

Effectiveness of Opioids in the Treatment of Chronic Non-Cancer Pain

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For thousands of years, opioids have been used to treat pain, and they continue to be one of the most commonly prescribed medications for pain. It is estimated that 90% of patients presenting to pain centers and receiving treatment in such facilities are on opioids. Opioids can be considered broad-spectrum analgesics that act at multiple points along the pain pathway. Unfortunately, opioids also have the potential for great harm, with multiple side effects and potential complications, some of which are lethal. They are also uniquely addictive, which can lead to misuse and diversion.

We reviewed the relevant English literature and did thorough manual searches of the bibliographies of known primary and review articles. We utilized pain relief as the primary outcome measure. Other outcome measures were functional improvement, improvement of psychological status, improvement in work status, and evidence of addiction. Short-term use and improvement was defined as less than 6 months and long-term relief was defined as 6 months or longer.

The 3 systematic reviews evaluating long-term effectiveness of opioids for chronic non-cancer pain provided unclear and weak evidence. The results of this review showed that many patients in the included studies were dissatisfied with adverse events or insufficient pain relief from opioids and withdrew from the studies. For patients able to continue on opioids, evidence was weak suggesting that their pain scores were lower than before therapy and that this relief could be maintained long-term (> 6 months). There was also weak evidence that long-term opioid therapy with morphine and transdermal fentanyl not only decreases pain but also improves functioning. Limited evidence was available for the most commonly used opioids, oxycodone and hydrocodone. Evidence for the ability to drive on chronic opioid therapy was moderate without major side effects or complications.

It is concluded that, for long-term opioid therapy of 6 months or longer in managing chronic non-cancer pain, with improvement in function and reduction in pain, there is weak evidence for morphine and transdermal fentanyl. However, there is limited or lack of evidence for all other controlled substances, including the most commonly used drugs, oxycodone and hydrocodone.

Key words: Opioids, opioid effectiveness, pain relief, functional improvement, adverse effects, codeine, morphine, hydrocodone, hydromorphone, fentanyl, methadone.

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Ballantyne (1), in writing about perspectives on right use and utility, of opioids wrote "when it became necessary, at the beginning of the twentieth century, to regulate addictive drugs (including opioids) because of rampant street use, opioid treatment of pain declined, especially in the United States." Kathleen Foley, one of the first of a generation of opioid advocates who responded to the iniquities of pain under-treatment brought about by twentieth century drug regulations, quotes one of her patients: "I would rather be in pain than be considered an addict" (1). Dr. Foley stated: "This clinical anecdote captures the reality of the under-treatment of pain, which is one of the serious, unintended consequences of the war on drugs."

Opioids have been used for thousands of years to treat pain and continue to be one of the most commonly prescribed medications for pain. However, the United States, which differs from other western countries, made it illegal for physicians to prescribe opioids for addiction. Physicians in the United States could face loss of license, loss of practice, and possible imprisonment, and in fact, still do (1). Consequently, it has been stated that the chilling effect that these regulations had on opioid treatment of pain have been countered by pain (opiate) advocacy, which successfully restored opioid treatment of acute and cancer pain. Based on the ability of opioids to effectively and safely treat acute and cancer pain, several arguments have been made to support extending opioid treatment to patients with chronic pain, attempting to remove the previously exercised caution based on fears of addiction. It is argued that physicians should be encouraged to prescribe opioids because they are indispensable for the treatment of pain and suffering (1,2), because uncontrolled pain may have deleterious physical effects (1,3-5), and because persistent pain destroys people's autonomy, dignity, and decision-making capacity (1). It is also recognized that opioid therapy, specifically on a long-term basis for chronic pain, is associated with multiple side effects, drug abuse, and addiction. In fact, in Denmark, with free-flow of opioids, the results showed worse pain, higher healthcare utilization, and lower activity levels in opioid-treated patients compared to a matched cohort of chronic pain patients not using opioids. This provides prima facie evidence that when opioids are prescribed liberally, even if a small number of patients benefit, the overall population does not (6). However, due to politics and the emotional issues involved with efforts

to improve awareness and treatment of chronic pain, the availability of opioids has increased dramatically in the past few decades (7).

In the United States, the therapeutic use of opioids has exploded as witnessed by the increased sales of hydrocodone by 244% from 1997 to 2006, while at the same time methadone usage increased 1177% and oxycodone increased 732% (7). In addition, the estimated number of prescriptions filled for controlled substances increased from 222 million in 1994 to 354 million in 2003 (7-9). Consequently, the milligram per person use of therapeutic opioids in the United States increased from 73.59 milligrams in 1997 to 329.23 milligrams in 2006, an increase of 347% (7). And, while hydrocodone is the most commonly used opioid in the United States, oxycodone is the most commonly used opioid based on milligrams per person and methadone is the drug which is most rapidly increasing in its use. In pain management settings, it has been reported that as many as 90% of patients receive opioids for chronic pain management in spite of the numerous issues involved (10-35). In the same vein, it has been shown that a majority of these patients were on opioids prior to presenting to an interventional pain management setting (11).

A systematic review of opioid treatment for chronic back pain by Martell et al (35) showed variable prescribing patterns for opioids ranging from 3% to 66% (36-39). The prevalence estimates were highest in specialty treatment centers, ranging from 11% to 66%, and lowest in primary care settings, ranging from 3% to 31%. Other studies (40-44) also evaluated prescription patterns and trends of opioid use in managing chronic pain, showing significant increases in opioid prescriptions as well as costs.

Prescription opioids are associated with multiple long-term adverse consequences which include hormonal and immune system effects, abuse and addiction, tolerance, and hyperalgesia. More importantly, opioid use has been associated with increased disability, medical costs, subsequent surgery, and continued or late opioid use (40-45). Numerous investigations (8,11-28,35,46-49) have illustrated drug abuse in 18% to 41% of patients receiving opioids for chronic pain. Martell et al (35) estimated the prevalence of lifetime substance use disorders to range from 36% to 56%, with an estimate of 43% current substance use disorders and 5% to 24% of the patients with aberrant medication-taking behaviors. Further, patients on chronic opioid therapy have been shown to also

abuse illicit drugs (13-28). The results showed that illicit drug use in patients without controlled substance abuse was found in 14% to 16% of patients, and illicit drug use in patients with controlled substance abuse was present in 34% of patients (13,15,16). Contrary to popular belief, illicit drug use was significant in chronic pain patients in general, and was similar in patients using either long-acting or short-acting opioids (26). Consequently, the cost of opioid abuse is enormous, reaching \$300 billion a year, with the federal government spending \$12-13 billion each year on its National Drug Control Policy since 1998 (6,8,46).

The deleterious effects of chronic opioid use, abuse, and diversion extend into increased emergency room visits (50-54) and also contribute to increasing deaths. In fact, opioid-related deaths have topped deaths due to motor vehicle injuries with enormous increases (55,56) specifically secondary to methadone-induced deaths (57-60).

