

ASIPP - Opioid Guidelines 2012

American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part I – Evidence Assessment

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Background: Opioid abuse has continued to increase at an alarming rate since the 1990s. As documented by different medical specialties, medical boards, advocacy groups, and the Drug Enforcement Administration, available evidence suggests a wide variance in chronic opioid therapy of 90 days or longer in chronic non-cancer pain. Part 1 describes evidence assessment.

Objectives: The objectives of opioid guidelines as issued by the American Society of Interventional Pain Physicians (ASIPP) are to provide guidance for the use of opioids for the treatment of chronic non-cancer pain, to produce consistency in the application of an opioid philosophy among the many diverse groups involved, to improve the treatment of chronic non-cancer pain, and to reduce the incidence of abuse and drug diversion. The focus of these guidelines is to curtail the abuse of opioids without jeopardizing non-cancer pain management with opioids.

Results:

- 1) There is good evidence that non-medical use of opioids is extensive; one-third of chronic pain patients may not use prescribed opioids as prescribed or may abuse them, and illicit drug use is significantly higher in these patients.
- 2) There is good evidence that opioid prescriptions are increasing rapidly, as the majority of prescriptions are from non-pain physicians, many patients are on long-acting opioids, and many patients are provided with combinations of long-acting and short-acting opioids.
- 3) There is good evidence that the increased supply of opioids, use of high dose opioids, doctor shoppers, and patients with multiple comorbid factors contribute to the majority of the fatalities.
- 4) There is fair evidence that long-acting opioids and a combination of long-acting and short-acting opioids contribute to increasing fatalities and that even low-doses of 40 mg or 50 mg of daily morphine equivalent doses may be responsible for emergency room admissions with overdoses and deaths.
- 5) There is good evidence that approximately 60% of fatalities originate from opioids prescribed within the guidelines, with approximately 40% of fatalities occurring in 10% of drug abusers.
- 6) The short-term effectiveness of opioids is fair, whereas the long-term effectiveness of opioids is limited due to a lack of long-term (> 3 months) high quality studies, with fair evidence with no significant difference between long-acting and short-acting opioids.
- 7) Among the individual drugs, most opioids have fair evidence for short-term and limited evidence for long-term due to a lack of quality studies.

- 8) The evidence for the effectiveness and safety of chronic opioid therapy in the elderly for chronic non-cancer pain is fair for short-term and limited for long-term due to lack of high quality studies; limited in children and adolescents and patients with comorbid psychological disorders due to lack of quality studies; and the evidence is poor in pregnant women.
- 9) There is limited evidence for reliability and accuracy of screening tests for opioid abuse due to lack of high quality studies.
- 10) There is fair evidence to support the identification of patients who are non-compliant or abusing prescription drugs or illicit drugs through urine drug testing and prescription drug monitoring programs, both of which can reduce prescription drug abuse or doctor shopping.

Disclaimer: The guidelines are based on the best available evidence and do not constitute inflexible treatment recommendations. Due to the changing body of evidence, this document is not intended to be a "standard of care."

Key words: Chronic pain, persistent pain, non-cancer pain, controlled substances, substance abuse, prescription drug abuse, dependency, opioids, prescription monitoring, drug testing, adherence monitoring, diversion

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1.0 INTRODUCTION

The American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing for chronic non-cancer pain are systematically developed statements designed to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances. These guidelines also focus on various aspects of opioid use, misuse, abuse, overuse, and resulting fatalities. Thus, these guidelines focus not only on physicians and practitioners, but on law enforcement agencies, lawmakers, and regulators who need to better understand the role of opioids in non-cancer pain management. The guidelines present statements of best practice based on a thorough evaluation of the evidence from published studies on outcomes of treatments. For further information and detailed analysis, readers may review the related publications, including systematic reviews and individual articles.

1.1 Purpose

Evidence-based clinical practice guidelines for responsible chronic opioid prescribing of 90 days or longer in chronic non-cancer pain are statements which have been developed in order to improve quality of care, patient access, treatment outcomes, appropriateness of care, efficiency and effectiveness, and achieve cost containment by improving the cost-benefit ratio. Other purposes include providing a better understanding of the risks and benefits of curtailing opioid abuse while at the same time not jeopardizing access to opioids for patients for whom they are medically indicated. These guidelines are provided in 2 parts: Part 1 assesses the evidence and Part 2 provides guidance.

1.2 Objectives

The objectives of these guidelines are to provide clear and concise guidelines to physicians to improve patient access and to avoid diversion and abuse. The perceived benefits of these guidelines include:

- ◆ Increased physician awareness about current issues involving opioids and non-cancer pain
- ◆ Improved patient access
- ◆ Reduced level of opioid abuse with responsible prescribing
- ◆ Improved ability to manage patient expectations
- ◆ Reduced diversion
- ◆ Improved understanding by law enforcement about proper prescribing patterns
- ◆ Improved cooperation among patients, providers, and regulatory agencies
- ◆ Improved understanding by patients regarding their rights, but also an increased awareness of responsibilities and adverse consequences that may occur while taking opioid medications.

1.3 Population and Preferences

The population covered by these guidelines includes all patients with chronic moderate to severe pain of non-cancer origin who may be eligible for appropriate medically necessary opioid analgesic management, within an algorithmic approach of chronic pain management, and within the boundaries of responsible opioid prescribing. This management may include or be independent of other modalities of treatments including interventional techniques.

1.4 Application

These guidelines are developed for use by physicians practicing interventional pain management and do not constitute inflexible treatment recommendations. The guidelines may, however, also be applied to other physicians, as well as practitioners involved in prescribing opioids. These guidelines are not intended to address all possible clinical situations where opioids might be used for non-cancer pain in clinical practices. It is expected that a provider will establish a plan of care on a case-by-case basis, with consideration of individual patients' medical conditions, personal needs, and preferences, as well as the physician's experience. Based on individual patients' needs, a treatment different from the guidance provided and outlined here could be warranted. Thus, these guidelines do not represent the "standard of care."

1.5 Implementation and Review

The dates for implementation and review were established:

- ◆ Effective date – July 1, 2012
- ◆ Scheduled review – July 1, 2014
- ◆ Expected revision date on or before June 30, 2015.

1.6 Focus

The focus of these guidelines is to curtail the abuse of opioids without jeopardizing non-cancer pain management. It is recognized that the management of non-cancer pain takes place in a wide context of health care situations, involving multiple specialties and multiple techniques. However, providers managing acute pain must be cognizant of the fact that once opioid use commences, they are continued in the majority of patients in the chronic phase and throughout their lifetime frequently. Consequently, these guidelines cannot be applied to all patients. The decision to implement a particular management approach should be based on a comprehensive assessment of the patient's overall health status, disease state, preference, and physician training and skill. Multiple guidelines have been published, along with extensive literature on opioids, and the related adverse effects in clinical practice.

1.7 Chronic Pain

Chronic pain is defined by the International Association for the Study of Pain (IASP) as, "pain that persists beyond an expected time frame for healing" (1). Recognizing the complexity of chronic pain, ASIPP defines chronic pain 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 pathologies; may not be amenable to routine pain control methods; and healing may never occur" (2,3). Based on multiple regulations and definitions, chronic may be considered as continued pain after 90 days.

The true burden of chronic pain has not been accurately estimated due to numerous variations in the definition, severity, interference with activities of daily living and the ability to work. Thus, estimates of chronic pain have ranged from 11% to 55% (4,5). However, it has been well documented that chronic persistent pain can cause significant impairment of physical activities, psychological health, and performance of social responsibilities including work and family life (2,4-34). The Institute of Medicine (IOM) report on relieving pain in America (6) noted that not only is the magnitude of pain in the United States astounding, with more than 100 million Americans with pain that persists for weeks to years, but that it also has estimated financial costs ranging from \$560 billion to \$630 billion per year with Americans constituting only 4.5% of the global population. Harkness et al (8) reported a modest increase in prevalence in follow-up studies over a 40 year period, with low back pain having increased from 8.1% to 17.8% in males and 9.1% to 18.2% in females. In contrast, Freberger et al (9), in an evaluation in North Carolina households conducted in 1992 and repeated in 2006, showed a significant and rapid overall increase for low back pain of 162% from 3.9% in 1992 to 10.2% in 2006. These findings have been echoed in numerous studies. Hoy et al (10-12), in multiple publications evaluating spinal pain, showed variable prevalence with a significant recurrence of 24% to 80%; a significant increase in prevalence as the population ages. Manchikanti et al (2), in a comprehensive review of epidemiology, described the adult population as ranging from 2% to 40%, with a median point-prevalence of 15%, and lifetime prevalence of 54% to 80%. Studies of the prevalence of low back and neck pain and its impact in the general population have shown 23% of patients reporting Grade II to IV low back pain with a high pain intensity and disability compared to 15% with neck pain. In addition, age-related prevalence of persistent pain has been shown to be more common in the elderly when associated with functional limitations

and difficulty in performing daily life activities. Chronic persistent low back and neck pain is seen in 25% and 60% of patients, one year or longer after the initial episode.

Chronic pain is often confused with chronic pain syndrome (2). Chronic pain syndrome has been defined as a complex pain condition with physical, psychological, emotional, and social components. Even though both chronic pain and chronic pain syndrome can coexist and are defined in terms of duration and the persistence of the sensation of pain and the presence or absence of psychological and emotional components, they are 2 separate entities. Chronic pain syndrome, as opposed to chronic pain, encompasses the added components of certain recognizable psychological and socioeconomic influences and characteristic psychological and sociological behavioral patterns. These features, while to some extent may distinguish both conditions, overlap each other in multiple aspects.

1.8 Therapeutic Opioid Use

The global epidemic of chronic pain with its related disability and opioid use and related fatalities, are the issues of modern medicine, specifically in the United States (13-45). This is illustrated by the fact that overwhelming data points to an increased supply of opioids, high medical users, and doctor shoppers. One example of the therapeutic opioid explosion is the fact that sales of opioid analgesics quadrupled between 1999 and 2010. The data on sales and distribution of opioids show an increase from 96 mg of morphine equivalents per person in the United States in 1997 to 710 mg per person in 2010 (39,46). In fact, this is equivalent to 7.1 kg of opioid medication per 10,000 people, or enough to supply every adult American with 5 mg of hydrocodone every 6 hours for 45 days. In addition, sales of hydrocodone have increased by 280% from 1997 to 2007, while methadone usage has increased 1,293% and oxycodone usage increased by 866% (36). Moreover, the estimated number of prescriptions filled for opioids exceeded 256 million in the United States in 2009 (47-49). The data becomes even more convincing when compared from 2002 to 2009, showing an increase from 9.3 million for extended-release (ER) opioids to 22.9 million, a 146% increase; and from 164.8 million to 234 million for immediate release (IR) opioids, a 42% increase with an annual increase of 21% for ER opioids and 6% for IR opioids. Furthermore, the data illustrates an 8-fold increase in stimulant prescriptions from 1999 to 2009 (47). As repeatedly illustrated, hydrocodone with ac-

etaminophen was the number one prescription from 2006 through 2011 (50). Opiate analgesics constituted number 4 in the proportion of patients treated in selected therapies with hypertension, topping at 42.4 million; and opiate analgesics at 15.6 million, constituting number 10 in spending in leading therapy areas; with oncologicals constituting 23.2 billion, and opiate analgesics constituting 8.3 billion in 2011 (50). In addition to this, with respect to the world's supply of opioids, the United Nations Office on Drugs and Crime shows that 90% of the global consumption of morphine, fentanyl, and oxycodone registered in 2009 occurred in Australia, Canada, New Zealand, the United States, and several European countries (51,52). In addition, a UN report illustrates that the U.S. population, constituting 4.6% of the world's population consumed 83% of the world's oxycodone, and 99% of hydrocodone in 2007 (53). It has been illustrated that global pharmaceutical companies produced more than 75 tons of oxycodone in 2007 compared with 11.5 tons in 1999. The consumption of hydrocodone, the most commonly prescribed opioid in the United States, is about 27.4 million grams annually compared to 3,237 grams for Britain, France, Germany, and Italy combined (53).

The explosive use of therapeutic opioids, however, is complicated by a lack of evidence regarding their effectiveness, long-term efficacy, and safety data in the treatment of chronic non-cancer pain, but there is irrefutable evidence of adverse consequences (46,54-123). While the IOM report (6) is a blueprint for transforming prevention, care, education, and research claiming that effective pain management is a moral imperative, a professional responsibility, and the duty of the people in the healing professions, it also, on the other hand, recognizes the serious problem of diversion and abuse of opioid drugs and questions their long-term usefulness.

The IOM also believes that when opioids are used as prescribed, they can be safe and effective for acute postoperative pain, procedural pain, and patients near the end of life who desire more pain relief, but not for chronic non-cancer pain. Thus, although proponents of opioids argue that the IOM is promoting pain treatments including opioids, the IOM clearly acknowledges that there is no evidence for their effectiveness and acknowledges abuse patterns and adverse effects in chronic pain settings.

There have been dramatic increases in the number of opioid prescriptions for non-cancer pain over the past 2 decades, coinciding with the liberalization

of laws governing opioid prescribing for the treatment of chronic non-cancer pain by the state medical boards in the late 1990s (124). In addition, the escalation of opioid use in the United States has been fueled by the introduction of new pain management standards for inpatient and outpatient medical care issued by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in 2000 (125), by multiple physicians and organizations advocating increased use of opioids in the treatment of chronic non-cancer pain, by aggressive marketing by the pharmaceutical industry, with the development of long-acting opioids, and by a growing awareness of the right to pain relief empowered by JCAHO standards (126-131). While these positions are largely based on relatively poor science and misinformation, in relation to the safety and effectiveness of opioids when prescribed by physicians and taken appropriately, they have unexpectedly fueled explosive increases in the utilization of opioids (52,64,65,67-70,126-150). This overwhelming misinformation is illustrated by the fact that language in the model guidelines (124) states, "No disciplinary action will be taken against a practitioner based solely on the quantity and/or frequency of opioids prescribed." This has provided a misleading and false sense of security to widely prescribe these drugs even with weak or no indications of their utility. The recent revelation that the pharmaceutical industry was involved in the development of opioid guidelines as well as the bias observed in the development of many of these guidelines illustrate that the model guidelines are not a model for curtailing controlled substance abuse and may, in fact, be facilitating it (59-62,69,70,72). Actually, while proponents continue to advocate increased opioid therapy, responsible opioid prescribers and opponents have been discussing the postmortem analysis of the opioid epidemic and its consequences (59-62). Most agree that there have been gross miscalculations and misinformation behind the provision of therapy on a wide scale without evidence and proven safety.

Thus, therapeutic opioid use, specifically in high doses over long periods of time in chronic non-cancer pain starting with acute pain, not only lacks scientific evidence, but is in fact associated with serious health risks including multiple fatalities, and is based on emotional and political propaganda under the guise of improving the treatment of chronic pain. Despite widespread concerns and increasing deaths, the availability and utilization of opioids has increased exponentially in the past few decades (2,4,5,7-33,35,36,42,43,64,71-77).

2.0 METHODS

The objective of these guidelines was to synthesize the available evidence on the comparative effectiveness and safety of chronic opioid therapy in the treatment of chronic non-cancer pain. The focus of these guidelines is to curtail the abuse of opioids without jeopardizing non-cancer pain management with opioids.

2.1 Panel Composition

ASIPP convened a multidisciplinary panel of 56 experts in various fields to review the evidence and formulate recommendations for chronic opioid therapy in non-cancer pain. The panel has been instructed to answer questions and develop evidence pertaining to important aspects of opioid therapy. Members of the panel were also requested to develop comprehensive reviews on various related subjects in preparation for the opioid guidelines (44,62,78-86). Other independent submissions were also considered (45,117,151-158). The panel members convened in person on 3 occasions in Memphis, Tennessee, during other workshops conducted by ASIPP, and also had 5 webinars and/or telephone conferences. The majority of the participants attended multiple meetings.

The committee provided a broad representation of academic and non-academic clinical practitioners, representing a variety of practices and geographic areas, all with interest and expertise in opioid use and management of patients with chronic non-cancer pain. The committee formulated the elements of the guidelines preparation process, including literature searches, literature synthesis, consensus evaluation, open forum presentations, and formal endorsement by the ASIPP Board of Directors and peer review.

2.2 Evidence Review

These guidelines were developed utilizing the evidence review conducted by ASIPP with multiple comprehensive reviews (44,62,64,78-86) and other independent submissions (45,117,151-160) to Pain Physician. The guidelines also utilized multiple previously published guidelines and systematic reviews (60,62,64,65,73,87,88,97,98,113,161-226). The panel screened over 10,000 abstracts from searches for systematic reviews and primary studies from multiple electronic databases, reference lists of relevant articles, and suggestions from expert reviewers. Multiple systematic reviews and primary studies were included in the evidence synthesis with regards to pain relief, side effects, and functional outcomes when treated with opi-

oids. Guidelines and treatment recommendations were based on these reviews. During the process, the panel reviewed published randomized controlled trials (RCTs), meta-analyses, narrative reviews, and clinical practice guidelines concerning the use of opioid analgesics in patients with chronic non-cancer pain.

The process also incorporated information from the much publicized Clinical Practice Guidelines We Can Trust, published by the IOM (227). The IOM provided a new definition for clinical practice guidelines, which are as follows:

Clinical practice guidelines are statements that include recommendations intended to optimize patient care, and that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. The new definition provides a clear distinction between the term "clinical practice guidelines" and other forms of clinical guidance derived from widely disparate development processes (e.g., consensus statements, expert advice, and appropriate use criteria). Furthermore, it underscores systematic review and benefits and harms assessment as essential characteristics of clinical practice guidelines.

To be trustworthy, guidelines should:

1. Be based on a systematic review of the existing evidence
2. Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups
3. Consider important patient subgroups and patient preferences, as appropriate
4. Be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest
5. Provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of recommendations
6. Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations

The IOM committee derived several recommendations directly relevant to the ultimate effectiveness of the 8 standards in increasing the quality and trustworthiness of CPGs and enhancing health care quality and patient outcomes (227).

