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Updated Opioid Guidelines 2023

Comprehensive, Evidence-Based, Consensus Guidelines for Prescription of Opioids for Chronic Non-Cancer Pain from the American Society of Interventional Pain Physicians (ASIPP)

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Background: Opioid prescribing in the United States is decreasing, however, the opioid epidemic is continuing at an uncontrollable rate. Available data show a significant number of opioid deaths, primarily associated with illicit fentanyl use. It is interesting to also note that the data show no clear correlation between opioid prescribing (either number of prescriptions or morphine milligram equivalent [MME] per capita), opioid hospitalizations, and deaths. Furthermore, the data suggest that the 2016 guidelines from the Centers for Disease Control and Prevention (CDC) have resulted in notable problems including increased hospitalizations and mental health disorders due to the lack of appropriate opioid prescribing as well as inaptly rapid tapering or weaning processes. Consequently, when examined in light of other policies and complications caused by COVID-19, a fourth wave of the opioid epidemic has been emerging.

Objectives: In light of this, we herein seek to provide guidance for the prescription of opioids for the management of chronic non-cancer pain. These clinical practice guidelines are based upon a systematic review of both clinical and epidemiological evidence and have been developed by a panel of multidisciplinary experts assessing the quality of the evidence and the strength of recommendations and offer a clear explanation of logical relationships between various care options and health outcomes.

Methods: The methods utilized included the development of objectives and key questions for the various facets of opioid prescribing practice. Also utilized were employment of trustworthy standards, and appropriate disclosures of conflicts of interest(s). The literature pertaining to opioid use, abuse, effectiveness, and adverse consequences was reviewed. The recommendations were developed after the appropriate review of text and questions by a panel of multidisciplinary subject matter experts, who tabulated comments, incorporated changes, and developed focal responses to questions posed.

The multidisciplinary panel finalized 20 guideline recommendations for prescription of opioids for chronic non-cancer pain.

Summary of the results showed over 90% agreement for the final 20 recommendations with strong

consensus. The consensus guidelines included 4 sections specific to opioid therapy with 1) ten recommendations particular to initial steps of opioid therapy; 2) five recommendations for assessment of effectiveness of opioid therapy; 3) three recommendations regarding monitoring adherence and side effects; and 4) two general, final phase recommendations.

Limitations: There is a continued paucity of literature of long-term opioid therapy addressing chronic non-cancer pain. Further, significant biases exist in the preparation of guidelines, which has led to highly variable rules and regulations across various states.

Conclusion: These guidelines were developed based upon a comprehensive review of the literature, consensus among expert panelists, and in alignment with patient preferences, and shared decision-making so as to improve the long-term pain relief and function in patients with chronic non-cancer pain. Consequently, it was concluded – and herein recommended – that chronic opioid therapy should be provided in low doses with appropriate adherence monitoring and understanding of adverse events only to those patients with a proven medical necessity, and who exhibit stable improvement in both pain relief and activities of daily function, either independently or in conjunction with other modalities of treatments.

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

Disclaimer: The guidelines presented are based upon the best available evidence, and do not constitute or represent inflexible treatment recommendations. This document is not intended to be regarded and/or used as a "standard of care."

Pain Physician Opioid Special Issue 2023; 26:S7-S126

SUMMARY OF RECOMMENDATIONS:

i. ***Initial Steps of Opioid Therapy***

1. Comprehensive evaluation of pain history, medical history, psychosocial history, functional assessment, and appropriate consultations are recommended prior to initiation of opioid therapy. **(Evidence Level: Strong; Strength of Recommendation: Strong)**
2. Review of Prescription Drug Monitoring Program (PDMP) data prior to initiating any/all controlled substance prescriptions and periodically or as mandated by regulations during treatment in order to provide information on patterns of prescribing from all providers registered with the system. **(Evidence Level: Moderate to strong; Strength of Recommendation: Strong)**
3. Risk stratification as part of patient management is essential for opioid and controlled substance medication management. **(Evidence Level: Limited; Strength of Recommendation: Moderate)**
4. Urine drug monitoring (UDM) should be implemented at the initiation of opioid therapy and conducted periodically for monitoring therapeutic compliance as per available guidance referential to mode and frequency of testing. **(Evidence Level: Moderate; Strength of Recommendation: Strong)**
5. Prior to starting opioid therapy, clinicians should discuss the realistic benefits, and known risks with patients; should establish clear treatment goals for pain and/or function and should consider – and discuss - how opioid therapy will be discontinued if benefits do not outweigh risks. **(Evidence Level: Strong; Strength of Recommendation: Strong)**
6. It is essential to establish goals of opioid therapy related to pain relief, improvement in function if and as possible, improvement in quality of life, and a plan for opioid tapering and cessation if and when meaningful, realistic improvement is not achieved from opioid therapy. **(Evidence Level: Strong; Strength of Recommendation: Strong)**
7. A controlled substance agreement that is detailed with each item, including safe storage and disposal, and initialed and signed by the patient is essential prior to initiating therapy. **(Evidence Level: Strong; Strength of Recommendation: Strong)**
8. Once medical necessity is established, opioid therapy may be initiated using low doses and short-acting drugs, with appropriate monitoring to provide effective relief and avoid side effects. **(Evidence Level: Moderate; Strength of Recommendation: Moderate to Strong)**
9. Long-acting opioids should not be utilized for the initiation of opioid therapy. **(Evidence Level: Strong; Strength of Recommendation: Strong)**
10. Methadone is recommended for use after failure of other opioid therapies only if EKG and evaluation of QT intervals and drug interactions have been conducted and evaluated; commencing with low doses, with dose adjustments with repeat EKG performed at least 6-12 months thereafter. Only clinicians with specific training in methadone prescribing, use, and risk management should offer this agent for treatment of noncancer pain that is resistant to effect(s) of other opioids. **(Evidence Level: Strong; Strength of Recommendation: Strong)**

ii. ***Assessment of Effectiveness of Opioid Therapy***

11. Physicians should evaluate meaningful benefit (i.e., least 30% benefit in pain and/or function) produced by opioid treatment and should ensure that opioid therapy does not incur aberrant behaviors and/or adverse effects. **(Evidence Level: Moderate; Strength of Recommendation: Moderate)**
12. Clinicians must understand the effectiveness, viability, limitations, adverse consequences, and relative value (versus burden/risk) of long-term opioid therapy in chronic non-cancer pain. **(Evidence Level: Strong; Strength of Recommendation: Strong)**
13. The evidence of effectiveness is similar for short-acting and long-acting opioids, with increased incidence and prevalence of adverse consequences evidenced with the use of long-acting opioids. **(Evidence Level: Moderate; Strength of recommendation: Moderate)**
14. The administration of high doses of long-acting opioids is recommended in limited circumstances wherein severe intractable pain is not responsive or mitigated by short-acting opioids or moderate doses of long-acting opioids. **(Evidence Level: Moderate; Strength of Recommendation: Moderate)**
15. Tapering or weaning processes must be initiated slowly after appropriate criteria have been met and should entail slow tapering of the dosage across a specified period of time. Reinstitution of opioid therapy can be considered when such treatment is deemed medically necessary if the patient's behavior and pattern of drug use are shown to be stable, and if results of at least two consistent urine drug tests are negative (for opioids and/or illicit drugs). **(Evidence Level: Moderate; Strength of Recommendation: Moderate)**

iii. ***Monitoring Adherence and Side Effects***

16. Adherence monitoring to assess and sustain appropriate use must be instituted at proper intervals, as based on risk stratification and indication(s) of other issues that may be regarded as negatively influencing therapeutic compliance. **(Evidence Level: Moderate; Strength of Recommendation: Moderate)**

17. It is essential to monitor and manage side effects appropriately; such management may include discontinuation of opioids if indicated. **(Evidence Level: Strong; Strength of Recommendation: Strong)**
18. Bowel function must be closely monitored to assess opioid-induced constipation, and a bowel regimen should be initiated as soon as deemed necessary. **(Evidence Level: Strong; Strength of Recommendation: Strong)**

iv. ***Final Phase***

19. Chronic opioid therapy may be maintained, with continuous adherence monitoring, and modified at any time during this phase, in conjunction with - or after failure of - other modalities of pain care, for those patients demonstrating reasonable improvement in physical and functional status, and minimal adverse effects. **(Evidence Level: Moderate; Strength of Recommendation: Moderate)**
20. Chronic opioid therapy should be monitored for (burdensome and adverse) side effects, and these side effects should be managed appropriately. **(Evidence Level: Strong; Strength of Recommendation: Strong)**

Index - Opioid Guidelines 2023

1.0 Introduction

The COVID-19 pandemic caused many challenges to public health and economic systems worldwide.. During the pandemic, the International Narcotics Control Board considered ensuring access to and availability of controlled substances for medical and scientific purposes (1). The tremendous scope and scale (and often paucity) of resources utilized to mitigate the effects of the SARS CoV-19 virus, coupled to exacerbation of worldwide opioid overdose deaths resulted in two concomitant public health emergencies affecting patients suffering with chronic pain (2). The pandemic brought into stark relief the need to focus on facts, a lesson that should be learned beyond the bounds of COVID, so as to address the extant opioid drug crisis (3).

Ghada Waly, Executive Director of the United Nations' Office on Drugs and Crime (UNODC), has noted that drug use was the cause of almost a half a million deaths in 2019, while drug use disorders resulted in the loss of 18 million years of healthy life; and these effects were mostly due to opioids, and serious, often lethal illnesses are more common among drug users. In addition, the illicit drug trade continues to impact global economic and social development, often disproportionately affecting the most vulnerable and marginalized. Taken together, these factors establish the opioid crisis as a fundamental threat to national stability and security, with manifest effects upon the contemporary global stage (4-10).

The United States' Centers for Disease Control (CDC) published a document to further understanding of the opioid epidemic and characterized 3 distinct waves (4). Manchikanti et al (5) described an evolution of a fourth wave, beginning in 2016 and which has been steadily expanding due to multiple factors, including misapplication of the 2016 CDC Guidelines, an increased availability of illicit drugs, spill-over effects of the COVID-19 pandemic, and policies that have served to reduce access to interventional procedures for treating chronic pain (Fig. 1) (5-15).

There has been contradictory literature focusing on prescription opioids that has frequently explicated that prescription drug use/misuse is responsible for the opioid epidemic. Of note, United States overdose deaths in 2021 increased half as much as in 2020, and declined modestly in 2022, even though they continue to be higher than earlier years (13,15). As the data show, an estimated 79,117 Americans died from drug overdoses between January and September 2022, fewer than the 81,155 people who died during the first 9 months of 2021; but still 50% higher than pre-2020 deaths (14). For the entirety of 2021, a record 106,699 lives were lost due to overdose deaths. Figure 2 shows the total number of overdose deaths between January to September 2016 to 2022. In contrast, prescription opioids - other than methadone - decreased from 13,722 in 2020 to 13,503 in 2021.