Concrete evidence of the effectiveness and safety of opioids in chronic pain has not been demonstrated. The foundation of the argument for use of opioids is the unique analgesic efficacy of opioids. And, based on surveys, case series, occasional open-label follow-up studies, as well as some randomized controlled trials and epidemiological studies, opioid use has escalated in the United States. It is also argued, based on the clinical experience of opioid maintenance treatment for addicts that patients on stable regimens can be fully functional in society and in the workplace despite their chronic use of substances known to affect cognitive function. Nevertheless, the argument to apply the same knowledge to chronic pain patients seemed to be reasonable (61-65). In addition, the early experience with tolerance to the analgesic effects of opioids was treated by dose escalation as a therapeutic maneuver, while the ongoing experience suggests a less rosy state of affairs (1).

In recent years, multiple reviews have been published to evaluate the effectiveness of opioid therapy in chronic pain (1,35,66-70). However, very few of them evaluated long-term opioid therapy. Chou et al (68) performed the first comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain in a systematic review including the literature through October 2002. They concluded that there was insufficient evidence to prove that different long-acting opioids are associated with different efficacy or safety profiles. Further, they concluded that there was also insufficient evidence to determine whether long-act-

ing opioids as a class are more effective or safer than short-acting opioids. They also showed that long-acting and short-acting oxycodone provided equally effective pain control with fair evidence.

The latest systematic review and metaanalysis of efficacy and safety of long-term opioid therapy for chronic non-cancer pain by Noble et al (66) provided significant insights into long-term chronic opioid therapy. The results showed that many patients withdrew from the clinical trials due to adverse effects or insufficient pain relief. They concluded there is weak evidence that oral opioids reduce pain long-term in the relatively small proportion of individuals with chronic non-cancer pain that continue treatment.

Martell et al (35), in their systematic review, concluded that opioids were ineffective in chronic low back pain, for long-term use of 16 weeks or longer. Ballantyne (1), after directly comparing the efficacy of different opioids, concluded that a nonsignificant reduction in pain was present from baseline. Kalso et al (69), in a systematic review evaluating the data up to September 2003 regarding opioids in chronic non-cancer pain, studied 8 trials that had open-label follow-up of 6 to 24 months. Their results showed a mean decrease in pain intensity in most studies of at least 30% with opioids, which was comparable in neuropathic and musculoskeletal pain, noting that about 80% of patients experienced at least one adverse event. However, only 44% of the 388 patients on open-label treatments were still on opioids after therapy for between 7 and 24 months. They concluded that the short-term efficacy of opioids was good in both neuropathic and musculoskeletal pain conditions, while, only a minority of patients in these studies went on to long-term management with opioids.

The evidence has been evaluated extensively for short-term efficacy, however the evaluation of long-term effectiveness is scant.

SHORT-TERM EFFECTIVENESS

Multiple randomized trials have been conducted to test the analgesic efficacy of opioids for various chronic pain conditions for short periods of time. Ballantyne (1) evaluated 28 studies and described the characteristic features, however all of them were short-term. Measured pain scales from the randomized controlled trials showed a statistically significant improvement across all the studies, in both painful arthritis and neuropathic pain. The randomized studies made it clear that neuropathic pain is indeed opioid

responsive, although larger doses are required than those needed to treat nociceptive pain.

Furlan et al (70) included 41 randomized trials involving 6,019 patients with nociceptive, neuropathic, mixed pain, and fibromyalgia. With a dropout rate of 33% in the opioid groups, opioids were judged to be more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain or fibromyalgia over an average duration of 5 weeks with a range of 1 to 16 weeks. Kalso et al (69) reported short-term efficacy of opioids as good in both neuropathic and musculoskeletal pain, however, only 44% of the patients continued treatment and 80% of the patients experienced at least one adverse event with constipation in 41%, nausea in 32%, and somnolence in 29%. Martell et al (35) also showed that opioids were efficacious for short-term pain relief, but with significant abuse, addiction, aberrant behaviors, and side effects. Chou et al (68) were only able to support that short-acting oxycodone and long-acting oxycodone were equally effective for pain control.

Eisenberg et al (71) studied 23 trials meeting the inclusion criteria and were classified as short-term (less than 24 hours; n=14) or intermediate-term (median=28 days; range=8 to 70 days; n=9). They studied opioids for neuropathic pain and reported contradictory results for short-term. However, for the intermediate-term ranging from 8 to 70 days, all 9 trials demonstrated opioid efficacy for spontaneous neuropathic pain. They concluded that intermediate-term studies demonstrated significant efficacy of opioids over placebo. However, the intermediate-term ranging from 8 to 70 days with median of 28 days, is considered as short-term for assessment of these guidelines.

Deshpande et al (72), in studying opioids for chronic low back pain for the Cochrane collaboration, included 4 trials. Three trials (73-75) compared tramadol to placebo. Pooled results supported that tramadol was more effective than placebo for pain relief and improvement of function. One trial (76) comparing morphine or oxycodone to Naprosyn showed no significant benefit either for relieving pain or improving function.

Cepeda et al (77) also evaluated the role of tramadol for osteoarthritis in a systematic review and meta-analysis, concluding that patients who received tramadol reported less pain associated with a higher degree of global improvement. They also concluded that decreasing pain intensity produced not only symptom relief, but also improved the function in patients with

osteoarthritis, even though these benefits were small.

Sandoval et al (78) reported one randomized controlled trial of methadone for chronic non-cancer pain and numerous observational reports. The duration of the controlled trial was for 20 days with a well-defined analgesic effect compared to placebo with methadone 20 mg/day (79).

However, the second most commonly used opioid, hydrocodone, was not studied for its effectiveness, while it was studied for its side effects. Adams et al (80) evaluated a comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in 11,352 patients with chronic pain. They showed that the abuse liability of hydrocodone as 4.9% compared to 2.7% for tramadol and 2.5% for NSAIDs. Even though the effectiveness of opioids was not specifically studied, based on methodology it appears that hydrocodone was effective.

LONG-TERM EFFECTIVENESS

At least 3 systematic reviews looked at long-term effectiveness of opioids (35,66,69). Martell et al (35) concluded that the effectiveness of opioids for a period lasting 16 weeks or longer was unclear. Kalso et al (69), showed a mean decrease in pain intensity of at least 30% with opioids, noting that about 80% of patients experienced at least 1 adverse event. They also showed that only 44% of the 388 patients on open-label treatments were still on opioids after therapy for between 7 and 24 months. They concluded that only a minority of patients went on to long-term management with opioids. Noble et al (66) provided somewhat better evidence, though weak. The evidence suggested that oral opioids reduced pain long-term in the relatively small proportion of individuals with chronic non-cancer pain that continued treatment. However, for oral opioids they evaluated morphine in 3 studies (81-83), tramadol in one study (84), methadone in one study (85), extended release oxymorphone in one study (86), controlled release oxycodone in one study (87), and dihydrocodeine and buprenorphine in another study (83). For evaluation of the effectiveness of transdermal fentanyl they included 3 studies (81,88,89). The conditions treated included low back pain, osteoarthritis, diabetic neuropathy, and neuropathic pain. Only 2 studies utilized pain relief of 50% or greater as their significant criteria (81,83). Table 1 illustrates the characteristics of studies included in this systematic review. Due to high withdrawal rates, they first analyzed withdrawal rates for the 2 most com-

Table 1. Characteristics of included studies in the evaluation of long-term effectiveness by Noble et al (66).

