ASIPP - Opioid Guidelines 2012

American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part 2 - Guidance

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Results:

Part 2 of the guidelines on responsible opioid prescribing provides the following recommendations for initiating and maintaining chronic opioid therapy of 90 days or longer.

1. A) Comprehensive assessment and documentation is recommended before initiating opioid therapy, including documentation of comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history. (Evidence: good)
   B) Despite limited evidence for reliability and accuracy, screening for opioid use is recommended, as it will identify opioid abusers and reduce opioid abuse. (Evidence: limited)
   C) Prescription monitoring programs must be implemented, as they provide data on patterns of prescription usage, reduce prescription drug abuse or doctor shopping. (Evidence: good to fair)
   D) Urine drug testing (UDT) must be implemented from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy. (Evidence: good)
2. A) Establish appropriate physical diagnosis and psychological diagnosis if available prior to initiating opioid therapy. (Evidence: good)
   B) Caution must be exercised in ordering various imaging and other evaluations, interpretation and communication with the patient; to avoid increased fear, activity restriction, requests for increased opioids, and maladaptive behaviors. (Evidence: good)
   C) Stratify patients into one of the 3 risk categories – low, medium, or high risk.
   D) A pain management consultation, may assist non-pain physicians, if high-dose opioid therapy is utilized. (Evidence: fair)
3. Essential to establish medical necessity prior to initiation or maintenance of opioid therapy. (Evidence: good)
4. Establish treatment goals of opioid therapy with regard to pain relief and improvement in function. (Evidence: good)
5. A) Long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain that is not amenable to short-acting or moderate doses of long-acting opioids, as there is no significant difference between long-acting and short-acting opioids for their effectiveness or adverse effects. (Evidence: fair)
   B) The relative and absolute contraindications to opioid use in chronic non-cancer pain must be evaluated including respiratory instability, acute psychiatric instability, uncontrolled suicide risk, active or history of alcohol or substance abuse, confirmed allergy to opioid agents,

coadministration of drugs capable of inducing life-limiting drug interaction, concomitant use of benzodiazepines, active diversion of controlled substances, and concomitant use of heavy doses of central nervous system depressants. (Evidence: fair to limited)

6. A robust agreement which is followed by all parties is essential in initiating and maintaining opioid therapy as such agreements reduce overuse, misuse, abuse, and diversion. (Evidence: fair)
7. A) Once medical necessity is established, opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid side effects. (Evidence: fair for short-term effectiveness, limited for long-term effectiveness)
   B) Up to 40 mg of morphine equivalent is considered as low dose, 41 to 90 mg of morphine equivalent as a moderate dose, and greater than 91 mg of morphine equivalence as high dose. (Evidence: fair)
   C) In reference to long-acting opioids, titration must be carried out with caution and overdose and misuse must be avoided. (Evidence: good)
8. A) Methadone is recommended for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. (Evidence: limited)
   B) Monitoring recommendation for methadone prescription is that an electrocardiogram should be obtained prior to initiation, at 30 days and yearly thereafter. (Evidence: fair)
9. In order to reduce prescription drug abuse and doctor shopping, adherence monitoring by UDT and PMDPs provide evidence that is essential to the identification of those patients who are non-compliant or abusing prescription drugs or illicit drugs. (Evidence: fair)
10. Constipation must be closely monitored and a bowel regimen be initiated as soon as deemed necessary. (Evidence: good)
11. Chronic opioid therapy may be continued, with continuous adherence monitoring, in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse effects. (Evidence: fair)

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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Evidence-based clinical practice guidelines for responsible opioid prescribing in non-cancer pain are statements developed to improve the quality of care, patient access, treatment outcomes, appropriateness of care, deficiency and effectiveness, and achieve cost containment by improving the cost-benefit ratio. The objectives of these guidelines are to provide clear and concise guidelines to physicians to improve patient access and to avoid diversion and abuse. Part 1 of these guidelines describes evidence assessment (1), whereas Part 2 of these guidelines - the present manuscript, describes guidance for responsible opioid prescribing.

The global epidemic of chronic pain with its related disability and opioid use and its related fatalities, are the predominant issues of concern in modern medicine, specifically in the United States (2-40). The escalating use of therapeutic opioids in the United States is correlated to an increase in the supply of opioids, from 96 mg of morphine equivalence per person in the United States in 1997 to 710 mg per person in 2010 (34,41). This is equivalent to 7.1 kg of opioid medication per 10,000 population or enough to supply every adult American with 5 mg of hydrocodone every 6 hours for 45 days. Sales have increased 280% for hydrocodone, 1,293% for methadone, and 866% for oxycodone from 1997 to 2007 (31), with the estimated number of prescriptions filled for opioids exceeding 256 million in the United States in 2009 (42-44). From 2006 to 2011, hydrocodone was the number one prescription in the United States (45). In 2007, based on a study by the International Narcotics Control Board (46), American's, constituting 4.6% of the global population, accounted for over 99% of the global consumption of hydrocodone and 83% of the global consumption of oxycodone,.

The explosive use of therapeutic opioids, however, is accompanied by increasing fatalities and adverse consequences, and a lack of evidence regarding long-term effectiveness and safety in the treatment of chronic non-cancer pain (46-115). Even the Institute of Medicine (IOM) report, considered a blueprint for transforming prevention, care, education, and research on

chronic pain recognizes the serious problem of diversion and abuse of opioid drugs and has questions about their long-term usefulness, all the while maintaining that effective pain management is a moral imperative, a professional responsibility, and the duty of the people in the healing professions (4,47). 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, opioid prescriptions have seen dramatic increases for non-cancer pain over the past 2 decades (116). In addition, the introduction of new pain management standards for inpatient and outpatient medical care implemented by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in 2000 (117), multiple physicians and advocacy organizations promoting increased use of opioids in the treatment of chronic non-cancer pain, the introduction of long-acting opioids with aggressive marketing by the pharmaceutical industry, and a growing awareness of right to pain relief, empowered by JCAHO standards, have fueled the explosion in opioid use, at least in the United Sates (118-121). It has been alleged, however, that these positions are largely based on poor science and misinformation in relation to the safety and effectiveness of opioids when prescribed by a physician and taken appropriately (51,60,62-65,118-132).

Opioid use for non-therapeutic purposes and also for chronic pain has increased over the years (63,66-68,70,76-79,85,106,127-176). It has been shown that 90% of patients present to pain management settings with prior opioid therapy, with a similar number of patients on opioids in treatment (159-174). Further, Deyo et al (30) illustrated that approximately 61% of patients with low back pain in primary care settings were on a course of opioids and that of these, 19% were long-term users. Multiple surveys have illustrated that the majority of prescriptions are from primary specialties, followed by surgical specialties rather than pain physicians (42-45). As shown in Figure 1, 42% of immediate release opioids and 44% of long-acting opioids were prescribed by primary care physicians, whereas specialties identified as pain management, including anesthesiology and PMR, contributed to 6% of immediate release opioids and 23% of long-acting opioids (42-45).

Multiple guidelines have been published with advice for long-term opioid therapy in chronic non-cancer pain. Stein et al (59) assessed recently published guidelines, which included the guidelines by the American Pain Society (APS)-American Academy of Pain Medicine (AAPM) guidelines (50), British Pain Society's guidelines (52), Canadian National Opioid Use Guideline Group (NOUGG) (54), German guidelines (49), and guidelines

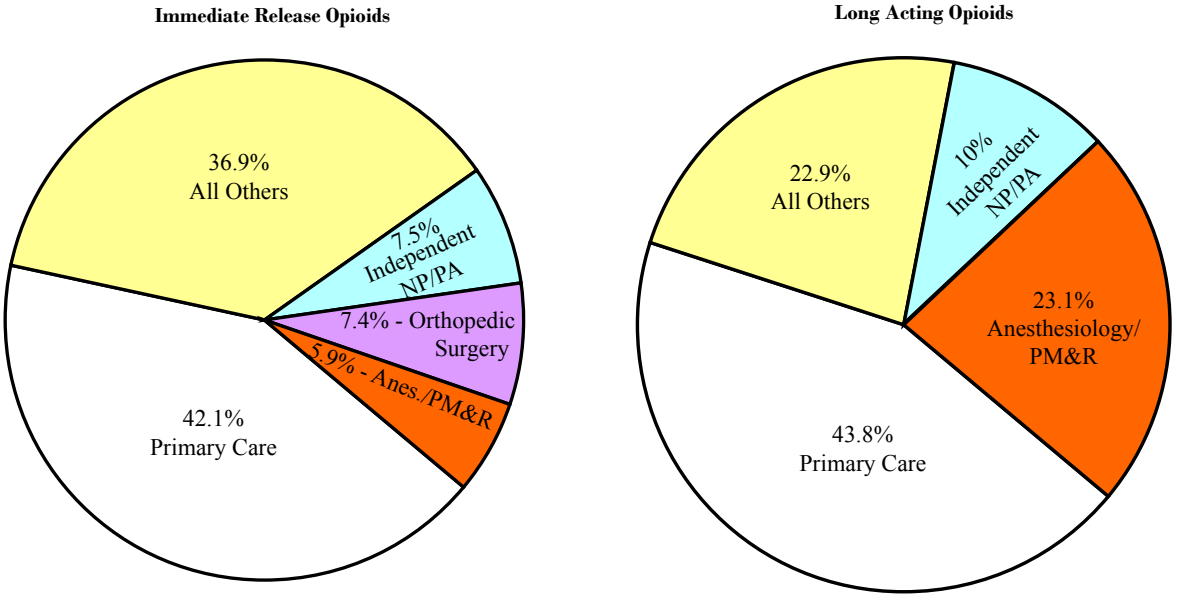


Fig. 1. *Total number of prescriptions dispensed in the U.S. by various specialties for IR and ER/LA opioids in 2009*

by the American Society of Interventional Pain Physicians (55). It should be noted that this document serves, in part, to update the American Society of Interventional Pain Physicians' guidelines. Sorgatz and Maier (57) summarized that the 5 guidelines impact assessment of opioids in chronic non-cancer pain only in diction. They stated the following:

- APS-AAPM: "Although evidence is limited, an expert panel (...) concludes that chronic opioid therapy can be an effective therapy for carefully selected and monitored patients with chronic non-cancer pain. However, opioids are also associated with potentially serious harms (...) "(50).
- The British Pain Society guidelines state "There is evidence from clinical trials that opioids can be effective in the short and medium term (...) However, the safety and efficacy of opioids in the long-term is uncertain (...)" (52).
- The guidelines by American Society of Interventional Pain Physicians state: "Opioids are commonly prescribed for chronic non-cancer pain and may be effective for short-term pain relief. However, long-term effectiveness of 6 months or longer is variable ..." (55).
- The Canadian guidelines National Opioid Use Guideline Group (NOUGG) state that "opioids showed only small to moderate benefits for nociceptive (...) neuropathic (...) improving function and relieving pain" (58).

In APS-AAPM guidelines for the use of chronic opioid therapy in chronic non-cancer pain (50,51), despite scant evidence, the expert panel concluded that chronic opioid therapy could be effective therapy for carefully selected and monitored patients with chronic non-cancer pain. They provided recommendations and guidance on patient selection and risk stratification; informed consent and opioid management plans, initiation and titration of chronic opioid therapy, use of methadone, monitoring of patients on chronic opioid therapy, dose escalations, high-dose therapy, opioid rotation, and indications for discontinuation of therapy, prevention and management of opioid-related adverse effects, driving and work safety, identifying a medical home and when to obtain consultation, management of breakthrough pain, chronic opioid therapy in pregnancy and opioid-related policies.

Canadian Guidelines (54) for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain have analyzed the evidence and have provided recommendations with 5 clusters. Cluster 1 dealt with deciding to initiate opioid therapy with comprehensive assessment, addiction-risk screening, urine drug screening, opioid efficacy, risks, adverse effects, complications, and benzodiazepine tapering. Cluster 2 dealt with conducting an opioid trial with titration and driving, stepped opioid selection, optimal dose, watchful dose, and opioid misuse. Cluster 3 described monitoring of long-term opioid therapy with monitoring, switching or discontinuing opioids, impact on driving, revisiting opioid trial steps, and collaborative care. Cluster 4 described treating specific populations with long-term opioid therapy including the elderly, adolescents, pregnant patients, and patients suffering with comorbid psychiatric conditions. Finally, Cluster 5 described managing opioid misuse and addiction with addiction treatment options, prescription fraud, unacceptable patient behavior, and acute care opioid prescribing policies.

The British Pain Society's Opioids for Persistent Pain (52) described the pharmacology of opioids, necessity to prescribe opioids, adverse effects of opioid therapy, practical aspects of prescribing, non-medical prescriptions of opioids, and opioids and problem drug use.

Hughes et al (177) also performed a systematic review of treatment guidelines, published in 2011. They included 6 clinical guidelines meeting inclusion criteria with one duplicate (50,54,55,58,178-180).Three of the guidelines, including Canadian guidelines and APS-AAPM guidelines were included by Stein et al (59), whereas 3 other guidelines were not included by Stein et al (178-180). Hughes et al (177) concluded that since evidence supporting efficacy for the use of opioids as treatment for chronic non-cancer pain was limited, opioids for chronic non-cancer pain should be reserved for select patients with moderate or severe pain that significantly affects function or quality of life. They also concluded that continuation of opioid therapy is indicated if documentation supports the opioid results in improvement in those limitations. Furthermore, their recommendations included a comprehensive pre-treatment assessment, identification of contraindications, obtaining informed consent, establishing a written treatment plan with goals and objectives, using an opioid treatment agreement, obtaining specialist referral when indicated, and establishing a follow-up plan that includes monitoring for adverse effects, titration and rotation of medication, prescription use monitoring, use of drug screening, and thorough record keeping which includes documentation of functional improvement.