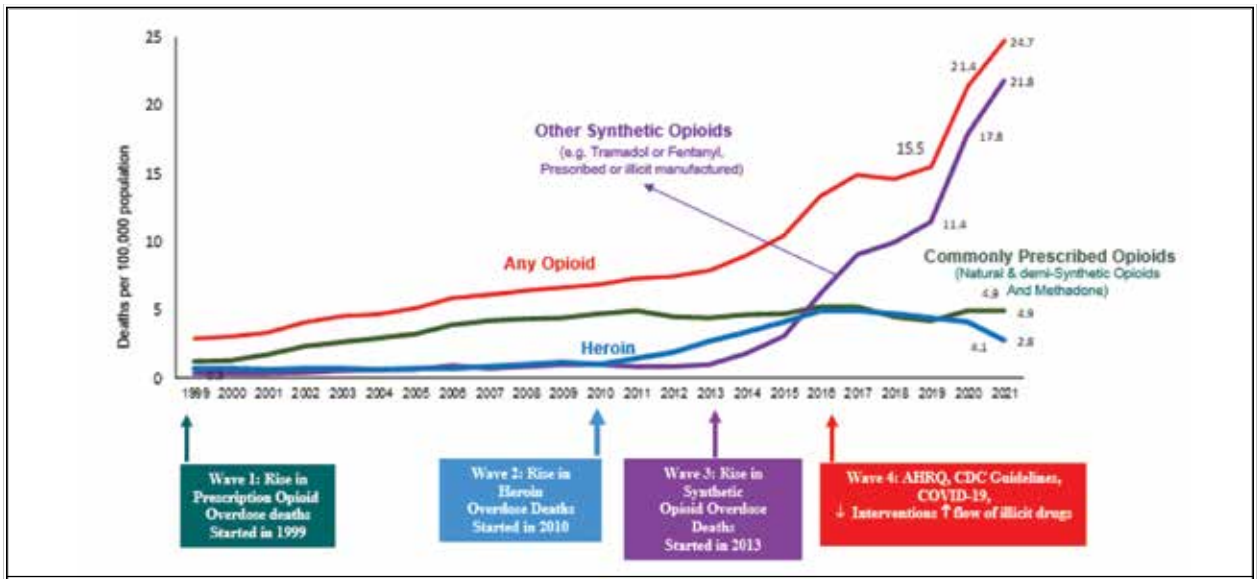
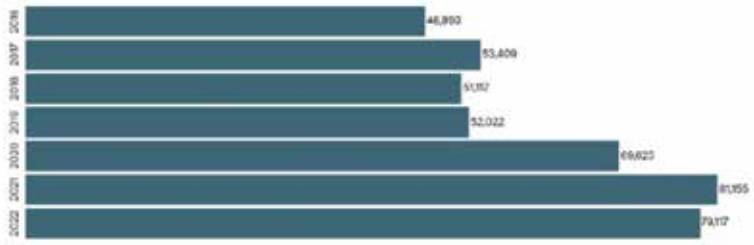


Fig. 1. *Four waves of rise in opioid overdose deaths.*
Redrawn and modified from CDC figure.



Data: Jan. – Sept., 2016 thru 2021 final totals: CDC WONDER; Estimated Jan.– Sept. 2022 totals: Calculations based on National Vital Statistics System Provisional Drug Overdose Death Counts, CDC WONDER.

Fig. 2. *Total number of overdose deaths between January to September (nine-month period), by year.*

Source: Baumgartner JC, Radley DC. Overdose Deaths Declined but Remained Near Record Levels During the First Nine Months of 2022 as States Cope with Synthetic Opioids." To the Point (blog), Commonwealth Fund, Mar. 13, 2023. Accessed 4/11/2023. https://www.commonwealthfund.org/blog/2023/overdose-deaths-declined-remained-near-record-levels-during-first-nine-months-2022-states (14).

Despite reports of increasing overdoses ranging from 60% to 130% (9), the updated 2022 CDC Clinical Practice Guidelines "assumed" credit for the declining use of opioids, yet did not accept any responsibility for adverse impacts (5,13,16,17); mentioning only that some policies reportedly drawn from the 2016 guidelines have, in fact, been notably inconsistent with those guidelines and in the severity of restrictions of clinical practices for interventional care of chronic pain, have gone well beyond its stated recommendations. Such misapplication of extant recommendations included extension to patient populations not covered in the 2016 CDC guidelines. And, although compliance with CDC guidelines is explicitly defined as voluntary, they have become de facto policy - as mandatory regulations - in many states.

Aubry and Carr (7) studied the relationship(s) of opioid overdoses, opioid treatment admissions, and prescriptions of opioids (for chronic pain) in the United States from 2010 to 2019. They clearly showed that there is no longer a direct correlation. Prior data led the CDC to conclude that prescription opioids are the principal determinate for opioid overdose deaths, total overdose deaths (TOD), and OTA/addiction (7). In 2015, then CDC Director, Tom Frieden stated, "Overprescribing opioids—largely for chronic pain—is a key driver of America's drug-overdose epidemic (18)." Previously, in 2005, the U.S. Department of Health and Human Services (HHS) declared that "there is a clear correlation between opioid prescribing rates and overdose death rates in the United States (19)".

Herein, based upon extensive review of the data, we posit that the CDC assertion of a continued direct relationship between these factors simply is not valid. As shown in Figs. 3 and 4, the relationships between total opioid doses, any opioid deaths (AOD), prescription opioid deaths (POD), opioid treatment admissions (OTA), and annual prescription opioid sales (i.e., morphine milligram equivalents (MME) per capita) are either non-existent, or significantly negative/inverse (20). As Fig. 3 depicts, the data from 2010 to 2019 – notably concurrent with initiation of CDC guidelines in 2016 – demonstrate that TOD, AOD, and OTA in 1,000s continued to escalate with distinct decline in both POD and MME per capita of prescription opioids.

As shown in Fig. 4, there is a significant negative relationship between prescription opioids and TOD versus MME per capita; AOD with MME; and a non-significant relationship with prescription opioids.

Related to the complex (clinical, psychological, and socio-economic) consequences of chronic pain, it is essential that clinicians have the education, training, guidance, and resources necessary to provide appropriate, comprehensive, and compassionate care for patients with chronic pain (2,5,13,21-25). The HHS Pain Management Best Practices Inter-Agency Task Force has advanced a comprehensive approach to improved management of both acute and chronic pain, proposing a 5-point strategy to combat the opioid crisis (23). Essential to this approach is an understanding of the important objectives of pain management, and the provision of person-centered care that are built upon trust between patient and clinicians, and which includes appropriate evaluation to identify causes of pain, establish a diagnosis, and the articulation of measurable treatment outcomes that focus on optimizing each patient's function and quality of life (QOL) (13,21,23).

Axiomatic to this approach are the needs for (1) clinicians to consider the full range of pharmacological and non-pharmacological treatments for the management of chronic pain; (2) health systems, payers, and governmental programs and entities to make available the full spectrum of evidence-based treatments (inclusive of those treatments based on accepted clinical con-

sensus) accessible to patients with pain; and (4) regulatory policies and laws that empower treating clinicians to prudently employ such interventions as dictated by their patients' need and best interest(s) (13,21).

In preparation of these guidelines, we have focused on the means to reduce the abuse and diversion of opioids, without curtailing access for those patients suffering from non-cancer chronic pain for whom there is medical indication for necessary opioid use. In 2022, the Veterans Administration (VA)/Department of Defense (DOD) published the Clinical Practice Guideline for the Use of Opioids in the Management of Chronic Pain. These guidelines have taken an approach similar to that of the CDC (13) and provided recommendations which were even more restrictive (14). These guidelines recommend against (1) the initiation of opioid therapy for the management of chronic non-cancer pain; (2) long-term opioid therapy, particularly for patients with chronic pain who have a substance use disorder (SUD); (3) concurrent use of benzodiazepines and opioids for chronic pain; and (4) long-term opioid therapy, particularly for younger age groups, as age is inversely associated with the risk of opioid use disorder (OUD) and overdose. Similar to the CDC guidelines (13), the VA guidelines also emphasize healthcare equity.

However, in contrast to the CDC guidelines, the VA

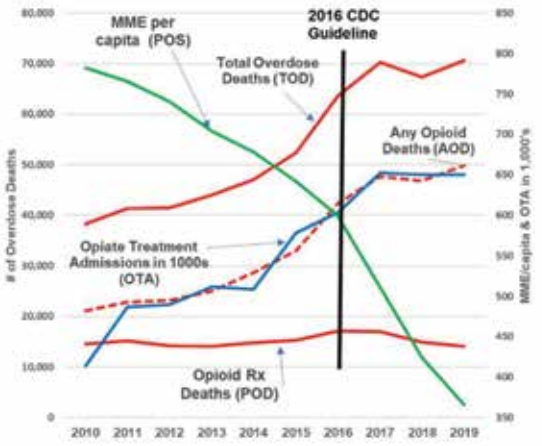


Fig. 3. *2010–2019 update. The green line represents opioid prescribing (POS, MME/capita); the red lines are opioid deaths (POD, AOD, and TOD); the blue line represents opioid addiction (OTA) (20).*

Over the past decade, as the green line (prescription opioids) declined by +50%, prescription opioid deaths remained flat while opioid addiction, any opioid and total overdose deaths continued increasing "exponentially (20)".
Source: Aubry L, Carr BT. Overdose, opioid treatment admissions and prescription opioid pain reliever relationships: United States, 2010-2019. *Front Pain Res (Lausanne)* 2022; 3:884674 (7).

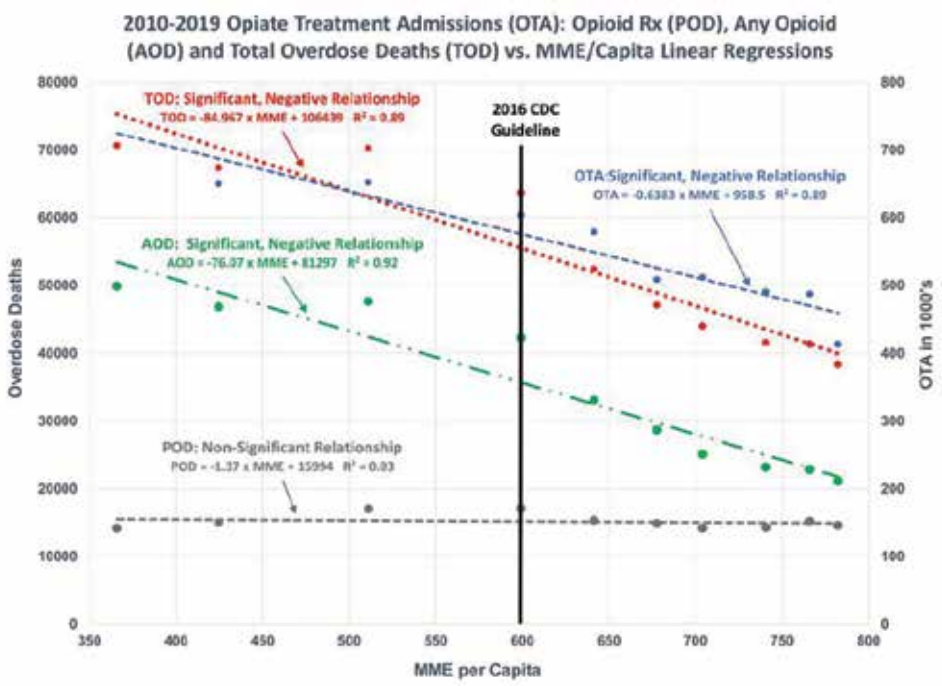


Fig. 4. *2010–2019 regression models: Illustrates the regression of OTA, POD, AOD, and TOD as functions of POS.*

Significant, negative relationships were found for OTA, AOD, and TOD. No significant relationship exists between POD and POS.
Source: Aubry L, Carr BT. Overdose, opioid treatment admissions and prescription opioid pain reliever relationships: United States, 2010-2019. *Front Pain Res (Lausanne)* 2022; 3:884674 (7).

recommends interventional pain care (e.g., joint injection, radiofrequency ablation). The VA guideline describes that from 2004 to 2012, the prevalence of opioid prescriptions among veterans increased from 18.9% to 33.4%, an increase of 76.7%; in response, the VA has since reduced prescription opioid use in patients within the VA healthcare system by 64% from 2012 to 2020. However, the VA has not reported adverse consequences of such restrictions on opioid prescriptions and the consequent cases of rapid withdrawal in the veteran population. The VA guideline workgroup and development team appears to have consisted of mostly non-physicians and an overwhelming number of non-pain physicians.

