

Focused Review

Effectiveness of Long-Term Opioid Therapy for Chronic Non-Cancer Pain

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Background: Opioids have been utilized for thousands of years to treat pain and their use continues to escalate. It is estimated that 90% of the patients who present to pain centers and receive treatment in such facilities are on opioids. However, in contrast to increasing opioid use and the lack of evidence supporting long-term effectiveness in chronic non-cancer pain, is the escalating misuse of prescription opioids, including abuse and diversion. There is also uncertainty about the incidence and clinical salience of multiple, poorly characterized adverse drug events, including endocrine dysfunction, immunosuppression, infectious disease, opioid-induced hyperalgesia, overdoses, deaths, and psychosocial and economic implications.

Study Design: A comprehensive review of the literature.

Objective: The objective of this comprehensive review is to evaluate the clinical effectiveness and safety of chronic opioid therapy in chronic non-cancer pain.

Methods: A comprehensive review of the literature relating to chronic opioid therapy in chronic non-cancer pain. The literature was collected from various electronic and other sources. The literature that was evaluated included randomized trials, observational studies, case reports, systematic reviews, and guidelines.

Outcome Measures: Pain relief was the primary outcome measure. The secondary outcome measures were functional improvement and adverse effects. Short-term effectiveness was considered to be less than 6 months; long-term effectiveness was considered to be at least one year.

Results: Given the complexity and widespread nature of opioid therapy, there is a paucity of qualitative and/or quantitative literature. The available evidence is weak for pain relief combined with improvement in functional status. Only one drug, tramadol, is effective for pain relief and improvement of functional status.

Limitations: This is a narrative review without application of methodologic quality assessment criteria. Even so, a paucity of literature exists concerning both controlled and observational literature for multiple drugs and multiple conditions of chronic non-cancer pain.

Conclusions: This comprehensive review illustrates the lack of literature on long-term opioid therapy; thus, opioid therapy should be provided with great restraint and caution, based on the weak evidence available.

Key words: Chronic non-cancer pain, opioids, opioid effectiveness, adverse effects, morphine, hydrocodone, hydromorphone, fentanyl, tramadol, methadone, oxycodone

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Chapman et al (1) have described that opioid use in recent years has escalated, making opioids one of the most commonly prescribed medication classes in the United States. They also pointed to the many issues associated with this increased opioid use, which include the lack of evidence supporting their long-term effectiveness, escalating misuse of prescription opioids, and uncertainty about the frequency and severity of multiple, poorly characterized adverse drug events associated with long-term opioid use such as endocrine dysfunction, immunosuppression, and opioid-induced hyperalgesia. They described that chief among the limitations of current evidence is sparse evidence on long-term opioid effectiveness in chronic pain patients due to the short-term timeframe of clinical trials, insufficiently comprehensive outcome assessments, and incomplete identification and quantification of adverse drug reactions. Consequently, they recommended improvements in evidence-generation methodology for long-term opioid pharmacotherapy, and they cautioned that the need for a strong evidence base is urgent.

It is argued that physicians should be encouraged to prescribe opioids because they are indispensable for the treatment of pain and suffering, because uncontrolled pain could have deleterious physical effects, and because persistent pain destroys people's autonomy, dignity, and decision making capacity (2). 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, a country that has a free flow of opioids, the results showed worse pain, higher health care utilization, and lower activity levels in opioid-treated patients, compared with a matched cohort of chronic pain patients not using opioids (3). This provides *prima facie* evidence that when opioids are prescribed liberally, even if a small number of patients benefit, the overall population does not (3). 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 (4-6).

In the United States, the therapeutic use of opioids has exploded as witnessed by the increased sales of hydrocodone by 280% from 1997 to 2007, while at the same time methadone usage increased 1,293% and oxycodone increased 866% (5). In addition, the estimated number of prescriptions filled for controlled substances increased from 222 million in 1994 to 354 million in 2003 (5). 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% (5). And, while hydrocodone is the most commonly used opioid in the United States, based on milligrams per person, oxycodone is the most commonly used drug with methadone use rapidly increasing the most. 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 (7-20). Similarly, it has been shown that a majority of these patients were on opioids prior to presenting to an interventional pain management setting (7). However, the claims of undertreatment of pain and the campaign for increased availability of opioids and so-called assessment for proper treatment of pain continue (21-25). Consequently, Americans, constituting only 4.6% of the world's population, have been consuming 80% of the global opioid supply, and 99% of the global hydrocodone supply, as well as two-thirds of the world's illegal drugs (4-6,26-29). In addition, the liberalization of the laws governing opioid prescribing for the treatment of chronic non-cancer pain by state medical boards in the late 1990s (2), the introduction of new pain management standards for inpatient and outpatient medical care implemented by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in 2000, and the advocacy efforts of many physicians and organizations for increased usage of opioids in the treatment of chronic pain (2-6,25,29) has resulted in escalating use, abuse, and overuse of therapeutic opioids. Opioids in general, and the most potent forms of opioids, including Schedule II drugs in particular, have dramatically increased (30-40).

This comprehensive review has been undertaken to evaluate the effectiveness and safety of long-term opioid therapy for chronic non-cancer pain.

1.0 METHODS

The methodology utilized here follows a narrative review process; however, considering the numerous deficiencies with narrative reviews, some aspects of the systematic review process derived from evidence-based systematic reviews of randomized trials (41-44), the standards of reporting of randomized trials (45), standards of reporting of observational studies and systematic reviews of observational studies (46-52), and other guidance along with previous systematic reviews were used (50-52).