However, the Interagency Guideline on Opioid

Dosing for Chronic Non-Cancer Pain (53), also provided guidance sponsored by the Washington State Agency Medical Directors Group (AMDG). This guideline is provided in 2 parts: Part 1 included guidance for initiation, transition, and maintenance of oral opioids for chronic non-cancer pain, and Part 2 describes guidance for optimizing treatment and when opioid doses are greater than 120 mg morphine equivalence per day.

Thus, in order to curtail opioid abuse but at the same time provide appropriate treatment for pain patients, the focus must be on misuse, abuse, and diversion, and should be addressed in 4 fronts: education, establishing medical necessity, supply, and drugs. These guidelines have been prepared with these aspects as the primary focus and with consideration of up-to-date literature, with special attention being given to the effectiveness of opioids in long-term therapy in conjunction with adverse consequences. Chronic opioid therapy has been defined as daily or near-daily use of opioids for at least 90 days, often indefinitely (50).

In fact, Franklin et al (181) showed that this guidance is effective in bending prescription opioid dosing and reducing mortality. In this study, Franklin et al (181) showed a substantial decline in both the morphine equivalent dose per day of long-acting Schedule II opioids by 27% and the proportion of workers on doses equal to or greater than 120 mg per day of morphine equivalent dosage by 35%, compared prior to 2007. Further, there was also a 50% decrease from 2009 to 2010 in the number of deaths.

Opioid prescribing may be different for different specialities and settings based on the speciality and training. Consequently, additional modalities may be utilized instead of high dose opioid therapy, leading to low or moderate dose opioid therapy and avoiding multiple complications (182). These include various techniques of rehabilitation with therapeutic exercise programs, physical therapy, occupational therapy; cognitive behavioral therapy with psychological interventions, surgical interventions, or interventional techniques.

In interventional pain management, patients may receive not only opioid analgesics, but also other controlled or non-controlled drugs, to manage comorbid psychiatric and psychological disorders. Consequently, the effectiveness studies of opioids published thus far may not apply in the majority of interventional pain management patients. Indeed, in an interventional pain practice, controlled substances may be prescribed at lower doses, particularly opioid analgesics, in conjunction with interventional techniques (182). It has also been shown that interventional techniques may reduce psychological distress and improve functional status (183-201). More likely than not, the requirement for opioids and adjuvant drugs may be reduced or at least become stable. Hence, interventional pain physicians probably should not compare patients in their settings undergoing interventional techniques with others receiving drug therapy as mainstay treatment. Monotherapy, particularly with opioids, may be appropriate for only a small subgroup of those with chronic pain. Additionally, in interventional pain management, the majority of the patients are presented on opioid therapy and it is well understood that once patients are on opioids, they will not be weaned off of them regardless of reported improvements in pain relief and functional status.

The concept of "universal precautions," first seen in medicine with the explosion of HIV and hepatitis tainted blood, was introduced to counter the misconception that a provider would be able to predict "by looking" who might have a communicable blood-borne disease. This led to the use of "precautions" (gloves, etc.) for all patients, regardless of their age or socioeconomic class. A rational approach to the treatment of chronic pain with opioids has been described using a pain and addiction continuum and a substance use assessment in a pain patient leading to the implementation of "universal precautions" in pain medicine (202).

The current guidelines manuscript focuses on responsible chronic opioid therapy, chronic opioid prescribing of 90 days or longer in chronic non-cancer pain, 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. The objectives of these guidelines are to provide clear and concise guidelines to physicians, to improve patient access and to avoid diversion and abuse. Consequently, these guidelines are developed to be used by physicians practicing interventional pain management/pain medicine or other specialists involved in chronic opioid therapy. Thus, the focus of these guidelines and also for physicians dealing with chronic opioid therapy should be to curtail the abuse of opioids without jeopardizing non-cancer pain management. These guidelines only recommend proper use and do not recommend total elimination of opioids in managing chronic pain. Various principles of opioid use with appropriate evidence-based recommendations are illustrated in Figure 2 showing guid-

ance to opioid therapy. Since evidence supporting the efficacy for use of opioids as treatment of chronic non-cancer pain is limited and based on short-term studies, long-term opioid therapy for chronic non-cancer pain should be reserved for select patients with moderate or severe pain that significantly affects function or quality of life. In addition, continuation of opioid therapy is indicated if documentation supports the opioid results in

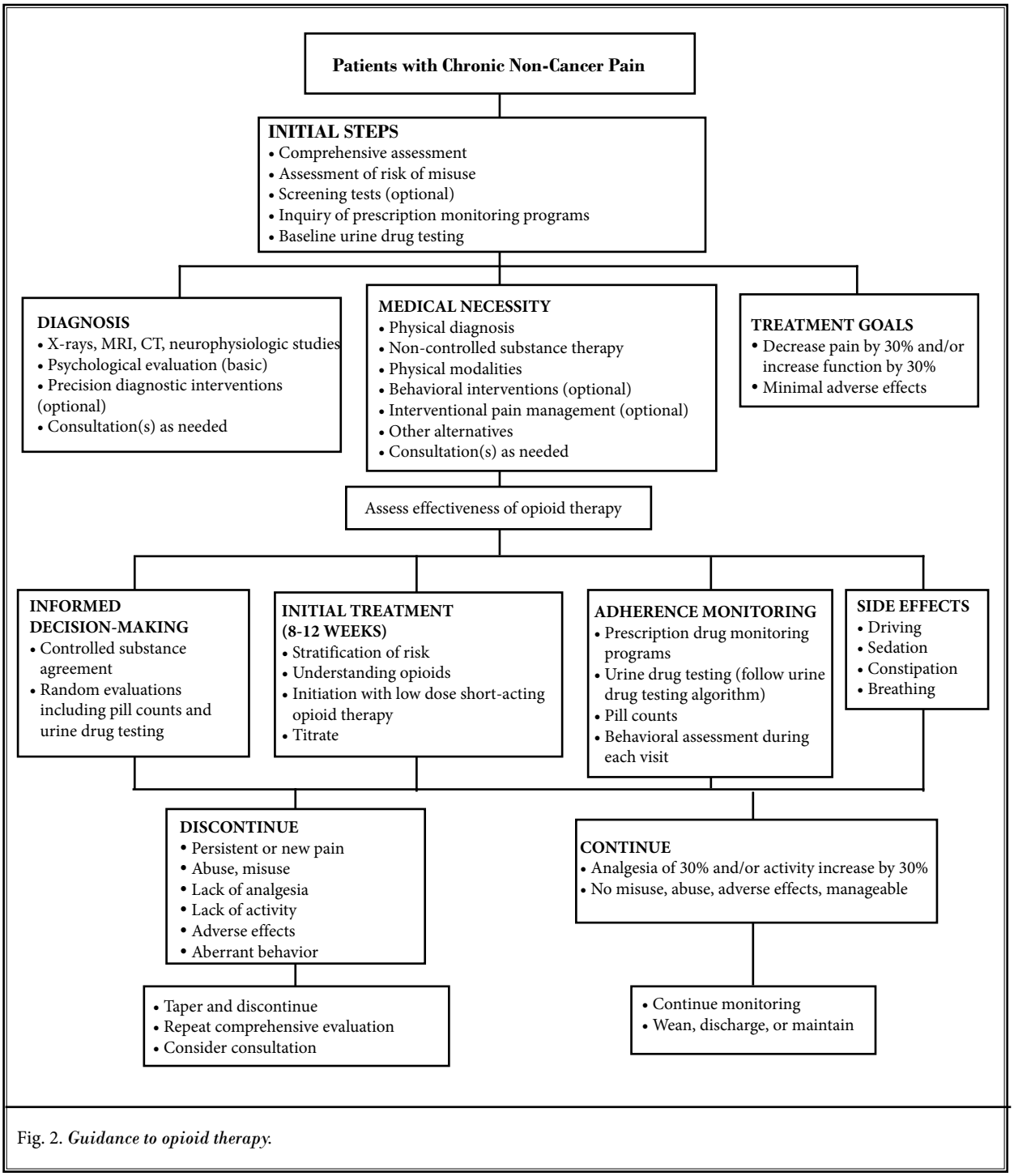


Fig. 2. *Guidance to opioid therapy.*

improvement in pain and function. If opioid therapy is indicated, for initiation or continuation, recommendations in this document may be followed.

1.0 Initial Steps of Opioid Therapy

Before the initiation of opioid therapy it is essential that comprehensive assessment and documentation of the patient's physical condition, general medical condition, psychological history, psychiatric status, substance use and abuse history of the patient and family be obtained (50,52,53,55,58,177-180).

1.1 Comprehensive Assessment

1.1.1 Pain Condition

A thorough history and physical examination must be documented to determine the type, cause, and nature of the pain, including questions about past investigations and interventions for pain. This history also should include medication trials and the pain intensity and the functional impairment that arises from it (i.e., impact of pain on activities of daily living, work, and other aspects of life). In addition, various circumstances which increase or exacerbate the pain and conditions which lead to diminution of pain must be documented (203-206). A physical diagnosis must be established prior to initiating opioid therapy. The diagnosis should not be non-specific such as low back pain, knee pain etc., but should be objective and somewhat specific based on the type of pain and abnormalities identified. This will assist in future treatments based on whether the pain is nociceptive, neuropathic, somatic, radicular, widespread, or localized.

1.1.2 General Medical History

General medical history includes questions about general physical health, emotional health, and medication usage (203-206). Chronic pain patients tend to have multiple medical comorbid conditions which may increase the pain levels or may interact with multiple other drugs.

1.1.3 Psychosocial History

Psychosocial history includes information regarding their upbringing, family and social support, family obligations, work status, use of alcohol, smoking, and living arrangements.

1.1.4 Functional Status

A history of the functional status of a patient includes information about their ability to perform activities of daily living, work, play, and socialization. Assessment may be performed utilizing the Oswestry Disability Index, Neck Disability Index, or another measure.

1.1.5 Sleep Patterns

Sleeping is an important function, specifically in patients with generalized pain problems such as fibromyalgia and with the elderly.

1.1.6 Psychological Evaluation

Psychological evaluation may be performed with a simple evaluation for depression, anxiety, and somatization. Patients with major personality disorders need further evaluation and appropriate consultations (203-206).

Psychiatric status includes information regarding the patient's current and past history of psychiatric disorders and treatments and family history of psychiatric disorders.

1.1.7 Substance Use History

Substance use history includes multiple questions in reference to current, past, and family history of substance use, abuse, and addiction to alcohol, tobacco, prescription drugs, street drugs, illicit drugs, over-the-counter medications, solvents, etc. Furthermore, history in reference to attendance at a treatment program for addiction or treatment in an outpatient office detoxification etc., must be documented (203-206).

1.1.8 Addiction Risk Screening

Before initiating opioid therapy, a physician may consider using a screening tool to determine the patient's risk for opioid addiction. This evaluation is part of the comprehensive assessment. Comprehensive history also includes a thorough review of the patient's alcohol and other substance use. The history is important in assessing the patients risk for opioid misuse or addiction. Various screening tools may help with the determination. Most of the screening tools have not been studied in depth, validated, or been compared to each other. Thus, the evidence is poor as to their reliability (1,40,77-79,207-214).

1.1.9 Prescription Monitoring Programs

Before initiating therapy, a physician must obtain data from the prescription monitoring program. If a prescription monitoring program is not available, the physician must request information from all previous

physicians as well as pharmacies a patient uses or has used. While the evidence shows a general lack of reliability and accuracy for the multiple screening tools for opioid abuse, there is good evidence that prescription monitoring programs provide data on patterns of prescription usage, and fair evidence that prescription drug monitoring programs (PDMPs) can reduce prescription drug abuse or doctor shopping (1). However, the evidence that PDMPs reduce emergency room visits, drug overdoses, or deaths is poor. PDMPs collect statewide data about prescription drugs and track their flow (213,215-224). There are 3 components of these programs. The first component involves collecting data for prescriptions, documenting the physicians who wrote them and the pharmacies that dispensed them. With the enactment of the National All Schedules Electronic Reporting (NASPER) Act, physicians will have access to a database that has the capacity to monitor all transactions. In fact, some states are already mandating such use of prescription monitoring programs (221). To date, in the United States 38 states have functioning PDMPs, with 48 states with legislation passed (224), but there is a significant difference in the manner and frequency with which the data is collected.

1.1.10 Urine Drug Screening

In initiating and maintaining chronic opioid therapy, urine drug testing (UDT) must be used to establish a baseline measure of risk or to monitor compliance (40,51,54,149,172,173,207-213,225-234). However, it is essential to understand pharmacology, pharmacodynamics, drug interactions, and to have knowledge of interpretation and a plan in place to use the results, without financial considerations as the driving force (235-239).

UDT has been described in Part I and other manuscripts (40,53,54,225-231,237-240). Various details of interpretation of UDT are shown in Tables 1–3.

Physicians face multiple issues when utilizing UDT. In particular, the implication that the physician does not trust his or her patient. Information gained from UDT is limited regarding whether a patient is taking the dosages prescribed, or if they are a high metabolizer. UDT can reveal whether they are taking illicit substances.

- Drug screening should not imply that a physician does not trust the patients or that patients are not trustworthy. The literature, however, shows that self-reporting of drug use and behavioral monitor-

Table 1. *Urine drug testing: Typical screening and confirmation cut-off concentrations and detection times for drugs of abuse.*

Drug	Screening cut-off concentrations ng/mL urine	Confirmation cut-off concentrations ng/mL	Urine detection time	Immunoassay (I) Chromatography (C)
Hydrocodone	300	50	1–2 days	I & C
Oxycodone	100	50	1–3 days	I & C
Morphine	300	50	3–4 days	I & C
Methadone	300	100	5–10 days	I & C
Hydromorphone	300	100	1–2 days	I & C
Meperidine	300	100	1–2 days	I & C
Codeine	300	50	1–3 days	I & C
Benzodiazepines	200	20–50	Up to 30 days	I
Barbiturates	200	100	2–10 days	I & C
Marijuana	50	15	1–3 days for casual use; up to 11 weeks for chronic use	I & C
Cocaine	300	50	1–3 days	I & C
Amphetamine	1,000	100	2–4 days	I & C
Methamphetamine	1,000	100	2–4 days	I & C
Heroin*	10	25	1–3 days	I & C
Phencyclidine	25	10	2–8 days	I & C

*6-MAM, the specific metabolite is detected only for 6 hours.