Reference	Opioid	Type of Predominant Pain	Number of Patients Enrolled	Outcomes Used in Evidence Synthesis			
				Withdrawal Due to Adverse Events	Withdrawal Due to Insufficient Pain Relief	Pain	
						Continuous/Categorical	>50% Relief
Oral Administration							
Allan et al (81)	Morphine ^a	Low back pain	342	✓	✓	<i>b</i>	✓
Caldwell et al (82)	Morphine ^a	Osteoarthritis	(295) ^c 181	✓	✓	<i>d</i>	
Harati et al (84)	Tramadol	Diabetic neuropathy	(131) ^c 117	✓	✓	✓	
Fredheim et al (85)	Methadone	Low back pain	12	✓	✓	<i>e</i>	
McIlwain and Ahdieh (86)	Extended-release oxycodone	Osteoarthritis	(491) ^c 153	✓	✓	✓	
Roth et al (87)	Controlled-release oxycodone	Osteoarthritis	(133) 106	✓	✓	✓	
Zenz et al (83)	Dihydrocodeine, ^a buprenorphine, or morphine ^a	Neuropathic or back pain	100		✓		✓
Transdermal Administration							
Allan et al (81)	Fentanyl	Low back pain	338	✓	✓	<i>b</i>	
Milligan et al (88)	Fentanyl	Unspecified	532	✓	✓	<i>f</i>	
Mystakidou et al (89)	Fentanyl	Unspecified	529	✓	✓	✓	

^aSustained release.

^bNot analyzed because of number of patients at follow-up times not reported.

^cN in parentheses denotes number of patients randomized in original RCT; second number is that enrolled in open-label extension.

^dNot meta-analyzed because reported units are statistically incompatible with the 3 other studies meeting inclusion criteria.

^eNot analyzed because data were reported for fewer than 10 patients at follow-up times.

^fNot analyzed because instrument used not validated.

Adapted and modified from Noble et al (66). Long-term opioid therapy for chronic noncancer pain: A systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage* 2008; 35:214-228.

mon reasons cited for leaving a study, namely, adverse events and insufficient pain relief. Consequently, the patients who reported long-term pain outcomes represent only a subset of the patients initially enrolled in the studies. They also included open-label extensions of randomized controlled trials (82,84,86,87). Among individuals with chronic non-cancer pain taking oral opioids, approximately a third did not continue long-term treatment with a follow-up time ranging from 6 to 18 months because of the intolerable adverse effects. In reference to pain relief, these authors were unable to formulate evidence-based conclusions on long-term efficacy of transdermal opioids for chronic pain, because only 2 studies contributed data on this analysis. However, for oral administration of opioids, data was sufficient for analyzing long-term pain score data, and the included studies assessed pain sever-

ity. Consequently, studies were combined for meta-analysis. Patients treated with long-term oral opioid therapy for 16 to 18 months showed approximately a 63.4% mean reduction in pain scores, even though substantial heterogeneity was observed in the studies. Further, the heterogeneity of oral opioid studies could not be resolved using meta-regression by follow-up time. In summary, it was evident that long-term opioids are associated with some degree of pain relief, because even the smallest summary affects sizes yielded by the sensitivity, and analysis remained large for oral opioids, and statistically significant.

Thus, it appears that it is necessary to utilize less rigorous forms of evidence to evaluate long-term effectiveness, since it is not feasible to conduct randomized controlled trials over prolonged periods. Other drawbacks of long-term effectiveness is that in open-

label follow-up studies, as many as 56% of patients abandon the treatment because of lack of efficacy or side effects (66,69). Further, many opioid trials utilize enrichment in their protocols (patients who do not respond are selected out during pre-trial phase), and there is an unusually high dropout rate across opioid trials during enrichment, likely reducing the internal validity of the trials (90). Another issue related to long-term opioid therapy is lack of improvement in functional status and escalation of opioid dosage. Generally, treatment in the long-term studies has been based on the traditional premise that dosage should be titrated upwards to overcome pharmacological tolerance, this being an inevitable consequence of long-term opioid treatment (1). Thus, the majority of patients are able to reach a stable, non-escalating, effective dose, and analgesic tolerance seems to stabilize over a period of time (1). However, some patients continue to fail dose escalation, reporting no change or worsening of their pain, despite high doses of opioids (91,92) with a paradoxical response of actual improvement in pain once opioid treatment is discontinued (93,94). This phenomenon is explained by rampant tolerance or opioid-induced hyperalgesia (91), thus the premise that tolerance can always be overcome by dose escalation is unreliable (67).

Despite multiple evaluations on long-term effectiveness of opioid therapy, hydrocodone, the most commonly utilized, has not been studied for its effectiveness. However, one of the largest studies to date (80), which included more than 11,000 patients with chronic pain, 3,000 of whom were taking hydrocodone-containing preparations, found relatively low levels of abuse, indicating long-term effectiveness.

Morphine

Allan et al (81) compared 342 strong-opioid naïve patients with chronic low back pain on a 12-hour, 30-mg dosage of sustained release oral morphine with those using a transdermal fentanyl. Doses were adjusted according to response. Participants assessed pain relief, quality of life, disease progression, and side effects including bowel function. Among these, approximately 70% of the participants did not work. Sustained release morphine provided significant improvement of mean VAS scores for patients who remained in the study for 56 weeks. However, use of concomitant, strong, short-acting opioids were frequently used in 50% of the patients as rescue medication. Quality of life scores showed improvement in

physical health from baseline of $25.7 + 0.4$ to $30.5 + 0.6$ at a statistically significant difference. However, there was no significant difference with mental health. At end point, investigators considered 45% of patients had stable disease, 8% deteriorated, and 23% had improved. They concluded that strong opioids may be indicated for chronic low back pain that is not relieved by other forms of analgesia.

Caldwell et al (82), in an open-label extension trial evaluated Avinza®, an extended-release morphine formulation, in 181 patients during the 26-week open-label extension trial with an option to increase their dose to optimize pain control. Of the 181 patients entering the open-label trial, 91 patients received Avinza in the morning and 90 patients in the evening. Forty-nine percent remained on the initial 30 mg Avinza dose throughout the open-label trial, whereas 7 patients increased their daily dose to 120 mg, the highest dose administered during the trial. Significant reductions in pain intensity and improvement on several sleep measures were observed. However, improvements were not observed in physical function. Stable average daily dose was approximately 50 mg per day of Avinza. Twenty-eight or 15% of patients were excluded entirely from the subset analysis due to concomitant therapy with NSAIDs and/or acetaminophen use. Constipation and nausea were the most frequent adverse effects reported in over 80% of the patients.