- Establishing transparency
- Management of conflict of interest with appropriate disclosures reflecting all current and planned

commercial, non-commercial, intellectual, institutional, and patient/public activities pertinent to the potential scope of the guidelines, with exclusion criteria to exclude members with conflicts of interest

- Guideline development group composition
- Clinical practice guideline – systematic review intersection
- Establishing evidence foundations for rating the strength of recommendations
- Articulation of recommendations
- External review
- Updating.

Even though the IOM committee recognized that other forms of clinical guidance might have value, the process was not described in the report. The IOM also acknowledged that for many clinical domains, high quality evidence was lacking or even non-existent. However, given such constraints, guideline developers may still produce trustworthy clinical practice guidelines if their development reflects the committee standards.

2.3 Methodological Assessment

The methodology utilized here follows the systematic review process derived from AN evidence-based review of systematic reviews and meta-analysis of randomized trials and observational studies (228-246), Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of randomized trials (247-253), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (254-258), Cochrane guidelines (223), and Chou and Huffman's guidelines (64).

The guideline preparation considered systematic reviews, comprehensive reviews, and RCTs, and observational studies of critical importance that were published after the publication of the systematic reviews.

2.3.1 Analysis of Evidence

The analysis of the evidence was performed based on United States Preventive Services Task Force (USPSTF) criteria (259) as illustrated in Table 1, criteria which have been utilized by others (64,260).

The analysis was conducted using 3 levels of evidence; good, fair, or limited (i.e., lack of evidence or poor).

2.4 Guideline Development Process

The guidelines panel met on multiple occasions. At the first meeting, the panel defined the scope and de-

velopment of recommendations for important aspects to guide the systematic evidence review and synthesis. During the course of multiple meetings the sub-panels reviewed the results of the evidence review and drafted potential recommendations. The final consensus was carried out by electronic communication with further discussions, revisions, and final recommendations approved by at least two-thirds of the majority.

3.0 EVIDENCE ASSESSMENT

The evidence synthesis and analysis resulted in the following conclusions and recommendations with unanimous consent. Ten of the 55 authors provided information that they received funding from the industry; however, of these, only 2 (less than 4%) were receiving funding from drug makers with multidisciplinary authorship (18%) receiving funding for research or engaged in speaking from the industry.

Editorially, appropriate measures were taken to avoid any conflicting opinions from authors receiving funding from the industry. The panel was multidisciplinary with academicians, practitioners, and geographically diverse. Of the 55 members involved in preparing the guidelines, there were 2 pharmacists, 2 psychologists, 2 registered nurses, one statistician, one physical therapist, 2 research coordinators, one librarian, one academic radiologist, 3 residents or fellows, and the remaining (40) were practicing interventional pain physicians, either in an academic setting or in private practice. Many of the practitioners are also involved in drug detoxification.

The first author of the 2008 opioid guidelines, Andrea Trescot, MD, who has not participated initially, has withdrawn her name due to time constraints. A second

author, Xiulu Ruan, MD, who participated sporadically, withdrew his name due to time constraints and lack of appropriate involvement.

3.1. The Extent of Opioid Abuse

Results of the 2010 National Survey on Drug Use and Health (NSDUH) (261) showed that an estimated 22.6 million or 8.9% of Americans aged 12 or older were current (past month) illicit drug users. Illicit drugs in the survey included marijuana, cocaine, heroin, hallucinogens, and inhalants, or prescription-type psychotherapeutic drugs (defined in this survey as prescription-type pain relievers), tranquilizers, stimulants, and sedatives used non-medically. Marijuana was the most commonly used illicit drug with 17.4 million current (past month) users, or 6.9% of the US population. Next to marijuana, 7.0 million (2.7%) persons age 12 or older had used prescription-type psychotherapeutic drugs non-medically in the past month (current use). Of these, 5.1 million used pain relievers.

There is an increase in incidences of driving under the influence of illicit drugs. In 2010, 10.6 million persons, or 4.2% of the population aged 12 or older, reported driving under the influence of illicit drugs during the past year. The rates were highest among adults aged 18 to 25 with 12.7% (261). Also in 2010, 15.7% used marijuana on 300 or more days within the past 12 months, translating to 4.6 million using marijuana on a daily or almost daily basis over a 12-month period. In addition, 39.9%, or 6.94 million, used the drug on 20 or more days in the past month. Persons with any type of psychological distress including major depression have utilized higher doses of psychotherapeutic drugs.

Table 1. *Method for grading the overall strength of the evidence for an intervention.*

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least 2 consistent, higher-quality RCTs or studies of diagnostic test accuracy).
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (at least one higher-quality trial or study of diagnostic test accuracy of sufficient sample size; 2 or more higher-quality trials or studies of diagnostic test accuracy with some inconsistency; at least 2 consistent, lower-quality trials or studies of diagnostic test accuracy, or multiple consistent observational studies with no significant methodological flaws).
Limited, lack of evidence, or poor	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Adapted and modified from methods developed by U.S. Preventive Services Task Force (64,259,260).

The source of prescription drugs was an important issue in 2009-2010. Among persons aged 12 or older who used pain relievers non-medically in the past 12 months, 55% reported that they received the drug for free from a friend or relative (261), while another 11.4% bought or took the drug from a friend or relative. Only 17.3% reported that they got the drug from just one doctor. In contrast, 4.4% procured the pain relievers from a drug dealer or other stranger and 0.4% reported buying the drug on the Internet. Thus, over 79% obtained prescription pain relievers from sources other than doctors. However, Becker et al (262) showed that in a large community sample, 31% of respondents reporting non-medical use of opioids obtained these medications directly from a physician, and 20% reported obtaining opioid analgesics exclusively from a physician.

Martell et al (73), in a systematic review of opioid treatment for chronic back pain, estimated the prevalence of lifetime substance use disorders to range from 36% to 56%, with a 43% current substance use disorder rate. Furthermore, aberrant medication taking behaviors also ranged from 5% to 24%. In a study of opioid prescriptions for chronic pain and overdose (263), the authors identified 51 opioid-related overdoses, including 6 deaths. They concluded that patients receiving higher doses of prescribed opioids were at an increased risk for overdose, which underscored the need for close supervision of these patients. In a review of opioid dependence and addiction during opioid treatment of chronic pain (37), it was concluded that problematic opioid seeking and addiction arise often enough during chronic treatment to be of considerable concern. However, Fishbain et al (264), in a structured evidence-based review of 67 studies, concluded that chronic opioid therapy exposure will lead to abuse and addiction only in a small percentage of chronic pain patients (3.3%), but a large percentage (11.5%) will demonstrate aberrant drug-related behaviors and illicit drug use. Moreover, they showed that the percent of urine drug screens with illicit drugs present was 14.5%, while the percent of urine drug screens with a non-prescribed opioid or no opioid present, suggesting the possibility of diversion, was 20.4%. In a study of substance use disorders in a primary care sample of patients receiving daily opioid therapy (265), it was found that the frequency of opioid use disorders was 4 times higher in patients receiving opioid therapy when compared with general population samples (3.8% versus 0.9%). A study evaluating risks for possible and probable opioid misuse among recipients of chronic opioid therapy in

commercial and Medicaid insurance plans (266) showed an estimated possible misuse of 20% to 24%.

Degenhardt and Hall (113) described the extent of illicit drug use and dependence and its contribution to the global burden of disease. They showed that in high-income countries, illicit drug use contributes to the burden of disease with major adverse health effects of dependence, psychotic disorders, and other mental disorders. In the United Kingdom (221), most prescribing fell within current guidelines with increasing prescriptions of benzodiazepines and opioids resulting in addiction. It was stated that addiction to prescription drugs can be every bit as dangerous and distressing as addiction to illegal drugs.

Edlund et al (92) in a large national represented cross-sectional survey of over 9,000 subjects found that the prevalence of problematic substance use was higher among those on prescribed opioids than among non-opioid users. This included problematic use of alcohol and non-opioid substances as well as opioids. Controlling for comorbid mental disorders, the association with non-opioid substances disappeared, suggesting that the higher prevalence of mental disorders in opioid users mediates their higher risk for problematic substance use.

In an "empirical view of opioid dependence," Ruetsch (222) described that approximately 20% of Americans report using prescription opioids for non-medical use and that 6% to 15% of people in the United States abuse drugs. This is associated with annual costs of nearly half a trillion dollars, taking into account the medical, economic, social, and criminal impact of this abuse. Numerous other studies also have reported the abuse of opioids in various groups, along with the impact of this abuse on various aspects of the society (267-278).

The abuse of opioids in chronic non-cancer pain has been estimated to range from 5% to 41% of patients receiving opioids for chronic pain (52,68,75,145,279-307). In addition, illicit drug use in patients in chronic pain management settings without controlled substance abuse was found in 5% to 16% of patients and illicit drug use in patients with controlled substance abuse was present in 34% of the patients (279-281,290-293,297-299,304-306). Multiple evaluations with urine drug testing (UDT) in recent years have shown significant abnormalities indicating the inappropriate intake of prescribed opioids, benzodiazepines, and use of illicit drugs. However, recent monitoring trends have shown reduced doctor shopping and illicit drug use at least in some settings (284,287,293).

3.1.1 Conclusions

1. There is good evidence that non-medical use of opioids is extensive.
2. There is good evidence that approximately one-third of chronic pain patients may not use prescribed opioids as prescribed or may abuse them.
3. There is good evidence that illicit drug use in chronic pain patients is significantly higher than in the general population and that such use is high in patients receiving opioids and higher in those abusing opioids.

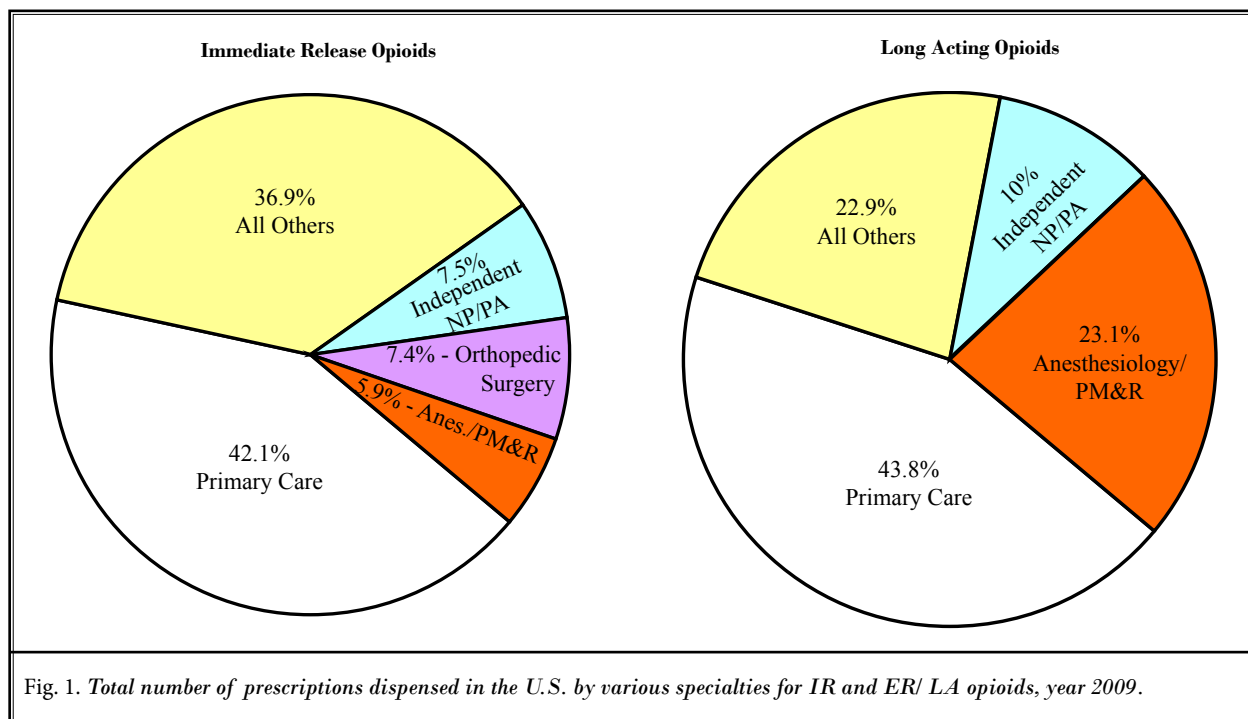
3.2 Prescribing Patterns

In pain management settings, it has been reported that as many as 90% of patients received opioids for chronic pain management in spite of numerous issues involved (36,68,279-284,286,287,289-293,303-307). In addition, it also has been illustrated that the majority of these patients were on opioids prior to presenting to an interventional pain management setting (289).

Deyo et al (35) illustrated that approximately 61% of patients in primary care settings with low back pain received a course opioids and 19% were long-term users. They also showed that psychological distress, un-

healthy lifestyles, and utilization were associated incrementally with duration of opioid prescription, not just with chronic use. Among long-term opioid users, 59% received only short-acting drugs, 39% received both long and short-acting drugs, and 44% received a sedative/hypnotic. Of those with any opioid use, 36% had an emergency visit. Multiple studies (7,73,92,262) have described that many patients in primary care settings also abuse illicit drugs. In a 2009 survey, it was reported that the majority of the opioids were prescribed by multiple specialties, including family practice, internal medicine, dentistry, emergency medicine, and orthopedic surgeons, rather than pain physicians (47-49). As shown in Figure 1, 42% of IR opioids and 44% of long-acting opioids were prescribed by primary care physicians, whereas specialties identified as pain management, including anesthesiology and physical medicine and rehabilitation, contributed to 6% of IR opioids and 23% of long-acting opioids.

Multiple studies illustrate increasing or escalating use of therapeutic opioids. Caudill-Slosberg et al (308), in one of the earliest evaluations, demonstrated that opioid use doubled from 8% in 1980 to 16% in 2000. Further data illustrates that from 1999 to 2002, 4% of



U.S. adults reported use of opioid analgesics for pain within the past month (309). In another study from Utah (310), the results illustrated that 28.8% of adults had been prescribed an opioid in the last year and 29.1% of these prescriptions were for long-term pain. Other studies have illustrated the proportion of insured people receiving opioids with the diagnosis of chronic non-cancer pain with a corresponding increase of opioid prescriptions (311). In settings of managing young veterans, it was reported that the prevalence of chronic opioid use increased from 3% in 2003 to 4.5% in 2007 (312). Patients on average were exposed to 2 different opioids and had 3 different prescribers. Further, 80% of opioid prescriptions during the study were prescribed by family care providers, and less than 1% was from pain specialists.

Boulanger et al (66) in a retrospective analysis of factors for opioid and non-opioid therapy for fibromyalgia showed that 78,511 of 117,305 patients were on opioids.

3.2.1 Conclusions

1. There is good evidence that opioid prescriptions are increasing rapidly.
2. There is good evidence that the majority of prescriptions are from non-pain physicians.
3. There is good evidence that many patients are on long-acting opioids.
4. There is good evidence that many patients are provided with combinations of long-acting and short-acting opioids.

3.3 Relationship of Therapeutic Opioid Use and Adverse Consequences

The overuse of opioids and the escalation of the therapeutic use of opioids have been briefly described earlier in this manuscript and extensively in other manuscripts (34,36,44,45). The majority of cases involving injury and death frequently occur with people using opioids exactly as prescribed, not just with those misusing or abusing them (67). Even more importantly, most studies indicate that patients on long-term opioid therapy are unlikely to stop even if analgesia and function are poor and safety issues arise (36). On the other hand, patients reporting pain relief and improvement in function with other modalities or surgical or non-surgical interventions continue to use opioids (260,313-325).

Higher doses and a combination of short-acting and long-acting opioids are likely to lead to abuse, and also cause serious dose-related adverse effects includ-

ing death. Commencing long-acting opioid therapy is often the starting point for high dose opioid therapy, a practice that growing evidence suggests is harmful to patients and increases the black market availability of opioids through diversion (67).

In 2012, the Centers for Disease Control and Prevention (CDC) (39) reported the percentage of prescription drug overdoses patients by risk group in the United States. Approximately 80% of prescribed low doses (less than 100 mg of morphine equivalent dose per day) by a single practitioner accounted for an estimated 20% of all prescription overdoses (Fig. 2). In contrast, among the remaining 20% of overdose patients, the 10% prescribed high doses (greater than 100 mg morphine equivalent dose per day) by single prescribers account for an estimated 40% of prescription opioid overdoses (94,326-329), whereas the remaining 10% of patients seeing multiple doctors and typically involved in drug diversion contribute to 40% of overdoses (326). Finally, among persons who died of opioid overdoses, a significant proportion did not have a prescription in their records for the opioid that killed them. In West Virginia, Utah, and Ohio, 25% to 66% of those who died of pharmaceutical overdose used opioids originally prescribed to someone else (95,326). While 100 mg or more morphine equivalent dosage was classified as a high dose in some published studies (45,328,329), emergency room admission for overdoses or deaths occurred at dosages of 40 mg (327), 50 mg (94,263), 120 mg (328), and 200 mg (329). Thus, there were significant fatalities even at the low doses (45,94,263,327).

The CDC also showed the relationship between increasing opioid sales and treatment admissions, along with deaths, as illustrated in Figure 3 (39,89,273). Further, it has been shown that medical and non-medical use of prescription opioids among high school seniors in the United States reached 17.6% with lifetime medical use of prescription opioids, while 12.9% reported non-medical use of prescription opioids (295).