Table 2. *Drug cross-reactants*.

Drug Group	Cross Reactivity Based on Product Insert	Cross Reactivity Based on Potential Cross-Reaction
Cannabinoids	Dronabinol (Marinol)	NSAIDs Efavirenz (Sustiva) Hemp Seed Oil (Cannabis seed) Pantoprazole (Protonix) Nexium Prilosec
Opioids	6-Acetylmorphine Ethyl morphine Oxymorphone Oxycodone Methadone Dextromethorphan	Fluoroquinolones Ofloxacin (Floxin) Papaverine Poppy Seeds Rifampicin & Rifampin (Rimactane, Rifadin, Rofact) Levofloxacin (Levaquin)
Amphetamines	Dextroamphetamine + amphetamine (Adderall)	Ephedrine Methylphenidate Trazodone Bupropion Desipramine Amantadine Ranitidine Phenylpropanolamine Vicks Vapor Spray Phentermine (Adipex/Obenix/Oby-Trim) Pseudoephedrine
Methamphetamine	d-Methamphetamine d-Amphetamine Chloroquine (Aralen) Desoxyephedrine MDMA (Ecstasy) Methamphetamine (Desoxyn)	Bupropion (Wellbutrin & Zyban) Chloroquine (Aralen) Chlorpromazine (Thorazine, Largactil) Desipramine (Norpramin) Dextroamphetamine (Dexedrine) Ephedrine (Ephedra and Ma Huang) Fenfluramine (Fen Phen) Labetalol (Labetalol) Mexiletine (Mexitil) n-acetyl procainamide (Procainamide) Phenylephrine (Neo-synephrine) Propranolol (Inderal) Pseudoephedrine (Claritin-D) Quinacrine (Atabrine, Mepacrine) Ranitidine (Zantac) Selegiline (Selegiline) Trazodone (Desyrel, Desyrel Dividose) Tyramine (Tyramine)
PCP	None	Chlorpromazine Meperidine Doxylamine Dextromethorphan Diphenhydramine (Benadryl) Thioridazine (Mellaril) Venlafaxine (Effexor)
Benzodiazepine	Bromazepam (Tenix) Clobazam (Mystan) Estazolam (ProSom)	Oxaprozin (Daypro) Sertraline (Zoloft) Some herbal agents
Cocaine	Benzoylecgonine Ecgonine Ecgonine Methyl Ester	TAC Solution (TAC Solution)
ETOH	None	Asthma inhalers (sometimes)
Methadone	None	Propoxyphene Seroquel

Table 2 (cont.). *Drug cross-reactants*.

Drug Group	Cross Reactivity Based on Product Insert	Cross Reactivity Based on Potential Cross-Reaction
Barbiturates	Alphenal	Phenytoin (Dilantin) Primidone (Mysoline)
Oxycodone	Hydrocodone Hydromorphone (Dilaudid) Oxymorphone (Numorphan) Codeine (Codeine)	

Source: DrugCheck® Cross Reactivity Chart (www.drugcheck.com/_images/DC145_Cross-Reactivity_chart.pdf)

Table 3. *Interpreting unexpected results of urine drug screens*.

	Unexpected Result	Possible Explanations	Actions for the Physician
1	UDS negative for prescribed opioid.	• False negative. • Non-compliance. • Diversion.	• Repeat test using chromatography; specify the drug of interest (e.g. oxycodone often missed by immunoassay). • Take a detailed history of the patient's medication use for the preceding 7 days (e.g., could learn that patient ran out several days prior to test). • Ask patient if they've given the drug to others. • Monitor compliance with pill counts.
2	UDS positive for non-prescribed opioid or benzodiazepines.	• False positive. • Patient acquired opioids from other sources (double doctoring, "street").	• Repeat UDS regularly. • Ask the patient if they accessed opioids from other sources. • Assess for opioid misuse/addiction. • Review/revise treatment agreement.
3	UDS positive for illicit drugs (e.g., cocaine, cannabis).	• False positive. • Patient is occasional user or addicted to the illicit drug. • Cannabis is positive for patients taking dronabinol (Marinol®), THC:CBD (Sativex®) or using medical marijuana.	• Repeat UDS regularly. • Assess for abuse/addiction and refer for addiction treatment as appropriate. • Ask about medical prescription of dronabinol, THC:CBD or medical marijuana access program.
4	Urine creatinine is lower than 2–3 mmol/liter.	• Patient added water to sample.	• Repeat UDS. • Consider supervised collection or temperature testing. • Take a detailed history of the patient's medication use for the preceding 7 days. • Review/revise treatment agreement.
5	Urine sample is cold.	• Delay in handling sample (urine cools within minutes). • Patient added water to sample.	• Repeat UDS, consider supervised collection or temperature testing. • Take a detailed history of the patient's medication use for the preceding 7 days. • Review/revise treatment agreement.

UDS=urine drug screen; THC=Tetrahydrocannabinol; CBD=cannabidiol

Source: Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain© 2010 National Opioid Use Guideline Group (NOUGG) (54).

ing fail to detect problems with drug misuse and abuse (53). Creating a UDT policy that is applicable universally and consistently with all patients assists to "de-stigmatize" UDT and can potentially convince patients that it has nothing to do with an individual patient or their trustworthiness (53,54). Consequently, the practice can explain to patients that drug testing is a routine procedure for all patients starting or maintained on opioid therapy and it is an important tool for monitoring the safety of opioid therapy. The UDT not only provides adherence monitoring, but it is also a monitoring tool for safety.

- As it is very difficult to correlate urine drug concentration with a patient's dose, it is not feasible for the physician to ascertain whether or not a patient has taken the dose of opioid appropriately using UDT. UDT can, however, detect the parent drug and/or its metabolites and demonstrate recent use of prescribed drugs and illegal substances. UDT will

not detect the amount of medication taken, when it was taken or identify the source of the drug.

- Some patients state that the expected drug is not found in the urine because they are high metabolizers. They may state that they are on diuretics and are drinking fluids to lose weight or on diet pills, and since they have so much fat, it cannot be detected. Most of the explanations are untrue, however, as only a small percentage of persons are considered ultra rapid metabolizers and may metabolize specific drugs more rapidly than typical patients (53). It would be rare for someone to take an opioid as prescribed and have a negative UDT. Moreover, diuretics, water intake, and excessive fat do not influence urine drug concentrations to an extent that one cannot influence urine drug concentrations. It is also crucial that the testing methodology used to identify the specific medication of interest have a low cut-off threshold. When possible, "no threshold" should be requested.

There is a misconception that short-acting opioids are not detected in the urine. In fact, most opioids are detectable in the body from one to 2 days. Short-acting opioids can be detected with no threshold testing.

- Confirmation of the results is a major issue. Proponents argue that each and every specimen must be sent to the lab and confirmed for a myriad of drugs; while others state that immunoassay testing is reliable and that confirmation should only be requested if there are questions with reference to results and patient history. If a patient admits that they have used a licit or illicit drug other than the prescriptions and if that drug is testing positive, there is no need to confirm this with laboratory testing. If, however, the patient denies any such use, it is essential that the result is confirmed through laboratory testing with LC/MS/MS. There is a significant correlation between immunoassay and chromatography for a majority of drugs (172,173). However, on occasion, it should be noted that even confirmatory testing requires expert assistance for interpretation (53). Most importantly with confirmation testing, while noting that financial incentives are put aside, understanding the pharmacology and metabolism of the drugs is essential.
- Some of the most common questions arise when dealing with marijuana. While for many people marijuana is a highly controversial and complex issue, the Drug Enforcement Administration (DEA) currently classifies it as a Schedule I drug. For that reason, many providers do not prescribe opioids to patients using marijuana or give them one opportunity to stop using them. Other providers reference state "medical marijuana" laws (http://apps.leg.wa.gov/RCW/default.aspx?cite=69.51A&full=true) (53) and feel comfortable prescribing opioids to marijuana users. Some providers adopt a "don't ask, don't tell" policy, whereas others request the lab to remove marijuana from the UDT so that positive results are not seen. While this may be a risky practice, physicians should create their office policies and disclose them to patients. These policies, should, of course, follow all state and federal regulations apart from policies addressing personal ethics and beliefs.

1.2 Recommendations

1. Comprehensive assessment and documentation is recommended before initiating opioid therapy, including documentation of comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history. (Evidence: good)
2. Despite limited evidence for reliability and accuracy, screening for opioid use is recommended, as it will identify opioid abusers and reduce opioid abuse. (Evidence: limited)
3. Prescription monitoring programs must be implemented due to regulations, as they provide data on patterns of prescription usage, reduce prescription drug abuse or doctor shopping, and PDMPs may reduce emergency room visits, drug overdoses, or deaths. (Evidence: good to fair)
4. UDT must be implemented from initiation along with subsequent adherence monitoring, in an in-office setting with immunoassay and confirmation for accuracy with chromatography in select cases, to identify patients who are non-compliant or abusing prescription drugs or illicit drugs, and UDT may decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy. (Evidence: good)

2.0 Establishing Diagnosis

Diagnosis may be established by various means including physical examination, x-rays, magnetic resonance imaging (MRI), computed tomography (CT), and neurophysiologic studies. Furthermore, psychological

evaluations and precision diagnostic interventions may also be applied. Diagnostic interventional techniques will assist in making the proper diagnosis by following an algorithmic approach. Research shows that in approximately 70% to 85% of patients with spinal pain, an accurate diagnosis may not be provided even with the available history, physical examination, electromyographic (EMG)/nerve conduction studies, and radiologic evaluation (179,240-269). With precise diagnostic interventional techniques, the chances of an accurate diagnosis may be improved substantially, and proper treatment may be offered (270-273). Once the diagnosis is established, various modalities of therapy may be offered with interventional techniques or other techniques. Whatever opioids are required will be prescribed in low doses or eliminated.

Given the degree to which routine imaging has been criticized, it may be appropriate that physicians follow the recommendations provided by professional organizations and governmental organizations. In ordering various investigations, being conservative may be prudent, along with their interpretation, due to findings in asymptomatic patients and also the psychological factors and nocebo effect introduced in these patients with graphic description of asymptomatic abnormalities (252-292). Guidelines provided by specialty societies are appropriate if they were peer-reviewed and developed utilizing guidance from IOM criteria. Early imaging is discouraged in all circles. It is also crucial to realize that numerous abnormalities are generally found on imaging in asymptomatic subjects (262-292). In the era of information disclosure and electronic media, findings which do not correlate with symptoms and do not provide certainty as a pathological entity should be addressed by qualified physicians, not by technologists and radiologists, without any clinical correlation. Irrelevant and non-corroborative findings create fear and activity avoidance, resulting in negative consequences including requests for increased opioid dosages.

The role of neurophysiologic testing is limited in chronic pain management, even though some insurers mistakenly focus on the neurophysiologic evaluation and findings (252-256,275).

2.1 Consultation(s)

Physicians should be willing to refer a patient as clinically indicated for additional evaluation to achieve treatment objectives. Special attention should be given to those patients who are at risk of misusing their medications and those whose living arrangements create a risk for medication misuse or diversion. The management of patients with a history of substance abuse or with a coexisting psychiatric disorder may require extra care, monitoring, documentation, and consultation with, or referral to, an addictionologist. The lack of well-trained psychologists and psychiatrists in chronic pain management in many regions of the country may make this referral difficult to obtain. Likewise, in many locations there are no clinically trained addiction specialists with whom to collaborate.

Interagency guidelines on opioid dosing for chronic non-cancer pain (53) have proven to be effective in reducing opioid usage and deaths, and include thresholds for pain consultation. The hallmark of this guideline (53) is a recommendation not to prescribe more than an average daily morphine equivalent dose of 120 mg without either the patient demonstrating improvement in function and pain or first obtaining a consultation from a pain management expert. This concept was based on the results of a study by Dunn et al (135), which showed that patients receiving 100 mg or more per day morphine equivalent doses had a 9-fold increase in overdose risk with 12% fatal overdoses and most overdoses being medically serious. Furthermore, high-dose opioid therapy can be ineffective and/or unsafe (53). Higher strength opioids may be associated with poorer functional outcomes and adverse consequences (26,32,33,90,135,293-296).

2.2 Recommendations

1. Establish appropriate physical diagnosis and psychological diagnosis if available prior to initiating opioid therapy. (Evidence: good)
2. Caution must be exercised in ordering various imaging and other evaluations, and only appropriate information in the realm of clinical relevance shall be provided by the treating physician to the patients when there is correlation of the symptoms with findings; to avoid increased fear, activity restriction, requests for increased opioids, and maladaptive behaviors. (Evidence: good)
3. A pain management consultation, for non-pain physicians, if high-dose opioid therapy is being utilized. (Evidence: fair)

3.0 Establishing Medical Necessity

To establish medical necessity for opioid therapy, it is essential to have a physical diagnosis and information of multiple modalities of treatments available including

conservative, various other alternatives, and consultations if necessary. These include non-controlled substance therapy, physical modalities, behavioral interventions, interventional pain management techniques, and any other alternatives.

Medical necessity is established only when the following criteria are met: pain of moderate to severe degree; suspected organic problem; documented failure to respond to non-controlled substance, adjuvant agents, physician ordered physical therapy, structured exercise program; and interventional techniques, specifically for long-term high-dose therapy.

Opioids may be used as a second-line treatment. For non-opioid controlled substance, appropriate documentation of psychological status must be documented.

Continued medical necessity depends on the following 4 "A's":

- Analgesia
- Activity
- Aberrant behavior
- Adverse effects

Behavioral interventions, interventional pain management, various other alternatives, and consultations as needed must be obtained.