An updated version of the CDC Clinical Practice Guidelines for Prescribing Opioids published in 2022 (13) focused on behavioral aspects of chronic pain, with descriptions of suicidal ideation and health disparities based on race, ethnicity, and gender. The document also noted that historically, the range of therapeutic options has been inaccessible to many patients because of factors such as inadequate clinician education, training, and guidance; unconscious clinical bias; a shortage of pain management specialists; insufficient access to treatment modalities such as behavioral therapy; siloed health systems; inadequate insurance coverage and reimbursement policy; and lack of clarity in evidence supporting different pain treatments. The report also focused on studies evaluating opioids and other interventions that were previously published by the Agency for Healthcare Research and Quality (AHRQ), as sponsored by the CDC and HHS, and which provided negative opinions. While multiple issues related to the previous guidelines were acknowledged, there was nevertheless continued focus on the same issues and this position has not changed significantly, except for expanding the guidance to all specialties. Thus, the new guidelines may not differ significantly when compared with the prior versions, and do not include appropriate modalities, ignore elements of drug abuse, and leave open to numerous other organizations to continue to mandate use of the 2016 or 2022 guidelines.

The American Society of Interventional Pain Physicians (ASIPP) guidelines presented herein are updated from the ASIPP 2017 publication (21) for prescription opioids for chronic non-cancer pain based on evidence and consensus.

2.0 Methods

2.1 Rationale

Pain is a complex phenomenon that is influenced by multiple biological, psychological, and social factors (9,13,20-29). There is substantial heterogeneity in the effectiveness of various modalities of treatment that are provided to reduce pain and increase function, depending at least in part upon the type of pain and/or condition being treated. The HHS has advanced a comprehensive approach that addresses improved pain management in both the acute and chronic settings with a 5-point strategy to combat the opioid crisis (23). The HHS report identified the lack of understanding of, and clinical education on effective use of non-opioid medications for acute and chronic pain management. Thus, chronic pain is often ineffectively managed for a variety of reasons, including clinician training, patient access, and socio-economic and organizational barriers to care.

The National Uniform Claims Committee (NUCC) has defined interventional pain management as, "the discipline of medicine devoted to the diagnosis and treatment of pain related disorders principally with the application of interventional techniques in managing subacute, chronic, persistent, and intractable pain, independently or in conjunction with other modalities of treatment" (30).

The Medicare Payment Advisory Commission (MedPAC) defined interventional pain management techniques as, "minimally invasive procedures including, percutaneous precision needle placement, with placement of drugs in targeted areas or ablation of targeted nerves; and some surgical techniques such as laser or endoscopic diskectomy, intrathecal infusion pumps and spinal cord stimulators, for the diagnosis and management of chronic, persistent or intractable pain" (31).

Multiple guidelines have been developed by various agencies and organizations (9,13,25,36-40), although some are incongruent and have led to discordant conclusions among reviewers and practitioners. To be sure, opioid prescriptions are provided by various medical specialties. Multiple studies (32-34) published prior to the publication of the CDC opioid guidelines and numerous state regulations showed that the majority of opioid prescriptions were written by primary care physicians and other providers, although the number of prescriptions per provider was highest among pain medicine specialists, followed by physical medicine and rehabilitation specialists, and finally orthopedic sur-

geons. Many physicians, including interventional pain specialists who manage chronic pain believe that the judicious, medically necessary use of opioids can be effective in controlling pain, and recognize the common adverse events of tolerance, physical dependence, and addiction (5,9,13,21,23,25,35).

Prior and current ASIPP clinical practice guidelines focus on safe and effective prescribing practices, in concordance with physician and patient preferences and a shared decision-making model of clinical practice (9,13,21,25,36-40).

The ASIPP guidelines for responsible opioid prescribing in chronic non-cancer pain published in 2012 (41) were updated in 2017 (21). Since the 2017 publication (21), new CDC guidelines have been established (13). Moreover, a number of developments have occurred in the opioid overdose crisis, which we believe has led to a fourth wave, due to changes in regulatory atmosphere, and effects of mandatory (mis)application of the CDC guidelines (5,9,13,15).

2.2 Objectives

The objectives of the current ASIPP guidelines are to synthesize the available evidence on the comparative effectiveness and safety, and adverse events of chronic opioid therapy in the treatment of chronic non-cancer pain, so as to provide direction for rational use in real world practice, and in this way curtail opioid abuse --without jeopardizing sound, safe, and appropriate use of these agents for the medical management of non-cancer pain.

These comprehensive evidence-based guidelines of prescription of opioids for chronic non-cancer pain address the following areas:

1. Initial steps of opioid therapy.
2. Assessment of effectiveness of opioid therapy.
3. Monitoring adherence and side effects.
4. Final phase intervention with continuation or discontinuation of opioid therapy based on the relative individual response, risk, and harms of opioid use.

2.2.1 Application

While these guidelines may be applied by any specialty, they are specifically intended for use by interventional pain physicians. These guidelines do not constitute inflexible treatment recommendations. It is expected that a clinician will establish a case-by-case plan of care, based upon each individual patient's medical condition, personal needs, preferences, and the physician's experience and expertise. Consequently, these guidelines do not represent a "standard of care." It is a well-known fact that while not all treatments are supported by existing evidence and grading, there may be strong clinical support for some interventions (even in the absence of formally graded evidence).

These guidelines are intended to provide practitioners, patients, payors, and regulators with information that can be used to determine whether available evidence supports the notion of a "standard" for chronic opioid therapy. In this context, "standard" refers to what is applicable to the majority of patients, with preference for patient facility, practicality and ease of administration without compromising treatment effectiveness or incurring additional morbidity (21,23,24). In this light, we emphasize the essentiality of recognizing the difference between "standard" – as employed herein, and "standard of care," which is often utilized in medico-legal contexts.

2.3 Key Questions

These guidelines focus on the following key questions:

1. What is the impact of chronic pain on healthcare resources?
2. What are statistics relevant to trends in the utilization of various treatment modalities in managing chronic pain?
3. What is the effectiveness of non-opioid and non-pharmacological treatments?
4. What is the effectiveness of interventional techniques in managing chronic pain?
5. What is the Controlled Substance Act (CSA) and its relation to opioid prescriptions?
6. How were CDC guidelines developed and what is their impact on prescription opioids?
7. Is there U.S. Food and Drug Administration (FDA) guidance on opioid prescriptions?
8. What are the utilization patterns, effectiveness, and adverse consequences of marijuana in the treatment of chronic pain?
9. What are the use patterns and adverse consequences of cocaine in chronic pain?
10. What are the utilization patterns and adverse consequences of various stimulants in chronic pain?
11. What are the use patterns and adverse consequences and effectiveness of kratom?
12. What are the use patterns and adverse consequences of psychedelics?
13. What are the utilization patterns and adverse con-

sequences and effectiveness of ketamine, designer drugs, and 3,4-methylenedioxy-methamphetamine (MDMA)?
14. What is the evidence for the therapeutic efficacy and/or effectiveness of opioids in managing chronic non-cancer pain?
15. What are the burdens, risks, adverse consequences, and harms of chronic opioid therapy?
16. What is the prevalence of opioid use disorder (OUD) in chronic non-cancer pain patients and what are the management options for such co-morbidity?
17. What constitutes responsible opioid prescribing and what management strategy is safest and most effective for long-term opioid therapy in managing chronic non-cancer pain?

2.4 Adherence to Trustworthy Standards

The Institute of Medicine (IOM) standards (42), and National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument were followed in the preparation of these guidelines (43). The NEATS instrument was developed and tested as a tool to be used by trained staff at the AHRQ National Guideline Clearinghouse to provide assessments focused on adherence to clinical treatment.

2.5 Disclosure of Guideline Funding Source

The guidelines for the prescription of opioids for chronic non-cancer pain guidelines were commissioned, prepared, edited, and endorsed by ASIPP without external funding sought or obtained. The guideline preparation committee and the writing of the guidelines were financially supported entirely by ASIPP without any industry involvement.

2.6 Disclosure and Management of Financial Conflicts of Interests

Potential conflicts of interest for all panel members within the last 5 years were compiled and distributed at the introductory panel meeting. Conflicts of interests were on interest confluence extending beyond financial relationships, so as to include personal experience, practice patterns, academic interests, and promotions.

Following review and discussion of these disclosures, the panel concluded that individuals with potential conflicts could remain on the panel. However, those panel members with potential conflicts of interest were recused from discussion or preparation of the guidelines relevant and relative to their conflict(s), and these members agreed not to discuss any aspect of the guidelines with industry before publication.

All the panel members were connected through e-mails, discussions and reviews were also performed through electronic communication. The discussions were carried out at multiple ASIPP related meetings; however, there were no specific travel arrangements made, there was no renumeration provided to the participants.

Disclosures and competing interests are provided at the end of the manuscript.

2.7 Composition of Guideline Development Group

A multidisciplinary panel of experts in various medical and pharmaceutical fields, convened by the ASIPP, reviewed the evidence, considered patient perspectives, and formulated recommendations for chronic opioid therapy in non-cancer pain. The panel, consisting of authors and committee members, has been instructed to assess the evidence pertaining to important aspects of opioid therapy. The panel members convened either in person or through e-seminars and telephone conferences.

The panel provided a broad representation of academic and non-academic clinical practitioners, scientists, and ethicists representing a variety of specialties, disciplines, practices, and geographic areas, all with interest and expertise in opioid use and management of patients with chronic non-cancer pain.

The multidisciplinary panel composition included methodologists (e.g., epidemiologists, statisticians, ethicists, and health services researchers) with experience in research and conduct of systematic reviews.

Editorially, appropriate measures were taken to avoid any conflicting opinions from authors receiving funding from the industry. The panel was multidisciplinary with academicians and practitioners, and geographically diverse. Of the 43 members involved in preparing the guidelines, there were 27 anesthesiologists, six physiatrists, one radiologist, one neurosurgeon, one general surgeon, one internal medicine specialist, one addictionologist, three scientists/researchers; two ethicists, three law and/or policy specialists, one psychiatrist, three pharmacists, and two statisticians, either in an academic setting or in private practice. All of them were involved in managing chronic non-cancer pain.