Multiple misunderstood safety issues include titration based on efficacy and tolerability rather than safety with hypotheses about pseudoaddiction, breakthrough pain, and denial of hyperalgesia (80,102). It has been reported that most deaths occur at night, suggesting that rather than provide improved sleep, long-acting drugs produce more adverse effects during the night. These adverse effects are also associated with the dangers of concomitant medication use, especially nighttime sedatives, in conjunction with the dangers of obesity and sleep apnea (67,103,104). Prolonged QTc in-

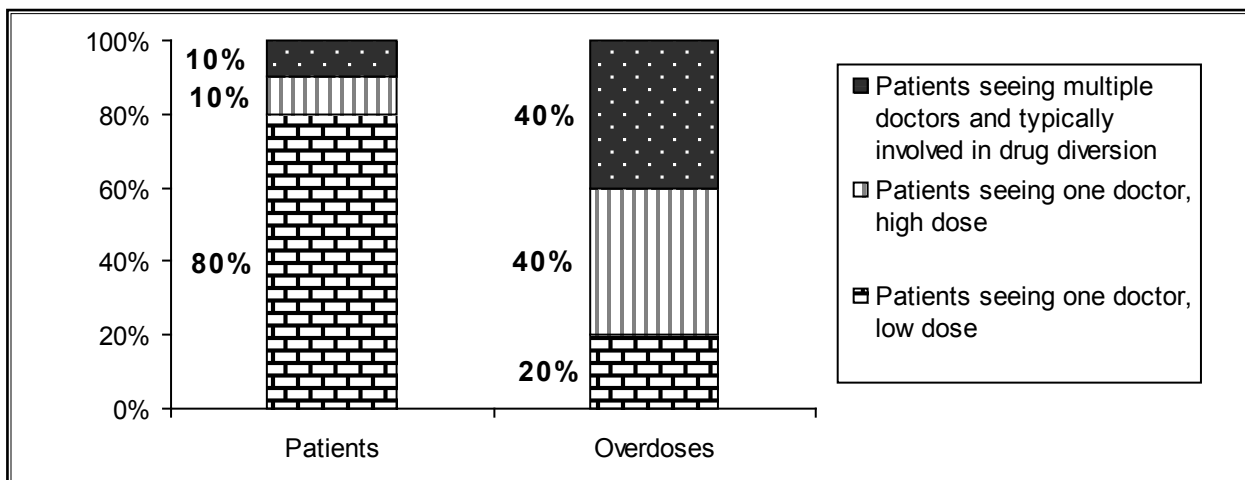


Fig. 2. Percentage of patients and prescription drug overdoses, by risk group – United States.

Source: Centers for Disease Control and Prevention. CDC grand rounds: Prescription drug overdoses – a U.S. epidemic. MMWR Morb Mortal Wkly Rep 2012; 61:10-13 (39).

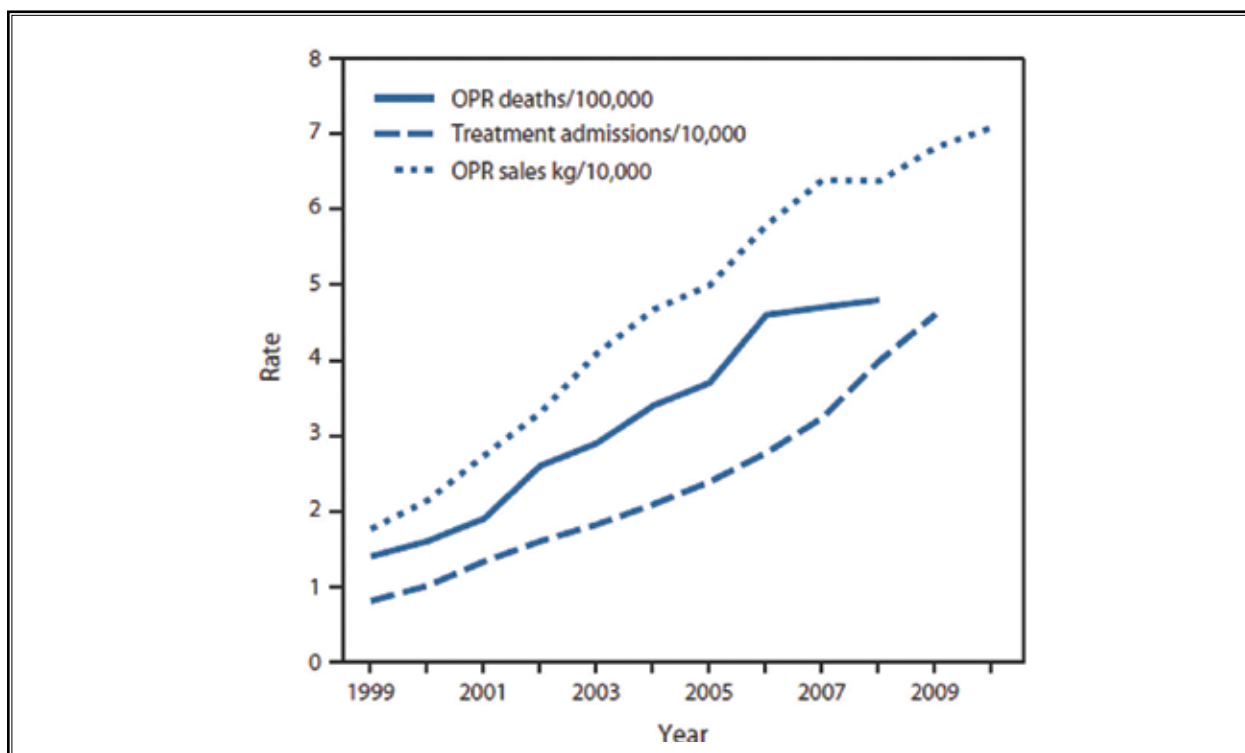


Fig. 3. Rates* of opioid pain reliever (OPR) overdose death, OPR treatment admissions, and kilograms of OPR sold --- United States, 1999—2010.

* Age-adjusted rates per 100,000 population for OPR deaths, crude rates per 10,000 population for OPR abuse treatment admissions, and crude rates per 10,000 population for kilograms of OPR sold.

Source: Centers for Disease Control and Prevention. Vital signs: Overdoses of prescription opioid pain relievers – United States, 1999-2008. MMWR Morb Mortal Wkly Rep 2011; 60:1487-1492 (89).

terval and sudden death is a potential problem for all opioids, even though it has been particularly described for methadone and buprenorphine, particularly at high doses (105-109). For all types of regular opioid therapy, there are risks associated not only with constipation, which does not resolve with time, but also with continued oversedation, impaired cognition, fractures, and serious bowel obstruction, all of which increase with larger doses (105,117,193,199-201,218-263).

Multiple studies in the literature (26,36,38,110,112,330-348) have reported an association between opioid prescribing and overall health status, with increased disability, medical costs, subsequent surgery, and continued or late opioid use. In fact, Franklin et al (348) reported that appropriate guidelines might bend the prescription opioid dosing and mortality curves. They showed that with the implementation of Washington State opioid dosing guidelines, there has been a substantial decline since 2007 of 27% in the morphine equivalent dose per day of long-acting Schedule II opioids, and a 35% decline in the proportion of workers on doses of greater than 120 mg per day morphine equivalent dosage. Moreover, the number of deaths was reduced by 50% from 2009 to 2010.

3.3.1 Conclusions

1. There is good evidence that the increased supply of opioids, use of high dose opioids, doctor shoppers, and patients with multiple comorbid factors contribute to the majority of fatalities.
2. There is good evidence that approximately 60% of fatalities originate from opioids prescribed within the guidelines.
3. There is good evidence that approximately 40% of fatalities occur in 10% of drug abusers.
4. There is fair evidence that long-acting opioids and a combination of long-acting and short-acting opioids contribute to increasing fatalities.
5. There is fair evidence that even low doses of 40 mg or 50 mg daily of morphine equivalent doses are responsible for emergency room admissions with overdoses and deaths.

3.4 Effectiveness of Opioids

Multiple manuscripts, systematic and comprehensive reviews, and guidelines have been published evaluating the effectiveness and safety of opioids. Only the most recent guidelines, systematic reviews, comprehensive reviews, and individual articles if not included in previous systematic reviews were considered here

(6,44-58,60,62,65,73,78-88,97,98,151-226,349-354).

Furlan et al (97) included 41 randomized trials involving 6,019 patients with various types of pain. Of all the studies, 90% were either funded by or had one or more co-authors affiliated with the pharmaceutical industry. Although all the trials included were described as randomized, patient assignment was judged adequate to be called random in only 17 trials and 39 trials were described as double-blind. Of these, 30 trials were judged as having adequate methods of double-blinding. Of the 6,019 patients with chronic non-cancer pain included in the systematic review, 80% were classified as having nociceptive pain (osteoarthritis, rheumatoid arthritis, and back pain without radiculopathy); 12% neuropathic pain (diabetic neuropathy, postherpetic neuralgia, phantom limb pain, and regional cervical brachial pain syndrome); 7% fibromyalgia; and 1% mixed nociceptive and neuropathic pain. The average age of the people involved was 58.1 years with a range of 40 to 71 years with 63% of participants being female and 85% white. Multiple opioid studies included codeine, morphine, oxycodone, tramadol, and propoxyphene. The duration of the studies was only 5 weeks on average, except for fibromyalgia studies, which had a mean length of approximately 9 weeks.

Meta-analysis of 28 studies meeting inclusion criteria showed results in favor of morphine and oxycodone with all other opioids considered weak evidence (97). The drop-out rates averaged 33% in the opioid groups and 38% in the placebo groups. The results illustrated that opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain or fibromyalgia. Only strong opioids, however, not weak opioids were significantly superior to Naprosyn, naproxen, and nortriptyline, and only for pain relief. The authors interpreted the results as weak, with strong opioids outperforming the placebo for pain and function in all types of chronic non-cancer pain. Other drugs produced better functional outcomes than opioids, whereas for pain relief they were outperformed only by strong opioids. Despite the relative shortness of the trials, more than one-third of the participants abandoned the treatment.

Even though this systematic review was well conducted and did include multiple studies, there were multiple limitations associated with the short duration of the studies. The authors also noted that most trials that compared opioids with other drugs were not adequately designed as equivalent or non-inferiority trials.

Kalso et al (98), in a study preceding the evalua-

tion by Furlan et al (97), evaluated opioids in chronic non-cancer pain to assess their efficacy and safety. Kalso et al (98) showed the mean decrease with opioids in pain intensity in most studies to be at least 30%, with comparable effects on neuropathic and musculoskeletal pain. However, the review did not include evidence from studies of weak opioids such as tramadol or codeine, nor did it assess the effectiveness of opioids compared with other analgesics. Six of the 15 included trials had an open-label follow-up for 6 to 24 months. The mean decrease in pain intensity in most studies was at least 30% with opioids and was comparable in neuropathic and musculoskeletal pain. Only 44% of 388 patients on open-label treatments were still on opioid therapy from between 7 and 24 months. The short-term efficacy of opioids was good in both neuropathic and musculoskeletal pain conditions.

Martell et al (73) performed a systematic review of the prevalence, efficacy, and association with addiction of opioid treatment for chronic back pain. This systematic review showed that opioid prescribing varied by treatment settings from 3% to 66%. Studies were conducted in various settings, including 4 multidisciplinary or specialty groups (332,355-357), 4 pain treatment centers (335,358-360), one across all disciplines (361), one in community dwelling elderly persons (362), and one in the primary care group (363). The most common concern in the studies was lack of internal validity due to limitations that are common in observational studies, along with recall bias, which was a major concern. Of the 2 multidisciplinary pain clinics (335,359), the prevalence of opioid prescriptions was 43% and 41%. The prevalence of opioid prescriptions was 15% in the National Ambulatory Medical Care Survey (361), 11% in academic multidisciplinary pain clinics (358), 28% in National Low Back Pain Study (357), 40% at the University of Washington tertiary care pain treatment center (360), and 66% in Minneapolis Orthopedic Spine Clinic (332). Others were at low levels. Meta-analysis of the 4 studies assessing the efficacy of opioids compared with a placebo or a non-opioid control did not show reduced pain with opioids. Meta-analysis of the 5 studies directly comparing the efficacy of different opioids demonstrated a non-significant reduction in pain from baseline. The authors concluded that opioids were commonly prescribed for chronic back pain and may be efficacious for short-term pain relief. Long-term efficacy of greater than 16 weeks was unclear. Substance use disorders were common in patients taking opioids for back pain, and aberrant medication-taking behaviors

also occurred in 24% of cases.

Eisenberg et al (177) studied 22 trials meeting inclusion criteria and classified as short-term (less than 24 hours; n=14) or intermediate-term (median=28 days; range=8 to 70 days; n=8). They studied opioids for neuropathic pain and reported contradictory results for short-term. For the intermediate-term ranging from 8 to 70 days, however, all 8 trials demonstrated opioid efficacy for spontaneous neuropathic pain. They concluded that intermediate-term studies demonstrated significant efficacy of opioids over placebo. 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.

Eisenberg et al (177) concluded that short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain, whereas intermediate-term studies (also considered as short-term) demonstrated significant efficacy of opioids over placebo, which was likely to be clinically important. Even though adverse effects were common, albeit not life threatening, they suggested that further RCTs were needed to establish long-term efficacy safety including addiction potential and effects on the quality of life (QOL).

Deshpande et al (179) evaluated the role of opioids in managing chronic low back pain. They included only 4 trials, of which 3 studied tramadol. They concluded that despite consensus surrounding the use of opioids for long-term management of chronic low back pain, there were very few high quality trials assessing the efficacy. Although the trials included in their review achieved high internal validity scores, they were characterized by a lack of generalizability, inadequate description of study populations, poor intention to treat analysis, and limited interpretation of functional improvement. Based on their results, the benefits of opioids in clinical practice for the long-term management of chronic low back pain was questionable. They also recommended that further high-quality studies more closely simulating clinical practice were needed to assess the usefulness and potential risks of opioids for individuals with chronic low back pain.

Cepeda et al (180) evaluated the role of tramadol for osteoarthritis in a systematic review and meta-analysis of 11 RCTs, 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 (181) included 21 papers, with one small randomized trial, 13 case reports, and 7 case series involving 545 patients with multiple non-cancer pain conditions. In 50% of the patients, however, no specific diagnosis was provided. In these patients, methadone was administered primarily even though previous opioid treatment was ineffective or produced intolerable side effects, with starting doses ranging from 0.2 to 80 mg per day and maximum doses ranging from 20 to 930 mg per day. The results of the review showed that pain outcomes were meaningful in 59% of patients in the uncontrolled studies; however, the only randomized trial (364) demonstrated a statistically significant improvement in pain for methadone at 20 mg per day compared to the placebo. Side effects were considered minor. The authors ultimately concluded that the figure of 59% effectiveness of methadone should be interpreted very cautiously, as it seems overrated due to the poor quality of uncontrolled studies and their tendency to report positive results. Thus, the utilization of oral methadone for non-cancer pain was based on primarily uncontrolled literature. Well-designed controlled trials may provide more accurate information on the efficiency of the drug for pain syndromes and in particular for neuropathic pain.

Chou and Huffman (64) identified 12 systematic reviews that primarily evaluated the short-term benefits of opioids for chronic non-cancer pain. 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 when compared to a placebo in patients with non-cancer pain. This was based on short-term (< 12 weeks) outcomes.

Manchikanti et al (78), 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 limited evidence.

3.4.1 Long-Term Effectiveness

Five systematic reviews of at least one-year follow-up looked at the long-term effectiveness of opioids

(73,78,98,190,223). There were also 4 comprehensive, but non-systematic reviews (151,158,350,351). Among the new studies, there were 5 studies evaluating buprenorphine (160,217,219,349,354). Among these 5 buprenorphine studies, one study evaluated controlled-released (CR) oxycodone and pregabalin (349) and another study evaluated hydromorphone (354). However, only one of these 5 evaluations was a RCT (219).

Chou and Carson (190), in their report of drug class review on long-acting opioid analgesics, identified 34 randomized trials enrolling 3,608 patients with chronic non-cancer pain, 8 trials compared one long-acting opioid to another, 7 trials compared a long-acting opioid to a short-acting opioid, and 22 compared a long-acting opioid to a non-opioid or placebo. The trials ranged in size from 12 to 683 evaluable enrollees with an average of 106 enrollees. Ten of the trials focused on osteoarthritis, 10 on back pain, 7 on neuropathic pain, one on phantom limb pain, one on chronic pancreatitis pain, and 5 on heterogenous chronic non-cancer pain. Nearly all of the trials were of relatively short duration ranging from 5 days to 24 weeks, except for one study evaluating transdermal fentanyl versus long-acting morphine that was 13 months in duration (365). They concluded that there was insufficient evidence to suggest that one long-acting opioid was superior to another in terms of efficacy in adult patients with chronic non-cancer pain. Moreover, they also concluded that there was no useful indirect evidence for determining the comparative efficacy of long-acting opioids. Multiple drawbacks of the included studies were insufficient quality, diverse study designs, patient populations, interventions, and outcomes assessment. They also evaluated the comparative effectiveness of short-acting opioids versus long-acting opioids and concluded that there was no good quality evidence to suggest the superior efficacy of long-acting opioids as a class over short-acting opioids. For oxycodone, there was fair evidence that short-acting and long-acting were equally effective for pain control. They (190) concluded that there was insufficient evidence to suggest that one long-acting opioid was superior in terms of adverse events in adult patients with chronic non-cancer pain. There was no convincing evidence to suggest lower adverse event rates with long-acting opioids as a class compared with short-acting opioids for all assessed adverse events.

Kalso et al (98), 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 ranging from between 7 and 24 months. They concluded that only a minority of patients went on to long-term management with opioids.

Noble et al (223) updated their previous systematic review (182) in 2009 and concluded that based on weak evidence, opioids might be effective in a small proportion of patients. They were concerned about many patients discontinuing long-term opioid therapy due to adverse events or insufficient pain relief. The updated review, however, 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, also including 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 (365-367), 2 studies of ER tramadol (368,369), one study of IR tramadol (370), 2 studies of CR oxycodone (371,372), one methadone study (373), one study of ER oxymorphone (374), another study of weak opioids for ER oxymorphone (375), and multiple other studies of dihydrocodeine, buprenorphine, and morphine for weak opioids. There were 3 studies evaluating the role of transdermal fentanyl (365,376,377).