3.1 Recommendations

It is essential to establish medical necessity prior to initiation or maintenance of opioid therapy. (Evidence: good)

4.0 Establishing Treatment Goals

It is essential to establish treatment goals. Treatment goals should combine pain relief with improvement in activity and minimal or no adverse effects. To achieve the treatment goals, outcomes assessment is essential. Outcomes may be assessed by numeric rating scale pain (0–10 scale), functional assessment using the Oswestry Disability Index (0–50 scale), Neck Disability Index (0–50 scale), employment status, and/or improvement in activity status. The minimum amount of change in pain score in order to be clinically meaningful has been described as a 2-point change on a scale of 0 to 10 (or 20 percentage points), based on findings in trials which have been commonly utilized studying general chronic pain (297), chronic musculoskeletal pain (298), and chronic low back pain (297-302). Consequently, for guideline purposes, it would be appropriate to use clinically meaningful pain relief of at least 30% and/or a 3-point change on an 11-point scale of 0–10, or as clinically significant and/or functional status improvement of 30% or more. For interventional techniques, significant improvement has been defined as 50% reduction in pain scores and disability scores for evaluation purposes.

Before starting opioids, physicians should insure that the patient's expectations are realistic. The goal of opioid therapy for chronic non-cancer pain is rarely the elimination of pain, but rather an improvement in function or a reduction of pain intensity by at least 30%. Before starting opioids, a discussion with the patient about specific goals related to pain reduction and functional improvement should address any unrealistic expectations. These goals, once established should be documented in the patient's record; they are critical in determining that opioids are effective and should be monitored over time (54).

4.1 Recommendations

It is essential to establish treatment goals of opioid therapy with regard to pain relief and improvement in function. (Evidence: good)

5.0 Assessment Of Effectiveness Of Opioid Therapy

The effectiveness of various types of opioids must be clearly defined. The evidence for various types of opioids is described as follows.

1. Nociceptive pain — Opioids showed only small to moderate benefits for nociceptive pain for improving function and relieving pain on a short-term basis of 3 months or less. If opioids are required, patients generally respond to moderate doses after failure of alternative techniques and non-opioid management (1,49-58,62,68,73,76,90,91,132,302-316).
2. Neuropathic pain — Opioids showed only small to moderate benefits for neuropathic pain (1,49-58,73,90,132,303,317-319). However, it is the general belief that opioids are resistant in neuropathic pain and these patients may require higher opioid doses in combination with tricyclic antidepressants or anticonvulsants.
3. Widespread soft tissue pain — The benefit of the weak opioid tramadol for fibromyalgia was small. Other pain-relief options should be considered (54).
4. Headache and other problems — Opioids are not usually indicated for migraine or tension headaches, or for patients with functional gastrointestinal problems (316).

Multiple manuscripts, systematic and compre-

hensive reviews, and guidelines have been published evaluating the effectiveness and safety of opioids (1,49-58,62,68,73,76,90,91,132,302-319). With extensive review as shown in Part 1 (1), it was concluded that the short-term effectiveness of opioids is fair, whereas long-term effectiveness of opioids is limited or poor. There is also fair evidence for lack of significant difference in effectiveness or adverse effects between long-acting and short-acting opioids. The evidence for improvement in quality of life parameters is fair for short-term and poor for long-term. There is no published evidence for opioid rotation.

An evaluation of individual drugs also showed variable evidence with lack of available evidence for hydrocodone, fair for short-term, and poor for long-term for oxycodone, morphine, and fentanyl. The evidence for tramadol is fair in osteoarthritis. The evidence for methadone, oxymorphone, hydromorphone, tapentadol, codeine, and buprenorphine is limited for either short-term or long-term improvement.

An evaluation of the effectiveness, adverse effects, and indications in special populations showed the evidence is fair for short-term and poor for long-term in the elderly, poor in children, adolescents, and in patients with generalized anxiety disorder, depression, and high risk psychological disorders such as personality disorders.

5.1 Recommendations

1. Clinicians must understand the effectiveness and adverse consequences of long-term opioid therapy in chronic non-cancer pain and its limitations. (Evidence: fair for short-term, limited for long-term)
2. The long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain that is not amenable to short-acting or moderate doses of long-acting opioids, as there is no significant difference between long-acting and short-acting opioids for their effectiveness or adverse effects. (Evidence: fair)
3. A trial of opioid rotation may be considered for patients requiring escalating doses. (Evidence: limited)
4. It is recommended that contraindications to opioid use in chronic non-cancer pain must be evaluated including respiratory instability, acute psychiatric instability, uncontrolled suicide risk, active or history of alcohol or substance abuse, confirmed allergy to opioid agents, coadministration of drugs capable of inducing life-limiting drug interaction, concomitant use of benzodiazepines, active diversion of controlled substances, and concomitant use of heavy doses of central nervous system depressants, such as benzodiazepines. (Evidence: fair to limited)

6.0 Informed Decision-Making

Informed decision-making with appropriate consent is not only essential but mandatory. A discussion about potential benefits, adverse effects, complications, and risks helps the physician and patient make a joint decision on whether to proceed with the opioid therapy (54). There have been substantial descriptions in reference to informed consent and treatment agreements and their effectiveness (1,320-327).

The following must be explained to patients and understood by patients before starting on opioids:

1) Opioids are used to improve the ability to be active and reduce pain, if appropriate criteria are met, in conjunction with or without various other modalities of treatments including cognitive behavioral therapy, behavior modification, therapeutic exercise program, increased activity, positive attitudes, physical therapy, psychotherapy, other drug therapy, or interventional techniques.
2) Opioids may help on a short-term basis, but they have substantial risks.
3) Common side effects include nausea (28%), constipation (26%), drowsiness (24%), dizziness (18%), dry-skin/itching (15%), and vomiting (15%) (54). However, these side effects can be minimized by slowly increasing the dose of the drug and starting a bowel regimen to manage constipation which may be the most long-lasting side effect of all. More serious complications include the effect on driving, respiratory depression, drug dependency, drug addiction, hormonal deficiency, fatigue, weakness, impotency, sexual dysfunction, etc., overdose, and death. Patients and physicians must take these complications and adverse consequences very seriously. Managing side effects through polypharmacy and the combination of various sedative hypnotics may not be useful.
4) The development of tolerance, dependency, addiction, and hyperalgesia are a major concern. Although the majority of patients believe that they can not develop addiction, many patients believe they develop tolerance and request higher doses believing that they are entitled for increase in doses and frequency with continued pain manage-

ment. However, physicians must educate patients on common aspects of addiction, hyperalgesia, and medication adjustment with emphasis on low dose or no opioid therapy and multidisciplinary management.

5) Abrupt stoppage of medication results in withdrawal states. Opioids overdoses are common, often resulting in various morbidities including death. Mixing opioids with alcohol or sedative drugs, such as antianxiety drugs and sleeping medications increase the risk of overdose significantly. Patients must understand the signs of overdosage.
6) Drugs prescribed to one patient may be disastrous to another person. Thus, medication should be safely secured by patients and never shared.

The informed consent and treatment agreement often includes clear descriptions of medication use and abuse, as well as the consequences for violating the contract, which are as follows:

1) One prescribing doctor and one designated pharmacy
2) Urine/serum drug screening when requested
3) No early refills and no medications called in
4) If medications are lost or stolen, then a police report could be required before considering additional prescriptions.

Additional items to be included in an agreement are listed in Table 4.

Overall, there is fair evidence to support the use of treatment agreements. Though in non-randomized studies (325), one found that treatment agreements

Table 4. *Sample controlled substance agreement.*

We are committed to doing all we can to treat your chronic pain condition. In some cases, controlled substances are used as a therapeutic option in the management of chronic pain and related anxiety and depression, which is strictly regulated by both state and federal agencies. This agreement is a tool to protect both you and your physician by establishing guidelines, within the laws, for proper controlled substance use. The words "we" and "our" refer to the facility, and the words "I", "you", "your", "me", or "my" refer to you, the patient.
1. i. I understand that chronic opioid therapy has been associated with not only addiction and abuse, but also multiple medical problems including the suppression of endocrine function resulting in low hormonal levels in men and women which may affect mood, stamina, sexual desire, and physical and sexual performance.
ii. For female patients: If I plan to become pregnant or believe that I have become pregnant while taking this medication, I am aware that, should I carry the baby to delivery while taking these medications; the baby will be physically dependent upon opioids. I will immediately call my obstetrician and this office to inform them of my pregnancy. I am also aware that opioids may cause a birth defect, even though it is extremely rare.
iii. I have been informed that long-term and/or high doses of pain medications may also cause increased levels of pain known as opioid induced hyperalgesia (pain medicine causing more pain) where simple touch will be predicted as pain and pain gradually increases in intensity and also the location with hurting all over the body. I understand that opioid-induced hyperalgesia is a normal, expected result of using these medicines for a long period of time. This is only treated with addition of non-steroidal anti-inflammatory drugs such as Advil, Ibuprofen, etc., or by reducing or stopping opioids.
iv. I understand that physical dependence is not the same as addiction. I am aware physical dependence means that if my pain medicine use is markedly decreased, stopped, or reversed by some of the agents mentioned above, I will experience a withdrawal syndrome. This means I may have any or all of the following: runny nose, yawning, large pupils, goose bumps, abdominal pain and cramping, diarrhea, irritability, aches throughout my body, and a flu-like feeling. I am aware that opioid withdrawal is uncomfortable, and could even result in heart attack, stroke, or death.
v. I am aware that tolerance to analgesia means that I may require more medicine to get the same amount of pain relief. I am aware that tolerance to analgesia does not seem to be a big problem for most patients with chronic pain; however, it has been seen and may occur to me. If it occurs, increasing doses may not always help and may cause unacceptable side effects. Tolerance or failure to respond well to opioids may cause my doctor to choose another form of treatment, reduce the dose, or stop it.
2. i. All controlled substances must come from the physician whose signature appears below or during his/her absence, by the covering physician, unless specific authorization is obtained for an exception.
ii. I understand that I must tell the physician whose signature appears below or during his/her absence, the covering physician, all drugs that I am taking, have purchased, or have obtained, even over-the-counter medications. Failure to do so may result in drug interactions or overdoses that could result in harm to me, including death.
iii. I will not seek prescriptions for controlled substances from any other physician, health care provider, or dentist. I understand it is unlawful to be prescribed the same controlled medication by more than one physician at a time without each physician's knowledge.

Table 4 (cont.). ***Sample controlled substance agreement.***

iv. I also understand that it is unlawful to obtain or to attempt to obtain a prescription for a controlled substance by knowingly misrepresenting facts to a physician or his/her staff or knowingly withholding facts from a physician or his/her staff (including failure to inform the physician or his/her staff of all controlled substances that I have been prescribed).

3. All controlled substances must be obtained at the same pharmacy where possible. Should the need arise to change pharmacies, our office must be informed. The pharmacy that you have selected is:
_____ Phone:_____

4. i. You may not share, sell, or otherwise permit others, including your spouse or family members, to have access to any controlled substances that you have been prescribed.

ii. Early refills will not be given. I will not consume excessive amount (I will follow prescribed instructions) and remain compliant to all aspects of treatment. Renewals are based upon keeping scheduled appointments. Please do not make phone calls for change in prescriptions unless you develop side effects or early refills and do not phone for refills after hours or on weekends.

iii. Medication changes will not be made between appointments unless medically necessary, which will be determined by the physician.

5. Unannounced pill counts, random urine or serum, or planned drug screening may be requested from you and your cooperation is required. Presence of unauthorized substances in urine or serum toxicology screens may result in your discharge from treatment by the facility and its physicians and staff.

6. I will not consume excessive amounts of alcohol in conjunction with controlled substances. I will not use, purchase, or otherwise obtain any other legal drugs except as specifically authorized by the physician whose signature appears below or during his/her absence, by the covering physician, as set forth in Section 1 above. I will not use, purchase, or otherwise obtain any illegal drugs, including marijuana, cocaine, etc. I understand that driving while under the influence of any substance, including a prescribed controlled substance or any combination of substances (e.g., alcohol and prescription drugs), which impairs my driving ability, may result in DUI charges.

7. Medications or written prescriptions may not be replaced if they are lost, stolen, get wet, are destroyed, left on an airplane, etc. If your medication has been stolen, it will not be replaced unless explicit proof is provided with direct evidence from authorities. A report narrating what you told the authorities is not enough.

8. In the event you are arrested or incarcerated related to legal or illegal drugs (including alcohol), refills on controlled substances will not be given.

9. I understand that failure to adhere to these policies may result in cessation of therapy with controlled substances prescribed by this physician and other physicians at the facility and that law enforcement officials may be contacted.

10. I also understand that the prescribing physician has permission to discuss all diagnostic and treatment details, including medications, with dispensing pharmacists, other professionals who provide your health care, or appropriate drug and law enforcement agencies for the purpose of maintaining accountability.

11. I affirm that I have full right and power to sign and to be bound by this agreement, that I have read it, and understand and accept all of its terms. A copy of this document has been given to me.

_____
Patient's full name

_____ _____
Patient's signature Date

_____ _____
Physician's signature Date

improve compliance (326), while another found that primary-care physicians were more willing to prescribe opioids to patients if the pain medicine physician also signed an agreement ("tri-lateral contract") (327).

Informed consent or agreements also mandate that multiple random evaluations, including pill counts and UDT, must be performed. Furthermore, based on the state regulation, evaluation of prescription drug patterns are monitored by state controlled substance monitoring programs.

6.1 Recommendations

A robust agreement which is followed by all parties is essential in initiating and maintaining opioid therapy, as such agreements reduce overuse, misuse, abuse, and diversion. (Evidence: fair)

7.0 Initial Treatment

Initiation of treatment is based on evaluation of stratification of risk, knowledge and understanding of opioids, initiation with low-dose, short-acting, opioid therapy, and titration during an 8 to 12 week period.