Consequently, the types of studies included were randomized controlled trials (RCTs), non-randomized

studies, systematic reviews, guidelines, and narrative reviews. All the studies utilizing adults aged at least 18 years with pain due to any cause other than cancer lasting for at least 3 months prior to inclusion, were included. Participants also should have received non-opioid pharmacotherapy, which failed to provide relief prior to the beginning of opioids. Only opioids administered either orally or topically were considered. The types of outcome measures included pain relief, proportion of patients with at least 50% pain relief, health related quality of life and function, and adverse events or side effects including discontinuation from the study due to adverse events and discontinuation from the study due to insufficient pain relief.

The search was similar to the one utilized for randomized trials (48) with inclusion of multiple sources, including PubMed from 1966, EMBASE from 1980, Cochrane library, ECRI Institute Library, the U.S Food and Drug Administration (FDA), the U.S. National Guideline Clearinghouse (NGC), previous systematic reviews and cross references, Database of Abstracts of Reviews of Effects (DARE), and clinical trials through November 2010. The search terminology included chronic non-cancer pain and opioids.

However, manuscripts were not reviewed extensively for selection criteria and methodologic quality assessment criteria.

The evaluation was for short-term effectiveness (< 6 months) and long-term effectiveness (at least one year).

2.0 EVIDENCE REVIEW

2.1 Prevalence of Prescription of Opioids

A systematic review of opioid treatment for chronic back pain by Martell et al (53) showed variable prescribing patterns for opioids ranging from 3% to 66% (54-60). 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%.

Among the reports, in a large U.S. survey, the proportion of office visits for chronic musculoskeletal pain in which opioids were prescribed doubled from 8% in 1980 to 16% in 2000. The proportion of office visits in which prescriptions for potent opioids were given increased from 2% to 9%. In a survey of over 1% of the U.S. population from 1997 to 2005 by 2 health plans of long-term opioid therapy for chronic non-cancer pain, it was concluded that long-term opioid therapy for non-cancer pain was increasingly prevalent; however, with

an inadequate understanding of the benefits and risks associated with such therapy, the incidence of long-term use increased from 8.5% to 12.1% per 100,000 enrollees (32).

In a study of commercial and Medicaid insurance plans from 2000 to 2005 (33), the proportion of enrollees with chronic pain who received opioids were 58% of commercial and 29% of Medicaid patients. There was an increase in the cumulative yearly opioid dose of 38% in commercial patients and 37% in Medicaid patients due to an increase in the number of days the opioids were prescribed. Short-acting opioids use grew more rapidly than others, despite no significant change in the underlying population's prevalence of chronic pain or new evidence of the efficacy of long-term opioid therapy. In an evaluation of analgesic usage for low back pain and its impact on health care costs and service use (34), in 2001 55.5% of the plan members who had claims for low back services received analgesics costing a total of \$1.4 million, of which 68% were opioids.

In a study of patterns and trends in opioid use among individuals with back pain in the United States (35), overall opioid use increased from 11.6% of individuals with back pain in 1996 to 12.6% in 1999. There was also an increase of prescriptions of oxycodone and hydrocodone but a decrease in propoxyphene. In Canada, opioid analgesic prescriptions in Ontario increased 29% from January 1991 to May 2007 (36). However, the number of oxycodone prescriptions increased more than 850% during the same period, along with increases of hydromorphone, fentanyl, and morphine. This study also illustrated that the addition of long-acting oxycodone to the drug formulary was associated with a 5-fold increase in oxycodone-related mortality and a 41% increase in opioid-related mortality, along with increasing health care services.

In a study of prescription patterns and concern about opioid analgesics for chronic non-malignant pain in general practice (61), 57.9% of general practitioners reported they sometimes, frequently, or always, prescribe strong opioids for chronic pain. Even though 83% of the general practitioners prescribing the opioids felt they were effective, they were worried about long-term commitment, addiction, and other adverse events.

2.2 Drug Abuse

Prescription opioids are associated with multiple long-term adverse consequences which include hormonal and immune system effects, abuse and addic-

tion, tolerance, and hyperalgesia. More importantly, opioid use has been associated with increased disability, medical costs, subsequent surgery, and continued or late opioid use (4,31,34,55,61-68). Numerous investigations (4,5,8-20,53,69-80) have illustrated drug abuse in 18% to 41% of patients receiving opioids for chronic pain. Martell et al (53) 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 patients with aberrant medication-taking behaviors. Further, patients on chronic opioid therapy have been shown to also abuse illicit drugs (8-20). 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 (8,10,11). 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 (19). Consequently, the cost of opioid abuse is enormous, reaching \$300 billion a year, with the federal government spending \$15.5 billion in 2010 on its National Drug Control Policy since 1998 (4,81).

The deleterious effects of chronic opioid use, abuse, and diversion translate into increased emergency room visits (5,6,26,27,40,82-86) and also contribute to increasing deaths (26,36,87-95). In fact, opioid-related deaths have topped deaths due to motor vehicle injuries with enormous increases (87,88,95) specifically secondary to methadone induced deaths (89-92,94,95).

2.3 Short-Term Effectiveness

Multiple systematic reviews, randomized trials, observational studies and guidelines have been conducted to test the analgesic efficacy of opioids for various chronic pain conditions for short periods of time.

Furlan et al (96) included 41 randomized trials involving 6,019 patients with nociceptive pain, neuropathic pain, mixed pain, and fibromyalgia. Even 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 one to 16 weeks.

Kalso et al (97) 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 including constipation in 41%, nausea in 32%, and somnolence in 29%.

Martell et al (53) also showed that opioids were efficacious for short-term pain relief, but with significant abuse, addiction, aberrant behaviors, and side effects.

Eisenberg et al (98) studied 23 trials meeting 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 range of 8 to 70 days, with a median of 28 days, is considered as short-term for the purpose of the present review.