In Manchikanti et al's (78) systematic review of 111 trials with administration of opioids either orally or topically, only 4 studies evaluated effectiveness beyond 6 months (365,378-380). Of these, one study evaluated tapentadol (380) with weak positive evidence, the second study evaluated morphine with negative evidence (378), the third study evaluated oxycodone with negative results (379), and the fourth study evaluated fentanyl and morphine with indeterminate results (365). Martell et al (73) in their systematic review concluded that long-term efficacy of greater than 16 weeks was unclear.

A critical review of the literature without a methodological quality assessment of the manuscripts, by Taylor et al (350) evaluated CR formulation of oxycodone in patients with moderate to severe chronic osteoarthritis. Out of a total of 3 studies; one was an open-label trial evaluating long-term relief (372,380,381). They concluded that the literature supports the fact that CR oxycodone is safe and effective and significantly reduces moderate to severe chronic pain in osteoarthritis patients with the expected side effects associated with other opioid agents.

Smith (151) in a contemporary opinion piece described the role of opioids in neuropathic pain. They showed that opioids are considered to be a second or third-line class of analgesics that may provide reasonable analgesia to some patients with chronic neuropathic pain. Even though opioids may alleviate chronic neuropathic pain, overall, neuropathic pain tends to be less opioid-responsive than nociceptive pain. They described that the mechanisms that may contribute to neuropathic pain may also simultaneously contribute to diminishing the antinociceptive properties of opioids for neuropathic pain. Thus, these mechanisms may also contribute to analgesic tolerance and/or opioid hyperalgesia by multiple mechanisms involving N-Methyl-D-aspartate (NMDA) receptor, neural hyperexcitation, and opioid-induced cholecystokinin (CCK) release. They concluded that there was no robust evidence that any specific opioid agent was better than any other opioid at effectively treating neuropathic pain, and that conceivably, opioids or opioid-like analgesic agents may be particularly suited to alleviate neuropathic pain in certain patients suffering from neuropathic pain.

Krashin et al (155) reviewed the role of opioids in the management of HIV-related pain. They concluded that pain is undertreated and more complex to manage in patients with HIV due to the complex anti-retroviral drug regimens, higher risks of side effects, and higher rates of comorbid psychiatric illness and substance abuse. Thus, in managing these patients, multiple factors should be taken into account and multimodal therapy must be provided, including non-opioid pain relievers, adjuvant medications, and psychosocial therapies, in addition to opioid analgesics. In general, patients with HIV-related pain require high doses of opioids not only to treat acute pain, but also chronic pain. Often they have increased tolerance, even when currently abstinent (155). There are no studies evaluating the effectiveness of individual drugs and their efficacy and adverse effect profile in HIV-related pain.

Pergolizzi et al (351) described the current considerations for the treatment of severe chronic pain and the potential for tapentadol. They described the investigation as 3 double-blind, randomized, placebo-controlled, multicenter trials in patients with chronic low back pain or osteoarthritis. In all the studies a 3-week titration phase enabled subjects with moderate to severe pain to reach their optimal dose of tapentadol prolonged release, oxycodone CR, or placebo. This was followed by a 12-week maintenance phase, when patients would adjust the dose, but were not allowed

rescue medication. The primary end-point was the mean change in pain intensity, using the last observation carried forward imputation. In the low back pain trial, optimal doses of opioids in both active treatment groups produced a statistically significant reduction in pain intensity compared to the placebo over the entire maintenance period, with a lower incidence of adverse events (382). A meta-analysis of the 3 studies demonstrated that tapentadol long-acting was non-inferior to oxycodone CR in terms of efficacy (383). A clinical study with a randomized-withdrawal design has investigated the efficacy and safety of tapentadol in 588 patients with painful diabetic neuropathy who were dissatisfied with their current treatment and had an average pain score above 5 (384). However, the study included only a greater than one point reduction in pain intensity for inclusion criteria for the randomized, double-blind phase. In the open-label phase of a randomized study in 1,117 patients with osteoarthritis or chronic low back pain, with patients being encouraged to stay for a 51 week maintenance phase, tapentadol provided stable pain relief over the study period and was also associated with significantly lower levels of constipation, nausea, and vomiting than oxycodone (385).

Among the new studies, transdermal buprenorphine was evaluated in a prospective evaluation (217) in patients with cancer and non-cancer pain with 81% of 4,030 patients with cancer pain. The second study (219) evaluated buprenorphine transdermal system for chronic moderate to severe low back pain in a randomized, double-blind evaluation. In this study, Steiner et al (219) evaluated the results in a phase III study with 1,160 opioid experienced patients with chronic moderate to severe low back pain in an open-label run-in period. The results showed that there was very little difference among the groups with regards to pain relief. However, the treatment group did not worsen with increased pain as did the control group. The authors concluded that based on the primary efficacy variable, there were statistically significant differences in buprenorphine transdermal system 20 compared with buprenorphine transdermal system 5.

The study of long-term CR oxycodone and pregabalin in the treatment of non-cancer pain was an observational study (349), which showed the effectiveness of a combination with pregabalin with a reduction in dosages. The study by Daitch et al (160) showed the effectiveness of sublingual buprenorphine in patients who were switched from long-term opioid management with superior improvement in patients who were

on lower doses of morphine (100 mg morphine equivalence or less compared to higher dosages). Finally, the clinical efficacy of hydromorphone was also studied in a routine clinical practice (354) in 197 patients who received osmotic controlled-release oral delivery system OROS (Osmotic-controlled Release Oral delivery System) hydromorphone (extended release) and were monitored for 90 days. Of these, 127 patients had non-malignant diseases, mostly degenerative joint disease, with the others being cancer pain patients. They (354) showed significant reductions in pain scores, although 17 patients stopped treatment due to adverse effects. The authors (354) concluded that the severity of the patients' pain decreased during treatment with OROS hydromorphone with few adverse effects. Further, the observed pain relief was accompanied by an improvement in the quality of the patients' lives.

3.4.2 Short-Acting Versus Long-Acting Opioids

Chou and Carson (190) in their drug effectiveness review project report evaluated 7 trials compared long-acting opioids to short-acting opioids (378,386-391). The results illustrated that long-acting opioids have not been shown to be superior to short-acting opioids. For oxycodone, there was no good quality evidence to suggest the superior efficacy of long-acting opioids as a class over short-acting opioids. Specifically, there was fair evidence from 3 trials where long- and short-acting oxycodone was equally effective for pain control. These 7 identified randomized trials included 568 patients, with all studies being rated as fair quality. The randomized trials directly compared the efficacy of long-acting opioids to short-acting opioids in patients with chronic pain of non-cancer origin. Three studies compared long-acting oxycodone to short-acting oxycodone (387,389-391). Two studies evaluated long-acting dihydrocodeine (388-390), one evaluated long-acting codeine (386), and one evaluated long-acting morphine (378). These trials showed no consistent trends demonstrating significant differences in efficacy between long-acting opioids as a class and short-acting opioids. In addition, the authors also concluded that there was no convincing evidence from 7 RCTs to suggest lower adverse event rates with long-acting opioids as a class compared with short-acting opioids for all assessed adverse events. There were no data comparing rates of addiction or abuse of long-acting and short-acting opioids.

Fine et al (174) reviewed the evidence with respect to long-acting opioids and short-acting opioids with their appropriate use in chronic pain management. In

another manuscript (192) the benefits of ER opioid analgesic formulations in the treatment of chronic pain were described; however, there were no comparative evaluations.

3.4.3 Opioid Rotation

Opioid rotation in the management of chronic cancer pain is common, although its prevalence and effectiveness in chronic non-cancer pain is unknown. Vissers et al (392) observed that opioid rotation could result in a better analgesic effect at a lower equipotent dose in cancer patients; however, there is no such evidence available in non-cancer patients. Moreover, the opioid rotation recommendations are often based on data derived from studies designed to evaluate acute pain relief, and sometimes on single-dose studies, which makes this information unreliable in chronic pain settings.

Webster and Fine (393) performed a focused literature review to identify reports of fatal or near-fatal outcomes that have occurred in conjunction with opioid rotation in order to evaluate clinician competence in opioid rotation, and to identify inconsistencies in published protocols for opioid rotation. An increasing body of literature showed that widely used opioid rotation practices, including the use of dose conversion ratios found in equianalgesic tables, may be an important contributor to the increasing incidence of opioid-related fatalities (394-396). These errors may be due, in part, not only to inadequate competence on the part of the prescriber, but also to the proliferation of inconsistent guidelines for opioid rotation, conflation of equianalgesic tables as conversion tables, and limitations inherent in the equianalgesic dose tables (397-399).

Canadian Guidelines (224) recommend that for patients experiencing unacceptable adverse effects or insufficient opioid effectiveness from one particular opioid, a different opioid should be prescribed or therapy discontinued.

Chou and Carson et al (190), in the drug review showed that opioid rotation, which has been proposed as a strategy to improve the balance between analgesia and side effects, was not supported by any clinical trials of opioid rotation in patients with non-cancer pain. Furthermore, they concluded that the supporting evidence primarily consisted of anecdotal data and uncontrolled observational studies.

Nalamachu (215) discussed opioid rotation with ER opioids. He posited that current scientific knowledge limits the ability to predict which patient will respond optimally to specific opioid analgesics and that, conse-

quently, opioid rotation is a necessary practice in the management of chronic non-cancer pain where therapeutic efficacy with the lowest possible dose is the desired result. He concluded that even patients who respond favorably to initial opioid therapy may require rotation to a new opioid over time to maintain adequate analgesia, which in essence may minimize the risks of adverse events and overdose associated with frequent dose escalations and higher opioid doses. Nalamachu et al (215) described various clinical considerations with multiple steps with opioid selection, supplemental analgesia to manage breakthrough pain, rotation to methadone, and managing withdrawals. None of this, however, is based on good scientific evidence, but it rather on case reports and opinions.

In another study reporting a 10-year experience of 345 patients in an acute palliative care unit with switching to methadone, Mercadante (400) concluded that switching to methadone from different opioids, using an initial fixed ratio, followed by flexible dosing, according to the clinical need, was highly effective and safe when performed in an acute pain relief and palliative care unit. This study contained multiple deficiencies and was not conducted in chronic non-cancer pain patients.

3.4.4 Impact on Quality of Life

While there is no significant evidence of long-term pain relief with opioids in chronic non-cancer pain, the impact of long-term opioid therapy on QOL is even less optimistic. QOL improvement has been evaluated less frequently than pain relief. Devulder et al (401) evaluated the impact of long-term use of opioids on QOL in patients with chronic non-malignant pain in a systematic review. They identified 11 studies that evaluated long-term treatment with opioids in patients with chronic pain. The total number of patients enrolled into these studies was 2,877. Of these 11 included studies, 6 were randomized trials (n=1,504) (365,402-406) and 5 studies were open-label, observational studies (n=1,373) (376,377,407-409). Of the 6 randomized trials, 4 trials were double-blinded (403-406) and 2 studies were open-label (365,402). Among the 6 randomized trials that were eligible, in 2 of the studies, baseline QOL was not measured and therefore the QOL change with treatment was not reported (144,405). In both of these trials, the primary study objective was the comparison of the impact of the 2 study interventions on the patient's QOL. Subsequently, the results were not presented in terms of any changes from baseline. How-

ever, in the remaining 4 randomized trials, 3 demonstrated an improvement in QOL with opioid treatment (402-404), even though this improvement was not always significantly greater than placebo (404). One study showed no treatment-related improvement in QOL or functionality (406). Thus, among the randomized trials, there was some improvement shown in 3 of the 6 studies evaluated.

Among the 5 studies described as observational or open-labeled, the results were only indicative at best, since their design implied less methodological rigor than seen with RCTs. In 4 of these studies, a statistically significant improvement in the overall QOL was seen with long-term opioid treatment (377,406,407,409). Only one of the studies failed to detect an overall change in QOL (376).

Thus, Devulder et al (401) concluded that there was both moderate/high quality and low quality evidence suggesting that the pain relief elicited by long-term (defined as greater than 6 weeks duration of opioid treatment) was accompanied by improvement in QOL. They also concluded that owing to the heterogeneity of the included studies, in terms of the population studied, study designs used, and outcome measures assessed and the methods used to assess them, it was not possible to determine the average magnitude of this QOL improvement. Based on these findings, the authors postulated that if an appropriate dose level is chosen for each patient, on an individual basis, pain relief elicited by long-term opioid treatment might offset the impact of common side effects of treatment to evoke an overall improvement in a patients' well-being.

Dersh et al (330) in a prospective outcomes study sought to determine whether prescription opioid dependence, assessed at the beginning of rehabilitation treatment, is associated with poorer treatment outcomes in patients with chronic disabling occupational spinal disorders attending an interdisciplinary rehabilitation program. They concluded that iatrogenic prescription opioid dependence might be a risk factor for less successful long-term work and health outcomes, even after detoxification from opioids as part of an interdisciplinary functional rehabilitation program. Chronic prescription opioid dependence in this patient population is also associated with a significantly higher prevalence of comorbid psychiatric conditions.

Among the other studies (333,335,366,367,410-418), the results were mixed. Among the studies with positive results, Dillie et al (410) reported a positive difference in relation to most health-related quality of

life (HRQoL) domains of the short form-36 (SF-36) with the administration of oxycodone. Rauck et al (411) also showed that both sustainable-release morphine and oxycodone led to a significant improvement in both physical and mental components of the SF-12, with physical functioning scores improving by approximately 20% to 30%. Caldwell et al (366) showed that the mean physical function scores improved by 18% at week 4 compared with an improvement of 8% with the placebo. Adams et al (414) showed that sustained-release (SR) morphine significantly increased the proportion of those who reported an improvement in their ability to undertake moderate-intensity activities. Zenz et al (367) have illustrated a close correlation between pain reduction and an increase in performance. Jensen et al (412) also showed that in a 10-year follow-up, opioid users had lower SF-36 scores than chronic pain patients who were not using opioids. Deshpande et al (413) concluded that pain relief could be expected to improve more in non-depressed patients.

Multiple other studies of the literature (26,36,38,110,112,333-347) have reported an association between opioid prescribing and deterioration of health status resulting in increased disability, medical costs, subsequent surgery, continued or late opioid use, and failure to respond to numerous interventions. Thus, epidemiologic studies provided mixed results with regards to improvement in function and QOL with opioids in chronic pain patients (60-65,78,81,87,97,98,187,189,190,260,341). In an epidemiologic study by Breivik et al (26) from Denmark where opioids are prescribed liberally for chronic pain, it was demonstrated that in patients receiving opioids, pain was worse, health care utilization was higher, and activity levels were lower compared to a matched cohort of chronic pain patients not using opioids. This study suggested that when opioids are prescribed liberally, even if some patients benefit, the overall population does not. Eriksen et al (37) also reported worse pain, higher health care utilization, and lower activity levels in opioid-treated patients compared to matched cohort of chronic pain patients not using opioids. Sjogren et al (38) in a study published in 2010 evaluating the role of opioids showed that the odds of recovery from chronic pain were almost 4 times higher among individuals not using opioids compared with individuals using opioids. Moreover, the strong opioids were associated with poor HRQoL and higher risk of death.

Apart from pain relief, functional status improvement and health care utilization, another important

function relevant to patients on chronic opioid therapy is driving capability (418,419). Fishbain et al (419) 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, these opinions did not correlate with a narrative review by Strassels (418), who reported that although the effects vary among drugs, cognitive function might be influenced by the use of opioid analgesics.

Wilhelmi and Cohen (158) described a framework for “driving under the influence of drugs” policy for the opioid using driver. They defined that driving under the influence of drugs is a term used to designate the action of driving an automobile after the consumption of drugs or medications other than alcohol that interfere with the capacity to operate a vehicle safely. They described that unlike recreational drugs, prescription medications pose a unique challenge to those attempting to harness their benefits, yet protect the driving public. They concluded that a sizable percentage of the driving public has detectable levels of opioids within their bodies. They also stated that the best available evidence demonstrates psychomotor impairment following acute administration of opioids or an increase in opioid dosage, but impairment diminishes with chronic, stable opioid usage. Thus, it is essential to balance the benefit of pain relief against the need for public protection, based on the evidence.

3.4.5 Summary of Effectiveness Evidence

In summary, based on the present systematic reviews, it appears that short-term opioid therapy is associated with a moderate degree of pain relief, although evidence is weak due to overall summary effects and sizes. Consequently, less vigorous forms of evidence have been used to evaluate long-term effectiveness based on assertions that it is not feasible to conduct RCTs over prolonged periods, even though, long-term RCTs are demanded for other interventions (3,63,64,227,232-235,420-422). Other drawbacks of assessment of long-term effectiveness are that in open label follow-up studies, as many as 56% of patients abandon treatment because of a lack of efficacy or side effects (98,223). Furthermore, many opioid trials utilize enrichment in their protocols (patients who do not respond 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 (422). Nevertheless, lingering issues remain related to opioids’ lack of effectiveness for improving functional status or QOL even when the dosage is escalated. The traditional premise that dosages should be titrated upwards to overcome pharmacological tolerance, an inevitable consequence of long-term opioid treatment, has been utilized in long-term studies (88). Consequently, at least some patients might be able to reach a stable, non-escalating, effective dose; analgesic tolerance seems to stabilize over time. Even then, many patients continue to fail dose escalation, reporting no change or worsening of their pain, despite high doses of opioids (80,420,423-426) with a paradoxical response of actual improvement in pain once opioid treatment is discontinued (427-429), secondary to a rampant tolerance or opioid-induced hyperalgesia. This shows that the premise that tolerance can always be overcome by dose escalation is unrealistic.