Zenz et al (83) evaluated long-term oral opioid therapy in patients with chronic non-cancer pain. They described 100 patients utilizing sustained-release morphine, dihydrocodeine, or buprenorphine, with 23 patients in the morphine group. Good pain relief was obtained in 51 patients, partial pain relief was reported by 28 patients, and 21 patients reporting no beneficial effect from opioid therapy. The most common side effects were constipation and nausea.

Maier et al (95) evaluated the responsiveness of morphine along with its efficacy and tolerability in patients with chronic non-tumor associated pain. Only 17 or 35.4% of the patients were judged to be responders with good reduction in pain, whereas an additional 17 or 35.4% were judged to be partial responders with moderate reduction in pain. Pain reduction also correlated with improvement of physical function. In another study, Maier et al (96) evaluated long-term efficacy of opioid medication in patients with chronic non-cancer pain, 5 years after the onset of medical treatment. In this report, a total of 121 patients with at least a 3-year history of morphine

use were evaluated by a standardized interview during a clinical visit or telephone call. Of 121 patients, frequency of withdrawal was 14.8% mainly due to lack of efficacy with an average treatment time of 66 months (37-105 months with 87% more than 5 years). In addition, this study reported that patients treated in the pain clinic stopped significantly less frequently than patients treated by general practitioners or other non-specialized physicians (5% versus 23%). The study showed that patients with long-term opioid intake exhibited significantly lower pain intensity and higher contentment with the pain management and improvement in physical status and quality of life. There were inconsistent changes in opioid dosages over the period of 5 years, without any change in 33% of the patients, with decrease in 16%, slight increase in 27%, and high increase in 19%. The survey

demonstrated a very low frequency of withdrawal in patients with long-term opioid medication after initial response without evidence for tolerance development, especially if their treatment was controlled in a pain center.

Tassian et al (97) evaluated the long-term effects of sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. Of the 28 patients initially included in the study, 18 patients received oral sustained morphine on a long-term basis with significant improvement in pain, function, and mood. Morphine induced persisting effects on pain, and to a lesser extent on quality of life and mood at 12 months, with no disruption of cognitive function.

Table 2 illustrates results of multiple studies evaluating the long-term effectiveness of morphine.

Table 2. Results of studies evaluating the long-term effectiveness of morphine.

Study/ methods	Participants	Opioids studied	Outcome(s)	Result(s)	Conclusion(s)	Complications
Allan et al (81) Open, randomized, parallel group multicenter study 13 months	Chronic low back pain N=680	Sustained release oral morphine versus transdermal fentanyl	Pain relief; bowel function, quality of life, disease progression, and side effects	Significant proportion of patients on sustained release morphine experienced pain relief.	Sustained release strong opioids can safely be used in opioid naive patients	Most common adverse events leading to discontinuation were nausea (37%), vomiting and constipation.
Caldwell et al (82) Double-blind trial, followed by open-label extension trial	184 with chronic osteoarthritis 181 patients entered the open-label trial	Placebo, Avinza, or MS Contin in double-blind trial	Pain relief; physical functioning; stiffness	Significant improvement in pain relief and sleep measures	Efficacy was comparable between two modes of administration.	Most common adverse effects were constipation and nausea
Zenz et al (83) Narrative descriptive report	100 patients who were chronically given opioids for treatment of nonmalignant pain, with 23 patients receiving morphine SR	Sustained release morphine, sustained release dihydrocodeine, buprenorphine	VAS, Karnofsky Performance Status Scale used to assess function	Good pain relief was obtained in 51 patients and partial pain relief was reported by 28 patients. Only 21 patients had no beneficial effect from opioid therapy	Results indicate that opioids can be effective in chronic nonmalignant pain, with side effects that are comparable to those that complicate the treatment of cancer pain	Common side effects were constipation and nausea
Maier et al (96) Narrative descriptive report	121 patients with chronic non-cancer pain	Sustained release morphine	Pain relief and quality of life.	Significantly lower pain intensity and improved physical state and quality of life	Pain relief correlated with improvement in functional status	There was no development of tolerance
Tassain et al (97) Long-term prospective study	28 chronic non-cancer pain patients, 18 received oral sustained morphine, 10 patients stopped morphine due to side effects and were followed as control group	Oral sustained morphine	Pain relief and cognitive functioning follow-up period of 12 months	Morphine produced persistent pain relief and improved quality of life and mood	There was no impairment of any neuropsychological variables over time	Side effects included constipation, loss of appetite, nausea, dry mouth, drowsiness, somnolence, fatigue, subjective memory impairment, sweating, and pruritus

Transdermal Fentanyl

Allan et al (81) evaluated 338 patients with chronic low back pain with transdermal fentanyl for a period of 13 months and also compared them with sustained release morphine. The proportion of patients experiencing a 50% or greater improvement in back pain was observed to be 40% in the patients with rest, 47% in patients on movement and during the day, and 53% in patients at night. Concomitant medication with possible analgesic effect and rescue medication during the trial was seen in greater than 80% of the patients with 52% using strong opioids.

Milligan et al (88) evaluated long-term efficacy and safety of transdermal fentanyl in the treatment of chronic non-cancer pain in an international, multicenter, open-label trial over a period of 12 months. The trial was completed by 301 (57%) of the patients. The main outcome measures were pain control assessment, global treatment satisfaction, patient preference for transdermal fentanyl, and quality of life. The mean dose of transdermal fentanyl increased from 48 to 90

mg/h during a period of 12 months. During treatment, on average, 67% of patients within the efficacy analysis group (n=524) reported very good, good, or moderate pain control, with global satisfaction reported in 42% of the patients. The majority (86%) of patients reported a preference for transdermal fentanyl over their previous treatment. There was significant improvement in the bodily pain scores of Short Form 36. The most frequent treatment-related adverse events were nausea (31%), constipation (19%), and somnolence (18%).

Mystakidou et al (89) evaluated the effectiveness of transdermal fentanyl in the long-term management of non-cancer pain. A total of 529 patients were recruited into this prospective open-label study. The mean duration of therapy for effective pain management was 10 months, and 90% of patients sustained effectiveness with improvement in quality of life scores and pain. Further, the improvements were not influenced by pain type or etiology.

Table 3 illustrates results of studies evaluating long-term effectiveness of transdermal fentanyl.

Table 3. Results of studies evaluating the long-term effectiveness of transdermal fentanyl.