Deshpande et al (99), in studying opioids for chronic low back pain for the Cochrane collaboration, included 4 trials. They concluded that the benefits of opioids in clinical practice for the long-term management of chronic low back pain remains questionable.

Cepeda et al (100) 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 function in patients with osteoarthritis, even though these benefits were small.

Sandoval et al (101) reported one RCT of methadone for chronic non-cancer pain and numerous observational reports. Their conclusions were that its effectiveness must be interpreted cautiously.

Chou and Huffman (102) identified 12 systematic reviews that primarily evaluated the short-term benefits of opioids for chronic non-cancer pain. Only one systematic review focused on the long-term benefits of opioids (103). Further, they identified 13 placebo-controlled randomized trials of opioids for chronic non-cancer pain not included in the systematic reviews. They indicated in the summary of evidence that many trials found opioids moderately effective for pain relief and slightly to moderately effective for functional outcomes compared to placebo in patients with non-cancer pain, even though almost all data were based on short-term (< 12 weeks) outcomes.

Noble et al (104) showed that of 3,026 participants receiving oral opioids in 11 studies, only 2,473 were eligible for analysis; they had a variety of painful conditions and were prescribed various different opioids. Many of

them discontinued long-term oral opioid therapy due to adverse events or insufficient pain relief. They also concluded that the weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. They summarized that the conclusions, with regards to the quality of life or functioning improvement, were inconclusive.

Manchikanti et al (41), in a systematic review, identified 111 randomized trials for consideration in the evaluation, of which only 20 met inclusion criteria for qualitative synthesis with a minimum of 12-week follow-up. They concluded that the results showed fair evidence for administration of tramadol in osteoarthritis, whereas, for all the agents including tramadol, in all conditions, the evidence was very weak or negative, leading to the conclusion of poor evidence.

Papaleontiou et al (105), in their systematic review and metaanalysis of outcomes associated with opioid use in the treatment of chronic non-cancer pain in older adults, evaluated 40 studies and concluded that in older adults with chronic pain and no significant comorbidity, short-term use of opioids is associated with a reduction in pain intensity and better physical functioning, but poorer mental health functioning. While they stated that adults age 65 and older were as likely as those younger than 65 to benefit from treatment, the long-term safety, efficacy, and abuse potential of this treatment practice in diverse populations of older persons remains to be determined.

Multiple systematic reviews recently evaluated various studies which met inclusion criteria (41,102,104,105). The characteristic features of these studies and evidence synthesis is illustrated in these systematic reviews.

2.4 Long-Term Effectiveness

Four systematic reviews looked at the long-term effectiveness of opioids of at least one year (41,53,97,104).

Martell et al (53) concluded that the effectiveness of opioids for a period lasting 16 weeks or longer was unclear. Kalso et al (97), showed a mean decrease in pain intensity of at least 30% with opioids, noting that about 80% of patients experienced at least one 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 (104) updated their previous systematic review (103) in 2009 and concluded that opioids might

be effective in a small proportion of patients based on weak evidence. They were concerned about many patients discontinuing long-term opioid therapy due to adverse events or insufficient pain relief. However, they included both randomized and observational studies. In this evaluation, they reviewed 26 studies with 27 treatment groups that enrolled a total of 4,893 participants, which also included intrathecal opioids apart from oral and transdermal opioids. Twenty-five of the studies were case series or uncontrolled long-term trial continuations; the other was an RCT comparing 2 opioids. They also included strong and weak opioids. There were 3 morphine studies (106-108), 2 studies of extended release tramadol (109,110), one study of immediate release tramadol (111), 2 studies of controlled release oxycodone (112,113), one methadone study (114), one study of extended-release oxymorphone (115), another study of weak opioids for extended release oxymorphone (116), and multiple other studies of dihydrocodeine, buprenorphine, and morphine for weak opioids. There were 3 studies evaluating the role of transdermal fentanyl (106,117,118).

In Manchikanti et al's (41) systematic review of 111 trials with administration of opioids either orally or topically, only 4 studies evaluated effectiveness beyond 6 months (106,119-121). Of these, one study evaluated tapentadol (121) with weak positive evidence, the second study evaluated morphine with negative evidence (119), the third study evaluated oxycodone with negative results (120), and the fourth study evaluated fentanyl and morphine with indeterminate results (106).

In summary, based on the present systematic reviews, it appears that long-term opioid therapy is associated with some degree of pain relief, though evidence is weak because of overall summary effects and sizes. Consequently, it appears that it is necessary to use less vigorous forms of evidence to evaluate long-term effectiveness, since it is not feasible to conduct RCTs over prolonged periods. Other drawbacks of long-term effectiveness are that in open label follow-up studies, as many as 56% of patients abandon the treatment because of a lack of efficacy or side effects (97,104,122). Further, many opioid trials utilize enrichment in their protocols (patients who do not respond or are selected out during the pre-trial phase) and there is an unusually high dropout rate across opioid trials during enrichment, likely reducing the internal validity of the trials (123). Yet, lingering issues remain related to opioids' lack of effectiveness for improving functional status or quality of life even when the dosage is escalated.

Further, the traditional premise that dosages should be titrated upwards to overcome pharmacological tolerance, which appears to be an inevitable consequence of long-term opioid treatment, has been utilized in long-term studies (2). Consequently, the majority of patients might be able to reach a stable, non-escalating, effective dose; analgesic tolerance seems to stabilize over time. Even then, some patients continue to fail dose escalation, reporting no change or worsening of their pain, despite high doses of opioids (22,100,124-128) with a paradoxical response of actual improvement in pain once opioid treatment is discontinued (129-131), secondary to a rampant tolerance or opioid-induced hyperalgesia; thus, it shows that the premise that tolerance can always be overcome by dose escalation is unrealistic (100,127).