In chronic pain patients, however, there is also debate in reference to exercise (159). Nijs et al (159) in a review of the available evidence addressing the effect of exercise on central pain modulation in patients with chronic pain showed diverse results. Exercise is considered as an effective treatment for various chronic pain disorders; including fibromyalgia, chronic neck pain, osteoarthritis, rheumatoid arthritis, and chronic low back pain. However, the clinical benefits of exercise therapy in these populations, though established based on evidence in some, continue to be unclear, specifically with reference to exercise and its potential effects on the processes involved in chronic pain (i.e., central pain modulation). Exercise activates endogenous analgesia in healthy individuals by the increased pain threshold due to the release of endogenous opioids and activation of supraspinal nociceptive inhibitory mechanisms orchestrated by the brain (159). Exercise triggers the release of beta-endorphins from the pituitary (peripherally) and the hypothalamus (centrally), which in turn enables analgesic effects by activating mu opioid receptors peripherally and centrally, respectively (159). Furthermore, the hypothalamus also has the capacity to activate descending nociceptive inhibitor mechanisms through its projections on the periaqueductal gray. This review (159) showed that several groups have shown dysfunctioning of endogenous analgesia in response to exercise in patients with chronic pain. Generally, with exercise, muscle contractions activate generalized endogenous analgesia in healthy, pain-free humans and patients with either osteoarthritis or rheumatoid arthri-

tis, but result in increased generalized pain sensitivity in fibromyalgia patients. It has been shown that in patients with local muscular pain, exercises with non-painful muscles activate generalized endogenous analgesia, whereas, when painful muscles are exercised, pain sensitivity is not changed either in the exercising muscles or at distant locations. Nijs et al (159) concluded that a dysfunctional response of patients with chronic pain and aberrations in central pain modulation to exercise has been shown, indicating that exercise therapy should be individually tailored with emphasis on prevention of symptom flares.

3.4.6 Conclusions

While there is significant short-term evidence available for all opioids, an assessment of long-term effectiveness is hindered due to the short 3 month duration of the studies.

1. The short-term effectiveness of opioids is fair.
2. The long-term effectiveness of opioids is limited due to lack of long-term (> 3 months) high quality studies.
3. There is fair evidence with no significant difference in effectiveness or adverse effects between long-acting and short-acting opioids.
4. There is limited published evidence for opioid rotation due to lack of quality publications.
5. The evidence for improvement in QOL parameters is fair for short-term and limited for long-term due to only short-term studies and lack of quality literature with long-term follow-up.

3.5 Evidence of Effectiveness of Individual Drugs

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

3.5.1 Hydrocodone

Despite multiple evaluations on the 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 (430), 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. These results support the hypothesis that the rate of abuse identified

with tramadol is not significantly greater than NSAIDs, but is less than the rate associated with hydrocodone.

3.5.2 Oxycodone

The long-term effectiveness of oxycodone was evaluated in multiple studies (349,372,374,379,411,431,432).

Portenoy et al (431) looked at SR oxycodone use over a 3-year period in 233 non-cancer patients who had participated earlier in clinical trials studying the same medication. At the 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 SR oxycodone.

Rauk et al (411), in a randomized, open-label, multicenter trial, studied the effectiveness of SR oxycodone compared with SR morphine in 266 patients for up to 8 months. Both groups showed significant improvement. They concluded that compared to twice-daily SR oxycodone, once-daily SR morphine resulted in significantly better physical function and QOL.

Roth et al (372) studied 133 patients with osteoarthritis with follow-up lasting up to 6 months. Fifty-eight patients completed 6 months of treatment, 41 completed a 12-month follow-up, and 15 completed an 18-month follow-up. They concluded that SR oxycodone provided sustained analgesia.

Hermos et al (374), in an observational review, reported the results of 47,000 veterans receiving opioids through the Veterans Affairs 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, those patients with concurrent benzodiazepines, psychogenic pain, alcohol abuse, and HIV/AIDS had more treatment management problems.

Vondrackova et al (379), 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 (432), 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.

In a study of CR oxycodone and pregabalin (349), the results showed the effectiveness of the combination with pregabalin to reduce the dosages of oxycodone.

Table 2 illustrates the results of studies evaluating the effectiveness of oxycodone.

3.5.3 Morphine

The long-term effectiveness of morphine has been evaluated in multiple studies (365-367,378,409,433).

Allan et al (365) compared 342 strong-opioid naïve patients with chronic low back pain on a 12-hour, 30 mg dosage of SR oral morphine with those using transdermal fentanyl. Doses were adjusted according to response. Participants assessed pain relief, QOL, disease progression, and side effects including bowel function. Among these, approximately 70% of the participants were not employed. SR 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 was frequently used by 50% of the participants as rescue medication. QOL 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 the end point, investigators considered that 45% of the participants had stabilized, 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 (366) evaluated Avinza, an ER 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. The 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 (367) evaluated long-term oral opioid therapy in patients with chronic non-cancer pain. They described 100 patients utilizing SR 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 reported no beneficial effect from opioid therapy. The most common side effects were constipation and nausea.

Maier et al (433) 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 a 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 opioids 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 QOL. There were inconsistent 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 the initial response was without evidence for tolerance development, especially if their treatment was controlled in a pain center.

Tassain et al (409) evaluated the long-term effects of SR 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

Table 2. Results of studies evaluating long-term effectiveness of oxycodone.

Study/Methods	Participants	Opioids Studied	Outcome(S)	Conclusion(S)	Complications	Result(S)
Rauck et al (411) Randomized, open-label, multicenter trial	Chronic, severe low back pain (n=266) Sustained release morphine vs. sustained release oxycodone Up to 8 mos.	Randomized to sustained release morphine (Avinza) or sustained release oxycodone (OxyContin) period of dose titration, then 8 wk evaluation and optional 4 mo. 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)
Gatti et al (349)	n=1051	Oxycodone + pregabalin		Combination of controlled release oxycodone + pregabalin could represent valuable long-term therapeutic addition to existing pharmacological options for non-cancer pain treatment.		The results showed the effectiveness of combination with pregabalin to reduce the dosages of oxycodone
Roth et al (372) Randomized, double blind, placebo controlled	133 patients with osteoarthritis 6 to 12 mos. 58 patients completed 6 mos. of treatments, 41 completed 12 mos., 15 completed 18 mos.	Sustained release oxycodone twice a day 10 mg (n=44) 20 mg (n=44) vs placebo (n=45)	Visual analog scale, 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 (374) Observational review	47,000 veterans receiving opioids through the Veterans Affairs 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 mos. (31% with cancer diagnosis); mean daily dose 3.9 tabs/day (0.5-13.0) with minimal change over time
Portenoy et al (431) 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, visual analog scale, med acceptability, adverse events, aberrant drug behavior (abuse, misuse, withdrawal)	There needs 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 33 mos. and 54% at 36 mos.
Ytterberg et al (432) 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 effective therapies for prolonged rheumatic disease treatment w/o major side effects.

mood. Morphine induced persisting effects on pain and to a lesser extent on QOL and mood at 12 months, with no disruption of cognitive function.

Table 3 illustrates the results of multiple studies evaluating the long-term effectiveness of morphine.

3.5.4 Tramadol

In a Cochrane Review of oral or transdermal opioids for osteoarthritis of the knee or hip (178) utilizing 10 randomized trials with meta-analysis of randomized trials, oral codeine was studied in 3 trials, and transder-

mal fentanyl and oral oxycodone in 2 trials. Overall, opioids were more effective than control interventions in terms of pain relief and improvement of function. The authors were not able to find substantial differences in effects according to the type of opioid, analgesic potency (strong or weak), daily dose, duration of treatment or follow-up, methodological quality of trials, and type of funding. Adverse events were more frequent in patients receiving opioids when compared to the control group. The authors concluded that the small to moderate beneficial effects of non-tramadol

Table 3. 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 (365) 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 (366) 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 (367) 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	Visual analog scale, 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 (433) 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 (409) 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

opioids are outweighed by large increases in the risks of adverse events. It was recommended that non-tramadol opioids should therefore not be routinely used, even if osteoarthritis pain is severe. The majority of the trials were of short-term duration (9 out of 10 trials), whereas only one trial was of longer duration (370).

Pergolizzi et al (352), in a review of ER formulations of tramadol in the treatment of chronic pain, provided the expert opinion that based on the literature cited, ER formulations of tramadol appear to offer a rational and important addition to analgesic armamentarium.

Harati et al (370) evaluated the long-term effectiveness of tramadol in 117 participants with painful diabetic neuropathy. This was a 6 month open extension, following 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 a placebo. The results illustrated that tramadol reduced mean pain scores, which were maintained throughout the study and were 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.

3.5.5 Methadone

Methadone is one of the most commonly utilized, but also rigorously debated drugs, because of its potential for abuse, adverse consequences, and pharmacodynamic variations (373,434-441). There have not been any RCTs evaluating methadone either on a short-term or a long-term basis.

Sandoval et al (181), 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. 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 (181) review 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. In fact, however, these results must be interpreted with great caution, as the results are derived from observational studies without control groups.

3.5.6 Transdermal Fentanyl

Transdermal fentanyl provides SR analgesia. It has been the subject of 3 studies, both randomized and non-randomized (365,376,377). Even though transdermal fentanyl has been evaluated in systematic reviews, there has not been any strong evidence for either short-term or long-term effectiveness.

Allan et al (365) evaluated 338 patients with chronic low back pain who took transdermal fentanyl for 13 months; they also compared them with SR 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 (376) evaluated the long-term efficacy and safety of transdermal fentanyl in the treatment of chronic non-cancer pain in an international, multi-center, 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 QOL. The mean dose of transdermal fentanyl increased from 48 to 90 mcg/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 SF-36. The most frequent treatment-related adverse events were nausea (31%), constipation (19%), and somnolence (18%).

Mystakidou et al (377) 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 QOL scores and pain. Further-

more, the improvements were not influenced by pain type or etiology. Fentanyl was assessed in only one low quality, randomized, parallel group trial evaluating low back pain (365).

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

3.5.7 Oxymorphone

Oxymorphone was first synthesized in Germany in 1914 and patented in the US in 1955. It was introduced in 1959 as a parenteral opioid analgesic. It became available as a short acting oral opioid, but removed from the market in the early 70s. Oxymorphone was reintroduced in 2006 in a short acting and long acting form. The use of oxymorphone in the treatment of non-cancer pain has escalated over the last several years. Only 2 studies have reviewed the effectiveness of oxymorphone (375,440) for long-term use.

Rauck et al (440) 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 (375), 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 might require long-term opioid therapy.

3.5.8 Hydromorphone

The clinical effectiveness of hydromorphone was studied in a routine clinical practice in 197 patients receiving OROS hydromorphone with monitoring lasting for 90 days (354). Of these, 127 patients with non-malignant disorders, mostly degenerative joint disease, showed a significant reduction in pain scores. However, 17 patients also stopped treatment due to adverse effects. The observed pain relief was accompanied by an improvement in the quality of the patients' lives.

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 (365) 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 (376) 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, Short form-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 (377) 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

3.5.9 Tapentadol

Pergolizzi et al (351) described that tapentadol was evaluated in 3 double-blind randomized placebo-controlled multicenter trials in patients with chronic low back pain or osteoarthritis. The studies included a 3-week titration phase followed by 12-week maintenance phase. In the low back pain trial, optimal doses of opioids in both active treatment groups produced a statistically significant reduction in pain intensity compared to the placebo over the entire maintenance period with a lower incidence of adverse events (382). A meta-analysis of 3 studies demonstrated that tapentadol long-acting was equal to oxycodone in terms of efficacy (383). It was also evaluated in patients with painful diabetic neuropathy (384). Moreover, for long-term safety in a phase 3, open-label, randomized study including over 1,100 patients with osteoarthritis or chronic low back pain, with an approximately 51-week follow-up, tapentadol was shown to provide stable pain relief over the study period and was also associated with a lower adverse profile (385).

Wild et al (380) 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 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. Wild et al (380) 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.

3.5.10 Codeine

There was only one study available evaluating codeine use by patients with chronic rheumatic disease pain (432). 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.

3.5.11 Buprenorphine

Transdermal buprenorphine was evaluated in a prospective evaluation in patients with cancer and non-cancer pain (217) with 81% of 4,030 patients with cancer pain with only 19% with non-cancer pain with 764 patients with various types of diagnosis. The results illustrated well controlled pain relief.

A randomized, active-control, double-blind evaluation of buprenorphine transdermal system for chronic moderate to severe low back pain (219) showed that there was very little pain relief difference among the groups with different doses of buprenorphine transdermal system in an open-label run-in period or with oxycodone.

3.5.12 Conclusions

While there is significant short-term evidence available for all opioids, the evidence for long-term effectiveness is inconclusive due to the relatively short (3 month) duration of the studies.

1. The evidence for hydrocodone is limited due to lack of quality studies.
2. The evidence for oxycodone is fair for short-term and limited for long-term due to lack of long-term or quality studies.
3. The evidence for morphine is fair for short-term and limited for long-term due to lack of long-term or quality studies.
4. The evidence for tramadol is fair in osteoarthritis.
5. The evidence for methadone is limited due to lack of quality studies.
6. The evidence for transdermal fentanyl is fair for short-term and limited for long-term due to short-term studies and lack of high quality studies.
7. The evidence for oxymorphone is limited due to lack of quality studies.
8. The evidence for hydromorphone is limited due to lack of quality studies.

9. The evidence for tapentadol is limited due to lack of quality studies.
10. The evidence for codeine is limited due to lack of quality studies.
11. The evidence for buprenorphine is limited due to lack of long-term or high quality studies.

3.6 Effectiveness of Opioid Therapy in Specific Populations

Opioids are not only administered in healthy adults, but also the elderly, children, and adolescents; during pregnancy; and patients with comorbid psychiatric conditions.

3.6.1 Effectiveness and Safety in the Elderly

Canadian guidelines for the safe and effective use of opioids for chronic non-cancer pain (224) concluded that opioid therapy for elderly patients can be safe and effective (Grade B evidence) with appropriate precautions, including lower starting doses, slower titration, long dosing intervals, more frequent monitoring, and tapering of benzodiazepines (Grade C). They showed that the evidence suggests that many elderly patients who might benefit from opioid therapy are not receiving it in Canada (19).

Moulin et al (19) in a national Canadian survey documented that 29% of Canadian adults experienced chronic pain, with increasing frequency in elderly patients. They illustrated that even though most of these patients had moderate to severe pain that interfered with function, only 7% were receiving opioids stronger than codeine. In another study in the United States of 83,000 patients in 12 primary care clinics in Wisconsin by Adams et al (441), only 201 patients were receiving opioid therapy for chronic pain. Solomon et al (442) showed that elderly patients most commonly receive weak opioids, and rarely strong opioids. However, a recent escalation in drug usage and abuse has reversed these statistics (272-274,443-465).

A single systematic review (207), a guideline (224), and a consensus statement (195) have been developed in reference to the use of opioids for non-cancer pain in older adults.

Papaleontiou et al (207), in their systematic review and meta-analysis 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.

Canadian guidelines (224) in a summary of peer reviewed evidence showed that based on the evidence many elderly patients might benefit from opioid therapy but that they are not receiving it. Moreover, they also concluded that CR opioids are preferred for the elderly for reasons of compliance. A consensus statement of an international expert panel with a focus on the 6 clinically most often used World Health Organization Step III opioids recommends a preference for SR prescriptions because they increase patient compliance, as dosing frequency can be reduced. This recommendation comes despite the fact that there is no evidence to support the use of long-acting analgesics over short-acting analgesics. Moreover, with the elderly and those with comorbid disorders often taking multiple medications, long-acting opioids may be an inappropriate proposition considering that most complications occur during the night and also due to the fact that there is an increased risk of the common adverse effects of oversedation and overdose with lower metabolism and greater sensitivity to the psychoactive and respiratory effects of opioids and a combination of benzodiazepines and psychotropic medications (457). Canadian guidelines also dealt with various options to reduce risks for the elderly. In reference to cognitive impairment, overdose, tolerance check, and renal function, the guidelines advise that these have to be prescribed cautiously with initial titration at no more than 50% of the suggested initial dose for adults. Among strong opioids, oxycodone and hydrocodone may be preferred (458), CR formulations are recommended for compliance purposes even though there is no evidence of improved compliance. Morphine solutions may be used in some situations when preferable to the oral tablets. For elderly patients on benzodiazepines, the benzodiazepines must be tapered or reduced with the dose to avoid cognitive impairment.

Pergolizzi et al (195) provided a consensus statement on opioids from an international expert panel for the management of chronic severe pain in the elderly with a focus on the 6 clinically most often used opioids. In an evaluation of opioids for non-cancer pain they considered common etiologies such as osteoarthritis, rheumatoid arthritis, spinal pain, and herpes zoster. In

one study, morphine was given for up to 6 years with a moderate dose of up to 195 mg per day (459) and even up to 360 mg and 2 grams per day (460). Cognitive function was relatively unaffected in patients taking stable, moderate doses, but was in some cases impaired for up to 7 days after the dose increase (461).

Oxycodone was evaluated in 2 short studies with doses up to 40 mg per day, illustrating effective analgesia with typical opioid adverse events (372,389). The second study (372) had a 6-month extension period with optional treatment for an additional 12 months, and found no evidence of tolerance.

Hydromorphone was evaluated in only one study (464), and showed adequate efficacy and tolerability in a mixed group of cancer and non-cancer patients.