2.8 Evidence Review

These guidelines were updated using evidence re-

view, and incorporation of other organizations and agencies' guidelines, and were ratified via consensus among the panel members. During that process, the panel also reviewed published randomized controlled trials (RCTs) that were not included in systematic reviews, meta-analyses, narrative reviews, and clinical practice guidelines addressing the use and safety of opioid analgesics in patients with chronic non-cancer pain (42-44). As well, the panel also considered evidence related to initiation and titration, adverse events, and preventive strategies.

The panel reviewed all available literature including recently developed guidelines for assessing effectiveness and risks, and prescription of long-term opioid therapy in chronic non-cancer pain, with key focus on studies addressing at least one-year (pain level, function, and quality of life) outcomes for long-term opioid. The effectiveness of short-term opioid therapy has been addressed in multiple previous studies and guidelines (9,13,21,25). Literature and document searches used PubMed, Cochrane Library, Google Scholar, and the search of websites including the HHS, the FDA, and the CDC resources. Search strategy terms included opioids, chronic opioid therapy in non-cancer pain, effectiveness of opioid therapy, adverse consequences, preventive strategies, monitoring, balancing opioid therapy, and abuse.

Questions and format of the previous (2017) guidelines were utilized in formulating the current guidelines (21,27-29). After preparation, the text and questions were reviewed by all authors. The survey of recommendations considered comments, incorporated changes, and developed 20 recommendations and reached a unanimous consensus on recommendations.

2.9 Grading or Rating the Quality or Strength of Evidence

The grading of evidence and recommendation were based on qualitative modified approach to grading of evidence described by ASIPP (45), the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (46-49), clinical relevance and pragmatism (50), and AHRQ strength of recommendations (43) methods.

Table 1 provides a guide for strength of recommendations as developed by the NEATS instrument (43), and as modified by the guideline panel.

Table 1. *Guide for strength of recommendations as modified for ASIPP guidelines.*

Rating for Strength of Recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent the panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation. **ASIPP Adaptation: Consensus was achieved that there is high certainty that the net benefit is substantial providing strong recommendation.** **Recommendation: Strong**
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) high certainty for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation. **ASIPP Adaptation: Consensus was achieved. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.** **Recommendation: Moderate to strong**
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation. **ASIPP Adaptation: The consensus achieved that there is potential improvement in certain individuals or groups of patients based on individual professional judgement and shared decision making.** **Recommendation: Weak to moderate**

Adapted and modified from National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument (43).

2.10 Assessment and Recommendations of Benefits and Harms

The guidelines intend to clearly describe the potential benefits, burdens, risks, and harms for the interventions addressed, and explicitly relate this information to specific recommendations.

2.11 Evidence Summary of Recommendations

Documents accompanying the guidelines summarize the relevant supporting evidence and explicitly relate this information to recommendations.

2.12 Rating or Grading the Strength of Recommendations

IOM standards demand that for each recommendation, a rating of the strength of the recommendation (i.e., considering benefits and harms, available evidence, and confidence in the underlying evidence) should be provided. In preparation of these guidelines, the rating schemes recommended by NEATS were utilized as modified by the ASIPP panel, as presented in Table 1 (43).

2.13 Specificity of Recommendations

Guideline recommendations are, to the largest extent possible, specific, and unambiguous, and are intended to provide guidance on what actions should or should not be taken in various clinical settings and situations of chronic opioid therapy in diverse populations of patients.

2.14 External Review

These guidelines have been subjected to external peer review as per the policies of the publishing journal, Pain Physician. In addition, the guidelines also have been published on ASIPP's website and in the ASIPP newsletter with active solicitation of comments from stakeholders, scientific and clinical experts, organizations, patients, and the public.

2.15 Updating Opioid Guidelines

ASIPP guidelines will be updated every 5 years, contingent upon significant changes in evidence, public policy, or events; and therefore, it is anticipated that the guidelines presented here will remain valid and viable through 2028.

3.0 Impact of Chronic Pain on Health Care

Key Question 1. What is the impact of chronic pain on health care resources?

As defined by the International Association for the Study of Pain (IASP) chronic pain is, "pain that exists beyond an expected time frame for healing" (51). However, more descriptive definitions include multiple dynamics. ASIPP has defined chronic pain as, "pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal, that is associated with chronic pathologic processes that cause continuous or intermittent pain for months or years, that may continue in the presence or absence of demonstrable pathologies; may not be amenable to routine pain control methods; and healing may never occur" (52,53). The concept of high-impact chronic pain has been developed to appropriately identify those individuals with substantial levels of restriction in daily activities including work, social, and/or personal care activities (54-59). Thus, the prevalence of impairment of physical and psychological abilities as constituent to the concept of high impact chronic pain has been evaluated (27-29,55-64).

Population-based studies have reported that chronic pain is common in adults, with prevalence reported to be between 11% and 40% (27-29,56,59,65-67). Epidemiological studies also have shown that chronic pain increases with age, is reported more by females than males, and that pain intensity and pain-related disabilities are more frequent in females (68,69). Further, individuals with lower socioeconomic status have been shown to exhibit higher levels of pain-related disability, and greater pain-related impact on QOL (70-76).

The CDC report describing chronic pain among adults in the United States from 2019 to 2021 (59) showed that during 2021, an estimated 20.9% of U.S. adults experienced chronic pain, which is similar to the estimate of 20.4% reported in 2016 (54). The estimated prevalence of high-impact chronic pain in 2021 (6.9%), was, however, lower than in 2016 (8%) (54). Age-adjusted prevalence of high-impact chronic pain in 2021 was 6.4%, which aligns with the goal set by Healthy People 2030 Objective (76). Figure 5 presents the prevalence of chronic pain and high impact chronic pain from 2019 to 2021. The report also highlighted important disparities in the prevalence of chronic pain among certain population groups. Consistent with previous studies, the prevalence of chronic pain and high impact chronic pain were higher among older adults, females, adults currently unemployed, but

who worked previously, veterans, adults living in poverty, those residing in non-metropolitan areas, those with public health insurance, adults with a disability, adults in poor health, and adults with a history of certain chronic medical conditions. To this latter point, among all the observed chronic medical conditions, adults with a history of encephalomyelitis and/or chronic fatigue syndrome (70%) and dementia (54.9%) were found to have the greatest prevalence of chronic pain.

The age-adjusted prevalence of both chronic pain and high impact chronic pain was notably higher among certain demographic population groups including American Indian adults, Alaskan native adults, adults identifying as bisexual, and adults who were divorced or separated. The age-adjusted prevalence of high impact chronic pain among American Indian or Alaskan native adults (12.8%) was six times higher than among non-Hispanic Asian adults (2.1%), and nearly two times higher than among non-Hispanic white adults (6.5%). Table 2 presents age-adjusted prevalence of chronic pain across various categories.

Figure 6 shows characteristic anatomic locations of chronic pain (which patients described severe). Table 3 present various pain management approaches utilized in the United States and shows physical therapy to be used to the greatest extent, followed by massage. All other approaches, including non-opioid pharmacological, opioids, interventional techniques, and/or surgery accounted for 39.1%.

Indubitably, the economic impact of chronic pain continues to be enormous (21,27-29,54-89).

The annual U.S. expenditures related to pain (including direct medical costs and lost wages) by some accounts may be higher than those for cancer, heart disease, and diabetes combined. Even then, the treatment covered by these expenditures doesn't fully alleviate pain in the United States or other countries. The IOM report of 2011, despite its inaccuracies, concludes that the epidemic of chronic pain demands public health approaches with public education to counter

Table 2. *Age-adjusted prevalence of chronic pain in the United States in 2021.*

	Chronic Pain	High-Impact Chronic Pain
Overall Prevalence	19.7%	6.4%
American Indian/Alaska Native, non-Hispanic	28.0%	12.8%
Asian, non-Hispanic	7.7%	2.1%
Black or African American, non-Hispanic	18.2%	7.6%
White, non-Hispanic	21.8%	6.5%
Hispanic or Latino	16.5%	5.7%
Other single and multiple race	20.9%	10.5%

Source: Rikard SM, Strahan AE, Schmit KM, Guy GP Jr. Chronic pain among adults – United States, 2019-2021. *MMWR Morb Mortal Wkly Rep* 2023; 72:379-385 (59).

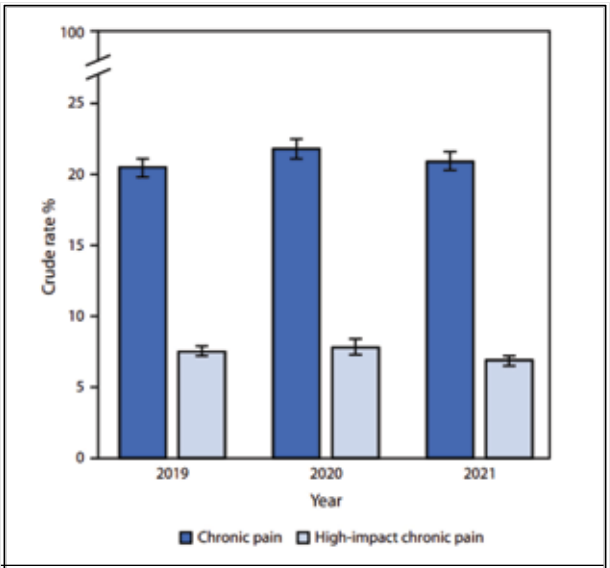


Fig. 5. *Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2019-2021.*¶.

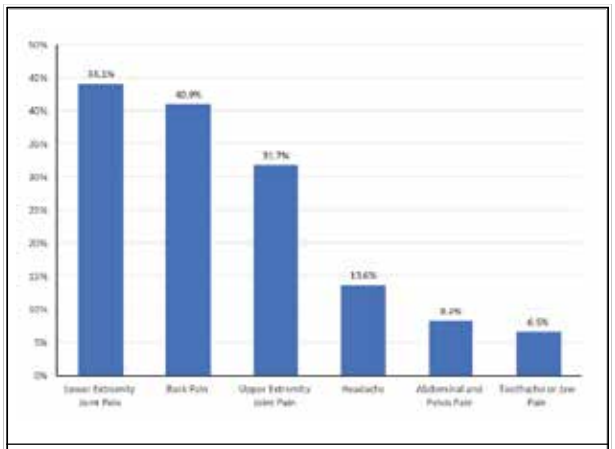


Fig. 6. *Characteristics of location of chronic pain described as "a lot."*

Source: Yong RJ, Mullins PM, Bhattacharyya N. Prevalence of chronic pain among adults in the United States. *Pain* 2022; 163:e328-e332 (55).