Study/methods	Participants	Opioids studied	Outcome(s)	Result(s)	Conclusion(s)	Complications
Allan et al (81) Open, randomized, parallel group multicenter study 13 months	338 patients were studied with transdermal fentanyl with chronic low back pain	Evaluation of transdermal fentanyl in strong-opioid naïve patients with chronic low back pain	Pain relief, bowel function, quality of life, disease progression, and side effects	Transdermal fentanyl provided significant pain relief	Transdermal fentanyl can safely be used in opioid naïve patients	Most common side effects included constipation and vomiting.
Milligan et al (88) International, multicenter, open-label trial	524 patients w/chronic non-cancer pain studied over 12 months 57% completed trial. 25% withdrew because of adverse events	Transdermal fentanyl compared to previous medication (over 40 different opioids)	Preference of medication, pain control, SF-36, global satisfaction, requirement for break-through pain	67% rated pain relief as very good to moderate on transdermal fentanyl, 86% preferred transdermal fentanyl, SF-36 showed improvement for body pain only	Long-term treatment with transdermal fentanyl offered majority of patients at least moderate relief	Nausea 31%; constipation 19%; somnolence 18%; respiratory depression, abuse, or less 1%; withdrawal 3%
Mystakidou et al (89) Prospective open-label study	529 patients being treated with oral codeine or oral morphine	Transdermal therapeutic system fentanyl	Quality of Life-Short Form 12, Greek Brief Pain Inventory	Transdermal therapeutic system-fentanyl significantly improves quality of life within 28 days, and pain management within 48 hours	Transdermal therapeutic system-fentanyl is a safe and effective pain management	Side effects, with constipation (range 4.6% -23.1%) and nausea were the most frequent

Methadone

Fredheim et al (85) studied 8 chronic nonmalignant patients experiencing insufficient pain control or intolerable side effects during treatment with oral morphine who switched to oral methadone. Electrocardiograms were obtained at baseline, at follow-up 2 weeks, and 3 and 9 months after the opioid switch. They showed that opioid switching from low doses of oral morphine to an equi-analgesic oral methadone causes a small, but statistically significant, increase in QTc time.

Fredheim et al (98) showed that, after switching 12 patients from morphine to methadone, their blood levels and metabolite levels remained steady for the 9-month study period, contradicting the hypothesis of metabolic tolerance and auto-induction of hepatic enzymes during long-term methadone therapy. However, they noted that the oral dose had a poor correlation with serum blood levels, confirming a large inter-individual variability of metabolism.

Sandoval et al (78), in a systematic review of oral methadone for chronic non-cancer pain included 21 articles that followed the inclusion criteria with 545 patients. However, some of them were short-term evaluations. Table 4 illustrates the characteristics of case series evaluating effectiveness of methadone over 6 months (99-103). Five studies with 234 patients who had more than 6 months of follow-up were included (Table 3). Of these, meaningful improvement was seen in 154 patients indicating 66% response. Sandoval et al's review (78) showed that in all 21 studies, of the 526 patients included, 308 patients, or 59%, responded with meaningful relief.

In addition to relief in 59% of the patients, side effects or complications were reported in 50% of the studies. The most common side-effects were nausea or vomiting in 23.6% of the patients, sedation in 18.5% of the patients, itching and/or rash in 13% of the patients, and constipation in 11.7% of the patients. The number of meaningful "effects" obtained would normally be interpreted as indicating that the drug has a fair amount of effectiveness, with effectiveness demonstrated in 59% of patients with chronic non-cancer pain; however, these results must be interpreted with great caution. The results are derived from observational studies without control groups, and these studies may be flawed by the tendency to publish only studies with favorable results.

Tramadol

Cepeda et al (77) performed a systematic review and meta-analysis of 11 randomized controlled trials to determine the analgesic effectiveness, effect on physical function, duration of benefit, and safety of oral tramadol in patients with osteoarthritis. The study only included randomized controlled trials that evaluated the effect of tramadol or tramadol plus acetaminophen on pain levels in patients with OA. Studies that evaluated other types of arthritis (e.g., rheumatoid arthritis), non-osteoarthritic joint pain, or back pain were excluded. The study concluded that tramadol is more effective than placebo for the treatment of OA when pain is moderate. However, when OA pain is severe, there is only a small benefit to the patient. The study also notes that tramadol tolerability is increased when a slow titration regimen is implemented (e.g. 100 mg/day for 7-10 days, then 200 mg/day). The study found that this approach halves the proportion of people who interrupt therapy because of adverse events. Since only 2 studies evaluated tramadol for more than 8 weeks, the authors were unable to determine whether the clinical effectiveness of tramadol decreases with chronic use. Finally, another noted limitation was that only one of the 11 systematic reviews included in this study was not industry funded. Thus, it is possible for an overestimation of treatment effects of tramadol in patients with OA.

Controlled-release tramadol was evaluated by Beaulieu et al (104) in a multicenter, randomized, double blind, double dummy, 8-week crossover study, comparing it to immediate release tramadol. Overall pain scores were significantly better with the controlled release formulation. Since tramadol has a serotonin and norepinephrine reuptake inhibition action, continuous dosing (such as seen with extended release formulations) would be expected to be more effective than intermittent dosing (since the intermediate dosing does not allow for accumulation of serotonin and norepinephrine).

Adams et al (80), in a study funded by Ortho-McNeil, performed a double blind, 12-month crossover trial, looking at 3 different treatment arms: tramadol alone, tramadol randomized against NSAIDs, and tramadol randomized against hydrocodone. They looked at pain scores, SF-36, and what they called an "abuse

Table 4. Characteristics of case series evaluating the effectiveness of methadone use 6 months or over.