7.1 Stratification of Risk

Stratification of risk for patients initiated or maintained on chronic opioid therapy is crucial to prevent misuse and abuse. These principles may also be applied for patients who are treated for acute pain management, but also have other risk factors and for whom pain may become chronic. Chronic opioid therapy has been defined as therapy lasting for at least 90 days, on a daily, or on a near daily basis (50,328). Consequently, all guidelines recommend that before initiating chronic opioid therapy for any patient and in high-risk patients for acute pain therapy, a clinician should conduct a history, physical examination, and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction. Chou et al (50) provided strong recommendation with low-quality evidence. In addition, they also recommended that a benefit to harm evaluation including a history, physical examination, and appropriate diagnostic testing, which should be performed and documented before initiation and on an on-going basis during chronic opioid therapy. Atluri et al (40) describe risk stratification of patients into different categories as the first step. The risk stratification is justified in all patients due to the significant proportion of misuse and abuse, which may range as high as 50% (50,150,207-214,329). Chou et al (50) described that risk stratification pertaining to outcomes associated with abuse liability of opioids—misuse, abuse, addiction, and diversion — is a vital but relatively undeveloped skill for many clinicians (50,330).All clinicians prescribing opioids, however, should be knowledgeable about the risk factors for opioid abuse. Moreover, it is also essential to perform an assessment of risks for opioid-associated adverse effects, given their high prevalence (50,331), even though it is difficult to perform, often time consuming, and without any reliable evidence of tools. Atluri et al (40) described the 3 cornerstones for responsible prescribing or stratifying patients by using screening tools into high, medium, and low-risk groups; monitoring patients by using urine drug screening, prescription monitoring programs, and pill counts; and lastly, establishing dose limits.

Atluri et al (40) described that stratification of patients into different risk categories requires the use of existing screening tools designed specifically to screen for opioid misuse (subjective tools like Screener and Opioid Assessment for Patients with Pain (SOAPP) (332), Pain Medication Questionnaire (PMQ) (333), Prescription Drug Use Questionnaire-Patient Version (PDUQp) (334), or objective tools like Addiction Behaviors Checklist (ABC) (214), Diagnosis, Intractability, Risk Efficacy (DIRE) Score (335), and the tool by Atluri and Sudarshan (211) to classify patients as high-risk, medium-risk, and low-risk. They described that objective tools may be better than subjective tools. Solanki et al (77) and Sehgal et al (79) concluded that there was no single screening tool that can be applied universally. Similarly, Chou and Huffman also (51) concluded that most of the studies evaluating the screening tools had methodological flaws. However, some believe that screening tools may play an important role in curbing abuse.

In risk stratification, it is important to utilize multiple models incorporating psychological and behavioral factors to explain the pain experience (336). Positive psychology has highlighted the importance of personal resources in adapting to stressful situations. Thus, resilience has been defined as the ability to adapt to stressful circumstances and has been strongly associated with decreased perceptions of stress (337). Some also have defined resilience as a multidimensional construct composed of a constitutional variable such as temperament and personality accompanied by specific skills (338). Others (339) have observed that resilience can be seen as synonymous with reduced vulnerability (340), with the ability to adapt to adversity (341), or coping (342,343). In general, resilience is associated with less depression and greater wellbeing and mental health (338,339,344). Thus, Ramírez-Maestre et al (336) showed that adjustment to chronic pain is mainly explained by psychological variables such as resilience, pain acceptance, and coping, not the length of time in pain. Resilience prevents patients with chronic spinal pain from suffering emotional distress, because higher levels of resilience are associated with lower levels of depression and anxiety. The study showed that resilience is an important resource for recovery from distress for individuals with chronic spinal pain. Furthermore, the study also concluded positive personality characteristics could play a crucial role in patient adjustment and that clinicians

should take into account the positive path to improved capacity in order to better understand the chronic pain experience.

Based on the present evidence, regardless of use of screening tools, patients may be classified into 3 categories as follows:

- Low risk — Low risk patients include those with a definable physical pathology; objective signs and reliable symptoms; clinical correlation with diagnostic testing including MRI, physical examination, and interventional diagnostic techniques; with or without mild psychological comorbidities; with or without mild coexisting medical disorders; no or well defined and controlled personal or family history of alcoholism or substance abuse; age of 45 or greater; high levels of pain acceptance and active coping strategies; and well-motivated patients with willingness to participate in multimodal therapy and attempting to function at normal levels.
- Medium risk — Medium risk patients include those with significant pain problems with objective signs and symptoms confirmed by radiological evaluation, physical examination, or diagnostic interventions; with moderate psychological problems, well-controlled by medical therapy; moderate coexisting medical disorders well controlled by medical therapy and which are not affected by chronic opioid therapy such as central sleep apnea; those who develop mild tolerance but not hyperalgesia without physical dependence or addiction; past history of personal or family history of alcoholism or substance abuse; involvement of more than 3 regions of the body; with defined pathology with moderate levels of pain acceptance and coping strategies; and willing to participate in multimodal therapy and attempting to function in their normal daily lives.
- High-risk — High-risk patients include those with widespread pain without objective signs and symptoms (involvement of more than 3 regions of the body); aberrant drug-related behavior; history of misuse, abuse, addiction, diversion, dependency, tolerance and hyperalgesia and alcoholism; with major psychological disorders; age of less than 45; HIV related pain; high levels of pain exacerbation and low levels of coping strategies; unwilling to participate in multimodal therapy; and not functioning close to a near normal lifestyle.

The patients may be stratified into these categories with or without various tools, but with proper history, examination, and monitoring by PDMPs, UDT, and simple psychological evaluation.

7.2 Understanding Opioids

Table 5 shows commonly used opioids, and Table 6 shows commonly used benzodiazepines available in the United States with various generic and brand names. As illustrated in these tables, these drugs are available with multiple names. Consequently they may have multiple interactions with drugs (53,345-364). The literature is highly variable on combinations of acetaminophen and the total dose of acetaminophen. However on January 13, 2011, the Food and Drug Administration (FDA) announced that there is no data that indicates that taking more than 325 mg of acetaminophen per dosage unit provides more pain relief (345). Further, the FDA has stated that the maximum daily dose of acetaminophen be less than 4,000 mg for acute pain and 2,000 mg per day for chronic pain. The present consensus appears to be taking around 2,000 mg of acetaminophen per day (346-350,360). With recommended low-dose therapy, this should not be an issue unless patients take acetaminophen over the counter. Thus, they should be instructed not to use products with acetaminophen or take additional acetaminophen.Lower doses have been recommended specifically for tramadol and acetaminophen combinations as well as in patients with hepatic abnormalities and alcoholics.

Acetaminophen toxicity causes the majority of cases of acute renal failure in the United States (346,347). Sub-clinical liver toxicity has been shown to occur with doses below 4 grams per day (347,348). Alcohol also competes for the same metabolic pathway as acetaminophen placing heavy drinkers at higher risk for toxicity. Chronic alcohol use is an independent risk factor for mortality in acetaminophen poisoning (349).

7.3 Dose Limits

With overwhelming evidence for the misuse, abuse, and limited efficacy of chronic opioid therapy, the rationale for high-dose opioids is being re-examined (40,49-55,57,98,181,363). Generally, it is believed that patients who do not respond to a low or medium-dose of opioids will not respond to larger doses although individual circumstances also exist (40). In 2007, the state of Washington issued interagency guidelines that include the daily dose should not exceed 120 mg of morphine equivalent dose. The guidelines by APS and AAPM in 2009 defined the

Table 5. *Opioids with various generic and brand names available in the United States.*

DRUG (GENERIC NAME)	BRAND NAME(S)
Hydrocodone	
Hydrocodone with acetaminophen	Anexsia®, Co-Gesic®, Hycet®, Liquicet®, Lorcet®, Lorcet Plus®, Lortab®, Maxidone®, Norco®, Polygesic®, Stagesic®, Vicodin®, Vicodin ES®, Xodol®, Zamicet®, Zolvit®, Zydone®
Hydrocodone with ibuprofen	Vicoprofen®, Ibudone®
Hydrocodone with aspirin	Lortab ASA
Oxycodone	
Oxycodone HCL	OxyContin®, Oxy-IR®, Roxicodone®
Oxycodone HCL with acetaminophen	Endocet®, Percocet®, Percocet-Demi®, Tylox®, Roxicet®
Oxycodone HCL/ ASA	Endodan®, Percodan®, Percodan-Demi®, Roxiprin®
Oxycodone HCL with ibuprofen	Combunox®
Morphine	
Morphine sulfate	Avinza®, Kadian®, MS Contin®, MSIR®, Oramorph®, Rescudose®, Roxanol®
Morphine and Naltrexone	Embeda®
Fentanyl (transdermal)	Duragesic®, Actiq®, Fentora TM, Lazanda, Onsolis
Methadone HCL	Dolophine®, Methadose®
Hydromorphone HCL	Dilaudid®, Exalgo®, Hydrostat®, Palladone®
Oxymorphone	Opana®, Numorphan®
Codeine	
Codeine monohydrate/sulphate trihydrate	Codeine
Codeine phosphate/acetaminophen/ caffeine	Tylenol® (No. 1, 2, 3)
Codeine phosphate/acetaminophen without caffeine	Empracet®
Pentazocine HCL	Talwin®, Talxin NX®, Talacen®
Meperidine	Demerol®
Tramadol	
Tramadol	Rybix®, Ryzolt®, Ultram®, Ultram ER®
Tramadol/ Acetaminophen	Ultracet®
Dronabinol	Marinol®
Buprenorphine	Buprenex®, Subutex®, Suboxone®, Norspan®
Tapentadol	Nucynta®, Nucynta ER®

"high doses" to 100 mg morphine equivalent dose (51). The Canadian Guidelines in 2010 identified 200 mg morphine equivalent dose as a watchful dose (54). However, there has been only limited data verifying the safety of these recommended doses, especially in high-risk patients. Franklin et al (181) showed the effectiveness of dose limitation with reduction in dosage, frequency, and death rate. In addition, 5 studies showed that the rate of overdose was directly proportional to the prescribed opioid dose (87,135,364-366). Bohnert et al (87) in a national sample of Veterans Health Administration patients revealed that there was a dose-response relationship between the maximum daily prescribed dose of opioids and the risk of opioid overdose deaths. The overdose death rate for patients receiving a dose of less than 20 mg morphine equivalent dose was 0.11 per 1,000 compared to those getting more than 100 mg morphine equivalent dose, for whom the death rate was 1.24. This difference was even higher in those with a history of substance

Table 6. *Benzodiazepines with various generic and brand names available in the United States.*

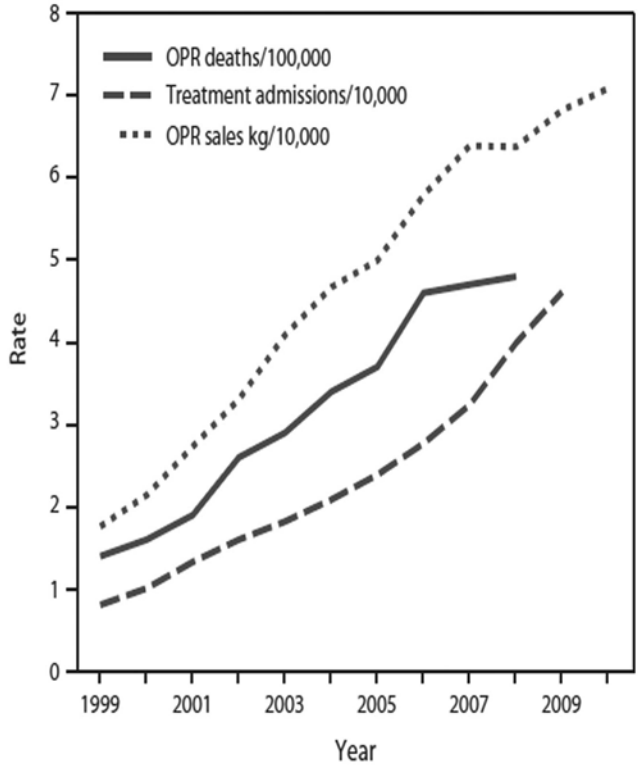
DRUG (GENERIC NAME)	BRAND NAME (S)
Alprazolam	Xanax®, Niravam®
Chlordiazepoxide	Librium®
Clonazepam	Klonopin®
Clorazepate	Tranxene®
Diazepam	Valium®, Valrelease®
Estazolam	ProSom®
Flurazepam	Dalmane®,
Lorazepam	Ativan®
Midazolam	Versed®
Oxazepam	Serax®
Quazepam	Doral®
Temazepam	Restoril®
Triazolam	Halcion®

abuse with 0.54% versus 2.9%. Based on these results, the authors concluded that the risk of opioid overdose increased when the opioid dose was equivalent to 50 mg morphine equivalent dose or higher. Dunn et al (135) in a population from a health maintenance organization (HMO) in Washington State, reported a 9-fold increase in opioid overdoses in patients receiving high dose opioids (> 100 mg morphine equivalent dose) when compared to those getting low dose (< 20 mg morphine equivalent dose). There was a 3.7-fold increase in overdose events in patients receiving doses between 50 to 99 mg morphine equivalent doses versus those getting less than 20 mg morphine equivalent dose. Paulozzi et al (364) found that compared to patients receiving lower opioid doses or no opioid prescriptions, the risk of overdose was greater if daily opioid doses were above 40 mg morphine equivalent dose. Braden et al (366) found that patients in Arkansas receiving morphine equivalent doses of more than 120 mg per day were more likely to have drug-related encounters than those getting lower doses. Gomes et al (365) found that patients from Ontario's Public Drug Plan receiving very high doses (> 400 mg morphine equivalent dose) and high doses (200 to 400 morphine equivalent dose) had a much higher overdose death rate than those getting moderate doses (< 200 mg morphine equivalent dose). Moreover, they also showed that in very high and high dose patients the opioid-related mortality rates were 9.94 per 1,000 population for very high and 7.92 for high. However, the opioid-related mortality rate was 1.63 per 1,000 in those with moderate doses. In addition, the overall death rate from any cause was much higher in patients receiving opioids (20.05) when compared to those who were not receiving any opioids (4.0) per 1,000 population. Franklin et al (181) showed that appropriate guidelines with dose limitation considering 120 mg morphine equivalent doses as high dose reduced overall opioids per day by 27% and long-acting Schedule II opioids by 37% in the proportion of the 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. Rome et al (363) in a report of outcomes of a chronic non-cancer pain rehabilitation program according to opioid use and status at admission stratified the participants into non-opioid grouping in 221 patients, low-dose (< 41 mg per day) in opioid users in 71 patients, and high-dose (> 41 mg per day, an average of 137.48 mg per day) in opioid users in 64 patients. The outcomes at discharge showed that patients taking higher doses reported significantly greater catastrophizing and greater pain severity than the non-opioid group. Two other studies conducted in the worker's compensation population also showed similar results (367,368). Adverse events were also reported more commonly at higher daily doses (369,370). Pascual et al (369) showed the increasing frequency of adverse effects of high dose tramadol (over 400 mg) compared with lower doses, with 2 patients ex-

periencing seizures. Huse et al (370) in a randomized trial showed that attention deficit was more common during morphine treatment compared to placebo, which was more pronounced when a higher dose was taken. Other studies (98,296,370-372) have shown that there was a dose-dependent relationship between chronic opioid use, specifically with high doses and sleep disorders. Ballantyne and Mao (296) in 2003 indicated that doses higher than 100 mg of morphine equivalent dose per day have not been validated in clinical trials and should be considered excessive.