Table 3. *Reported pain management strategies for respondents who reported chronic pain in the United States.*

Pain Management Strategy	N (millions)	% of population
Physical therapy	9.4	18.6
Massage	8.8	17.6
Meditation, guided imagery, or relaxation	7.8	15.6
Spinal manipulation or chiropractic care	5.8	11.6
Yoga or Tai Chi	4.3	8.6
A chronic pain self-management program or workshop	2.6	5.1
Talk therapy	1.9	3.8
Chronic pain peer support groups	0.9	1.8
Any other approaches (drugs, opioids, interventional techniques and/or surgery)	19.6	39.1

Source: Yong RJ, Mullins PM, Bhattacharyya N. Prevalence of chronic pain among adults in the United States. *Pain* 2022; 163:e328-e332 (55).

myths, stereotypes, and stigma that hinder better care (22). While the study of global burden of diseases and injuries of 2019 (64) shows continued increasing disability and significant overdose deaths in the United States accounting for 50% of deaths across the world due to assumed liberal prescribing of high dose opioids, inadequate provision of opioid substitution therapy, and the lacing of street drugs with highly potent opioids such as fentanyl are contributing to the public health crisis. However, a study by Weaver et al (80) evaluating healthcare spending effectiveness suggests that spending improved U.S. health from 1996 to 2016, yet low back and neck pain continue to be apar with ischemic heart disease for negatively affecting disability-adjusted life years (DALY).

Dieleman et al (81,82) evaluated the economic impact on healthcare in the United States and showed an estimated spending of $134.5 billion in 2016, a 53.5% increase from 2013 of $87.6 billion spent for managing spinal pain. The costs of other musculoskeletal disorders also increased by 43.5% from $183.5 billion in 2013 to $263.3 billion in 2016, as shown in Fig. 7.

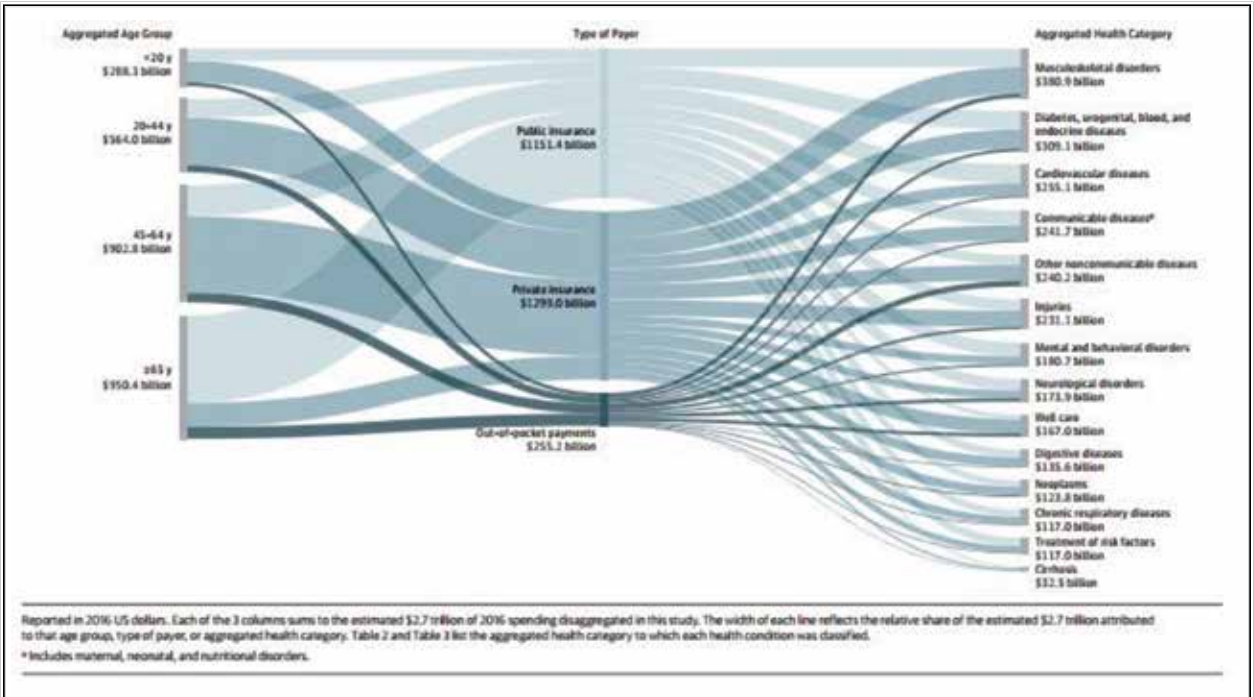


Fig. 7. *Estimated health care spending by aggregated age group, type of payer, and aggregated health category in 2016.*

Source: Dieleman JL, Cao J, Chapin A, et al. US health care spending by payer and health condition, 1996-2016. *JAMA* 2020; 323:863-884 (82).

4.0 Trends in Utilization of Health Care Modalities

Key Question 2. What are statistics relevant to trends in the utilization of various treatment modalities in managing chronic pain?

Overwhelming healthcare costs constitute a major burden on the United States' overall economy, and this has led the implementation of various healthcare reform measures and regulations. Notably, however, some guidelines have been based on public policy priorities to reduce healthcare costs and have not necessarily been based on the best evidence available to date (27-29). There has been escalating growth of various modalities for the treatment of spinal pain, including physical therapy, drug therapy, interventional techniques, and surgical interventions; and of these, surgery incurs the greatest net-impact economic and patient cost(s) (i.e., differential cost versus benefits).

4.1 Surgery

Since the description of the first discectomy to treat disc herniation in 1932 by Mixter, a neurosurgeon, and Barr, an orthopedic surgeon (90), surgical treatments for spinal pain have evolved with the evolution of multiple techniques and have evidenced a general trend toward increasing surgical interventions, which raises questions about the veridicality of effectiveness of such treatments (91).

The Spine Patient Outcomes Research Trial (SPORT) prospectively collected surgical data (92), which demonstrate that increasing national trends in surgical interventions (93-108); although the data lag, with the most current information presenting being from 2015 in most studies. Best et al (99) showed a 460% increase in surgical treatment of intervertebral disc disorders, and 910% increase in spinal stenosis surgeries from 1994 through 2006. Yoshihara and Yoneoka (94) showed a 2.4-fold population adjusted increase in surgical intervention for degenerative disc diseases from 2000 to 2009. Bae et al (102) showed 45% increase in lumbar spinal stenosis surgeries with 1.9% decrease in lumbar decompressions from 2004 to 2009. Similarly, Martin et al (95) showed an 62.3% increase in elective fusions, with greatest escalation (138.7%) seen among patients aged 65 or older from 2004 to 2015. They also showed aggregate hospital costs increased 177% during these 12 years, exceeding $10 billion in 2015 and averaging more than $50 per admission.

Studies by Lopez et al (93) from 2012 to 2017, showed a 24.2% increase in surgical interventions for chronic pain. In addition, re-operation rates for disc herniation and spinal stenosis varied from 10% to 23% (102) with data showing 40% of post-operative patients developing post-surgery syndrome or failed back surgery syndrome and requiring further treatment (101-107). These patients characteristically develop significant disability, requiring multiple modalities of treatment including physical therapy, drug therapy, interventional techniques, complex fusions, and neuromodulation techniques (102,109-126).

Paradigmatically, when caring for patients with chronic lower back pain, clinicians ideally should first exhaust all treatment modalities in the low to moderate risk tier before pursuing surgical intervention. A recent retrospective analysis of more than 75 million individuals, by Kim et al (127) found that nonadherence to clinical guidelines in treating patients with newly diagnosed low back pain (or lower extremity pain) contributed to substantial economic burden in the United States. Interestingly, 38.7% of patients that underwent surgery did not receive conservative management (neither physical therapy nor epidural steroid injections), thereby accounting for $265 million dollars' worth of healthcare expenses in the first 12 months after diagnosis (127). This gap in proper care utilization indicates the need for a more informed perspective regarding high-risk surgical solutions to achieve favorable outcomes more effectively and efficiently.

4.2 Interventional Techniques

Interventional techniques, including epidural injections, percutaneous adhesiolysis, facet joint interventions, sacroiliac joint interventions, and neuromodulation techniques have been frequently employed to manage spinal and non-spinal chronic pain.

Of note, however, is that the use of such techniques for the treatment of spinal pain increased until 2009, at which point utilization began to decrease (128,139-146). Recent analysis of the use of interventional techniques to manage chronic pain in the Medicare population (128) showed an overall decline in utilization from 2010 to 2019 of 4%, with an annual decline of 0.4% per 100,000 Medicare recipients, despite an increase of 0.7% per year of population growth (3.3% of those 65 years or older), and a 3% annual increase in Medicare participation from 2000 to 2019 (Fig. 8). Multiple investigators have attempted to assess the role of epidural injections in the prevention of surgery for spinal pain (129-138), and these systematic reviews, meta-analysis of RCTs and retrospective observational

studies reveal significant, but variable success rates of epidural injections to avoid surgery, with maximal effectiveness shown to be as high as 75%.

Further, analysis of utilization patterns of epidural procedures (139) showed a decline at a rate of 19% per 100,000 Medicare enrollees from 2019 to 2020, largely reflecting the impact of COVID-19, with an annual decline of 3% from 2010 to 2019. As shown in Fig. 9, overall declines from 2010 to 2019 showed a decrease in cervical and thoracic transforaminal injections, with an annual decrease of 5.6%; followed by 4.9% decreased in lumbar interlaminar and caudal epidural injections; 1.8% decrease in lumbar/sacral transforaminal epidurals, and 0.9% decrease in cervical and thoracic interlaminar epidurals.

Facet joint interventions decreased by 18.5% per 100,000 Medicare patients overall compared to 20.2 and 20.5% decreases in lumbar and cervical

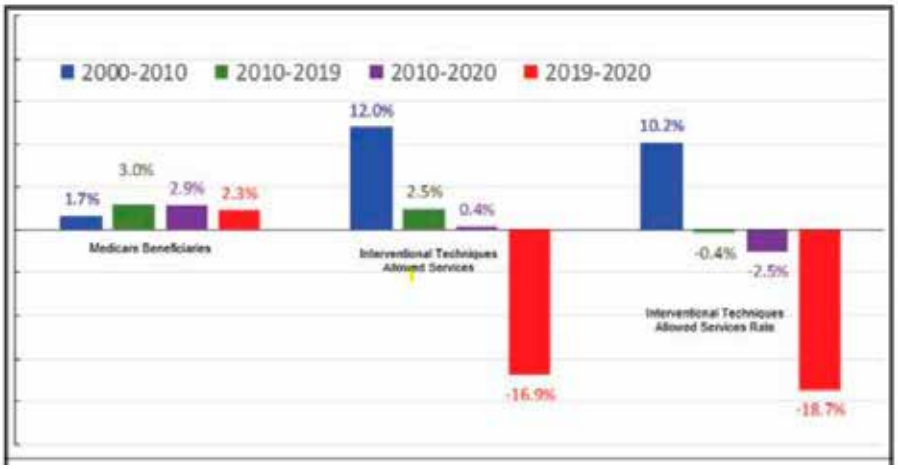


Fig. 8. *Comparative analysis of annual growth Medicare population, utilization of interventional pain management services, and rate (per 100,000 Medicare population) from 2000 to 2020 (geometric average annual change).*