Study/ Characteristics	Participants	Intervention	Outcomes	Effectiveness (no. Patients)
Robbins (99) Ambulatory setting	66 patients (53 F, 13 M), ages 26 to 58 y/o, with chronic headaches. Indication for methadone was ineffective pain relief with previous treatments: NSAIDs, calcium channel blockers, beta-blockers, valproate, and antidepressants	Average dose was 10 mg/day. Co-interventions: not described. Time: 6 months Side effects: fatigue, confusion nausea, constipation, profuse sweating, lightheaded/dizziness, and rash	Pain relief scale: 1-25% = no relief: 27 patients (41%) 25-50% = mild relief*: 5 patients (8%) 50-75% = moderate relief: 16 patients (24%) 75-100% = excellent relief: 18 patients (27%)	Meaningful = 34 Non-meaningful = 32 Unclassifiable = 0
Robbins (100) Ambulatory setting	148 patients. Only 42 remained on methadone after 6-mos period (33 F, 9 M). With chronic daily headache refractory to standard therapies such as NSAIDs, calcium channel blockers, divalproex, antidepressants, and methysergide	Average dose was 10 mg/day. Co-interventions: not described. Time: 6 months Complications and side effects: not described	42 reported moderate or excellent relief. Quality of work and home life in these 42 patients: 86% of patients had improvement in work performance; 71% improvement in relationship with partner; 81% improvement in relationship with children and friends; 60% improvement in sexuality	Meaningful = 42 Non-meaningful = 106 Unclassifiable = 0
Mironer et al (101) Ambulatory setting	47 patients (18 F, 29 M), 57 y/o on average (from 29 to 88), with neuropathic pain. Indication for methadone was ineffectiveness with previous treatments: opioids, anticonvulsants, antidepressants, calcium channel blockers, intravenous and oral lidocaine, etc.	Average daily intake of methadone was 27 mg/day (range 10-60 mg/day) The most common co-intervention: gabapentin (12 patients). Duration of treatment varied from 6 to 37 months	Patients reported on average 30% to 90% pain relief, with 34 out of 47 having more than 50% improvement in their pain scores. Side effects: not significant	Meaningful = 47 Non-meaningful = 0 Unclassifiable = 0
Quang-Cantagrel et al (102) Ambulatory setting	Methadone was given to 29 patients out of 86 (50 F, 36 M) with various non-cancer pain syndromes (back pain neuropathy: joint pain, visceral pain, reflex sympathetic dystrophy, headache, and fibromyalgia Indication for methadone was ineffectiveness with previous treatments	Doses of methadone were 39.0 6 17.0 mg/day. Co-interventions: not described. Duration of the treatment was an average of 49.4 wks	There was 1 case of addiction and no case of tolerance Complications and side effects (52%) included: nausea, vomiting, sedation, itching, and kidney alterations	Meaningful = 8 Non-meaningful = 21 Unclassifiable = 0
Moulin et al (103) Ambulatory Setting	50 patients (22 F, 28 M) with mean age of 52.7 and a variety of intractable neuropathic pains. The indications were ineffectiveness of previous medications and side effects	Initial dose of 20 mg/day. Maximum dose 160 mg/day Maintenance dose 121 mg/day. Co-interventions: tricyclic antidepressants, NSAIDs, SSRI, benzodiazepines, and anticonvulsants. Mean duration of treatment: 17.3 months	26 (52%) improved with methadone: 3 mild, 16 moderate, 6 marked, and 1 complete pain relief 16 patients (32%) reported improvement in function Complications and side effects: not described	Meaningful = 23 Non-meaningful = 27 Unclassifiable = 0

index.” They found that the prevalence of abuse/dependence over the 12-month period was equal for the tramadol and NSAIDs, but, as expected, the hydrocodone had twice as much abuse.

Table 5 illustrates the results of studies of tramadol.

Oxymorphone

Rauck et al (105) studied oxymorphone in an open-label, 6-month study looking at efficacy and side effects. They reported that 75% of patients could be stabilized on a dose of oxymorphone that provided effective pain relief with tolerable side effects.

Table 5. Results of studies evaluating long-term effectiveness of tramadol.

Study/ methods	Participants	Opioids studied	Outcome(s)	Result(s)	Conclusion(s)	Complications
Harati et al (84) 6-month open extension followed a 6-week double-blind, randomized trial	117 with painful diabetic neuropathy A total of 117 patients (56 former tramadol and 61 former placebo) entered the study	tramadol	Self-administered pain intensity scores (scale 0-4; none to extreme pain) and pain relief scores (scale 1-4; worse to complete relief) were recorded the first day of the open extension (last day of the double-blind phase) and at 30, 90, and 180 days.	Tramadol reduced mean pain scores which were maintained throughout the study	Tramadol provides long-term relief of the pain of diabetic neuropathy	The most common adverse events were constipation, nausea, and headache
Adams et al (80) Prospective	A total of 11,352 subjects were enrolled	NSAIDs, tramadol, hydrocodone	Abuse	Tramadol was effective with less abuse potential than hydrocodone	These results support the hypothesis that the rate of abuse identified with tramadol is less than the rate associated with hydrocodone	None described
Beaulieu et al (104) Multicenter randomized double blind, double dummy, crossover trial of tramadol controlled-release and tramadol immediate-release	Chronic non-cancer pain patients: (n=122) Completed study: n=65 8 weeks	Patients randomized to 2 groups: active tramadol controlled-release + placebo 4-6 hours prn or placebo plus active tramadol immediate-release 4-6 hours prn for 4 weeks and then switched to alternate treatment for another 4 weeks	Pain intensity; pain disability index; sleep quality and quantity; analgesic effectiveness; adverse events at each visit	Overall pain intensity scores significantly better with controlled-release tramadol No differences in total pain disability index, or overall pain and sleep scores	Significantly better pain control in chronic benign pain with tramadol controlled-release every 24 hours vs. Tramadol immediate-release every 4-6 hours prn Funded by Purdue Pharma	3 patients experienced serious adverse events. The only difference in adverse events was nausea seen more often in the tramadol controlled-release (p<0.021). 2 patients hospitalized with vomiting from the immediate-release group; one hospitalized for asthenia in the controlled-release group

McIlwain and Ahdieh (86), in a 52-week, multicenter open-label extension study of 153 patients with moderate to severe chronic osteoarthritis-related pain, showed improvement in pain. They found that oxymorphone ER provides a new 12-hour analgesic for the treatment of moderate to severe, chronic osteoarthritis-related pain in patients who may require long-term opioid therapy.

Oxycodone

The effectiveness of oxycodone was evaluated in multiple studies (87,106-108).

Portenoy et al (108) looked at sustained release oxycodone use over a 3-year period in 233 non-cancer patients who had participated earlier in clinical trials regarding the same medication. At study's end, pain was the same or improved in 70% to 80% of the patients. They noted that approximately half the patients who stopped the opioids due to side effects did so by the end of month 6. Adverse effects were seen in 88% of the patients on sustained release oxycodone.

Rauck et al (106), in a randomized, open-label, multicenter trial, studied the effectiveness of sustained release oxycodone compared with sustained release morphine in 266 patients up to 8 months. Both groups showed significant improvement. They concluded that compared to twice daily sustained release oxycodone, once daily sustained release morphine resulted in significantly better physical function and quality of life.

Roth et al (87) studied 133 patients with osteoarthritis with follow-up lasting up to 6 months. Fifty-eight patients completed 6 months of treatment and 41 completed a 12-month follow-up, whereas 15 completed an 18-month follow-up. They concluded that sustained release oxycodone provided sustained analgesia.

Hermes et al (107), in an observational review, reported the results of 47,000 veterans receiving opioids through the VA system, of which 2,200 received oxycodone for over 9 months (31% of these patients were diagnosed with cancer) with mean daily doses of 3.9 tablets per day with a range of 0.5 to 13 with minimum change over time. They concluded that among patients without cancer, patients with concurrent benzodiazepines, psychogenic pain, alcohol abuse, and HIV/AIDS had more treatment management problems.

Table 6 illustrates the results of studies evaluating the effectiveness of oxycodone.

Hydrocodone

There were no studies evaluating the effectiveness of hydrocodone, even though this is the most commonly used drug.

QUALITY OF LIFE IMPROVEMENT

Function and quality of life is even more difficult to assess and, not surprisingly, very few of the existing opioid studies have focused on this issue, with relatively scant data available. Even though multiple case series on function consistently report improvement, the quality of this type of evidence is always unreliable and questionable (109). Epidemiological studies are less positive, and report failure of opioids to improve quality of life in chronic pain patients (110). Systematic reviews and randomized controlled trials provide limited evidence. However, studies assessing cognitive function, including the ability to drive and operate machinery, find that cognitive function, manual dexterity and reaction times are maintained provided a stable dose of opioid is used (98,111-114). This does not apply if the patient is not following the instructions or dosing is irregular and escalates (111,115,116).