Candiotii and Gitlin (22) reviewed the effect of opioid-related side effects on the undertreatment of moderate to severe chronic non-cancer pain. They illustrated that the majority of patients treated with traditional opioids experienced gastrointestinal or central nervous system-related adverse events, most commonly constipation, nausea, and somnolence, often leading to discontinuation of opioid therapy. Further, they concluded that the pervasiveness of opioid-associated side effects and concerns related to tolerance, dependence, and addiction present potential barriers to the approval and use of opioids for the management of chronic non-cancer pain. The lower incidence of opioid-associated adverse events and possibly fewer withdrawal symptoms, combined with a satisfactory analgesic profile associated with tapentadol, suggests its potential utility for the management of chronic non-cancer pain.

In a systematic assessment of symptoms and side effects in chronic non-cancer pain (132), it was concluded that the number of symptoms reported using systematic assessment was 8-fold higher than those reported voluntarily. Fatigue, cognitive dysfunction, dry mouth, sweating, and weight gain were the most frequently reported side effects. In this study, a total of 62 patients and 64 controls participated in the study. The number of symptoms reported by the patients was significantly higher than those reported by the controls (9.9 ± 5.9 vs. 3.2 ± 3.9). The 6 most frequently reported symptoms were fatigue, memory deficits, dry mouth, concentration deficits, sweating, and weight gain. Of these, dry mouth was seen in 42% of the patients, sweating in 34%, weight gain in 29%, memory deficits in 24%, fatigue in 19%, and concentration deficits in 19%.

2.5 Effectiveness of Opioids (Individual Drugs)

In this evaluation, we reviewed the available literature for commonly utilized opioids – hydrocodone, oxycodone, morphine, tramadol, methadone, transdermal fentanyl, codeine, oxymorphone, buprenorphine, and tapentadol.

2.5.1 Hydrocodone

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 (133), 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.

2.5.2 Oxycodone

The long-term effectiveness of oxycodone was evaluated in multiple studies (113,115,120,134-136).

Portenoy et al (135) looked at sustained-release oxycodone use over a 3-year period in 233 non-cancer patients who had participated earlier in clinical trials studying 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.

Rauk et al (134), in a randomized, open-label, multicenter trial, studied the effectiveness of sustained release oxycodone compared with sustained release morphine in 266 patients for 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 (113) 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.

Hermos et al (115), in an observational review, reported the results of 47,000 veterans receiving opioids through the Veterans Affairs (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.

Vondrackova et al (120), in a randomized, double-blind, placebo-controlled trial, studied the analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release (PR) tablets in patients with moderate to severe chronic pain. They concluded that not only does oxycodone PR/naloxone PR demonstrate analgesic efficacy comparable with oxycodone PR, but it also improves opioid-induced bowel dysfunction, and might therefore improve the acceptability of long-term opioid treatment for chronic pain.

Ytterberg et al (136), in a retrospective cohort study, evaluated codeine and oxycodone use in patients with chronic rheumatic disease pain. They concluded that prolonged treatment of rheumatic disease pain with codeine or oxycodone was effective in reducing pain severity and was associated with only mild toxicity. Doses were stable for prolonged periods of time, with escalations of the opioid dose almost always related to worsening of the painful condition or a complication thereof, rather than the development of tolerance to opioids.

Table 1 illustrates the results of studies evaluating the effectiveness of oxycodone.

2.5.3 Morphine

The long-term effectiveness of morphine has been evaluated in multiple studies (106-108,119,137,138).

Allan et al (106) 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 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 were not employed. Sustained release morphine provided significant improvement of mean Visual Analog Scale (VAS) scores for participants who remained in the study for 56 weeks. However, use of concomitant, strong, short-acting opioids were frequently used by 50% of the participants as rescue medication. Quality of life scores showed improvement in physical health from a 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 the par-

ticipants had stable disease, 8% deteriorated, and 23% had improved. They concluded that strong opioids might be indicated for chronic low back pain that is not relieved by other forms of analgesia.

Caldwell et al (107) evaluated Avinza, an extended-release morphine formulation, in 181 participants during a 26-week open-label extension trial with an option to increase their dose to optimize pain control. Of the 181 participants who entered the open-label trial, 91 received Avinza in the morning and 90 received it 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 participants were excluded entirely from the subset analysis due to concomitant therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen use. Constipation and nausea were the most frequent adverse effects reported in over 80% of the participants.

Zenz et al (108) 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 (137) evaluated the 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 their pain management and improvement in physical status and quality of life. There were inconsis-

Table 1. Results of studies evaluating long-term effectiveness of oxycodone.