Evidence is more readily available for transdermal fentanyl than compared to other drugs used by the elderly (402,407,458,464,466-469). However, there are fewer non-cancer pain studies than cancer pain studies. In a randomized, open-label 2-way crossover study (470), both groups reported benefits from treatment. Patients switching to fentanyl from oxycodone/acetaminophen at the 3 month crossover point experienced better pain relief, while those switching from fentanyl did not. The results of the 8 studies in cancer and non-cancer pain were pooled (458) and demonstrated that pain scores were significantly reduced with fentanyl, but adverse events were high in the active and placebo groups. Many of these were not necessarily related to the treatment, and discontinuations were lower in the fentanyl group than with morphine. In an analysis of patients over 65 in the California Medicare database (467), oxycodone was associated with a 7-fold higher constipation rate than fentanyl. Jamison et al (468) investigated the psychomotor effects of long-term oxycodone with acetaminophen or transdermal fentanyl use in 144 patients with low back pain. These studies showed that neurophysiological test scores significantly improved, suggesting that long-term use of oxycodone with acetaminophen or transdermal fentanyl does not impair cognitive ability or psychomotor function. In a 6-month open-label, randomized, multicenter, 2-way crossover study with transdermal fentanyl or oxycodone (470), comparing HRQoL in 229 patients with chronic low back pain, patients receiving transdermal fentanyl showed a significant improvement with pain and disability during a 3- to 6-month trial period.

Transdermal buprenorphine also has been studied in 3 double-blind, placebo-controlled studies (471-473). These studies provided a good level of evidence dem-

onstrating good dose progression and responsiveness, and the ability to control adverse events with careful titration.

There were no adequate clinical studies available for methadone or for other opioids such as hydrocodone. The authors concluded that there is growing evidence that opioids are efficacious in non-cancer pain, but require individual dose titration and consideration of respective tolerability profiles.

3.6.2 Effectiveness and Safety in Adolescents

Canadian guidelines (224) state that opioids present hazards for adolescents (Grade B evidence); however, a trial of opioid therapy may be considered for adolescent patients with well defined somatic or neuropathic pain conditions when non-opioid alternatives have failed, risk of opioid misuse is assessed as low, close monitoring is available, and consultation if feasible is included in the treatment plan (Grade C). Non-medical use of opioids and psychotherapeutics is common among adolescents and may be a risk factor for future opioid addiction (261). Among adolescents, risk factors for opioid misuse include poor academic performance; higher risk-taking levels; major depression; and regular use of alcohol, cannabis, and nicotine (474).

Since persistent pain is a frequent complaint of adolescents in the pediatric population, it may require specialized treatment along with multimodal approaches (475). Reviews show that both psychological and medical interventions are efficacious in children and adolescents (476,477). Hechler et al (475) evaluated 275 children ages 4 to 18 years over a 12-month period utilizing a specialized multimodal outpatient treatment. They showed that at the 12-month follow-up, the majority of children improved and only a small number of children (12%) were still undergoing treatment or needed more intensive treatment. Furthermore, at a 12-month follow-up, almost 70% of children in the study group were able to attend school regularly. Pain intensity, pain related disability, and inappropriate coping strategies were significantly reduced at the 3-month visit and remained stable at subsequent time points. In the multimodal treatment modalities, participants were provided with drug treatment; however, the types of drugs provided were not specified. It appears that the majority of the drugs were either NSAIDs or other non-opioids.

The role of transdermal fentanyl in childhood and adolescents was also reviewed (478). The authors compiled the published evidence on pediatric application of

transdermal fentanyl in a comprehensive literature review. They identified 11 observational clinical or pharmacological studies for the purposes of this systematic review. There were no pediatric randomized or controlled cohort studies. The results showed that children may take longer to reach steady state fentanyl serum concentrations than adults, and younger children may require higher doses in relation to body weight than older children or adults. However the outcomes were not available.

In a review of clinical pharmacology for the buprenorphine transdermal therapeutic system (479), the authors found very few relevant pediatric buprenorphine data, particularly in children suffering with chronic pain. They concluded that buprenorphine was of interest in pediatric postoperative pain and cancer pain control because of its multiple administration routes, long duration of action, and metabolism largely independent of renal function.

In a description of the use of opioids for the management of pain in pediatric palliative care (480), the authors described various aspects of opioid therapy in pediatric patients including weak and strong opioids, but studies of chronic pain were minimal. The authors determined that morphine remains the gold standard starting opioid in pediatric palliative care. The transdermal fentanyl therapeutic system with a drug-release rate of 12.5 mcg per hour matches the lower dose requirements of pediatric cancer pain control, which may be associated with less constipation compared with morphine use. The authors also described that buprenorphine is of special clinical interest as a result of its different administration routes, long duration of action, and metabolism largely independent of renal function. Anti-hyperalgesic effects may contribute to its effectiveness in neuropathic pain. The authors noted that methadone also has a long elimination half-life and N-methyl-D-aspartate (NMDA) receptor activity, although dose administration is complicated by highly variable morphine equianalgesic equivalence ranging from equivalency for 1:2.5:20. They cautioned that opioid rotation to methadone requires special protocols that take this into account. Strategies to minimize adverse effects of long-term opioid treatment included dose reduction, symptomatic therapy, opioid rotation, and administration route changes.

Significant abuse and non-medical prescription drug use have been described in children and adolescents (481-488). It has been noted that more than 25% of kids and teens in the United States take prescriptions

on a regular basis (488-493). However, this abuse is not only limited to prescription drugs, but also illicit drugs and over-the-counter drugs, along with drug stimulants. In a survey of prescription drug abuse and diversion among adolescents in a southeast Michigan school district (487), 36% of students reported having a recent prescription for one of the 4 drug classes. A higher percentage of girls reported giving away their medication than boys; girls were significantly more likely than boys to divert to female friends, whereas boys were more likely than girls to divert to male friends. In addition, 10% of them diverted their drugs to parents.

3.6.3 Effectiveness and Safety in Pregnancy

The use of opioids during pregnancy is a highly debated subject. Canadian guidelines (224) recommend that pregnant patients taking long-term opioid therapy should be tapered to the lowest effective dose slowly enough to avoid withdrawal symptoms, and then therapy should be discontinued if possible (Grade B evidence). These guidelines showed that there is evidence that regular, scheduled opioid use for chronic non-cancer pain during pregnancy is associated with neonatal abstinence syndrome. In a study of 13 pregnant women on opioids for chronic pain, 5 of the neonates had neonatal abstinence syndrome (494). Codeine use also has been associated with fatal opioid toxicity in the neonate in breastfeeding women. It is converted to morphine by the cytochrome P450 system. Some patients are rapid converters, resulting in an accumulation of morphine in their breast milk (495). There have been several case reports of neonatal toxicity due to morphine accumulation. The key clinical features for the baby are not waking up to feed and limpness; and for the mother, signs of sedation and other signs of toxicity with symptoms worse by the fourth day (496). Furthermore, pregnant women addicted to opioids have improved obstetrical and neonatal outcomes when on methadone treatment. A number of studies have demonstrated that methadone treatment reduced the risk of premature labor, low birth weight, and neonatal mortality in heroin-dependent pregnant women (497-500).

Chou et al (64,187) also recommend that clinicians should advise women of childbearing potential about the risks and benefits of chronic opioid therapy during pregnancy and after delivery. Clinicians should encourage minimal or no use of chronic opioid therapy during pregnancy, unless potential benefits outweigh risks. In addition, Chou and Huffman (64,187) recommend that if chronic opioid therapy is used during pregnancy, cli-

nicians should be prepared to anticipate and manage risks to the patient and newborn (Strong Recommendation, low-quality evidence).

3.6.4 Effectiveness and Safety in High Risk Patients

Canadian guidelines describe patients with a psychiatric diagnosis as being at great risk for adverse effects from opioid treatment. Usually in these patients, opioids should be reserved for well-defined somatic or neuropathic pain conditions. They recommend that opioids should be titrated more slowly and monitored closely and that consultation should be obtained where feasible (Grade B evidence). However, patients on chronic opioid therapy have a higher prevalence of depression and other psychiatric conditions than the general population. A large population-based study found that self reported regular opioid use was strongly associated with both mood and anxiety disorders (501). Other studies (502,503) found that patients with low back pain who are receiving opioids were more likely to be depressed than those receiving only NSAIDs. Furthermore, patients with anxiety or depression may have a diminished analgesic response to opioid therapy or a heightened perception of pain (504). In a study of patients with sickle cell disease, it was shown that the severity of pain, functional disability, and use of opioids were correlated with the patients' depression and anxiety as reported during crisis and non-crisis days (505). In a review by Riley and Hastie (506) the most consistent finding was that depression and anxiety were associated with increased risk for drug abuse and decreased opioid efficacy. Moreover, improved mood and pain intensity have also been observed in multidisciplinary pain programs when patients were tapered off their medications (507).

Chronic pain is inherently associated with significant psychological and psychiatric comorbidity (296,508-535). A cross-sectional survey found that depression, panic disorder, social phobia, and agoraphobia were associated with non-medical use of prescription opioids (530). Another study found higher rates of opioid misuse and problematic drug use among patients on opioid therapy, with higher rates being mediated by higher rates of psychiatric disorders (531). In a study of 500 chronic pain patients on opioids, it was documented that anxiety and depression were associated with significantly higher rates of opioid abuse and illicit drug use (296). A study of chronic pain patients presenting to the emergency department for prescrip-

tion refills documented that a high proportion (81%) were abusing their opioids and that of these, a high proportion had depression and anxiety (532). Finally, a case controlled study found that patients on chronic opioid therapy are at a greater risk for suicide than control patients (533).

Sullivan et al (522) showed the association between common mental health disorders and problem drug use in the general population. They also showed that in the general population, depressive, anxiety, and drug abuse disorders were associated with increased use of regular opioids (501). Furthermore, they showed that depressive and anxiety disorders are more common and more strongly associated with prescribed opioid use than drug abuse disorders. Fenton et al (523) concluded that drug use disorders persisted in 30.9% of respondents in the United States. Based on the results of this study, they concluded that antisocial, borderline, and schizotypal personality disorders were specific predictors of drug abuse disorder persistence over a 3-year period. They also showed that deceitfulness and lack of remorse were the strongest antisocial criteria predictors of drug use disorder, that persistence, identity disturbance, and self-damaging impulsivity were the strongest borderline criteria predictors, and that social anxiety was the strongest schizotypal criteria predictor (523). In another study (524), the authors described that expanding the range of personality disorders beyond antisocial personality disorder appears essential in understanding the incidence and persistence of substance use disorders. They described that substance use disorders have low rates of treatment relative to major depression, but that they increase the likelihood of depression treatment among comorbid cases, a phenomenon that needs to be studied further. In a study of clinical and epidemiological assessment of substance misuse and psychiatric comorbidity (525), the results of most studies supported a high prevalence of substance misuse among individuals with psychiatric disorders and vice versa.

Even though psychological disorders have been associated with chronic pain, specifically depression and generalized anxiety disorder, multiple studies have reached different conclusions with regards to therapeutic and diagnostic responses to various types of interventions (522,535-548). Overall, it has been illustrated that the accuracy of the diagnosis may not be affected in patients on either opioid therapy or with a psychological diagnosis of depression, anxiety, and

solmization, and also with administration of sedation during interventional techniques (549-558).

Kroenke et al (526) evaluated the reciprocal relationship between pain and depression in a 12-month longitudinal analysis in primary care. They concluded that pain and depression have strong and similar effects on one another when assessed longitudinally over 12 months.

Braden et al (527) evaluated trends in long-term opioid use among patients with a history of depression from 2 large health plans. Using claims data, age- and gender-adjusted rates for long-term (n=90 days) opioid use, episodes were calculated for 1997–2005, comparing those with and without a diagnosis of depression in the 2 years prior. Opioid use characteristics were calculated for those with a long-term episode in 2005. Incident and prevalent long-term opioid use rates were 3 times higher in those with a history of depression. Prevalent long-term use per 1,000 in patients with a history of depression increased from 69.8 to 125.9 at Group Health and from 84.3 to 117.5 at Kaiser Permanente of Northern California between 1997 and 2005. Those with a history of depression were more likely to receive a higher average daily dose, greater days supply, and Schedule II opioids than nondepressed persons. They concluded that persons with a history of depression are more likely to receive long-term opioid therapy for non-cancer pain than those without a history of depression. Results suggest that long-term opioid therapy for non-cancer pain is being prescribed to a different population in clinical practice than the clinical trial populations where opioid efficacy has been established.

Starrels et al (528) examined 3 risk reduction strategies: (1) any UDT; (2) regular office visits (at least once per 6 months and within 30 days of modifying opioid treatment); and (3) restricted early refills (one or fewer opioid refills more than a week early). Risk factors for opioid misuse included: age < 45 years old, drug or alcohol use disorder, tobacco use, or mental health disorder. Associations of risk factors with each outcome were assessed in non-linear mixed effects models adjusting for patient clustering within physicians, demographics, and clinical factors. They concluded that the primary care physicians' adoption of opioid risk reduction strategies is limited, even among patients at increased risk of misuse.

Chou et al (187) described high-risk patients into one category. Their recommendations were that clinicians may consider chronic opioid therapy for patients with chronic non-cancer pain and a history of drug

abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist (Strong Recommendation, low quality evidence). Their second recommendation in this aspect is that clinicians should evaluate patients engaging in aberrant drug related behaviors for the appropriateness of chronic opioid therapy or need for restructuring of therapy, referral for assistance in management or discontinuation of chronic opioid therapy (Strong Recommendation, low quality evidence).

Chou et al (187) also described that chronic non-cancer pain is common in patients with suspected aberrant drug-related behaviors, psychosocial comorbidities, and history of substance abuse. Chou et al recommend that in some patients such as those actively using illicit drugs, potential benefits are outweighed by potential risks, and chronic opioid therapy should not be prescribed outside of highly controlled and specialized settings such as an opioid treatment program with directly observed therapy. In other patients, the potential benefits of chronic opioid therapy may outweigh potential risks; however, such patients have not been identified in any of the studies. Even though evidence is lacking as to the best methods for managing such patients, potential risks may be minimized by more frequent and intense monitoring compared with lower risk patients, authorization or limited prescription quantities, and consultation or comanagement with persons who have expertise in addiction or mental health issues. Moreover, Chou et al (187) recommend that in settings where local access to specialists is limited, clinicians may need to consider alternative methods such as telemedicine or web-based resources for obtaining consultative services, although there is no evidence evaluating the risks and benefits of such methods when compared with traditional face-to-face consultation.

While aberrant drug-related behaviors suggest the need for enhanced monitoring, reevaluation, and perhaps a change in therapy, these behaviors vary in seriousness. There is no evidence to guide optimal management strategies in these settings.

3.6.5 Conclusions

1. The evidence of effectiveness and safety of chronic opioid therapy in the elderly for chronic non-cancer pain is fair for short-term and limited for long-term due to lack of high quality studies.

2. The evidence of effectiveness and safety in children and adolescents is limited due to lack of quality studies.
3. The evidence of effectiveness and safety in pregnancy is poor; however, the evidence is good with regards to adverse effects.
4. Effectiveness and safety of opioids in patients with generalized anxiety disorder and depression is limited due to lack of high quality studies with fair evidence of increased risk.
5. The evidence of prevalence of high use of opioids in depression is fair.
6. The evidence of effectiveness and safety in high-risk psychological disorder patients with personality disorders and addiction disorders is limited due to lack of high quality studies, with good evidence of increased risk and adverse effects.

3.7 Adverse Effects and the Safety of Opioid Therapy

Candiotii and Gitlin (420) reviewed the influence of opioid-related side effects on 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, the most common of which were constipation, nausea, and somnolence, often leading to discontinuation of opioid therapy. Furthermore, 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 potential for 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 (421), it was concluded that the number of symptoms reported using a 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 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, concentra-

tion 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%.

Furlan et al (97) showed that among the side effects of opioids, only constipation and nausea were clinically and statistically significant. Kalso et al (98) showed that about 80% of patients experienced at least one adverse event, with constipation 41%, nausea 32%, and somnolence 29% being the most common with only 44% of patients continuing on a long-term basis. Martell et al (73) showed that the prevalence of life-time substance use disorders ranged from 36% to 56%, and that estimates of the prevalence of current substance use disorders were as high as 43%. Aberrant medication-taking behaviors ranged from 5% to 24%. The most common adverse events reported by Eisenberg et al (177) were nausea 33% opioid versus 9% control, constipation 33% opioid versus 10% control, drowsiness 29% opioid versus 12% control, dizziness opioid 21% versus 6% control, and vomiting 15% opioid versus 3% control. Whenever reported, the results showed that 11% of patients were withdrawn from their opioid therapy group and only 4% from the placebo group (177). Deshpande et al's (179) review showed that the 2 most common side effects of tramadol were headaches in 9% and nausea in 3%.

Commonly known side effects of opioids (559-575) include constipation, pruritus, respiratory depression, nausea, vomiting, delayed gastric emptying, sexual dysfunction (575), muscle rigidity and myoclonus (576,577), sleep disturbance (578), pyrexia, diminished psychomotor performance (418,419), cognitive impairment (579), hyperalgesia (88,224,580), dizziness, sedation, respiratory depression, death, and multiple drug interactions, all reflecting the effects of opioids on multiple organ systems (581).

Chou et al (187) described that an important goal of any chronic opioid therapy management plan is to maintain a favorable balance of benefits relative to harms. Among the multiple side effects, constipation is one of the most common opioid-related adverse effects (559). While most patients develop some degree of constipation after the initiation of opioid therapy or dose increases, amelioration of these constipating effects of opioids occurs in the majority of the patients. However, in some patients, constipation becomes a major issue with continued exposure to opioids. Furthermore, in older adults or other patients with additional reasons to develop constipation, physicians should consider ini-

tiation of a bowel regimen before the development of constipation. Even though the evidence for bowel regimen is anecdotal, regimens including increased fluid and fiber intake, stool softeners, and laxatives are often simple and effective. Even though multiple publications relate to opioid antagonists to prevent or treat opioid-induced bowel dysfunction (560,561), the evidence is insufficient to recommend such antagonists to prevent bowel dysfunction. However, randomized trials do suggest some potential benefit over placebo in managing bowel dysfunction (560,561).