Various aspects of quality of life were assessed in most studies. Several used validated quality of life questionnaires: the SF-36 (88,113,117,118), Short Form – McGill Pain Questionnaire (80), Short Form Health Survey (106), Brief Pain Inventory Short Form (105,108), Work Limitation Questionnaire (106), Sickness Impact Profile (119), Coping Strategy Questionnaire (120), and the CAGE-test (120). Only one study (118) reported a positive difference in relation to most health-related quality of life domains of the SF-36 with administration of oxycodone. The 10-year follow up by Jensen et al (120) showed that opioid users had lower SF-36 scores than chronic pain patients that were not using opioids. Deshpande et al (121) took the data from Gilron's study (122), and looked specifically at pain relief and mood, concluding that pain relief could be expected to improve mood in non-depressed patients.

In the study by Milligan et al (88), though overall QOL did not change, the SF-36 scores at 12 months for bodily pain and social functioning showed a significant improvement, as did the physical functioning summary score. It is also worth noting that, in a 10-year follow-up survey, Jensen et al (120) evaluated opioid use, health-related quality of life and health care utilization in chronic non-cancer pain patients.

Effectiveness of Opioids for Non-Cancer Pain

Table 6. Results of studies evaluating long-term effectiveness of oxycodone.

Study/ methods	Participants	Opioids studied	Outcome(s)	Result(s)	Conclusion(s)	Complications
Rauck et al (106) Randomized, open-label, multicenter trial	Chronic, severe low back pain (n=266) Sustained release morphine vs. sustained release oxycodone Up to 8 months	Randomized to sustained release morphine (Avinza) or sustained release oxycodone (Oxycontin) period of dose titration, then 8 week evaluation and optional 4 month extension (n=174)	Short Form-12, Work Limitation Questionnaire	Improvements seen in both groups (> in sustained release morphine)	Compared to twice a day sustained release oxycodone, once daily sustained release morphine resulted in significantly better physical function and quality of life activities.	None described
Roth et al (87) Randomized, double blind, placebo controlled	133 patients with osteoarthritis 6 to 12 months 58 patients completed 6 months treatments, 41 completed 12 months, 15 completed 18 months	Sustained release oxycodone bid 10 mg (n=44) 20 m (n=44) vs placebo (n=45)	VAS, mood, sleep, quality of life	Mood and quality of life improved. Analgesia was maintained and dose was stable	Sustained release oxycodone provided sustained analgesia	Typical opioid side effects were noted and decreased over time
Hermos et al (107) Observational review	47,000 veterans receiving opioids through the VA system	Oxycodone with APAP; concurrent use of long acting narcotics, benzodiazepines, tricyclic antidepressants, and anti-epileptic drugs	Number of doses	About 2,200 received oxycodone with APAP for > 9 months (31% with diagnosis of cancer); mean daily dose 3.9 tabs/day (0.5-13.0) with minimal change over time	Among patients without cancer, patients with concurrent benzodiazepines, psychogenic pain, alcohol abuse, and HIV/AIDS had more prescription management problems	None described
Portenoy et al (108) Open-label, uncontrolled registry	233 patients non-cancer pain Low back pain (68 patients) Neuropathic (67 patients) Osteoarthritis (84 patients)	Sustained release oxycodone 1 yr (141 pts) 2 yrs (86 pts) 3 yrs (39 pts)	Brief Pain Inventory Short Form, VAS, med acceptability, adverse events, aberrant drug behavior (abuse, misuse, withdrawal)	Brief Pain Inventory Short Form scores decreased after starting oxycodone. Pain scores improved in approximately 70 to 80% thru month 33 and 54% at month 36.	There need to be more data regarding efficacy of long-term opioids	Adverse events seen in 88% sustained release oxycodone. Constipation (15%), nausea (12%), somnolence (8%), vomiting (7%), depression (2%). 7 patients died, presumably not related to medication.

They evaluated 376 patients discharged from multidisciplinary pain centers, of whom 92 patients died during the follow-up period, and 5 patients could not be traced, with 160 patients agreeing to participate in the study with a response rate of 57%. The results showed opioid dose escalation occurred in a few opioid users, with increase and decrease being equally frequent. Only 60% of those discharged on long-acting opioids were still on that treatment at follow-up. The results also showed that occupational status was identified as a determining factor for future opioid use. Users of opioids had a significantly higher occurrence of depression. They also showed that the 10-year-incidence of being supplied by disability pension was more than halved when the patient had a job or was being rehabilitated at discharge, compared to a patient discharged on sickness or social security benefits. However, opioid treatment did not improve the health related quality of life to a level comparable with chronic pain patients not treated with opioids. This has been explained on the basis that it may have been a reluctance to prescribe opioids for people in a working position in favor of higher age and people receiving disability pension. This study showed that the reduction and stabilization of hospital admissions after the intervention was maintained even 10 years after the intervention.

Rauck et al (106), in a multicenter trial, compared the quality of life and work limitations of extended release morphine sulfate capsules, and twice daily controlled release oxycodone tablets in subjects with chronic, moderate to severe low back pain. In a 4-month extension survey, it was shown that both sustained release morphine and sustained release oxycodone lead to significant improvement on both physical and mental components of the SF-12, with physical functioning scores improving by approximately 20% to 30%. However, almost all of the gains were already achieved by the end of the opioid dose titration phase, when the first post-baseline assessment was performed. Rauck et al (123,124) have previously also reported that both sustained release morphine and oxycodone significantly improve pain and sleep scores during the 8-week evaluation phase of the study, but sustained release morphine resulted in significantly better improvement in pain and sleep scores while requiring a significantly lower daily morphine dose. Rauck et al (106) also noted that physical functioning continued to be noted in subsequent monthly assessments made over a total of more than 7 months

of follow-up study. Overall Rauck et al (106,123,124) appeared to favor sustained release morphine over sustained release oxycodone.