Study/methods	Participants	Opioids Studied	Outcome(s)	Conclusion(s)	Complications	Result(s)
Rauk et al (134) 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	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	Improvements seen in both groups (> in sustained release morphine)
Roth et al (113) Randomized, double blind, placebo controlled	<ul style="list-style-type: none"> • 133 patients with osteoarthritis • 6 to 12 months • 58 patients completed 6 months of treatments, 41 completed 12 months, 15 completed 18 months 	Sustained release oxycodone twice a day 10 mg (n=44) 20 mg (n=44) vs placebo (n=45)	VAS, mood, sleep, quality of life	Sustained release oxycodone provided sustained analgesia	Typical opioid side effects were noted and decreased over time	Mood and quality of life improved. Analgesia was maintained and dose was stable
Hermos et al (115) Observational review	47,000 veterans receiving opioids through the VA system	Oxycodone with acetaminophen; concurrent use of long acting narcotics, benzodiazepines, tricyclic antidepressants, and anti-epileptic drugs	Number of doses	Among patients without cancer, patients with concurrent benzodiazepines, psychogenic pain, alcohol abuse, and HIV/AIDS had more prescription management problems	None described	About 2,200 received oxycodone with acetaminophen for > 9 months (31% with diagnosis of cancer); mean daily dose 3.9 tabs/day (0.5-13.0) with minimal change over time
Portenoy et al (135) 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)	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.	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.
Ytterberg et al (136) Retrospective cohort study	644 patients with chronic rheumatic disease pain	Codeine and/or oxycodone	Pain relief, frequency and types of side effects	Prolonged treatment of rheumatic disease pain with codeine or oxycodone was effective in reducing pain severity and was associated with only mild toxicity	50% of the patients reported side effects, the most common being constipation, nausea, dyspepsia, sedation, headache, and dizziness	Codeine and oxycodone are effective therapies for prolonged treatment of rheumatic disease patients without major side effects.

tent changes in opioid dosages over the 5-year period, without any change in 33% of the patients, a decrease in 16%, a slight increase in 27%, and a high increase in 19%. The survey demonstrated a very low frequency of withdrawal in patients undergoing long-term opioid medication after initial response was without evidence for tolerance development, especially if their treatment was controlled in a pain center.

Tassian et al (138) 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 the 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)	Conclusion(s)	Complications	Result(S)
Allan et al (106) 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	Sustained release strong opioids can safely be used in opioid naïve patients	Most common adverse events leading to discontinuation were nausea (37%), vomiting and constipation.	Significant proportion of patients on sustained release morphine experienced pain relief.
Caldwell et al (107) Double-blind trial, followed by open-label extension trial	184 with chronic osteoarthritis 181 participants entered the open-label trial	Placebo, Avinza, or MS Contin in double-blind trial	Pain relief; physical functioning; stiffness	Efficacy was comparable between 2 modes of administration.	Most common adverse effects were constipation and nausea	Significant improvement in pain relief and sleep measures
Zenz et al (108) 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	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	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
Maier et al (137) Narrative descriptive report	121 patients with chronic non-cancer pain	Sustained release morphine	Pain relief and quality of life.	Pain relief correlated with improvement in functional status	There was no development of tolerance	Significantly lower pain intensity and improved physical state and quality of life
Tassain et al (138) 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	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	Morphine produced persistent pain relief and improved quality of life and mood

2.5.4 Tramadol

Despite numerous trials, the long-term effectiveness of tramadol has been evaluated in only one study in osteoarthritis (111).

Harati et al (111) evaluated the long-term effectiveness of tramadol in 117 participants with painful diabetic neuropathy. This was a 6 month open extension, which followed a 6 week double-blind, randomized trial. Of the 117 participants who entered the study, 56 had been taking tramadol and 61 had been taking placebo. The results illustrated that tramadol reduced mean pain scores, which were maintained throughout the study associated with the most common adverse events of constipation, nausea, and headache. The authors concluded that tramadol provides long-term relief of the pain of diabetic neuropathy; however, the evidence is very weak.

2.5.5 Methadone

Methadone is one of the commonly utilized, but also rigorously debated drugs, because of its potential for abuse, adverse consequences, and pharmacodynamic variations (114,139-144). There have not been any RCTs evaluating methadone either on a short-term or a long-term basis.

Sandoval et al (101), in a systematic review of oral methadone for chronic non-cancer pain, included 21 articles that followed inclusion criteria with 545 patients. However, some of them were short-term evaluations. Table 3 illustrates the characteristics of a case series evaluating the effectiveness of methadone over 6 months (114,139-144). Five studies with 234 participants who had more than 6 months of follow-up were included. Of these, meaningful improvement was seen in 154 participants indicating a 66% response. Sandoval et al's review (101) showed that in all 21 studies, of the 526 participants included, 308 participants, or 59%, responded with meaningful relief.

In addition to relief in 59% of the participants, side effects or complications were reported in 50% of the studies. The most common side-effects were nausea or vomiting in 23.6%, sedation in 18.5%, itching, and/or rash in 13%, and constipation in 11.7%. 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 participants with chronic non-cancer pain; however, these results must be interpreted with great caution. The results are derived from observational studies without control groups.

2.5.6 Transdermal Fentanyl

Transdermal fentanyl provides sustained release analgesia. It has been studied in 3 studies, both randomized and non-randomized (106,117,118). Even though transdermal fentanyl has been evaluated in systematic reviews, there has not been any strong evidence either for short-term or for long-term effectiveness. However, it has been shown to be superior to morphine, specifically with regards to some adverse effects.

Allan et al (106) evaluated 338 patients with chronic low back pain who took transdermal fentanyl for 13 months; they 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 patients who rested, 47% in patients who moved during the day, and 53% in patients at night. Concomitant medication with possible analgesic effect and rescue medication were taken by over 80% of the patients during the trial; 52% used strong opioids.

Milligan et al (117) evaluated the long-term efficacy and safety of transdermal fentanyl in the treatment of chronic non-cancer pain in an international, multicenter, open-label trial over 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 the 12 months. During treatment, on average, 67% of patients in the efficacy analysis group (n=524) reported very good, good, or moderate pain control, with global satisfaction reported in 42% of 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 the Short Form-36 (SF-36). The most frequent treatment-related adverse events were nausea (31%), constipation (19%), and somnolence (18%).

Mystakidou et al (118) 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 the patients sustained effectiveness with improvement in quality of life scores and pain. Further, the improvements were not influenced by pain type or etiology.