The above studies illustrate the dose-related effects at 40 mg morphine equivalent dose (364), 50 mg morphine equivalent dose (87,135), 120 mg morphine equivalent dose (177,366), and 200 mg morphine equivalent dose (365). Thus far, it appears that all the available literature correlates increasing mortality with increasing doses. In addition, several studies have demonstrated that for patients with severe pain on high opioid doses, tapering resulted in reduced pain and improved mood (54,363,373-375).

In 2008, opioid pain relievers were involved in 14,800 drug overdose deaths in the United States compared to 11,500 of 27,500 fatal unintended drug overdose deaths in 2007 — an increase of 3,300 in just one year (34). Consequently, based on statistics, it has been concluded that opioid analgesics contributed to fatalities based on opioid abuse and increases, doctor shopping, and other aspects of drug abuse as illustrated in Figure 3. The Centers for Disease Control and Prevention (CDC) (34) also reported the percentage of prescription drug overdoses by risk group in the United States.



* 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.

Fig. 3. *Rates of opioid pain reliever overdose death, opioid pain relief treatment admissions, and kilograms of opioid pain relievers sold – United States, 1999-2010.*

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 (83).

This concluded that approximately 80% of prescribed low doses (less than 100 mg morphine equivalent dose per day) were by a single practitioner, accounting for an estimated 20% of all prescription overdoses (Fig. 4). In contrast, among the remaining 20% of patients, 10% were prescribed high doses greater than 100 mg of morphine equivalent dose per day (85-87) of opioids by single prescribers accounting for an estimated 40% of the prescription opioid overdoses (87,135). The remaining 10% of patients seeing multiple doctors and typically involved in drug diversion contributed to 40% of overdoses (376).

Multiple studies in the literature have reported an association between opioid prescribing and overall health status, with increased disability, medical costs, subsequent surgery, and continued or late opioid use (23,31,33,36,167,293-295,367,368,377-387). Overall, epidemiologic studies are less positive with regards to improvement in function and quality of life with opioids in chronic pain patients (23,31,33,36,49,55,56,57,133,167,293-295,367,368,377-389). In fact, in an epidemiologic study from Denmark by Breivik et al (23) where opioids were 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. Eriksen et al (32) 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. Sjøgren et al (33) in a population based cohort study on chronic pain and 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. In addition, they also showed that use of strong opioids was associated with poor health-related quality of life and higher risk of death.

Therefore, we have reached a consensus on the following: low-dose is up to 40 mg of morphine equivalent dose, moderate dose is 41 to 90 mg morphine equivalent dose, and high dose is any dose after 91 or higher mg of morphine equivalent dosages. These doses are lower than described by the CDC, which shows >100 mg as high dose and Washington State guidelines, which show 120 mg as the high dose, but considered reasonable, based on current evidence, and a cautious approach, specifically when a patient is receiving multimodal therapy.

7.4 Initiation with Low-Dose Opioid Therapy

A physician should follow the principles of prescribing a low opiate dose as reasonably achievable or ALARA (as low as reasonably achievable) similar to radiation exposure guidelines to provide therapeutic effect without major side effects (390-402).

Low dose therapy may be effective with a reduction in the rate of complications, side effects, and ad-

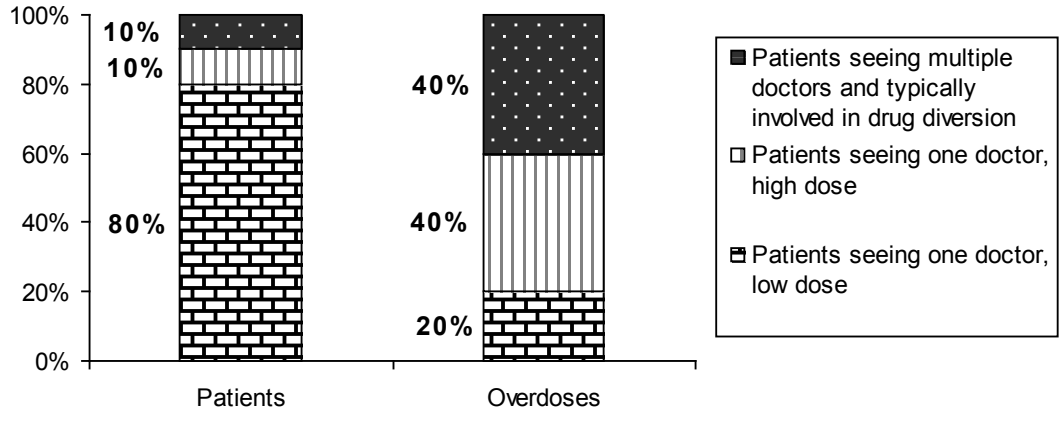


Fig. 4. *Percentage of patients and prescription drug overdoses, by risk group – United States.*

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 (34).

Table 7. *Recommended low-dose opioid therapy for select opioids showing starting doses and maintenance doses.*

Opioid	Recommended Starting Dose For Opioid-Naive Patients	Recommended Starting Dose For Opioid Exposed Patient's High Doses Leading To High Risks.	Recommended Maintenance Dose
Hydrocodone	5 to 10 mg, 2 to 3 times daily	5 to 10 mg, 3 to 4 times daily	30 to 40 mg for 24 hours
Morphine			
Morphine Immediate Release	Not recommended	10 mg, 2 to 3 times	30 to 60 mg per day
Morphine Sustained Release	Not recommended	15 to 30 mg twice daily	60 to 90 mg daily
Oxycodone			
Oxycodone	5 to 10 mg, 2 to 3 times daily	5 to 10 mg, 3 to 4 times daily	30 to 40 mg per day
Oxycodone Sustained Release	Not recommended	10 mg for 12 hours	30 to 60 mg for 24 hours
Methadone	Not recommended	2 to 5 mg, 2 to 3 times daily	10 to 30 mg per day
Transdermal Fentanyl	Not recommended	12.5 to 25 mcg q72h	25 to 50 mcg per 72 hours
Hydromorphone			
Hydromorphone Immediate Release	2 mg bid or tid	2 to 4 mg, 2 to 3 times daily	8 to 16 mg per day
Hydromorphone Sustained Release	Not recommended	5 mg to 10 mg, 2 times daily	20 to 40 mg daily
Codeine	15 mg bid or tid	30 mg bid to qid	120 to 160 mg daily
Oxymorphone			
Oxymorphone Immediate Release	5 mg bid or tid	5 to 10 mg 2 to 3 times daily	30 to 40 mg per day
Oxymorphone Sustained Release	Not recommended	10 mg q12h	40 to 60 mg per day
Tramadol			
Tramadol	50 mg bid or tid	50 mg 3 to 4 times daily	150 to 300 mg per day
Tramadol Sustained Release	Not recommended	200 mg daily	200 to 350 mg per day

verse effects, specifically when opioid therapy is combined with other modalities including interventional techniques. Consideration of higher dosage requires careful reassessment of the pain and risk of misuse, and frequent monitoring with evidence of improved patient outcomes if at all necessary.

Based on the available literature recommended low-dose therapy is shown in Table 7 for chronic non-cancer pain along with a description of dosing thresholds for selected opioids (1,49-55,58).

Thus, for mild to moderate pain, first line therapy should start with tramadol, codeine, or hydrocodone. For second line mild to moderate pain therapy, clinicians should start with hydrocodone or oxycodone. For severe pain, first line therapy may start with hydrocodone, oxycodone, hydromorphone, or morphine, with second line therapy leading to fentanyl and if absolutely necessary, the third line therapy for severe pain with methadone or buprenorphine (54). The literature illustrates that codeine and tramadol may have a lower abuse risk than more potent opioids (54,403-405).

Abuse rates measured from Drug Abuse Warning Network Data (DAWN) (405) showed that codeine and other low-potency opioids have low ratios of abuse to prescription use, related to oxycodone, hydromorphone, and hydrocodone. Tramadol also has a low risk of addiction, and experimental studies suggest that it has fewer psychoactive effects than other opioids (403,404). However, neither tramadol nor codeine are readily tolerated by the majority of patients long-term. In chronic pain management settings, the majority of patients have allegedly used these drugs (Tramadol and codeine) and refuse to try them. Oxycodone, hydrocodone, and hydromorphone have been shown to have higher abuse liability than other opioids (54,405-411). Butler et al (407) in a study of the 14 most desirable opioid formulations, found that prescription opioid misusers ranked controlled release oxycodone, immediate release hydromorphone, and oxycodone as the most desirable. Cicero et al (408) in a national surveillance study of addiction experts, law enforcement agencies, and poison control centers, identified hydrocodone and oxycodone (immediate release and controlled) as by far the most commonly abused opioids in the United States.

Morphine can cause toxicity in patients with re-

nal dysfunction (54,406). It has been shown that M-6 glucuronide, an active metabolite of morphine, accumulates in the serum of patients and causes central nervous system and respiratory depression. The degree of accumulation was related to the morphine dose and the extent of renal impairment (412).

Fentanyl, 80-100 times as potent as morphine can cause significant central nervous system and respiratory depression and also has been shown to contribute to numerous overdose deaths (54,349,413-416). Fentanyl was a contributing cause in 100 overdose deaths in Ontario between 2002 and 2004 with fentanyl intoxication being the sole cause of death in 54 of the patients with therapeutic and illicit use of fentanyl including chewing and ingesting fentanyl patches (414). In addition, fentanyl-laced heroin appeared simultaneously in various parts of the United States, beginning in 2005, with 55 drug overdose cases resulting in 12 deaths in the first half of 2006 (415). Fentanyl toxicity was related to 92% of the fentanyl-related deaths and is attributed partially due to cytochrome P450 3A4*1B and 3A5*3 variant alleles, resulting in variable fentanyl metabolism. Furthermore, the FDA (417), in July of 2005, issued a public health advisory calling attention to an increase in the number of fentanyl-patch-related overdoses and deaths, particularly among patients ignoring the product's boxed warnings and instructions for use. Another issue has been that up to 10% of Caucasians lack the enzyme CYP450 2D6 that converts codeine to morphine. Consequently, when switching from codeine to fentanyl, regardless of the codeine dose, caution must be exercised as patients may have little or no opioid tolerance (418-421).

In reference to methadone, even though it has not been shown to be more effective than other opioids, it has been used extensively in the United States and associated with multiple adverse consequences including prolonged QT interval (50,51,54,60,99,101,102,153,308,313,361,422-427). Methadone has been associated with numerous overdose deaths in pain patients with analgesic use increasing sharply in the United States, with a 1,293% increase from 1997 to 2007 (31). Methadone is also, however, dispensed in methadone clinics with very little regulation and supervision.

Meperidine is not recommended in chronic pain settings due to adverse neurological events resulting in confusion and seizures with long-term treatment secondary to accumulation of toxic metabolite Normeperidine. The adverse events with meperidine are also increased with long-term use, renal insufficiency, and concurrent benzodiazepine use (428).

Long-acting opioids are generally provided in high dose formulations, increasing the risk of abuse and overdose. Furthermore, long-acting opioids can easily be converted to immediate release by crushing or biting the tablet. Thus, OxyContin 80 mg tablet is equivalent to 16 Percocet tablets (54).

7.5 Titrate

Opioid medications must be started at low doses and titrated gradually to higher amounts if necessary. All attempts must be made to maintain patients on lower doses, including use of other drugs. Combinations of short- and long-acting, and high doses of long-acting opioids must be prescribed with extreme caution.

7.6 Recommendations

1. Once medical necessity is established, opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid side effects. (Evidence: fair for short-term effectiveness, limited for long-term effectiveness)
2. We are recommending up to 40 mg of morphine equivalent doses as low dose, 41 to 90 mg of morphine equivalent dose as a moderate dose, and greater than 91 mg of morphine equivalence as high doses. (Evidence: fair)
3. In reference to long-acting opioids, titration must be carried out with caution and overdose and misuse must be avoided. (Evidence: good)
4. Methadone is recommended for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. (Evidence: limited)

8.0 Adherence Monitoring

The role of adherence monitoring with various tools has been described as part of the initial evaluation. This must be continued through the treatment phase with PDMPs, UDT, pill counts, and behavioral assessment during each visit. Adherence monitoring is dependent on risk stratification. Monitoring based on risk stratification is illustrated in Figure 5 (40).An algorithmic approach to UDT is illustrated in Figure 6. However, regulations with stricter criteria take priority over these algorithmic approaches.

