodone	Oral, transdermal, or intravenous	From 4 days to 8 weeks	The short-term efficacy of opioids was good in both neuropathic and musculoskeletal pain conditions. However, only a minority of patients went on to long-term management with opioids; therefore, open-label follow-up data were too weak to make a definite conclusion.
Martell et al[7]	Back pain	Morphine, oxycodone, sustained-release morphine, controlled-release oxycodone, other opioids	Oral or transdermal	From 7 days to 16 weeks	Opioids may be efficacious for short-term pain relief. Long-term efficacy was unclear.
Noble et al[8]	Neuropathic pain, osteoarthritis, back pain	Morphine, tramadol, methadone, controlled-release oxycodone, extended-release oxymorphone, fentanyl, sufentanil, dihydrocodeine, buprenorphine	Oral, transdermal, or intrathecal	From 6–48 months	Weak evidence suggests that oral and intrathecal opioids reduce pain long-term in the relatively small proportion of individuals who continue treatment.
Nuesch et al[9]	Osteoarthritis	Codeine, morphine, oxycodone, oxymorphone	Oral or transdermal	From 3 days to 3 months	The small to moderate beneficial effects of opioids are outweighed by large increases in the risk of adverse events. Therefore, opioids should not be routinely used, even if osteoarthritic pain is severe.

Table 4 Editorials on opioid addiction in chronic pain patients

Years	Number of editorials	
	"Addiction"[a] AND "chronic pain"[b]	"Addiction"[a]
1973–1982	–	12
1983–1992	0	19
1993–2002	1[c]	63
2003–2012	4[d]	171

Notes: [a]OR "dependence" OR "abuse" OR "misuse;" [b]OR "neuropathic pain" NOT ("cancer pain" OR "terminal illness"); [c]reference 66; [d]references 67–70.

introduction of opioid treatment of chronic nonmalignant pain did not result in editorials on opioid addiction in chronic pain patients: there were five editorials related to this topic, four of them published only in 2003–2012. Compare this with 171 editorials on opioid addiction in general published during this period (Table 4).

Representation for all types of articles (including letters and commentaries) on opioid addiction in the top 20 journals was also insufficient: zero articles in 1993–2002 (10–15 years after the introduction of treatment) and five in 2003–2012 (Table 5).

The topic-in-title articles clearly announce the topic under discussion; however, if the topic is an undesirable problem, authors often try to avoid naming it explicitly in the title. The lack of topic-in-title publications indicates that the topic is a neglected one.[150] As indicated in the results of the present study, death associated with opioid addiction in chronic pain patients was not reflected in titles from 1983–2002; in 2003–2012, it was found in the titles of only four articles (Table 7). This tendency also applied to addiction, abuse, misuse, or dependence in opioid treatment of chronic pain. In 1983–1992, there were only two topic-in-title articles related

Table 5 Articles on opioid addiction in chronic pain patients in the top 20 journals[a]

Years	Number of articles	
	"Addiction"[b] AND "chronic pain"[c]	"Addiction"[b]
1973–1982	–	5
1983–1992	1[d]	5
1993–2002	0	12
2003–2012	5[e]	40

Notes: [a]List of top journals: *Addiction, The American Journal of Psychiatry, Annals of Internal Medicine, Annals of Neurology, Archives of General Psychiatry, BMJ, The Journal of Clinical Investigation, The Journal of Pharmacology and Experimental Therapeutics, JAMA: The Journal of the American Medical Association, Lancet, The New England Journal of Medicine, Nature Medicine, Nature Neuroscience, Nature Reviews Drug Discovery, Nature Reviews Neuroscience, Nature, Pharmacological Reviews, Proceedings of the National Academy of Science of the United States of America, Science* (New York, NY, USA), and *Trends in Pharmacological Sciences;* [b]OR "dependence" OR "abuse" OR "misuse;" [c]OR "neuropathic pain" NOT ("cancer pain" OR "terminal illness"); [d]reference 73; [e]references 74–78.