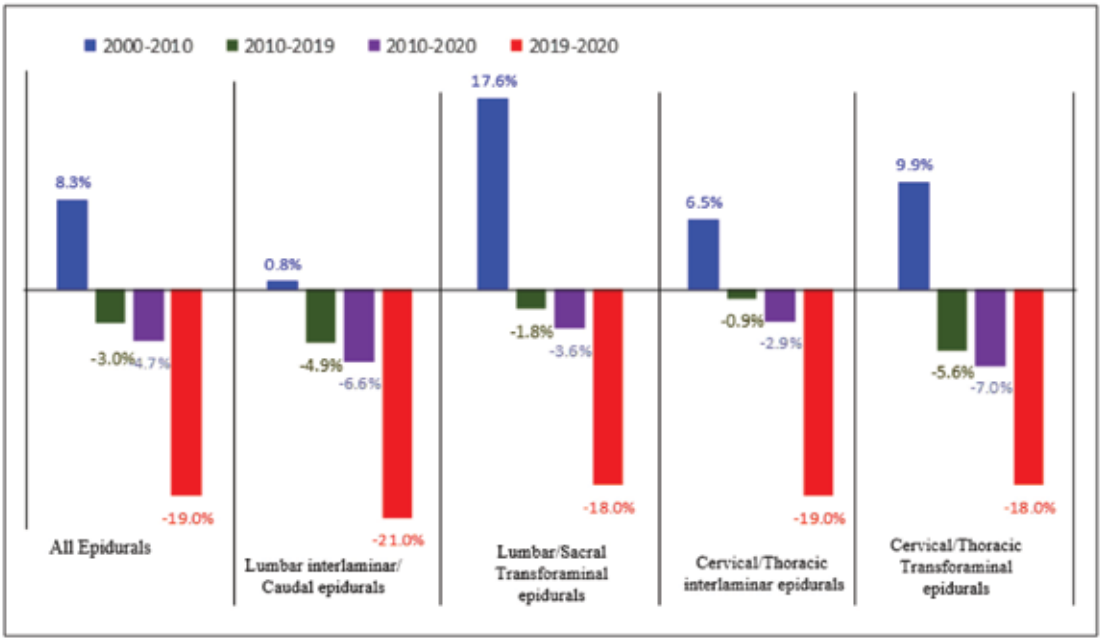


Fig. 9. *Change in the rate of frequency of utilization of epidural injections (annual change) per 100,000 Medicare beneficiaries stratified by the type of procedure.*

facet joint injections, 15 and 13.1% decrease in joint neurolysis procedures per 100,000 Medicare population patients with lumbosacral and cervicothoracic facet disorder-related pain (140). These findings are significant in that a comparative analysis from 2000 to 2010 and 2010 to 2019 showed a differential annual use of 14.4 vs. 2.2% for interventional procedures, illustrating a decreasing pattern of employment (Fig. 10). There were also significant decreases in the use of facet joint injections and nerve blocks, as compared to facet joint neurolytic procedures.

There was a 19.2% decrease in utilization of sacroiliac joint intraarticular injections from 2019 to 2020 (141); 23.3% increase in sacroiliac joint arthrodesis, and a 5.3% decrease in sacroiliac joint fusions from 2019 to 2020. However, data were not available for sacroiliac joint nerve blocks and sacroiliac joint radiofrequency neurotomy, as these codes were only available for use beginning in 2020. From 2010 to 2019, there was an overall annual increase in sacroiliac joint intraarticular injections of 0.9% per 100,000 Medicare population patients (Fig. 11). Sacroiliac joint arthrodesis and fusion increased 29% and 13.3% respectively per 100,000 Medicare population patients from 2010 to 2020.

The use of vertebral augmentation procedures declined 41%, (i.e.- at an annual rate of decline of 5.7%) per 100,000 Medicare population patients (145). Vertebroplasty interventions declined more dramatically than kyphoplasty from 2009 (Fig. 12). The use of vertebroplasty declined 66% (in number of operations), and evidenced a 74% decline in overall rate, with an annual decline of 11.4% and 13.9%. In contrast, kyphoplasty interventions decreased at an overall rate of 23%, and 2.9% annually. Evaluation of expenditures showed a net decrease of 8%, from 2009 to 2018. However, inflation-adjusted expenditures decreased overall by 21% (3% annually) from 2009 to 2018. Inflation-adjusted total expenditures per 100,000 Medicare population patients decreased 40% overall, with an annual decrease of 5%.

Utilization patterns showed that spinal cord stimulation trials 186% increased overall, with an annual increase of 12.4% (146). The rate of trials per 100,000 population increased 120%, at an annual increase of 9.1% from 2009 to 2018. The use of pulse generator implants increased 201%, with an annual increase of 13% (Fig. 13). In addition, percutaneous placement with pulse generator implants increased 252%, with an annual increase of 15%.

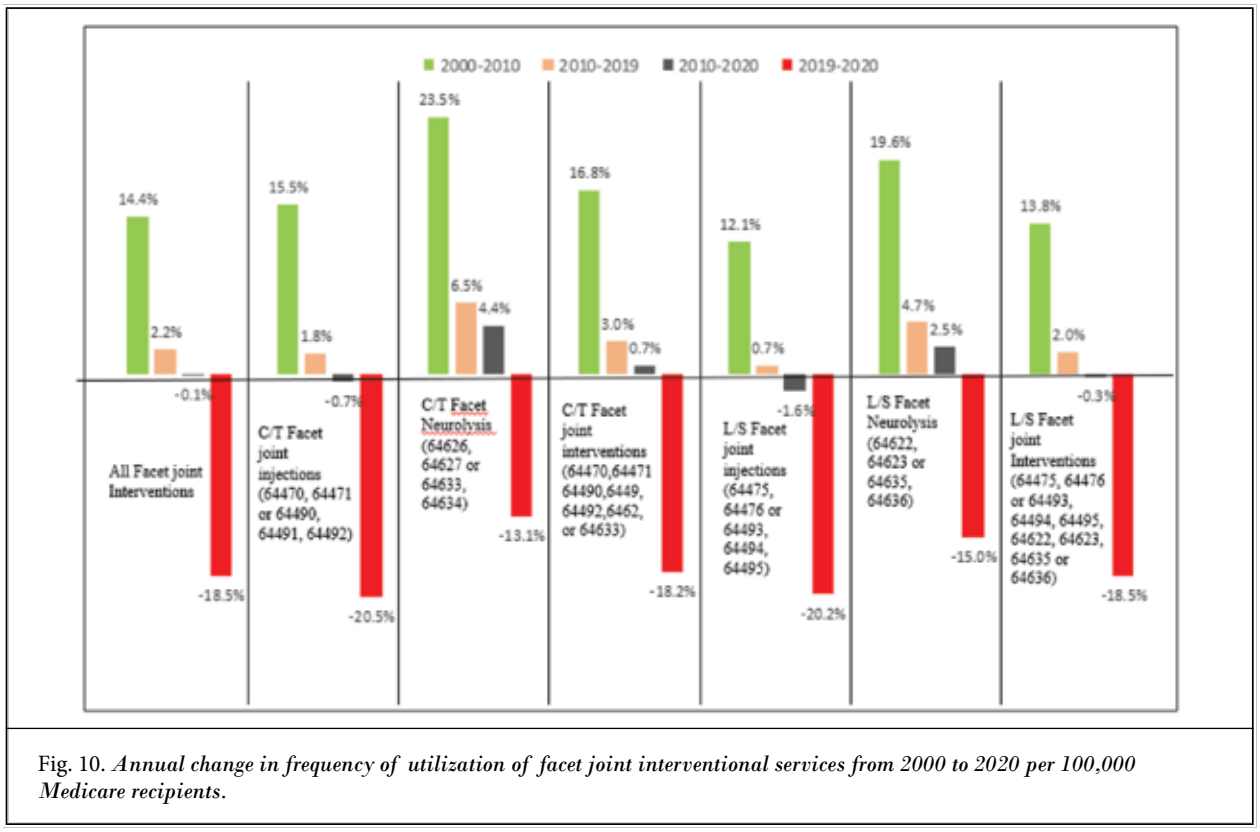


Fig. 10. *Annual change in frequency of utilization of facet joint interventional services from 2000 to 2020 per 100,000 Medicare recipients.*

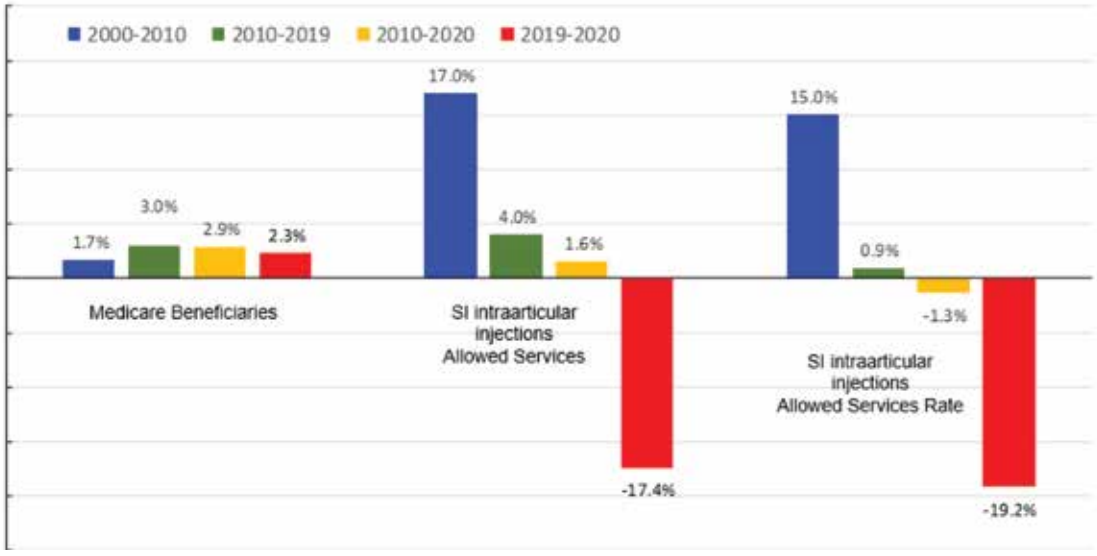


Fig. 11. *Comparative analysis of annual growth Medicare participation, utilization of sacroiliac joint intraarticular injections services, and rate (per 100,000 Medicare population) from 2000 to 2020 (geometric average annual change).*

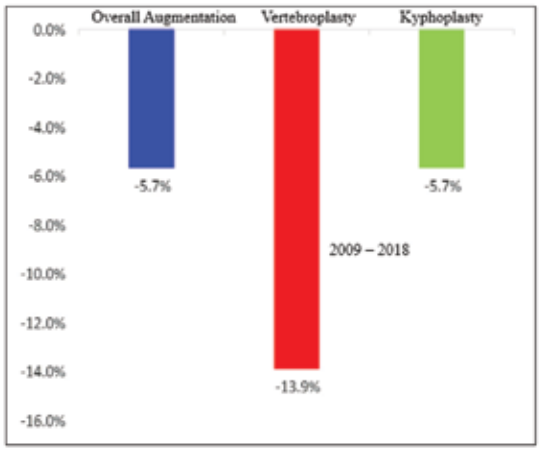


Fig. 12. *Annual change in relative utilization characteristics of kyphoplasty and vertebroplasty per 100,000 Medicare population.*

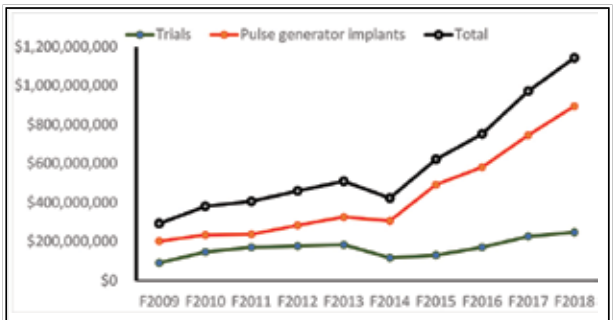


Fig. 13. *Increasing expenditures of spinal cord stimulator trials and pulse generator implants.*

In contrast, implantation of neurostimulator electrodes with paddle leads with laminectomy, and placement of spinal pulse generator increased 142% increase overall, with an annual increase of 10.3%.