Aberrant drug-related behaviors, include alteration of prescriptions or the route of delivery, doctor shop-

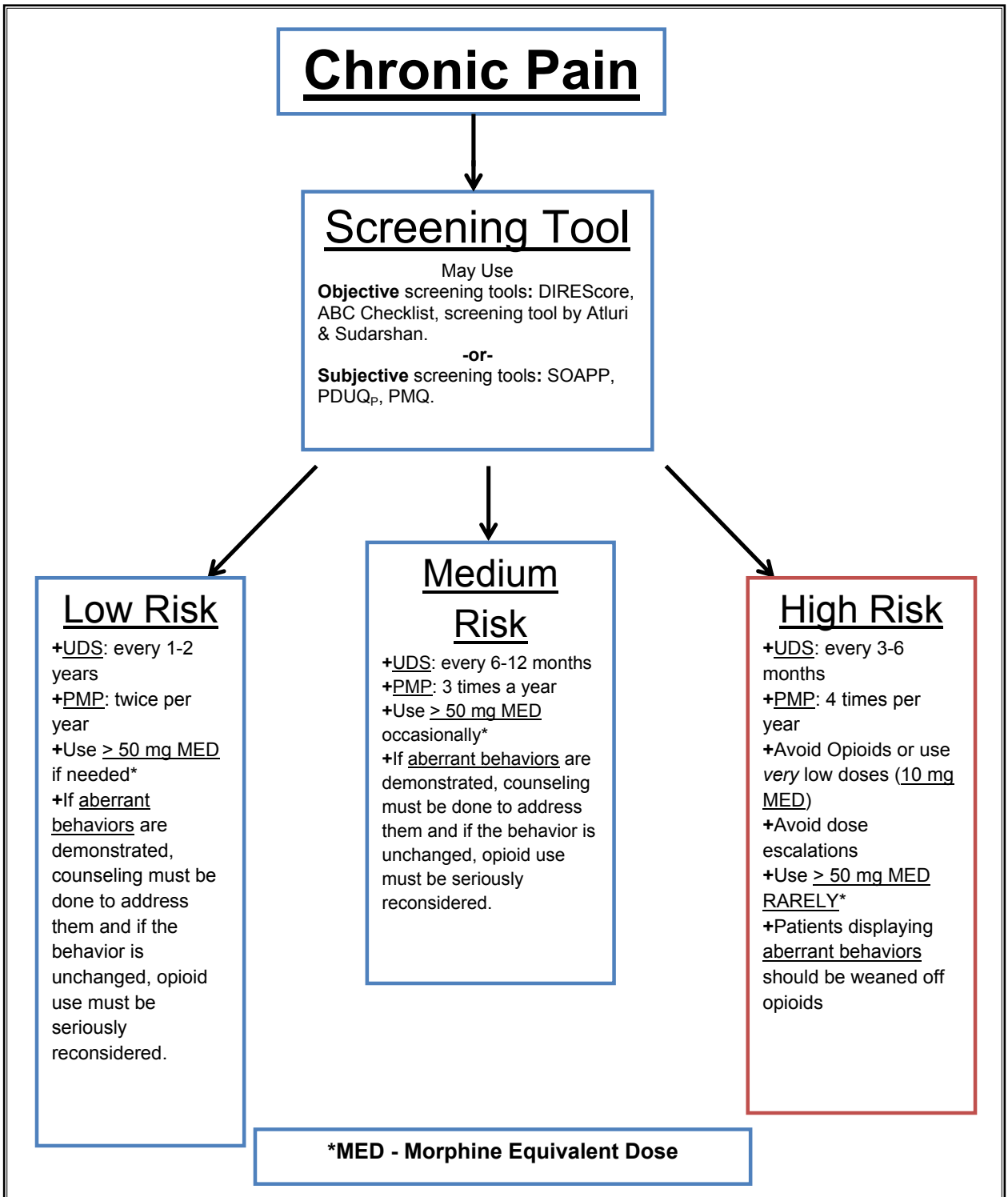


Fig. 5. *Risk stratification and adherence monitoring.*

Reproduced with permission from: Atluri SL, Akbik H, Sudarshan G. Prevention of opioid abuse in chronic non-cancer pain: An algorithmic, evidence-based approach. Pain Physician 2012; 15:ES177-ES189.

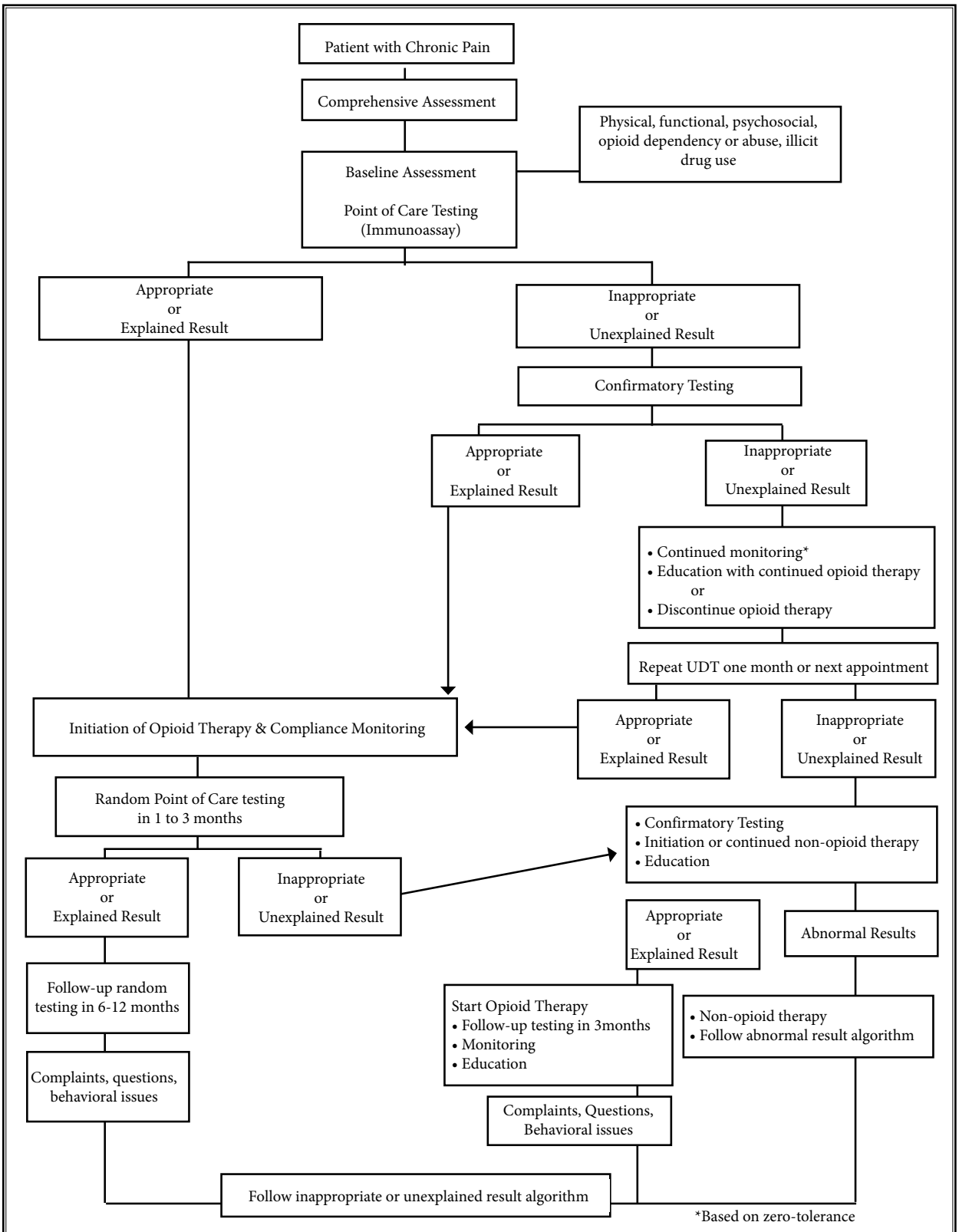


Fig. 6. ***Algorithmic steps in urine drug testing in chronic pain.***
Reproduced with permission from: Christo PJ, Manchikanti L, Ruan X, Bottros M, Hansen H, Solanki DR, Jordan AE, Colson J. Urine drug testing in chronic pain. Pain Physician 2011; 14:123-143 (226).

ping or accessing opioids from other sources, multiple unauthorized dose escalations, drug seeking behavior with focus on certain types of opioids and benzodiazepines, loss of prescriptions, requests for early refills, aggressive complaining, staff harassment, complaining about other patients, questioning rights and responsibilities, repeated withdrawal symptoms, exacerbation of underlying mood or anxiety disorders, alcohol use, poor social functioning, loss of job and loss of activities of daily living, emphatic views on opioid medication and illicit drugs as well as legalization of illicit drugs.

8.1 Recommendations

1. Monitoring recommendation for methadone prescription is that an electrocardiogram should be obtained prior to initiation, at 30 days and yearly thereafter. (Evidence: fair)
2. In order to reduce prescription drug abuse and doctor shopping, adherence monitoring by UDT and PMDPs provide evidence that is essential to the identification of those patients who are non-compliant or abusing prescription drugs or illicit drugs. (Evidence: fair)

9.0 Monitoring and Managing Side Effects

Multiple side effects, including effect on driving, sedation, constipation, and breathing specifically in patients with respiratory disorders, must be monitored.

Adverse effects have been commonly reported with nausea in 28%, constipation in 26%, somnolence/drowsiness in 24%, dizziness/vertigo in 18%, dry-skin/itching/pruritus in 15%, and vomiting in 15% of patients on relatively high-dose opioids. Low-dose opioids, however, have been accompanied by lesser complications (1,54,346-354,403-477). The majority of these adverse effects are resolved with continued treatment and dose adjustments. However, constipation may not be resolved and requires a bowel regimen. Furthermore, with long-term therapy and high doses, other complications may be noted including hypogonadism, neuroendocrine dysfunction, sleep disorders, and hyperalgesia (1,54,403-477). Other effects which are seen in less than 10% of the population 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 (54). The majority of these complications do resolve except for sexual dysfunction and fatigue, which increase with long-term treatment with hormonal imbalances. However, the complications are more frequent, longer lasting, and severe in long-term high-dose opioid therapy. Peripheral edema, though observed in a small proportion of patients, could be a major issue. Neuroendocrine abnormalities with erectile dysfunction must be taken into consideration and explained to the patient, with appropriate referral when indicated. Similarly sleep apnea and opioid-induced hyperalgesia (OIH) must be handled appropriately (1).

Neuroendocrine abnormalities and erectile dysfunction can be experienced with long-term opioid therapy in as many as 11% of the patients (296,430-435). Some outdated reports essentially state that patients taking opioid medications reported better sexual function, which was likely an improvement of well-being (429). Thus, in the short-term, a patient may notice improvement in many aspects including sexual function, but in the long-term, opioids may cause neuroendocrine dysfunction.

Smith and Elliott (478) described that opioid-induced androgen deficiency (OPIAD) is characterized by the presence of inappropriate low levels of gonadotrophin (follicle-stimulating hormone and leuteinizing hormone) leading to the inadequate production of sex hormones, particularly testosterone. Symptoms that may manifest in patients with OPIAD include reduced libido, erectile dysfunction, fatigue, hot flashes, and depression. Physical findings may include reduced facial and body hair, anemia, decreased muscle mass, weight gain, and osteopenia or osteoporosis. While the literature regarding OPIAD remains limited, OPIAD can have a significant negative impact on the quality of life of opioid users. Thus, clinicians should anticipate the potential for its occurrence whenever long-term opioid prescribing is undertaken and develop appropriate management strategies. Once diagnosed, treatment for OPIAD may be offered utilizing a number of androgen replacement therapy options including a variety of testosterone preparations and, for female patients, dehydroepiandrosterone (DHEA) supplementation.

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 (75,95).

Opioids can aggravate not just central sleep apnea, but frequently may also significantly aggravate obstructive sleep apnea. 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 (326,437-449). The most 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 that are associated with respiratory depression or that may potentiate opioid-induced respiratory depression such as benzodiazepines or abuse of opioids with or without other drugs (472-477). Many herbals and over-the-counters, including diphenhydramine preparations can contribute to a dose-dependant respiratory depression. 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. Furthermore, high opioid doses may contribute to sleep movement disorders including sleep apnea.

Part 1 with evidence assessment showed that the evidence is fair for existence of opioid hyperalgesia with chronic opioid therapy (1,75,95). However, debate continues on this aspect. Tompkins and Campbell (454) questioned whether OIH is clinically relevant or an extraneous research phenomenon, nothing that not all evidence supports the clinical importance of OIH, and that there is some doubt as to whether the phenomenon exists at all. Overall, there is growing evidence to support the presence and consequences of opioid hyperalgesia, along with the benefits of reducing opioid doses or weaning patients off of opioids.

Among the multiple side effects, constipation is one of the most common opioid-related adverse effects (331). Constipation may become a major issue with continued exposure to opioids in a significant proportion of patients. In addition, in older adults or other patients with additional reasons to develop constipation, constipation may be more frequent and also problematic. Consequently, a physician should consider the initiation of a bowel regimen even before the development of constipation and definitely after 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. Multiple publications have evaluated opioid antagonists in the prevention or treatment of opioid-induced bowel dysfunction (479,480), but the evidence is insufficient to recommend such antagonists to prevent bowel dysfunction.

During dosage titration in a trial of opioid therapy, advise the patient to avoid driving a motor vehicle or dangerous activities such as use of heavy machinery, until a stable dosage is established, it is certain the opioid does not cause sedation; and when taking opioids with alcohol, benzodiazepines, or other sedating drugs (54). When assessing safety to drive in patients on long-term opioid therapy, consider factors that could impair cognition and psychomotor ability, such as a consistently severe pain rating, disordered sleep, and concomitant medications that increase sedation (54).