Table 4 illustrates results of studies evaluating the long-term effectiveness of transdermal fentanyl.

Effectiveness of Long-Term Opioid Therapy for Chronic Non-Cancer Pain

Table 3. Characteristics of case series evaluating the effectiveness of methadone use 6 months or over.

Study/ Characteristics	Participants	Intervention	Outcomes	Effectiveness (No. Patients)
Robbins (142) Ambulatory setting	66 patients (53 F, 13 M), ages 26 to 58, 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, 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 (143) 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 (144) 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 (139) Ambulatory setting	Methadone was given to 29 of 86 patients (50 F, 36 M) with various non-cancer pain syndromes (back pain neuropathy: joint pain, visceral pain, reflex sympathetic dystrophy, headache, fibromyalgia) Indication for methadone: ineffectiveness with previous treatments	Doses of methadone were 39.0 ± 17.0 mg/day • Co-interventions: not described. • Duration of the treatment was an average of 49.4 wks	There was one case of addiction Complications and side effects (52%): nausea, vomiting, sedation, itching, kidney alterations	Meaningful = 8 Non-meaningful = 21 Unclassifiable = 0
Moulin et al (140) 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

Fentanyl was assessed in only one low quality, randomized, parallel group trial evaluating low back pain (106).

2.5.7 Oxymorphone

Oxymorphone is a relatively new drug and is not commonly prescribed. There is no significant evidence in systematic reviews. Only 2 studies have reviewed the effectiveness of oxymorphone (116,145) for long-term use.

Rauk et al (145) 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.

McIlwain and Ahdieh (116), in a 52-week, multi-center open-label extension study of 153 patients with moderate to severe chronic osteoarthritis-related pain, showed improvement in pain. They found that oxymor-

Table 4. Results of studies evaluating the long-term effectiveness of transdermal fentanyl.

Study/methods	Participants	Opioids Studied	Outcome(s)	Conclusion(s)	Complications	Result(S)
Allan et al (106) 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 can safely be used in opioid naïve patients	Most common side effects included constipation and vomiting.	Transdermal fentanyl provided significant pain relief
Milligan et al (117) 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	Long-term treatment with transdermal fentanyl offered majority of patients at least moderate relief	Nausea 31%; constipation 19%; somnolence 18%; respiratory depression or abuse, less than 1%; withdrawal 3%	67% rated pain relief as very good to moderate on transdermal fentanyl, 86% preferred transdermal fentanyl, SF-36 showed improvement for body pain only
Mystakidou et al (118) 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 is a safe and effective pain management	Side effects, with constipation (range 4.6% -23.1%) and nausea were the most frequent	Transdermal therapeutic system-fentanyl significantly improves quality of life within 28 days, and pain management within 48 hours

phone extended release (ER) provides a new 12-hour analgesic for the treatment of moderate to severe, chronic osteoarthritis-related pain in patients who might require long-term opioid therapy.

2.5.8 Tapentadol

Tapentadol was evaluated in one study for long-term effectiveness. Wild et al (121) in a randomized, controlled, comparative trial studied low back pain and osteoarthritis. Participants were randomized 4:1 to receive controlled, adjustable, oral, twice-daily doses of tapentadol ER (100 to 250 mg) or oxycodone HCl controlled release (CR; 20 to 50 mg) for up to one year. A total of 1,117 participants received at least one dose of the study drug. Mean (standard error) pain intensity scores in the tapentadol ER and oxycodone CR groups, respectively, were 7.6 (0.05) and 7.6 (0.11) at baseline and decreased to 4.4 (0.09) and 4.5 (0.17) at endpoint. The overall incidence of adverse effects was 85.7% in the tapentadol ER group and 90.6% in the oxycodone CR group. In the tapentadol ER and oxycodone CR groups, respectively, adverse events led to discontinuation in 22.1% and 36.8% of patients. They concluded that tapentadol ER (100 to 250 mg twice a day) was associated with better gastrointestinal tolerability than oxycodone HCl CR (20 to 50 mg twice a day) and provided sustainable relief of moderate to severe chronic knee or hip osteoarthritis or low back pain for up to one year.

2.5.9 Codeine

There was only one study available evaluating codeine use by patients with chronic rheumatic disease pain (136). In this study, codeine use and oxycodone use were studied retrospectively in a cohort of 446 rheumatology clinic patients. Prolonged treatment of rheumatic disease pain with codeine or oxycodone was effective in reducing pain severity and was associated with only mild toxicity. Doses were stable for prolonged periods of time, with escalation of the opioid dose almost always related to worsening of the painful condition or a complication thereof, rather than the development of tolerance to opioids. They concluded that doubts or concerns about opioid efficacy, toxicity, tolerance, and abuse or addiction should not be used to justify withholding opioids from patients with well-defined rheumatic disease pain.

2.5.10 Buprenorphine

There were no long-term studies evaluating buprenorphine.

2.6 Effectiveness of Quality of Life

Quality of life improvement has been evaluated less frequently than pain relief (146). Of the many reported studies, only one study reported a positive difference in relation to most health-related quality of life

(HRQoL) domains of the SF-36 with administration of oxycodone (146). A 10-year follow-up by Jensen et al (147) showed that opioid users had lower SF-36 scores than chronic pain patients who were not using opioids. Deshpande et al (148) concluded that pain relief could be expected to improve more in nondepressed patients. Milligan et al (117) showed improvement in bodily pain, social functioning and physical functioning on SF-36 scores for 12 months even though quality of life (QOL) scores did not change. In a 10-year follow-up survey of opioid use, Jensen et al (147) reported HRQoL and healthcare utilization in chronic noncancer pain patients, demonstrating that only 60% of those discharged on long-acting opioids were still on that treatment at follow-up. In fact, they showed that users of opioids had a significantly higher occurrence of depression. Rauck et al (134) showed that both sustained-release morphine and oxycodone led to significant improvement on both physical and mental components of the SF-12, with physical functioning scores improving by approximately 20-30%.