Fishbain et al (419), in a structured evidence-based review of impairment in driving-related skills in opioid-dependent or tolerant patients, concluded that the majority of 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 cognitive function of opioid-maintained patients. Moreover, the research was conclusive that there was no impairment with the psychomotor abilities of opioid-maintained patients. They also showed that there was no impairment of psychomotor abilities immediately after being given doses of opioids, and there was no greater incidence in motor vehicle violations or motor vehicle accidents. Furthermore, they illustrated that there was no impairment as measured in driving simulators and on-road driving by opioid-maintained patients. However, Strassels (418) showed that cognitive function can be influenced by the use of opioid analgesics, with varying effects among the drugs. Multiple other studies have also expressed diverse opinions with recommendations for counseling and development of evidence-based policies (582-589). Wilhelmi and Cohen (158) also showed that a sizable percentage of the driving public has detectable levels of opioids within their bodies. They concluded that the best available evidence demonstrates psychomotor impairment following acute administration of opioids or an increase in opioid dosage, but impairment diminishes with chronic, stable, opioid dosage.

Among the various other side effects, opioid-associated endocrinopathy, most commonly manifested as an androgen deficiency, referred to as opioid-associated androgen deficiency (OPIAD) is common. This syndrome is characterized by the presence of inappropriate low levels of gonadotrophins (follicle stimulating hormone and leuteinizing hormone) (154,562-564,590-598). The syndrome is characterized by the presence of inappropriately low levels of gonadotrophin (follicle

stimulating hormone and leuteinizing hormone) leading to inadequate production of sex hormones, particularly testosterone (154). Symptoms that may manifest in patients with OPIAD include reduced libido, erectile dysfunction, fatigue, hot flashes, and depression. Other findings may also include reduced facial and body hair, anemia, decreased muscle mass, weight gain, and osteopenia or osteoporosis. Further, OPIAD can also have a significant negative impact on the quality of life of opioid users. Khoromi et al (594) illustrated that the incidence of sexual dysfunction after morphine was present in 11% of the patients in a randomized trial. However, 2 other randomized trials suggested that patients taking opioid medications reported better sexual function, which was likely an improvement of feeling of wellbeing, at least in the initial stages (592,593). Thus, initially patients may notice improvement in sexual function as a consequence of improved analgesia. At present there is insufficient evidence to recommend a routine monitoring of asymptomatic patients on chronic opioid therapy for chronic non-cancer pain for hormonal deficiencies identified except that it is recommended to reduce the dosages or wean patients off of opioids as well as start hormonal supplemental therapy.

More serious complications include respiratory depression and death, which may occur when initial doses are too high, opioids are titrated too rapidly, or opioids are combined with other drugs such as benzodiazepines that are associated with respiratory depression or that may potentiate opioid-induced respiratory depression or abuse of opioids with or without other drugs (105,599-603). Patients with sleep apnea or with other pulmonary conditions may be at a higher risk for respiratory depression and opioids should be initiated, titrated, and monitored closely with as low a dose as possible.

Canadian guidelines (224) described adverse effects as shown in Table 5 ranging from 28% for nausea, 26% for constipation, 24% for somnolence/drowsiness, 18% for dizziness/vertigo, 15% for dry skin/itching/pruritus, and 15% for vomiting. They also showed that adverse effects where the difference was not clinically important (difference less than 10%) and are not statistically significant ($P > 0.05$) include dry mouth, headache, sexual dysfunction, hot flashes, loss of appetite, abdominal pain, fatigue, sleeplessness/insomnia, sweating, blurred vision/confusion, muscle contractions, diarrhea, ataxia, edema, difficulty urinating, restless legs, application site reaction, heartburn, anxiety, and weakness.

Apart from other complications as described, sleep apnea can be aggravated with opioids and becomes a

Table 5. *Adverse effects of opioids.*

Adverse effect	Number of Studies	Incidence in Opioid Group	Incidence in Placebo Group	Difference (95% CI)
Nausea	38	28%	9%	17% (13% to 21%) P<0.00001
Constipation	37	26%	7%	20% (15% to 25%) P<0.00001
Somnolence/drowsiness	30	24%	7%	14% (10% to 18%) P<0.00001
Dizziness/vertigo	33	18%	5%	12% (9% to 16%) P<0.00001
Dry-skin/ itching/pruritus	25	15%	2%	10% (5% to 15%) P<0.0001
Vomiting	23	15%	3%	11% (7% to 16%) P<0.00001

Source: Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain© 2010 National Opioid Use Guideline Group (NOUGG) (224).

serious issue. High opioid doses may contribute to sleep movement disorders including myoclonus and sometimes choreiform movement, and in combination with benzodiazepines and other drugs may significantly contribute to oxygen desaturation (105,599-603). Thus sleep studies may be considered in patients using high dose opioids specifically in combination with other drugs, elderly patients, obese patients, and patients with somnolence (224).

3.7.1 Conclusions

1. There is good evidence that the majority of the side effects of opioid therapy may be minor and are resolved, but some effects are long-lasting and increase with long-term use.
2. There is fair evidence that complications of long-term therapy or long-acting opioids are frequent.
3. There is fair evidence that serious complications are rare, but fatal when occur.
4. There is limited evidence to recommend a routine monitoring of asymptomatic patients on chronic opioid therapy for chronic non-cancer pain for hormonal deficiencies, due to only preliminary evidence and lack of high quality long-term follow-up.
5. There is fair evidence to reduce the dosages or wean patients off of opioids and also start hormonal supplemental therapy when hormonal deficiencies are identified.
6. There is fair evidence that somnolence and drowsiness may be associated with chronic opioid therapy.
7. There is fair evidence that central sleep apnea may be exacerbated with chronic opioid therapy.

3.8 The Role of Opioid Hyperalgesia and Breakthrough Pain

Opioid-induced hyperalgesia (OIH) and the treatment of breakthrough pain in chronic non-cancer pain

are controversial issues. OIH is more commonly accepted even though the concept of breakthrough pain continues to be mired in beliefs of pseudoaddiction and undertreatment of pain. The evidence is in contrast to the fact that pain may be essentially overtreated in many countries, specifically with opioids, even though overall there may also be an undertreatment of pain in some regions and segments of the population (80,102).

Lee et al (80) provided a comprehensive review of OIH in preparation of these guidelines. OIH is defined as a state of nociceptive sensitization caused by exposure to opioids. The condition is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain could actually become more sensitive to certain painful stimuli. The type of pain experienced might be the same as the underlying pain, or it might be different from the original underlying pain. The OIH appears to be a distinct, definable, and characteristic phenomenon that could explain loss of opioid efficacy in some patients (80). In a systematic review, Angst and Clark (604) reviewed the majority of publications available describing OIH in various animal models. They described their model for OIH that considers this process to be neurobiologically multifactorial. In another review of clinical evidence of OIH (605), the strongest evidence came from opioid infusion studies in normal volunteers as measured by secondary hyperalgesia. The authors concluded that there was not sufficient evidence to support or refute the existence of OIH in humans except in the case of normal volunteers receiving opioid infusions. Thus, the precise molecular mechanism of OIH, while not yet understood, varies substantially in the basic science literature, as well as in clinical medicine. It is generally thought to result from neuroplastic changes in the peripheral and central nervous system that lead to sensitization of pronociceptive pathways. While there are

many proposed mechanisms for OIH, 5 mechanisms involving the central glutaminergic system, spinal dynorphins, descending facilitation, genetic mechanisms, and decreased reuptake and enhanced nociceptive response have been described as the important mechanisms. Of these, the central glutaminergic system is considered the most common possibility. Another is the hypothesis that NMDA receptors in OIH include activation, inhibition of the glutamate transporter system, facilitation of calcium regulated intracellular protein kinase C, and cross talk of neural mechanisms of pain and tolerance.

Even though significant progress has been made in understanding OIH, findings of clinical prevalence of this condition are not available. Several observations, cross-sectional, and prospective controlled trials have examined the expression of potential clinical significance of OIH in humans, in studies using several distinct cohorts and methodologies utilizing former opioid addicts on methadone maintenance therapy, perioperative exposure to opioids in patients undergoing surgery, and of acute opioid exposure using human experimental pain testing. Furthermore, recent evidence has provided contradicting evidence with some studies showing increased sensitivity with chronic opioid therapy, some showing no change or only short-term change, and yet others showing that chronic opioid intake may only reduce the temperature sensitivity but not the pain sensitivity (153,605-617).

Breakthrough pain in chronic non-cancer pain continues to be controversial. In a focused review, Manchikanti et al (102) described that the philosophy of breakthrough pain in chronic non-cancer pain raises multiple issues leading almost all patients to be on high-dose long-acting opioids, followed by supplementing with short-acting drugs, instead of treating patients with only short-acting drugs as required. Thus, the subject of breakthrough pain in chronic non-cancer pain is looked at with suspicion due to the lack of evidence and inherent bias associated with its evaluation, followed by the escalating use and abuse of opioids. The present literature is extrapolated from cancer pain and also a few observational studies. This may be similar to the safety and effectiveness of opioids in chronic non-cancer pain, which was based on extremely weak evidence and exploded into an epidemic. Manchikanti et al (102) showed that there was no significant evidence for any type of breakthrough pain in chronic non-cancer pain based on available literature, methodology utilized, and response to opioids in chronic non-

cancer pain.

Thus, based on the available literature opioid hyperalgesia may be real to a great extent with high-dose opioid therapy, and there are no indications for breakthrough pain medication in chronic non-cancer pain.

3.8.1 Conclusions

1. The evidence is limited for existence and management of breakthrough pain in non-cancer pain, due to lack of quality studies.
2. The evidence is fair for existence of opioid hyperalgesia with chronic opioid therapy.

3.9 Screening for Opioid Abuse

The challenge of using opioid analgesic therapy lies in achieving a balance between 2 important public health concerns: responding to the need of relieving chronic pain and preventing the overuse or abuse of opioid medications (45,82,182,618-621).

Adherence monitoring may be carried out by multiple means including prescription drug monitoring programs (PDMPs), screening tools to monitor opioid adherence, and UDT. This may also be enhanced by the development of abuse deterrent formulations (ADFs) of opioids and also dispensing the medication in measured containers which control the dispensing aspect, thus avoiding misuse and abuse.

3.9.1 Prescription Drug Monitoring Programs

PDMPs collect state-wide data about prescription drugs and track their flow (622-628). There are 3 components of these programs. First is data collection for prescriptions that shows the physicians who wrote them and the pharmacies that dispensed them. Pharmacies are required to report the data by law. In the United States, 38 states have PMPs, but there is a significant difference in the manner and frequency with which the data is collected.

President George W. Bush signed into law the National All Schedule Prescription Electronic Reporting Act (NASPER) in 2005 which was created by ASIPP and enacted by Congress (629). This law requires states to collect prescription information for Schedule II, III, and IV medications. It also requires states to have the capability to share this information with each other. This can decrease cross-border narcotic trafficking. It is heartening to know that this program is now funded by the federal government.

At one point, only 3 states allowed physicians access with physician-friendly programs to monitor drug

utilization. These included Kentucky, Utah, and Idaho. Now, with enactment of NASPER and/or other funding from the Harold Rogers Prescription Monitoring Program, multiple states are operating physician-friendly programs where pain physicians can identify the risk of overuse and abuse (622-630).

Solanki et al (82) also evaluated various tools to assess the risk of substance misuse. They found 52 publications, of which 22 met the criteria to be included in the manuscript. There was only one study which was prospective, and compared various screening tools that were available to monitor opioid adherence. Further, in the majority of the studies, the number treated was small. There was not a single screening tool that could be applied universally to patients who are on opioid therapy for chronic non-cancer pain. Sehgal et al (84) also evaluated multiple screening tools as described above and concluded that the widespread use of prescription opioids in recent decades has been associated with a steady increase in prescription drug abuse and an increase in opioid-related deaths. Multiple approaches to identify and manage at-risk patients have been proposed. Experts recommend combining several different strategies to identify at-risk patients, including examining the underlying origins or implications of aberrant behaviors, and tailoring treatments accordingly. Informed consent forms, treatment agreements, risk documentation tools, and regular monitoring of the 4 A's (analgesia, activities of daily living, adverse side effects, and aberrant drug-related behaviors) will help to educate patients and guide management based on treatment goals. The application of universal precautions and awareness of aberrant behaviors will increase physician confidence in identifying and addressing problematic behaviors. Chronic pain treatments must be multimodal and combined with nonopioid medications. There should also be cognitive, behavioral, and interventional techniques to optimize outcomes, particularly for those who are unable to safely take their opioids in a structured fashion. Opioid formulations designed to deter and resist abuse are being marketed and may address some, but not all, aspects of inappropriate opioid use. The legal and regulatory environment surrounding opioid prescribing is in flux and the Food and Drug Administration (FDA) has adopted new approaches to control the growing problem of prescription opioid misuse and abuse. It is important that providers understand the dynamics surrounding pain management, and keep abreast of advances in opioid analgesia in order to treat pain effectively while minimizing abuse.

At present, screening for opioid abuse includes assessment of premorbid and comorbid substance abuse; assessment of aberrant drug-related behaviors; risk factor stratification; and utilization of opioid assessment screening tools. Various authors have developed multiple opioid assessment screening tools and instruments. In addition, UDT, monitoring of prescribing practices, PMPs, opioid treatment agreements, and utilization of universal precautions are essential. Presently, a combination of strategies is recommended to stratify risk, identify and understand aberrant drug related behaviors, and tailor treatments accordingly.

A critical issue in pain management is the ability of the clinician to identify patients who are most at-risk for developing prescription drug abuse. Several risk factors have been described and include sociodemographic factors, pain and drug-related factors, genetics and environment, psychosocial and family history, psychopathology, and alcohol and substance use disorders (631). However, none of these factors by themselves will increase the risk of drug abuse in a given individual. It is suggested that the risk of prescription drug abuse is greatest when risk factors in 3 categories, (i.e., psychosocial factors, drug related factors, and genetic factors) occur in the same individual. In the absence of psychosocial comorbidities and genetic predisposition, pain patients on stable doses of opioids in a controlled setting are unlikely to abuse opioids or develop addiction. On the other hand, patients with a personal or family history of substance abuse and psychosocial comorbidity are at increased risk, especially if treatment with opioids is not carefully structured and monitored (88). In a study of primary care patients with high levels of pain disability, unemployment, and psychosocial stressors, prescription drug use disorder was concentrated among those with a family history of substance use disorder, those who have spent time in jail, are current cigarette smokers, are male, white, and those with pain-related functional limitations and posttraumatic stress disorder. The vast majority had co-occurring substance use disorder (631).

Although several formal screening instruments that identify aberrant drug-related behaviors in patients on opioid therapy have been described, there is no well-tested, reliable, and easily administered screening tool to detect drug-seeking behaviors in primary care patients taking long-term opioids or being considered for such therapy. Evidence on prediction and identification of aberrant drug-related behaviors is limited; the definitions for aberrant drug-related behaviors are

not standardized across studies and do not account for the seriousness of identified behaviors. In general, the psychometric properties of published questionnaires and interview protocols are weak and, quite unlike other tests and protocols, have not been subjected to stringent scrutiny consistent with the practice of evidence-based medicine (230-235,253,255). Furthermore, most studies that evaluated these instruments are limited by methodological shortcomings (632). In terms of tools for screening patients before initiating chronic opioid therapy, a tool which has been described to have a reasonably high-quality deviation which may be used in conjunction with clinical assessment is the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) (187). It is suggested that opioid assessment screening tools should be used, jointly with other measures, to guide and monitor therapy. Two tools, Pain Assessment and Documentation Tool (PADT) and Current Opioid Misuse Measure (COMM) with strong content, face, and construct validity, are recommended for these purposes (187). PADT is a simple charting device based on the "4 A's" concept and designed to help clinicians consistently document various significant domains over time (633,634).

Chou et al (187) evaluated 9 studies ($n = 1,530$) for the accuracy of screening tools for identifying aberrant drug-related behavior in patients who were on long-term opioid therapy for chronic non-cancer pain. They found that none of the investigators were blinded to the results of the screening instruments. There was a significant variation in the aberrant drug-related behavior across the studies. Only 2 studies out of 9 made evaluations using the Pain Medication Questionnaire. Out of the 8 instruments studied, 2 were self-administered, 4 were interviewer-administered, and in the remaining 2 studies the methodology was not described. Pain scores were recorded in only one study, and none of the studies documented the doses of the opioids used. In one higher quality study, self-administered COMM was used to determine the diagnostic test characteristics of this instrument (635). It showed a sensitivity of 0.75 (95% CI, 0.63-0.84) and specificity of 0.73 (95% CI, 0.65-0.80). In another lower quality study, the interviewer-administered Addiction Behavior Checklist showed a sensitivity of 0.88 and specificity of 0.86 (636). Screening instruments in 4 studies showed limited diagnostic accuracy.