Analysis showed that total inflation-adjusted expenditures for these procedures increased 291% from 2009 to 2018, with 16.4% annual increase (146). These were 125% higher than for facet joint interventions, and 138% higher than epidural interventions in 2018 (Fig. 14). In contrast, these expenditures were 55% below the expenditures for facet joint interventions, and 66% lower than for epidural injections in 2009. Trial to implant ratio improved from 42.5% in 2009 to 63.6% in 2018. An overwhelming majority of trials (90%) were performed by nonsurgical physicians, whereas only 56% of implants were performed by non-surgeons.

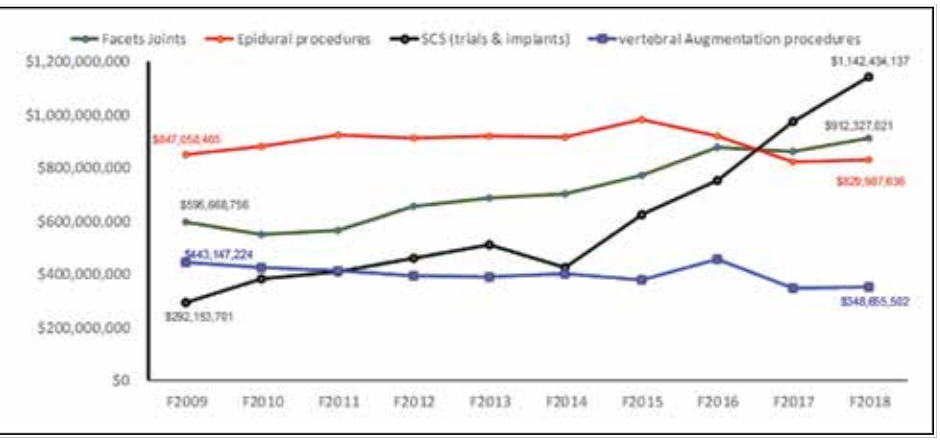


Fig. 14. *Total cost for facet joints interventions, epidural services, spinal cord stimulators and vertebral augmentation procedures on Medicare beneficiaries.*

5.0 Effectiveness of Non-Opioid and Non-Pharmacological Therapies

Key Question 3. What is the effectiveness of non-opioid and non-pharmacological treatments?

5.1 Non-Opioid Pharmacologic Therapy in Chronic Pain

Non-opioid, pharmacologic therapies commonly prescribed for chronic pain include oral and topical agents. The most utilized modalities are nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, including serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclics (TCAs), anticonvulsants, acetaminophen, and muscle relaxants (147-150). Other commonly used pharmacological agents are topical preparations, including diclofenac, capsaicin, and lidocaine. Non-opioid pharmacologic therapies are associated with risks, particularly in older adults, pregnant patients, and patients with certain cardiovascular, renal, gastrointestinal, and hepatic comorbidities (13). NSAIDs have been widely used both in the United States and multi-nationally, since the isolation of salicylate in the early nineteenth century, and subsequent formulation of aspirin (acetyl salicylate) by Felix Hoffman in 1897 (150,151). NSAIDs have been associated with serious gastrointestinal and major coronary events (13,151,152) and have been associated with 30% of hospital admissions for preventable adverse drug reactions (153). The CDC guidelines (13) show moderate quality evidence (with small improvement) for the use of NSAIDs in treating chronic low back pain (154). For other pain conditions, the evidence is moderate for short-term use, and despite this level of evidence, the guidelines strongly recommend the use of NSAIDs in treating such disorders.

Antidepressants including have been associated with nausea and sedation (147,152). Pregabalin and gabapentin are frequently prescribed with hopes that they can provide opioid-sparing effects. Notably in this regard, on December 19, 2019, the FDA issued the following warning: FDA In Brief: FDA requires new warnings for gabapentinoids about risk of respiratory depression: "Reports of gabapentinoid abuse alone, and with opioids, have emerged and there are serious consequences of this co-use, including respiratory depression and increased risk of opioid overdose death." Increases in non-serious adverse events have been found with anticonvulsants pregabalin (blurred vision, cognitive effects, sedation, weight gain, dizziness, and peripheral edema) and gabapentin (blurred vision, cognitive effects, sedation, and weight gain) (13,147).

In an AHRQ review utilized in CDC guidelines, McDonagh et al (147) described the following for the use of non-opioid pharmacological treatments for chronic pain:

- In the short term, improvement in pain and function was small with specific anticonvulsant, moderate with specific antidepressants in diabetic peripheral neuropathy/post-herpetic neuralgia and fibromyalgia, and small with NSAIDs in osteoarthritis and inflammatory arthritis.
- In the intermediate term, evidence was limited, with evidence of benefit for the use of memantine in fibromyalgia, and for serotonin/norepinephrine reuptake inhibitor (SNRI) antidepressants in treating low back pain and fibromyalgia.
- In the long term, there was insufficient evidence to draw conclusions. In general, evidence on QOL was limited, and no treatment achieved a large improvement in pain or function.
- Small to moderate, dose-dependent increases in withdrawal due to adverse events were found with

the SNRIs duloxetine and milnacipran, anticonvulsants pregabalin and gabapentin, and NSAIDs. Large increases in withdrawal signs and symptoms were seen with oxcarbazepine. Also, NSAIDs have increased risk of serious gastrointestinal, liver, and cardiovascular adverse events.

5.2 Non-Pharmacologic and Non-Interventional Techniques in Managing Chronic Pain

There are many non-invasive or non-interventional techniques for managing chronic pain including exercise programs, physical therapy, acupuncture, massage, transcutaneous electrical nerve stimulation (TENS), biofeedback therapy, and chiropractic treatments.

5.2.1 Exercise Programs

Structured exercise programs can be crucial in managing chronic pain. In fact, all guidelines, local coverage determinations (LCDs), and medical policies mandate some form of physical therapy and structured exercise programs prior to employing any type of interventional techniques or opioid therapy. The CDC guidelines (13) describe high quality evidence for exercise therapy for back pain, fibromyalgia, and hip and/or knee osteoarthritis, for reducing pain and improving function immediately after treatment and for sustained improvement for at least 2 to 6 months (152,155-158). Multiple guidelines published in the past have recommended aerobic, aquatic, and/or resistance exercises for persons with various types of chronic pain, including osteoarthritis of the knee or hip, back pain, and fibromyalgia (154,159-161). In addition, motor control exercise for low back pain has been reported to be more effective (for improvement in function) than minimal intervention (162,163).

Studies of the effectiveness of exercise therapy have shown moderate effectiveness for treatment of chronic low back pain, but there is no clear evidence to indicate that one form of exercise is more effective than another. A review of 217 RCTs, with 20,969 participants with non-specific low back pain of > 12 weeks concluded that Pilates, McKenzie, and functional restoration approaches were more effective than other types of exercise in reducing pain intensity and functional limitations (164). A systematic review with meta-analysis (with inclusion of 79 RCTs) of exercise-based interventions as compared to placebo noted exercise training to be more effective than true control or standard medical care in reducing chronic musculoskeletal pain (165).

5.2.2 Physical Therapy

Physical and occupational therapy have been long regarded as a supportive modality to treat acute and chronic pain. The goals of these modalities are to decrease pain, and increase function to prevent unnecessary disability, facilitate activities of daily living, and improve overall quality of life. A systematic review of the effects of occupational therapy interventions on chronic pain recommended individualization of techniques, and education on biomechanics as important for therapeutic success (166). Evaluating the use of physical therapy and rehabilitative interventions in 83 studies with 8,816 patients with chronic low back pain, it was found that exercise therapy reduced pain intensity, disability and improved long-term function when compared to non-exercise conventional care; and behavioral therapy was effective, at least in the short-term, for decreasing pain intensity as compared to no treatment (167).

But physical therapy is considered a high-cost treatment option. A randomized trial found no difference in reduction of chronic low back pain intensity, frequency, or disability between patients assigned to relatively low-cost group aerobics and those assigned to individual physiotherapy or muscle reconditioning sessions (168). Still, physical therapy can be helpful for patients who are not well motivated, non-drug compliant, have limited access to safe public spaces or public recreation facilities for exercise, and/or whose pain has not improved with low intensity physical exercise (13). A randomized trial (169) demonstrated that a stepped exercise program, in which patients were initially offered an internet-based exercise program and progressively advanced to bi-weekly coaching calls, and subsequent in-person physical therapy as needed (if not improved by these previous modalities) reported meaningful reductions in pain caused by osteoarthritis of the knee, with 35% of patients ultimately requiring in-person physical therapy.

5.2.3 Acupuncture

Acupuncture has been increasingly used to treat patients with chronic pain. Acupuncture is the most popular supplemental alternative therapy and has been widely used to treat various types of pain (170,171). There has been abundant literature evaluating acupuncture to alleviate non-specific musculoskeletal pain (172), osteoarthritis (173), chronic headache (174), and shoulder pain (175). In addition, it has been shown that acupuncture may lead to reduced use of opioids

(176). A clinical study found that among patients with migraine without aura, (true) acupuncture is associated with a long-term reduction in migraine recurrence, compared with sham acupuncture (177). Analgesic effectiveness of acupuncture on chronic pelvic pain has been assessed in a systematic review and meta-analysis (178), which showed that monotherapy with acupuncture produced a significantly lower pain level than in controls. Another systematic review and meta-analysis of acupuncture for chronic prostatitis or chronic pelvic pain syndrome (179) evaluated 11 high quality RCTs and showed that acupuncture has demonstrably measurable benefits in reducing pain in chronic prostatitis, and chronic pelvic pain.

Acupuncture also has been evaluated for its effectiveness against fibromyalgia (180); it was shown that in both fibromyalgia patients and animal models, acupuncture may improve pain symptoms by regulating afferent and descending inhibitory pain pathways, as well as by modulating peripheral inflammation and the autonomic involvement.

A review by Trivedi et al (181) concluded that acupuncture is effective for short-term treatment (i.e., lasting 3 to 5 months) of chronic pain.

Several guidelines have been published with differing recommendations for the treatment of low back pain with acupuncture (182-184), as based to varying degrees upon multiple systematic reviews that have shown the effectiveness of acupuncture (versus sham treatments), although the evidence was somewhat inconsistent across these reviews. Further, among the 16 systematic reviews, 7 showed that acupuncture produces greater pain relief and functional improvement than no treatment in short-term follow-up; and 5 systematic reviews found that acupuncture (when used in addition to conventional therapy) provided short-term improvements in pain and function in patients with chronic low back pain (185-188). A meta-analysis of 25 studies of 6,200 patients (189) compared acupuncture to sham treatments, and showed significant although small, positive differences, between patients treated with acupuncture, and controls who received NSAIDs, muscle relaxants, and other analgesics.