Table 6 Topic-in-title articles[a] on opioid addiction in chronic pain patients

Years	Number of articles	
	"Addiction"[b] AND "chronic pain"[c]	"Addiction"[b]
1973–1982	–	893
1983–1992	2[d]	536
1993–2002	13[e]	628
2003–2012	51[f]	1,404

Notes: [a]Articles with titles clearly indicating that they are devoted to the addiction in chronic pain patients; [b]OR "dependence" OR "abuse" OR "misuse;" [c]OR "neuropathic pain" NOT ("cancer pain" OR "terminal illness"); [d]references 79–80; [e]references 81–93; [f]references 94–144.

to opioid addiction in chronic pain patients, at a time when there were 536 topic-in-title articles on opioid addiction in general (right side of Table 6). There were also profound differences in the numbers of addiction articles related specifically to chronic pain patients and to opioid addiction in general for the periods 1993–2002 and 2003–2012. Especially interesting was the decrease in the number of topic-in-title articles on opioid addiction in general during 1983–2002 (right side of Table 6) when opioid treatment for chronic nonmalignant pain was being introduced. Could the acceptance of this new indication for opioid treatment be responsible for such a change?

Estimates of the rate of addiction problems among chronic pain patients extremely varied. Hojsted and Sjogren reported that the rates of addiction associated with long-term opioid treatment were 0%–50% in noncancer patients and 0%–7.7% in cancer patients, depending on the subpopulation studied and the criteria used.[108] This uncertainty is similar to that with the rate of iatrogenic addiction in patients treated with opioids for acute or subacute pain. A systematic review on this topic concluded, "It is not known whether the risk for iatrogenic addiction among patients treated with opioids for acute or subacute pain is relatively high (>10%) or low (0.1%)."[151] The difficulty of estimating the risk of opioid addiction and abuse (see Jamison et al)[152] calls into question the accuracy of reported rates of risk for opioid addiction.

Table 7 Topic-in-title articles[a] on death associated with opioid addiction in chronic pain patients

Years	Number of articles	
	"Death"[b] AND "addiction"[c] AND "chronic pain"[d]	"Death"[b] AND "addiction"[c]
1973–1982	–	4
1983–1992	0	3
1993–2002	0	2
2003–2012	4[e]	4

Notes: [a]Articles with titles clearly indicating that they are devoted to death associated with addiction in chronic pain patients; [b]OR "mortality" OR "fatality;" [c]OR "dependence" OR "abuse" OR "misuse;" [d]OR "neuropathic pain" NOT ("cancer pain" OR "terminal illness"); [e]references 145–148.

One author of a study on the use of opioids in chronic nonmalignant pain has asked: "Is this treatment a lifetime sentence?"[153] If not, another question should be: "Has the withdrawal syndrome after long-term opioid use been adequately studied?"; and not only acute withdrawal syndrome, but protracted withdrawal as well? The latter (also called protracted abstinence or chronic withdrawal syndrome) is characterized by generalized symptoms (eg, discomfort, fatigue, decreased blood pressure, pulse rate, and body temperature) lasting 3–9 months.[154–156] Long-lasting (3–4 months) neurobiological alterations following withdrawal from opioids have been well confirmed in animal experiments.[157] Lack of knowledge regarding the risk of addiction and even greater uncertainty regarding protracted withdrawal following cessation of long-term opioid treatment of chronic pain call for studies with high-quality evidence that supports reliable recommendations.

This study has a limitation related to the absence of exact definition of chronic nonmalignant pain. It is associated with the lack of definition for chronic pain in general. For example, the International Association for the Study of Pain Task Force on Taxonomy – in the classification of chronic pain – has chosen not to define chronic pain.[158]

Conclusion

There is no high-quality evidence on the efficacy of long-term opioid treatment of chronic nonmalignant pain. As a result, the strength of any recommendation regarding this treatment is weak. The safety of opioid treatment in terms of risk of addiction and overdose death has not properly been assessed due to the complexity of these outcomes. Until 2003, opioid addiction associated with the treatment of chronic nonmalignant pain was clearly a neglected topic of publication. However, this topic is now beginning to receive the attention it deserves.

Disclosure

The author reports no conflicts of interest in this work.

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Supplementary material

List of articles on long-term opioid treatment of chronic nonmalignant pain (1983–2012)

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