Atluri et al (45) in developing an algorithmic evidence-based approach to the prevention of opioid abuse in chronic non-cancer pain described that useful tools included Screener and Opioid Assessment

for Patients with Pain (SOAPP) (637), Pain Medication Questionnaire (PMQ) (638,639) Prescription Drug Use Questionnaire patient version (PDUQp) (640), Addiction Behaviors Checklist (ABC) (636), Diagnosis, Intractability, Risk, Efficacy (DIRE) Score (641), and an instrument by Atluri and Sudarshan (651). They concluded that the screening tool Current Opioid Misuse Measures (COMM) (635) and SOAPP (642) were not considered because many of the questions were not related to abuse diversion and fell under the category of psychological queries. In addition, they also stated that the PADT (633) is not a screening tool as it addresses the level of analgesia, adverse events, and the activities of daily living, along with the aberrant drug-related behavior. They also noted that the section of abuse is a small component of the whole tool in PADT. They felt that the screening tool by Michna et al (643) addressed only 3 items, and was not comprehensive enough to identify abuse. Another tool commonly recommended is the Opioid Risk Tool (ORT) (644) is a 5-item tool, which was felt to be not comprehensive by Atluri et al (45). Further, they also stated that the items in this tool were not predictors of abuse. Additionally, they described that PDUQ and PDUQp tools were developed by the same group, with modification of PDUQp from PDUQ (639,640). In addition, all the questions are related to abuse, and questions related to psychopathology were eliminated. Among the multiple tools selected, the first 3 tools were considered as subjective (PMQ, PDUQp) (638-640) and the last 3 were considered as objective tools (DIRE score, ABC checklist, and the tool by Atluri and Sudarshan) (636,641,645). Atluri et al described that even though there has been a call for the use of these subjective tools (172,275,646,647), abusers tend not to be truthful in subjective questionnaires (648-652). Consequently, they concluded that the screening tool developed by Wu et al (636), the DIRE Score (641), and the screening tool created by Atluri and Sudarshan (653) may have more value since they incorporate objective measures. They felt that these tools can be used singularly or in combination. They also described that generic screening tools for drug and alcohol abuse are not as useful as those specifically designed for prescription opioid abuse. However, the tool developed by Atluri and Sudarshan (645) to detect the risk of inappropriate use of prescription opioids in chronic pain patients utilizing 6 clinical criteria was evaluated in 2 prospective evaluations (653,654) utilizing 500 patients. The results of these studies showed that it was a reliable tool for screening for the potential for drug abuse

in an interventional pain management setting. Atluri and Sudarshan's tool (645) while it predicted substance abuse, it did not identify illicit drug use.

The White House in April 2011 announced a plan to curb prescription drug abuse called "Epidemic: Responding to America's Prescription Drug Abuse Crises" (655). The key elements of the plan are expansion of state-based PMDPs, recommending convenient and environmentally responsible ways to remove unused medications from homes, supporting education for patients and health care providers, and reducing the number of "pill mills" and doctor-shopping through law enforcement. In concert with the White House plan, the U.S. FDA announced a new risk reduction program, called Risk Evaluation and Mitigation Strategies (REMS), for all ER and long-acting opioid analgesics (646). The new REMS concentrates on educating physicians about proper pain management, patient selection, other requirements, and improving patient awareness regarding the safe use of opioid analgesics (646). As part of the plan, the FDA directed manufacturers of certain ER opioids and methadone to give patients educational materials, including a medication guide that uses consumer friendly language to explain safe use and disposal. Physician training, patient counseling, and other risk reduction measures developed by opioid manufacturers as part of the REMS are expected to become effective in 2012. They will be required for the various brand names of generic opioids: oxycodone, morphine, hydromorphone, oxymorphone, methadone, transdermal fentanyl, and transdermal buprenorphine. At this time physician training is not mandatory under the REMS plan. Other federal agencies are working to get Congress to link mandatory opioid physician training to the already required Drug Enforcement Administration (DEA) registration number needed to prescribe controlled substances. The FDA will also require risk management to include a way to determine if the education programs are helping to reduce problems associated with long-acting and ER opioids, while allowing patients who need opioids to get them (656).

3.9.2 Conclusions

1. There is limited evidence for reliability and accuracy of available instruments in screening for opioid abuse or illicit drug use due to lack of high quality studies.
2. There is limited evidence that screening for opioid abuse by any of the instruments will reduce the abuse, with lack of long-term published quality

literature.

3. There is good evidence that PMPs provide data on patterns of prescription usage.
4. There is fair evidence that prescription drug monitoring programs may reduce prescription drug abuse or doctor shopping.
5. There is limited evidence that prescription drug monitoring programs reduce emergency room visits, drug overdoses, or deaths, due to lack of high quality literature.

3.10 Urine Drug Testing

The role of UDT has been described by multiple authors (45,82,87,152,224,618,631,654,657-659). Consequently, as part of compliance monitoring, UDT is crucial in managing opioid therapy.

Screening for opioid misuse and abuse is an exercise to strengthen the patient-physician relationship. This should not be confrontational and the patient has to understand that this is like any other laboratory test. Thus, a physician would respond to adherence monitoring or screening for opioid abuse similar to how one would respond to an abnormal liver function test or anemia.

While routine UDT has become standard in the addiction treatment setting, it has not been universal in chronic pain management centers or with internists or family practitioners that treat a smaller number of chronic pain patients. In fact, in a systematic review of treatment agreements and UDT to reduce opioid misuse in patients with chronic pain (209), the evidence was relatively weak in supporting the effectiveness of opioid treatment agreements and UDT in reducing opioid misuse by patients with chronic pain. It was concluded that family medicine physicians who order UDT to monitor their patients on chronic opioid therapy are not proficient in their interpretation (660). Another study evaluating drug testing of adolescents in ambulatory medicine (661) concluded that primary care physicians do not always use proper urine sample collection and validation procedures, and they are not aware of the important limitations of drug testing. In a survey conducted in 2008 by the Biomedical Research and Education Foundation, based on a questionnaire distributed to 99 attendees (655), it was concluded that most urine testing was motivated more by a desire to detect undisclosed substances than to evaluate appropriate opioid use. However, some responders never urine-tested their opioid patients, and about two-thirds of the respon-

dents had no formal training in urine testing of patients on opioid therapy (662).

3.10.1 Limitations of Application of Urine Drug Testing

Nafziger and Bertino (663) described various scientific principles of pain medicine pharmacology that affect UDT findings and are important to consider. These include sources of variability in pharmacokinetics, pharmacodynamics (pharmacologic effects), pharmacogenetics (the effect of genetics and the environment on pharmacokinetics and pharmacodynamics), and also issues relating to the collection, handling, and assay methodologies for urine. In addition, it is essential to avoid adulteration and subversion of UDT, and to ensure validity. As important a tool as UDT is in the treatment of chronic pain, it nevertheless remains only one of many tools.

Multiple variables affecting the results of urine testing include cutoff selection; pharmacokinetics, pharmacodynamics, and pharmacogenetics; laboratory technology used in the urine drug test; and subversion and adulteration of the urine specimen.

3.10.2 Diagnostic Accuracy of Urine Drug Testing

Diagnostic accuracy evaluations comparing immunoassay testing with chromatography have not been frequently performed in a prospective manner; however, there are multiple reports with retrospective evaluations. Manchikanti et al (304) prospectively studied the diagnostic accuracy of point of care (POC) testing with immunoassay, comparing it with laboratory testing with chromatography in 1,000 patients. Compared with laboratory testing for opioids and illicit drugs, immunoassay in-office testing at high specificity and agreement, but variable sensitivity, demonstrates the value of immunoassay drug testing, but a cautious approach is advocated. Agreement for prescribed opioids was high with the index test (80.4%). The reference test of opioids improved the accuracy by 8.9% from 80.4% to 89.3%. Overall, results showed a necessity for 32.9% of the specimens to be sent for a reference test confirmation due to either abnormal opioid or illicit drug results. The abnormal specimens of patients receiving opioids improved the accuracy by 8.9% from 80.4% to 89.3%; for illicit drugs, the index test false-positive rate was 0% for cocaine, whereas it was 2% for marijuana, 0.9% for amphetamines, and 1.2% for methamphetamines. There was only a slight improvement in the accuracy data with laboratory intervention utilizing chromatography.

Manchikanti et al (305) showed that approximately 36% of specimens required confirmation. The index test's efficiency for prescribed benzodiazepines was 78.4%. Reference testing improved accuracy to 83.2%, a 19.6% increase, and 8.9% of participants were found to be taking non-prescribed benzodiazepines. The index test's false-positive rate for benzodiazepines use was 10.5% in patients receiving benzodiazepines. They concluded that clinicians should feel comfortable conducting in-office UDT immunoassay testing. The present study shows that it is reliable, expedient, and fiscally sound for all involved. In-office immunoassay testing compares favorably with laboratory testing for benzodiazepines, offering both high specificity and agreement. However, clinicians should be vigilant and wary when interpreting results, weighing all factors involved in their decision.

3.10.3 Practical Aspects

In clinical settings, UDT is utilized for compliance, as well as forensic testing to monitor therapeutic activity, misuse, and illegal drug use (279,303,307,654,664-670). Consequently, the initial and confirmatory testing levels, as well as the number of drugs tested, can be customized and are usually different from those evaluated under federal testing programs. Drug screening can be an important tool to ensure patient compliance with prescription regimens.

Drug screening or testing can be effectively performed in the physician's office using POC urine (dipstick immunoassay) testing. However, practitioners using POC testing need to be aware of whether the system used is compliant with methods and assurances established by the Clinical Laboratory Improvement Advisory Committee (CLIAC). A Clinical Laboratory Improvement Amendments (CLIA) waiver is required to perform certain tests including urine immunoassay. Only immunoassay tests for certain drugs are CLIA waived, and these may be performed in the office only if and when a certificate of waiver is first obtained by the physician or facility. Generally these tests do not require extensive training for office personnel.

UDT has become the standard of care for patients on controlled substances; however, the relative value of in-office screening and laboratory confirmation of those tests is sometimes unclear or controversial for physicians. The POC manufacturers recommend that their test needs to be confirmed; however, advantages and cost benefits have not been independently evaluated and confirmed.

Of particular concern to clinicians in this context of UDT is that the cost of UDT in the office, followed by a confirmatory test, can be expensive, with costs ranging from \$250 to \$1,400 (280,303,307,671-675). The Centers for Medicare and Medicaid Services (CMS) have changed codes for UDT from the old code (80101) used by pain physicians to a new code (G0431) effective January 10, 2010 (673). This action has been taken by CMS due to excessive use of UDT and abuse (280,303,307,671-675). While the earlier code included chromatographic methods and its descriptions, the new G-code descriptor states, "drug screen, qualitative; single drug class method (e.g., immunoassay, enzyme assay), each drug class" and excluded chromatography (674).

Collen (675) described that clinicians often require patients to sign a controlled substance agreement in order to receive opioid therapy (676). The majority of agreements contain a stipulation requiring patients to consent to random or unscheduled drug screens (677,678) that search for licit and illicit drugs. Due to the lack of efficacy of UDT in preventing adverse consequences, profit motive has been described as a driver for physician drug-screening behavior. Medicare data reveals that between the years 2000 and 2009, the total number of drug screens under Current Procedural Terminology (CPT) code 80101, including both CLIA-waived and non-waived tests, reimbursed by Medicare Part B increased approximately 4,537%, with geometric average growth rate 53%, with 186,629 tests (102 waived, 186,527 non-waived) in 2000 and 8,653,743 tests (3,820,793 waived, 4,832,950 non-waived) in 2009. In contrast to the UDT, Medicare category of pathology and laboratory services increased approximately 48% (679), while the Medicare population increased approximately 16% (680). Further, Collen (677) describes that a deeper examination finds that between 2000 and 2009, the total number of CLIA-waived drug tests (CPT Code 80101QW) paid for by Medicare conducted in physicians' offices increased approximately 3,172,910% with geometric average growth rate 216% (681). However, the base year, which was 2000, had only 101 tests performed, skewing the results. In 2009, the top 4 medical specialties that conducted the greatest number of drug screens were anesthesiology, family practice, internal medicine, and neurology, respectively. Among these, medical oncology did not conduct any tests at all, whereas addiction medicine conducted in 2009 only 10,126, in contrast to anesthesiology or pain medicine of 636,880. Other issues also include physician kickbacks (682,683) and increased regulations and enforcement.

3.10.4 Conclusions

1. There is fair evidence for the diagnostic accuracy of UDT.
2. There is fair evidence to identify patients who are non-compliant or abusing prescription drugs or illicit drugs.
3. There is fair evidence that UDT may decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy.

4.0 SUMMARY

Assessment of the evidence in providing opioid guidelines focused on various means to curtail abuse of controlled substances without jeopardizing pain management. This evidence synthesis provides evidence for various issues related to misuse, abuse, and diversion (44,684,685).

4.1. The Extent of Opioid Abuse

1. There is good evidence that non-medical use of opioids is extensive.
2. There is good evidence that approximately one-third of the chronic pain patients may not use prescribed opioids as prescribed or abuse them.
3. There is good evidence that illicit drug use in chronic pain patients is significantly higher than in the general population and such use is high in patients receiving opioids and higher in those abusing opioids.

4.2 Prescribing Patterns

1. There is good evidence that opioid prescriptions are increasing rapidly.
2. There is good evidence that the majority of prescriptions are from non-pain physicians.
3. There is good evidence that many patients are on long-term opioids.
4. There is good evidence that many patients are provided with combinations of long-term and short-term opioids.

4.3 Relationship of Therapeutic Opioid Use and Adverse Consequences

1. There is good evidence that the increased supply of opioids, use of high dose opioids, doctor shoppers, and patients with multiple comorbid factors contribute to the majority of the fatalities.
2. There is good evidence that approximately 60% of the fatalities originate from the opioids prescribed within the guidelines.

4. There is good evidence that approximately 40% of the fatalities occur in 10% of the drug abusers.
5. There is fair evidence that long-acting opioids and combination of long-acting and short-acting opioids contribute to increasing fatalities.
6. There is fair evidence that even low doses of 40 mg or 50 mg daily of morphine equivalent doses are responsible for emergency room admissions with overdoses and deaths.

4.4 Effectiveness of Opioids

1. The short-term effectiveness of opioids is fair.
2. The long-term effectiveness of opioids is limited due to lack of long-term (> 3 months) high quality studies.
3. There is fair evidence with no significant difference in effectiveness or adverse effects between long-acting and short-acting opioids.
4. There is limited published evidence for opioid rotation due to lack of quality publications.
5. The evidence for improvement in QOL parameters is fair for short-term and limited for long-term due to only short-term studies and lack of quality literature with long-term follow-up.

4.5 Evidence of Effectiveness of Individual Drugs

1. The evidence for hydrocodone is limited due to lack of quality studies.
2. The evidence for oxycodone is fair for short-term and limited for long-term due to lack of long-term or quality studies.
3. The evidence for morphine is fair for short-term and limited for long-term due to lack of long-term or quality studies.
4. The evidence for tramadol is fair in osteoarthritis.
5. The evidence for methadone is limited due to lack of quality studies.
6. The evidence for transdermal fentanyl is fair for short-term and limited for long-term due to short-term studies and lack of high quality studies.
7. The evidence for oxycodone is limited due to lack of quality studies.
8. The evidence for hydromorphone is limited due to lack of quality studies.
9. The evidence for tapentadol is limited due to lack of quality studies.
10. The evidence for codeine is limited due to lack of quality studies.

11. The evidence for buprenorphine is limited due to lack of long-term or high quality studies.

4.6 Effectiveness of Opioid Therapy in Specific Populations

1. The evidence of effectiveness and safety of chronic opioid therapy in the elderly for chronic non-cancer pain is fair for short-term and limited for long-term due to lack of high quality studies.
2. The evidence of effectiveness and safety in children and adolescents is limited due to lack of quality studies.
3. The evidence of effectiveness and safety in pregnancy is poor; however, the evidence is good with regards to adverse effects.
4. Effectiveness and safety in patients with generalized anxiety disorder and depression is limited due to lack of high quality studies with fair evidence of increased risk of opioids in this group of patients.
5. The evidence of prevalence of high use of opioids in depression is fair.
6. The evidence of effectiveness and safety in high-risk psychological disorder patients with personality disorders and addiction disorders is limited due to lack of high quality studies, with good evidence of increased risk and adverse effects.

4.7 Adverse Effects and the Safety of Opioid Therapy

1. There is good evidence that the majority of the side effects of opioid therapy may be minor and are resolved, but some effects are long-lasting and increase with long-term use.
2. There is fair evidence that complications of long-term therapy or long-acting opioids are frequent.
3. There is fair evidence that serious complications are rare, but fatal when occur.
4. There is limited evidence to recommend a routine monitoring of asymptomatic patients on chronic opioid therapy for chronic non-cancer pain for hormonal deficiencies, due to only preliminary evidence and lack of high quality long-term follow-up.
5. There is fair evidence to reduce the dosages or wean patients off of opioids and also to start hormonal supplemental therapy when hormonal deficiencies are identified.
6. There is fair evidence that somnolence and drowsiness may be associated with chronic opioid therapy.
7. There is fair evidence that central sleep apnea may be exacerbated with chronic opioid therapy.

4.8 The Role of Opioid Hyperalgesia and Breakthrough Pain

1. The evidence is limited for existence and management of breakthrough pain in non-cancer pain, due to lack of quality studies.
2. The evidence is fair for existence of opioid hyperalgesia with chronic opioid therapy.

4.9 Screening for Opioid Abuse

1. There is limited evidence for reliability and accuracy of available instruments in screening for opioid abuse or illicit drug use due to lack of high quality studies.
2. There is limited evidence that screening for opioid abuse by any of the instruments will reduce the abuse, with lack of long-term published quality literature.
3. There is good evidence that PMPs provide data on patterns of prescription usage.
4. There is fair evidence that prescription drug monitoring programs can reduce prescription drug abuse or doctor shopping.
5. There is limited evidence that prescription drug monitoring programs reduce emergency room visits, drug overdoses, or deaths, due to lack of high quality literature.

4.10 Urine Drug Testing

1. There is fair evidence for the diagnostic accuracy of UDT.
2. There is fair evidence to identify patients who are non-compliant or abusing prescription drugs or illicit drugs.
3. There is fair evidence that UDT may decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy.

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Author withdrawals: The first author of the 2008 opioid guidelines, Andrea Trescot, MD, who has not participated initially, has withdrawn her name due to time constraints. A second author, Xiulu Ruan, MD, who participated sporadically, withdrew his name due to time constraints and lack of appropriate involvement.

Conflicts of Interest:

Ten of the 55 authors provided information that they received funding from the industry; however, of these, only 2 (less than 4%) were receiving funding from drug makers and with multidisciplinary authorships (18%) receiving funding for research or engaged in speaking from the industry.

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