Wilhelmi and Cohen (481) in a focused review described a framework for "driving under the influence of drugs" policy for the opioid-using driver. 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. Unlike recreational drugs, prescription medications, specifically opioids and benzodiazepines, pose a unique challenge to those attempting to harness their benefits, yet protect the driving public. Wilhelmi and Cohen (481) concluded that a sizable percentage of the driving public has detectable levels of opioids within their bodies. 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. Thus, it is essential to take into account the evidence in chronic pain patients when balancing the benefit of pain relief against the need for public roadway protection. Similarly, policy makers also should take into account these issues during drafting driving under the influence of drugs legislation.

9.1 Recommendations

1. It is essential to monitor for side effects and manage them appropriately including discontinuation of opioids if indicated. (Evidence: fair)
2. Constipation must be closely monitored and a bowel regimen be initiated as soon as deemed necessary. (Evidence: good)
3. It is recommended that a policy of driving under the influence of drugs be developed and monitored during initiation of therapy, changes in the dosages, and addition of other centrally acting agents. (Evidence: good)

10.0 The Final Phase

After initiation of opioid therapy and stable maintenance for 8 to 12 weeks with appropriate outcomes, it is essential to arrive at a conclusion to either continue or to discontinue the opioids.

If the patient continues with persistent pain or there is new pain, a comprehensive evaluation must be repeated or a referral may be made. Similarly, if there is any indication of abuse, misuse, lack of analgesia, lack of activity, adverse effects, or aberrant behavior, the physician must taper the drug therapy and discontinue. Alternate modalities must be pursued at this stage.

Opioid therapy is continued if appropriate analgesia and functional status is achieved either with opioid therapy alone or in conjunction with other modalities. Minimal requirements for continued opioid therapy are analgesia of at least 30%, and/or activity improvement of 30% without misuse/abuse, or major adverse effects. However, if treatment is successful, one may attempt to wean from opioids if necessary. If necessary to continue, monitoring must be continued and the patient be discharged either with improvement or with any deficiencies.

Patients on high doses, obtaining inadequate analgesia, and with other issues may be converted to sublingual buprenorphine. Daitch et al (482) described conversion of chronic pain patients from full opioid agonists to sublingual buprenorphine. They described the results from clinical records of 100 chronic pain patients with 60 men and 44 women aged 21 to 78 and who had previously been treated with opioid agonist drugs. They were converted to buprenorphine sublingual tablet form during the study. After initiation of buprenorphine sublingual therapy for more than 2 months, the mean pain scores on a scale from 0 to 10 decreased by 3 points. However, patient quality of life was not significantly affected by buprenorphine sublingual therapy. The success rate was highest for patients using morphine, oxycodone, and fentanyl before buprenorphine sublingual induction. These patient groups had a 3.7-point decrease in pain for those taking morphine, a 2.5-point decrease in pain for those taking oxycodone, and a 2.2-point decrease for those taking fentanyl. The smallest pain reduction was seen in the patient groups using oxymorphone. In addition, patients taking between 100 to 199 mg morphine equivalent per day experienced the greatest reduction (2.7 points) in pain scores. Patients taking between 200 to 299 mg of morphine equivalent before buprenorphine sublingual induction exhibited a decrease of over 2 points on average. Patients taking greater than 400 mg morphine equivalent reported the smallest reduction in pain scores, on average a 1.1 point decrease.

In patients with dependency, office-based opioid dependence treatment may be provided. In a narrative review, Colson et al (483) described that office-based opioid dependence treatment is a viable alternative to methadone treatment or rehabilitation programs. However, office-based treatment of opioid dependency requires a special licensure from the DEA. Thus, for physicians providing opioid management of pain, the use of buprenorphine/naloxone is an important tool to consider for opioid dependence issues, which arise in treating chronic pain.

If it is required, tapering or discontinuation of opioid therapy may be considered; however, for a patient who has not been taking medication on a long-term basis, tapering or weaning is not necessary and discontinuation may be carried out. Tapering may be carried out slowly with a decrease by 10% of the original dose per week. This is generally well tolerated with minimal adverse physiological effects. However, some patients can be tapered or weaned more rapidly without any major problems over a 6 to 8 week period. During this period, if opioid abstinence syndrome is encountered, it is rarely medically serious, even though symptoms may be quite unpleasant. The symptoms of abstinence syndrome, including nausea, diarrhea, muscle pain, and myoclonus, can be managed with clonidine 0.1 to 0.2 mg orally every 6 hours or clonidine transdermal patch 0.1 mg - 24 hours weekly during the taper. Patients should be monitored often for significant hypotension and anticholinergic side effects. While rare, in some patients it may be necessary to slow the tapering and weaning timeline from weekly to monthly dosage adjustments. If the patient is not following the tapering dosages and abusing them, then tapering is going to be unsuccessful and patients must be referred to detoxification facilities or advised to do so.

Symptoms of mild opioid withdrawal occasionally may persist for 6 months after opioids have been discontinued. The physician may also consider using adjuvant agents such as antidepressants to manage irritability and sleep disturbance, or antiepileptics for neuropathic pain. However, physicians should be cautious and preferably not treat withdrawal symptoms with opioids or benzodiazepines once the weaning process or discontinuation of opioids is started. The patient may be referred for counseling or other support during the weaning period if there are significant behavioral issues. If such issues arise, the physician should refer the patient to a chemical dependency center for complicated withdrawal symptoms.

Physicians not trained in pain management may refer their patients with these issues to pain management specialists or addictionologists.

10.1 Recommendations

1. Chronic opioid therapy may be continued, with continuous adherence monitoring, modified at any time during this phase, with fair evidence showing effectiveness of opioids in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse effects. (Evidence: fair)
2. Methadone is recommended for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. (Evidence: limited)
3. A trial of opioid rotation may be considered for patients requiring escalating doses. (Evidence: limited)
4. Chronic opioid therapy should be monitored for adverse effects and to manage them appropriately. (Evidence: good)

11.0 Documentation

The physician should keep accurate and complete medical records, which include all aspects of interventional pain management and medical care. These comprise, but are not limited to:

- Medical history and physical examination
- Diagnostic, therapeutic, and laboratory results
- Evaluations and consultations
- Treatment objectives
- Discussion of risks, benefits, and limitations of treatments
- Details of different treatments and medications, including date, type, dosage, and quantity prescribed
- Instructions to the patient
- Periodic reviews of outcomes, including documentation of functional status, preferably using validated tools.

Records should remain current and be maintained in an accessible manner and readily available for review, not only for the physician and other members of the practice, but also for authorities.

To be in compliance with controlled substance laws and regulations required to prescribe, dispense, or administer controlled substances, the physician must have an active license in the state and comply with applicable federal and state regulations. Various licensure boards have published regulations and recommendations for prescribing controlled substances. Physicians are advised to refer to those regulations for their respective state. Physicians should not prescribe scheduled drugs for themselves or immediate family except in emergency situations.

The following criteria should be considered carefully in providing controlled substances:

1. Complete initial evaluation, including history and physical examination
2. Psychological evaluation
3. Physiological and functional assessment, as necessary and feasible
4. Indications and medical necessity
5. The use of the lowest possible dose to provide adequate analgesia with minimum side effects should be the goal of opioid therapy
6. In general, do not combine opioids with sedative-hypnotics, benzodiazepines, or barbiturates for chronic, non-cancer pain unless there is a specific medical indication for the combination
7. Adherence to the controlled substance agreement with patients understanding the risks and benefits of controlled substances and the policy and regulations of the practitioner, including controlled substances being prescribed by only one practitioner and being obtained from only one pharmacy
8. Monitoring for drug abuse or diversion should be routine, and if confirmed, referral to rehabilitation centers may be made, with termination of prescriptions of controlled substances.

12.0 Summary

The evidence synthesis and guidance preparation provides the following recommendations with 10 steps to opioid therapy:

12.1 Initial Steps of Opioid Therapy

- Comprehensive assessment and documentation is recommended before initiating opioid therapy, documentation of comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history. (Evidence: good)
- Despite limited evidence for reliability and accuracy, screening for opioid use is recommended, as it will identify opioid abusers and reduce opioid abuse. (Evidence: limited)
- Prescription monitoring programs must be implemented due to regulations, AS they provide data on patterns of prescription usage, reduce prescrip-

tion drug abuse or doctor shopping, and PDMPs may reduce emergency room visits, drug overdoses, or deaths. (Evidence: good to fair)
- UDT must be implemented from initiation along with subsequent adherence monitoring, in an in-office setting with immunoassay and confirmation for accuracy with chromatography in select cases, to identify patients who are non-compliant or abusing prescription drugs or illicit drugs, and UDT may decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy. (Evidence: good)

12.2 Establish Diagnosis

- Establish appropriate physical diagnosis and psychological diagnosis if available prior to initiating opioid therapy. (Evidence: good)
- Caution must be exercised in ordering various imaging and other evaluations, and only appropriate information in the realm of clinical relevance shall be provided by the treating physician to the patients when there is correlation of the symptoms with findings, to avoid increased fear, activity restriction, requests for increased opioids, and maladaptive behaviors. (Evidence: good)
- A pain management consultation, for non-pain physicians, if high-dose opioid therapy is being utilized. (Evidence: fair)

12.3 Establishing Medical Necessity

It is essential to establish medical necessity prior to initiation or maintenance of opioid therapy. (Evidence: good)

12.4 Establishing Treatment Goals

It is essential to establish treatment goals of opioid therapy with regard to pain relief and improvement in function. (Evidence: good)

12.5 Assessment of Effectiveness of Opioid Therapy

- Clinicians must understand the effectiveness and adverse consequences of long-term opioid therapy in chronic non-cancer pain and its limitations. (Evidence: fair for short-term, limited for long-term)
- The long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain that is not amenable to short-acting or moderate doses of long-acting opioids, as there is no significant difference between long-acting and short-acting opioids for their effectiveness or adverse effects. (Evidence: fair)
- A trial of opioid rotation may be considered for patients requiring escalating doses. (Evidence: limited)
- It is recommended that contraindications to opioid use in chronic non-cancer pain must be evaluated including respiratory instability, acute psychiatric instability, uncontrolled suicide risk, active or history of alcohol or substance abuse, confirmed allergy to opioid agents, coadministration of drugs capable of inducing life-limiting drug interaction, concomitant use of benzodiazepines, active diversion of controlled substances, and concomitant use of heavy doses of central nervous system depressants, such as benzodiazepines. (Evidence: fair to limited)

12.6 Informed Decision-Making

A robust agreement which is followed by all parties is essential in initiating and maintaining opioid therapy as such agreements reduce overuse, misuse, abuse, and diversion. (Evidence: fair)

12.7 Initial Treatment

- Once medical necessity is established, opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid side effects. (Evidence: fair for short-term effectiveness, limited for long-term effectiveness)
- We are recommending up to 40 mg of morphine equivalent doses as low dose, 41 to 90 mg of morphine equivalent dose as a moderate dose, and greater than 91 mg of morphine equivalence as high doses. (Evidence: fair)
- In reference to long-acting opioids, titration must be carried out with caution and overdose and misuse must be avoided. (Evidence: good)
- Methadone is recommended for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. (Evidence: limited)

12.8 Adherence Monitoring

- Monitoring recommendation for methadone prescription is that an electrocardiogram should be obtained prior to initiation, at 30 days and yearly thereafter. (Evidence: fair)
- In order to reduce prescription drug abuse and doctor shopping, adherence monitoring by UDT

and PMDPs provide evidence that is essential to the identification of those patients who are non-compliant or abusing prescription drugs or illicit drugs. (Evidence: fair)

12.9 Monitoring and Managing Side Effects

- It is essential to monitor for side effects and manage them appropriately including discontinuation of opioids if indicated. (Evidence: fair)
- Constipation must be closely monitored and a bowel regimen be initiated as soon as deemed necessary. (Evidence: good)
- It is recommended that a policy of driving under the influence of drugs be developed and monitored during initiation of therapy, changes in the dosages, and addition of other centrally acting agents. (Evidence: good)

12.10 The Final Phase

- Chronic opioid therapy may be continued, with continuous adherence monitoring, modified at any time during this phase, with fair evidence showing effectiveness of opioids in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse effects. (Evidence: fair)
- Methadone and buprenorphine are recommended for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. (Evidence: limited)
- A trial of opioid rotation may be considered for patients requiring escalating doses. (Evidence: limited)
- Chronic opioid therapy should be monitored for adverse effects and to manage them appropriately. (Evidence: good)

13.0 CONCLUSION

These guidelines were developed based on an extensive review of the literature, consensus among the panelists, and practice patterns. There are numerous fatalities with increasing therapeutic use and abuse, this may be related to a lack of understanding and education in the proper application of opioid therapy. Furthermore, the evidence supporting efficacy for use of opioids as a treatment for chronic non-cancer pain is fair for short-term to improve pain and function, whereas it is limited due to lack of literature in reference to long-term efficacy or effectiveness. For practitioners considering opioid use, multiple recommendations for opioid management are summarized. The majority of treatment recommendations are based on evidence consensus and practice patterns, rather than high quality evidence alone. Thus, opioids for chronic non-cancer pain should be reserved for select patients with moderate or severe pain that significantly affects function or quality of life. Appropriate evaluation, documentation, screening, and risk stratification is indicated from initiation through the continuation of opioid therapy.

In conclusion, the focus of these guidelines has been to objectively evaluate the evidence with the application of consensus and practice patterns to curb opioid abuse, misuse, and overuse, and at the same time maintain access to opioids for patients who are in need of them.

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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.

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.

Dr. Benyamin is a clinical investigator with Epimed and receives research support from Cephalon/Teva, BioDelivery Sciences International, Inc., Mundipharma Research GmbH & Co., AstraZeneca, Purdue Pharma, LP, and Theravance.

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