Other studies have also shown improved physical functioning associated with pain relief after therapy with sustained release morphine in patients with different types of chronic, moderate to severe non-cancer pain. In a randomized, double-blind, phase-3 trial conducted in osteoarthritis subjects, Caldwell et al (82) showed that the mean physical function score improved by 18% at week 4, compared to an improvement of 8% with placebo. In addition, an evaluation of 492 patients with nonmalignant chronic pain, Adams et al (125) showed that sustained release morphine significantly increased the proportion of subjects who reported an improvement in ability for moderate-intensity activities such as climbing a flight of stairs, bending, kneeling, or stooping. Further, Adams et al (125) also reported a significant decrease in the proportion of subjects with decreased functioning occurring 7 days a week from 81% at baseline to 67% at 3 months, in a randomized trial conducted in subjects with various chronic, nonmalignant pain comparing sustained release oxycodone with sustained release morphine. Allan et al (81) evaluating 680 patients with chronic low back pain utilizing transdermal fentanyl or sustained release morphine, showed that while both drugs provided significant pain relief, the proportion of participating reporting more than 3 weeks of off work at baseline decreased from 34% and 25% at baseline to 16% for transdermal fentanyl and sustained release morphine at endpoint. In addition, the proportion of working participants who reported no loss of working days due to low back pain increased from baseline to endpoint, from 35% to 59% in the transdermal fentanyl group, and from 49% to 67% in the sustained release morphine group. However, the differences not statistically significant, but 70% of the participants in the study did not work with 30% being retired, 34% disabled and 6% unemployed. They also showed significant improvement in overall physical health as determined by SF-36 with improved physical functioning, and social functioning. Zenz et al (83) showed a close correlation with pain reduction with an increase in performance. Tassain et al (97), in an evaluation of the long-term effect of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain reported persistent effects on pain relief, with persisting effects on the quality of life and mood to a lesser extent. Thus,

they concluded that morphine does not disrupt cognitive functioning in patients with chronic non-cancer pain and instead results in moderate improvement of some aspects of cognitive functioning as a consequence of the pain relief and concomitant improvement of well-being and mood.

Transdermal fentanyl was also studied for long-term effectiveness and improvement in functional status. Allan et al (81) showed significant improvement in quality of life measures with physical health. Milligan et al (88), however, showed no significant change in the quality of life parameters even though transdermal fentanyl provided significant pain relief and also satisfaction with the treatment. In contrast, Mystakidou et al (89) in a study of transdermal fentanyl in the treatment of chronic non-cancer pain, showed sustained efficacy of pain relief in 90% of the patients, with median duration therapy for effective pain management of 10 months, in 529 patients with significant improvement in quality of life measures.

Overall, though not surprisingly, epidemiological studies are less positive with regards to function and quality of life and report the failure of opioids to improve quality of life in chronic pain patients (6,7,35,66-70). Further, Eriksen et al (6) in an epidemiological study from Denmark, where opioids are prescribed liberally for chronic pain, demonstrated worse pain, higher healthcare utilization, and lower activity levels in opioid treated patients compared to a matched cohort of chronic pain patients not using opioids, suggesting that when opioids are prescribed liberally, even if some patients benefit, the overall population does not. More importantly, instead of improving functional status, opioid use has been associated with increased disability, medical costs, subsequent surgery, and continued or late opioid use (40,41,43-45). It was shown that patients receiving more than 450 mg equivalent of morphine over a period of several months were, on average, disabled 69 days longer than those who received no early opioids, had 3 times increased risk for surgery, and had 6 times greater risk of receiving late opioids (38,40,41,43-45). In a study of the association between opioid prescribing and an increase in overall health care costs for low back pain, overall, higher levels of health care utilization were reported (41). In a study evaluating an association between opioid use for more than a week for acute low back pain and disability duration in a worker's compensation cohort, there was significant association between opioid use initially and continued

disability (45). In yet, another study it was shown that opioid use was associated with greater self-reported disability and poorer functioning (38).

Another important function evaluated is driving capability when patients are on chronic opioid therapy (126,127). Fishbain et al (127) in a structured, evidence-based review of impairment in driving-related skills in opioid-dependent or tolerant patients, concluded that the majority of the reviewed studies appeared to indicate that opioids do not impair driving-related skills in opioid-dependent or tolerant patients. Further, the evidence was consistent in 4 out of 5 research areas investigated, but inconclusive in one. Research was conclusive for no impairment of psychomotor abilities of opioid maintained patients, no impairment of psychomotor abilities immediately after being given doses of opioids, no greater incidence in motor vehicle violations or motor vehicle accidents versus comparable controls of opioid-maintained patients, and no impairment as measured in driving simulators of and on road of driving by opioid-maintained patients. Inconclusive evidence was present in multiple studies for no impairment in cognitive function of opioid-maintained patients. In contrast, Strassels (126), based on a narrative review, indicated that cognitive function can be influenced by the use of opioid analgesics, although the effects vary among drugs. The most significant drugs described were mixed-activity drugs, such as codeine, propoxyphene, and meperidine, which are generally most concerning during the first few days after starting the opioid therapy, before tolerance develops. Thus, Strassels (126) recommended to address this issue on a patient-specific basis and advised against blanket policies regarding the activities of driving and working. However, Fishbain et al (127) utilized a structured, evidence-based review by categorization of the criteria according to guidelines developed by the Agency for Healthcare Policy Research (128).

DISCUSSION

The recognition that opioid therapy can relieve pain and improve mood and functioning in many patients with chronic pain has led pain experts to recommend that such patients not be denied opioids (67). Consequently, opioids have been used extensively with arguments that physicians should be encouraged to prescribe opioids because they are indispensable for the treatment of pain and suffering, because uncontrolled pain may have deleterious physical effects,

and because persistent pain destroys peoples' autonomy, dignity, and decision-making capacity (1,3-5). Consequently, not only the availability, but the use of opioids have increased substantially along with abuse, misuse, addiction, diversion, and all other associated complications including increasing disability (7). This review, along with the currently available literature, does not provide enough evidence to guide the prescribing physicians in choosing opioids for long-term management. The review of all the studies show at best weak evidence for long-term opioid therapy lasting over 6 months. Thus, for patients able to continue on opioids, morphine and transdermal fentanyl provide weak evidence on a long-term (> 6 months) basis and moderate evidence for short-term (< 6 months) basis. Overall, the literature describing long-term safety and efficacy of opioids for chronic non-cancer pain is limited in terms of quantity and quality, precluding the formation of evidence-based conclusions supported by strong qualitative or stable quantitative evidence. Consequently, all the evidence is of low quality, and thus weak. Further, the generalizability of findings of these studies to chronic non-cancer population in real world settings is unclear; weak evidence is available only for morphine and transdermal fentanyl, showing improvement in pain and function. The evidence is inconclusive for methadone. Further, the evidence is limited for the most commonly used drugs oxycodone and hydrocodone. However, there is weak evidence for the long-term effectiveness of tramadol specifically in osteoarthritis. In addition, the studies

evaluating long-term opioid therapy for chronic non-cancer pain (66) also demonstrated that these findings are applicable only in patients without a history of addiction or abusive behaviors.

Given the complexity of opioid therapy, the non-availability of qualitative or quantitative literature, and with only weak evidence of pain relief, combined with improvement in functional status, for only 2 drugs evaluated (morphine and transdermal fentanyl), the evidence-based approach to chronic opioid therapy for longer than 6 months provides a weak recommendation.

CONCLUSION

It is concluded that, for long-term opioid therapy of 6 months or longer in managing chronic non-cancer pain, with improvement in function and reduction in pain, there is weak evidence for morphine and transdermal fentanyl. However, there is limited evidence for all other controlled substances, including the most commonly used oxycodone and hydrocodone.

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