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 noncancer pain. Caldwell et al (107) showed that the mean physical function score improved by 18% at week 4 compared with an improvement of 8% with placebo. Adams et al (149) showed that sustained release morphine significantly increased the proportion of those who reported an improvement in their ability to undertake moderate-intensity activities. Allan et al (106), in an evaluation of transdermal fentanyl and sustained-release morphine, demonstrated that both drugs provided significant pain relief. Zenz et al (108) have also shown a close correlation between pain reduction and an increase in performance.

Overall, it appears that epidemiological studies are less positive with regard to function and QOL and report the failure of opioids to improve QOL in chronic pain patients (150). By contrast, Eriksen et al (3) demonstrated worse pain, higher health care utilization, and lower activity levels in opioid-treated patients compared with a matched cohort of chronic pain patients not using opioids. Other studies have also shown that instead of improving functional status, opioid use has been associated with increased disability, medical costs, subsequent surgery, and continued or late opioid use (34,63,64,151).

Apart from pain relief, functional status improve-

ment and health care utilization, another important function when patients are on chronic opioid therapy is driving capability (152,153). Fishbain et al (153), 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. However, the research was inconclusive in one of the 5 areas relating to potential impairment in the cognitive function of opioid-maintained patients. The research was conclusive that there was no impairment to the 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 and on-road driving by opioid-maintained patients. These opinions did not correlate with a narrative review by Strassels (152), indicating that cognitive function can be influenced by the use of opioid analgesics, although the effects vary among drugs.

2.7 Complications and Side Effects

Complications due to opioid administration concern all medical practitioners (90-92,154-172). Commonly known side effects of opioids include constipation, pruritus, respiratory depression, nausea, vomiting, delayed gastric emptying, sexual dysfunction (154), muscle rigidity and myoclonus (173,174), sleep disturbance (175), pyrexia, diminished psychomotor performance (152,153), cognitive impairment (176), hyperalgesia (2,154,165,177), dizziness, and sedation, all reflecting the effects of opioids on multiple organ systems (178).

Adverse events, in general, appear to fall into 2 broad categories: non-life-threatening and life-threatening. Hydrocodone can cause sensorineural hearing loss due to possible genetic polymorphisms (179). More serious adverse events, such as respiratory depression and death, have been seen with the use of fentanyl buccal tablets for breakthrough pain. Drug deaths from opioids are a serious and increasing issue (91,92,157-159,161,162).

Opioids have also been described to have multiple drug interactions. A drug interaction occurs when the amount or the action of a drug is altered by the administration of another drug or multiple drugs. Multiple hepatic drug interactions might influence opioid drug

levels (154,178).

3.0 Discussion

Chronic pain has been defined by the American Society of Interventional Pain Physicians (ASIPP) (180) as, "pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal, that is associated with chronic pathologic processes that cause continuous or intermittent pain for months or years that may continue in the presence or absence of demonstrable pathology; may not be amenable to routine pain control methods; and healing may never occur."

Chronic pain's prevalence and associated disability continue to increase. Harkness et al (181), in a 2000 publication, showed that there was a large difference in the prevalence of musculoskeletal pain over a 40-year period under investigation. The results showed that overall, the prevalence of low back pain increased from 8.1% in males to 17.8%, and in females, it increased from 9.1% to 18.2%. Similarly, Freburger et al (182) reported the rising prevalence of chronic low back pain following an evaluation of North Carolina (U.S.) households conducted in 1992 and repeated in 2006. The results showed a 162% increase in the prevalence of chronic impairing low back pain over the 14-year interval, going from 3.9% in 1992 to 10.2% in 2006 and an annual average increase of 11.6% associated with care-seeking and disability.

Opioids have been used for thousands of years to treat pain, and continue to be one of the most commonly prescribed medications for pain. In the United States and other countries, opioid prescriptions have been restricted. Despite the regulations and restrictions, during the past 20 years or so, opioids have been used increasingly to treat chronic pain with an unprecedented number of patients being prescribed long-term opioids and an explosion of therapeutic opioid use, abuse, and non-medical use.

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 (183). Consequently, opioids have been used extensively as a result of arguments that physicians should be encouraged to prescribe opioids because they are indispensable for the treatment of pain and suffering, because uncontrolled pain can have deleterious physical effects, and because persistent pain destroys a person's autonomy, dignity, and decision-making capacity (2,3) Con-

sequently, not only the availability, but also the use of opioids have increased substantially along with abuse, misuse, addiction, diversion, and other associated complications including increased disability (5).

3.1 Scientific Evidence

Proven scientific evidence for the effectiveness and safety of opioids in chronic pain has not been demonstrated. The foundation of the argument for the use of opioids is their unique analgesic efficacy. And, based on surveys, case series, occasional open-label followup studies, as well as some RCTs and epidemiological studies, opioid use has escalated in the United States. It is also argued, based on the clinical experience of opioid maintenance treatments 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. Therefore, the argument to apply the same knowledge to chronic pain patients seemed to be reasonable (122,184-187). In addition, early experience with tolerance to the analgesic effects of opioids was treated by dose escalation as a therapeutic maneuver, while ongoing experience suggests a less rosy state of affairs (2).

In recent years, multiple reviews have been published to evaluate the effectiveness of opioid therapy for chronic pain (2,29,97-99,102-104,164-170,188-191). However, very few of them evaluated long-term opioid therapy. Chou et al (191) performed the first comparative efficacy and safety review of long-acting oral opioids for chronic non-cancer pain in a systematic review that included literature published 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-acting 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.

Chou and Huffman (102), in a recent guideline development, concluded that even though evidence is limited, chronic opioid therapy can be effective for carefully selected and monitored patients with chronic non-cancer pain. However, they cautioned that opioids are also associated with potentially serious harms, including opioid-related adverse effects and outcomes related to the abuse potential of opioids. Further, they provided a perspective that safe and effective chronic

opioid therapy for chronic non-cancer pain requires clinical skills and knowledge in both the principles of opioid prescribing and the assessment and management of risks associated with opioid abuse, addiction, and diversion. Consequently, most of the recommendations in many areas related to the use of opioids for chronic non-cancer pain, developed by Chou and Huffman for the American Academy of Pain Medicine (AAPM) and American Pain Society (APS) guideline, provide recommendations developed by a multidisciplinary expert panel based on a consensus after a systematic review of the evidence.

Noble et al (103) provided significant insights into long-term chronic opioid therapy. Noble et al in an updated systematic review (104) reviewed 26 studies with 27 treatment groups that enrolled a total of 4,893 participants; the review also included intrathecal opioids apart from oral and transdermal opioid therapy. Of these, 25 studies were case series or uncontrolled long-term continuations, whereas one was an RCT comparing 2 opioids. They reported that many participants discontinued due to adverse effects, 22% taking oral opioids, and 12.1% taking transdermal opioids. Signs of opioid addiction were reported in 0.27% of the participants in the studies that reported that outcome. Their results showed that both modes of administration were associated with clinically significant reductions in pain, but the amount of pain relief varied among studies. In their systematic review, findings regarding quality of life and functional status were inconclusive due to an insufficient quantity of evidence for oral administration studies and inconclusive statistical findings for transdermal administration studies. They concluded that many patients discontinue long-term opioid therapy, especially oral opioids, due to adverse events or insufficient pain relief. However, they also concluded that the weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. They were uncertain with regards to the improvement in quality of life or functioning. They provided the conclusion that many minor adverse events occurred, but serious adverse events, including iatrogenic opioid addiction, were rare. In a plain language summary, they reported that the findings of their systematic review suggest that proper management of any type of strong pain killer (opioids) in well-selected patients with no history of substance addiction or abuse can lead to long-term pain relief for some patients with a very small (though not zero) risk of developing addiction, abuse, or other serious side effects. Once again,

they cautioned that the evidence supporting the conclusions is weak, and longer-term studies are needed to identify the patients who are most likely to benefit from treatment (104). 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.

Trescot et al (29,165) looked at available evidence and 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. Further, they concluded that there was limited evidence for all other opioids including the most commonly used ones, oxycodone and hydrocodone.

Martell et al (53), in their systematic review, concluded that opioids were ineffective for chronic low back pain, for long-term use of 16 weeks or longer. Balantyne (2), after directly comparing the efficacy of different opioids, concluded that a nonsignificant reduction in pain was present from baseline. Kalso et al (97), 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 for both 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 that lasted between 7 and 24 months. They concluded that the short-term efficacy of opioids was good for both neuropathic and musculoskeletal pain conditions, while only a minority of patients in these studies went on to long-term management with opioids.

Manchikanti et al (41) performed a systematic review of randomized trials of opioid management for chronic non-cancer pain with at least 12 weeks of follow-up. Based on the review of 20 trials meeting the inclusion criteria, they concluded that the indicated level of evidence was fair for tramadol in managing osteoarthritis. However, for all other drugs, including tramadol, for all other conditions, the evidence was poor based on either weak positive evidence, indeterminate evidence, or negative evidence. They concluded that the recommendations for opioid therapy must be based on non-randomized studies due to a paucity of evidence at

the present time. Further, they were unable to locate any studies evaluating hydrocodone. The evidence for the most commonly utilized opioids—oxycodone, hydrocodone, morphine, fentanyl—was inadequate.

Papaleontiou et al (105), in a systematic review and meta-analysis, evaluated outcomes associated with opioid use in the treatment of chronic non-cancer pain in adults aged 60 and older. They concluded that in older adults with chronic pain and no significant comorbidity, short-term use of opioids is associated with a reduction in pain intensity and better physical functioning, but poorer mental health functioning. However, they also stated that the long-term safety, efficacy, and abuse potential of this treatment practice in diverse populations of older persons remain to be determined. However, of all these, only 6 studies met inclusion criteria by Manchikanti et al (41) in their systematic review. Thus, most of the studies are considered very short-term – less than 6 weeks.

The present review, along with currently available literature, does not provide enough evidence to guide 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 these studies' findings to chronic non-cancer populations in real world settings is unclear. 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 (103) also demonstrated that these findings are applicable only in patients without a history of addiction or abusive behaviors.

Safe administration of opioids in low to moderate doses can be accomplished in conjunction with interventional techniques (155). Manchikanti et al (155) described the prevalence of side effects of prolonged low or moderate dose opioid therapy with concomitant benzodiazepine and antidepressants in chronic non-cancer pain. They concluded that moderate or low dose opioid therapy in conjunction with or without benzodiazepines, antidepressants, or in combination, are associated with minor side effects in a study of 1,000 patients. In addition, interventional pain management literature illustrates its effectiveness and safety profiles (50,51,192-234).

4.0 CONCLUSION

Even though opioids have been used for thousands of years to treat pain, and continue to be one of the most commonly prescribed medications, the evidence is lacking for multiple opioids and it is weak for long-term effectiveness in relieving pain and improving functional status. Thus, based on weak evidence, opioids must be used with great restraint and caution.

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