5.2.4 Massage

Massage has been traditionally thought to provide pain relief through physical and mental relaxation, and by increasing the pain thresholds via the release of endogenous opioids (i.e., endorphins and enkephalins) (190). The putative analgesic mechanism of massage involves the local stimulation of large nerve fibers that incur an inhibitory effect on both nociceptive primary afferents, as well as mastocytes and/or T-cells (191). Massage may also influence the autonomic nervous system by inducing a shift from sympathetic to parasympathetic response or vice versa (192). Despite not yet fully knowing mechanisms involved, there have been numerous trials, literature reviews, and systemic meta-analyses that have investigated its efficacy and/or effectiveness (193-195).

A meta-analysis by Farber et al (193) found the quality of evidence to be low to very low primarily because of experimental/study bias and imprecision. It was found, for example, that for acute low back pain, massage was better for pain control than inactive controls in the short term but was not of benefit for improving function. It was also shown that in patients with subacute and chronic low back pain, massage was better than inactive treatments in the short term but not in the long term. The analysis also showed that when compared to active controls, massage was better for pain both in the short term and at long term follow-up. Functional improvement was found in patients with sub-acute and chronic low back pain as compared with inactive controls, but only at short-term follow-up.

A review by Furlan et al (194) indicated that 8 of 13 articles revealed a high risk of bias. In two of the studies, massage was reported to be superior in reducing pain and incurring functional improvements at short and long-term follow-ups. Eight studies showed that massage was similar to exercise, and better than joint mobilization, relaxation therapy, physical therapy, acupuncture, and self-care education for decreasing symptoms, when compared to other active treatments. When positive effects of massage were obtained, these effects were shown to be durable for up to one year after the end of treatment. Two studies showed that acupuncture and massage elicited better results than Swedish massage alone, and another trial concluded that Thai massage produces similar results to Swedish massage. Overall, there was moderate evidence of short and long-term improvement in pain and function with massage as compared to sham or other treatments, but the differences in degree of improvement were small. The review showed that massage might be beneficial for those patients with subacute and chronic low back pain, especially when combined with exercise and (pain control, and activity of daily living) education.

5.2.5 Transcutaneous Electrical Nerve Stimulation (TENS)

Despite the common use of TENS for pain management, evidence for its effectiveness remains not conclusive. Due to this lack of optimal evidence TENS is not a treatment that is typically covered by insurance and is often restricted for use in RCTs. Previous health technology assessments and meta-analyses have found no benefit of TENS in patients with chronic pain (196,197). Some have criticized the recent meta-analysis for a paucity of RCTs, and the fact that the assessment did not compare the effectiveness of TENS with other nerve stimulation therapies.

Overall, multiple systematic reviews and meta-analyses (167,198-201) showed lack of significant improvement of pain with TENS use; however, there was some evidence to support that it may improve functional disability in the short-term, as compared to control treatments. Contrarily however, one systematic review (201) showed that TENS was indeed effective in reducing pain intensity immediately post treatment in patients with neck pain; however, in these cases, TENS was employed as an adjunct therapeutic modality. Similarly, another review (202) concluded that there was moderate certainty of evidence that pain intensity is lower during or immediately after TENS as compared to placebo.

5.2.6 Chiropractic Treatments

Mobilization and manipulation therapies are widely employed to treat patients with chronic pain; however, debate continues around their actual effectiveness, dosing, and safety.

It is important to differentiate different types – and putative mechanisms - of manipulative treatments that are utilized in osteopathic and/or chiropractic practice. The effectiveness of spinal manipulative therapy (SMT) for treating chronic low back pain is debated and recommendations for use are heterogeneous. According to a systematic review by de Luca et al (203) there is moderate evidence supporting the use of manual therapy to reduce pain levels and alleviate disability.

In some health systems, SMT is treated as a first line option but in others it is most often recommended along with other spinal treatments, or not recommended at all (154,204). There is also at least one recent review of guidelines that suggests that SMT should be considered as a second-tier treatment option after exercise and behavior therapy (205).

As noted, there are many theories as to the mechanism of action of SMT and most address biomechanical and/or neurophysiological processes (206). The biomechanical theory proposes that SMT acts to reduce the mechanical stresses, and the neurophysiological theory suggests that SMT affects the primary afferent neurons from the paraspinal musculature to engage systems that control pain processing (207,208). It remains unclear if and to what extent (1) these putative mechanisms are distinct, or work in tandem/synergy; (2) the differential use of certain forms of manipulative therapies may selectively engage either of these mechanisms; and (3) such differing techniques have therapeutic utility against particular types of pain.

A Cochrane review by Rubinstein et al (209) found that there was moderate quality evidence indicating that SMT was no different than other treatments for short term pain relief, but that it produced a small improvement in function. They also found high quality evidence that SMT had a small positive effect for short term pain relief, and small to moderate positive effects for improvement in function when compared to other (non-recommended) therapies. These results were similar for intermediate and long-term outcomes.

Most adverse events seen with SMT were transient and of mild to moderate severity, although there has been considerable consideration and concern about the safety of certain types of SMT in patients with demonstrable existing anatomical variation in cervico-cerebral vasculature. Overall, it was found that SMT produces similar clinical results when compared to recommended therapies for patients with chronic low back pain and seemed to be better than non-recommended interventions for improvement of short-term function.

Coulter et al (210) published a systematic review and meta-analysis of manipulation and mobilization for treating chronic low back pain with inclusion of 51 trials meeting criteria, and 9 trials with 1,176 patients. It was concluded that there is moderate quality evidence that manipulation and mobilization are likely to reduce pain and improve function for patients with chronic low back pain. In addition, it was shown that manipulation appears to produce a larger effect than mobilization, even though both therapies appear safe and multimodal programs may be a promising option.

Coulter et al (211) also performed a systematic review and meta-analysis of the use of manipulation and mobilization for treating chronic nonspecific neck pain. They included 47 randomized trials (with low risk of bias), which included 4,460 patients with nonspecific chronic neck pain. With acknowledgement of the aforementioned caveats focal to evaluating patients for

existing contraindications for cervical manipulation/mobilization, it was concluded that studies published since January 2000 provide low-moderate quality evidence that various types of manipulation and/or mobilization can reduce pain and improve function in patients with chronic nonspecific neck pain, as compared to other interventions. Further, it appears that multimodal approaches, in which multiple treatment approaches are integrated, might have the greatest potential impact.

A RAND review by Sherbourne et al (212) also addressed coping and management techniques used by chronic low back pain patients receiving chiropractic treatment. It was found that respondents reported using an average of 9 coping behaviors in the prior 6 months. Persons with chronic low back pain were proactive in their coping strategies and frequently used self-care coping strategies, such as those provided in patient education provided by chiropractors. Another RAND publication showed that 79% of patients assigned positive responses to the time spent with a chiropractic provider, and the majority of the patients rated their provider at the top of the scale. These results also showed that more chiropractic patients reported positive impressions of their clinical encounters, with key factors being always getting prompt answers to their questions, and always being seen within 15 minutes of their scheduled appointment time.

5.2.7 Biofeedback Therapy

Behavioral and psychological treatments have been shown to be effective in decreasing pain, improving function, and reducing psychological distress (212). There is some evidence that psychological treatments are more effective than medication and physical therapy in the short term (213).

Biofeedback is a psychological treatment that may be performed independently or as an adjunctive therapy with interventional and non-interventional medical approaches, physical therapy and/or cognitive behavioral therapy. During biofeedback treatments, patients receive information about physiological processes such as respiratory rate, heart rate, and/or muscle tension. Biofeedback teaches the patient to self-regulate their physiological processes with the assistance of the information that is "fed back" to them, thereby providing an informational-regulatory loop, in which patients actively respond to informational cues about their physiological state (213). The goals of biofeedback are to teach patients to consciously modulate physiological processes in order to positively affect their responses, functions, and (psychological and behavioral) coping mechanisms.

There are different types of biofeedback treatments including electromyographic, heart rate variability respiratory biofeedback, and neurofeedback, with electromyographic biofeedback and neurofeedback currently being most common. Somato-cognitive, and somato-neurocognitive and neurocognitive-somatic regulator processes have been described as putative mechanisms of biofeedback and neurofeedback, respectively. The benefits of biofeedback/neurofeedback have been shown in the treatment of several different chronic pain conditions (214). In previous meta-analyses, such modalities have been shown to be more effective than cognitive behavioral therapy and physical therapy (215,216). It has been difficult to establish conclusions on the general effectiveness of these therapies due to the heterogeneity of the treatments, mechanisms involved (as relevant and specific to particular types of pain), and the common practice of including such treatment as an adjunctive to with other interventions.

A meta-analysis by Sielski et al (216) evaluated short term and long-term effects of biofeedback on pain and focused on studies that reported biofeedback as a stand-alone intervention, or an intervention comprising at least one-fourth of the total treatment plan (216). The goal was to determine the efficacy of biofeedback as compared to different control groups and to identify important components of observed treatment effects. It was found that biofeedback incurred a significant small-to-medium reduction of pain that was durable to eight-months follow-up, and that it was also effective in reducing signs and symptoms of depression, disability, and muscle tension, and in improving patients' cognitive coping skills (216). The moderator analyses showed that longer biofeedback treatments were more effective for decreasing disability, and that a greater proportion of biofeedback in the overall treatment strategy was more effective for reducing depression. Thus, it was concluded that biofeedback treatment can be used as a standalone therapy or as an adjunctive intervention and can produce improvement on various pain-related outcomes both in the short and long term.

5.2.8 Multidisciplinary Rehabilitation

As has been explicitly recognized, addressed, and advocated, the multi-disciplinary approach to pain management is effective, efficient, and ethically appropriate – and arguably warranted -- given the multi-dimensional

realities, factors, dimensions, and problems of chronic pain. A randomized controlled trial of 521 patients with chronic low back pain (217) demonstrated that the use of multi-modal (non-pharmacological) interventions, inclusive of cognitive therapy, mindfulness-based stress reduction, and behavior therapy produced reductions in pain and improvements in physical function, mood, and sleep disturbance. To be sure, such an integrative multidisciplinary approach can, and should, include some construct and means to provide coordination of, and access to not only cognitive-behavioral therapies, but each and all of the aforementioned therapeutic modalities. Multidisciplinary rehabilitation for pain management involves coordinated care by a team of clinicians, physical and/or occupational therapists, mental health and behavior therapists, and additional specialist services when needed (13,218,219). CDC guidelines support the idea that multimodal therapies and multidisciplinary biopsychosocial rehabilitation can reduce long-term pain and disability, as compared to usual care and/or with physical treatments alone. Apropos this multidisciplinary approach, non-pharmacological therapies can also provide synergistic benefits when non-opioid, and/or opioid pain medications are used (13,23). CDC guidelines recommend that medications should ideally be combined with non-pharmacologic therapies to provide greater benefits in improving patients' pain and function.

But as noted in CDC guidelines, multimodal therapies are not always available or reimbursed by insurance and, if and when used iteratively, can be time consuming and costly for patients, and there are disparities in abilities to access multimodal care (13,23). In practical terms, multidisciplinary therapies are the least available and are expensive (and such non-availability and expense can be time and cost inefficient - and in these ways both economically and ethically problematic, particularly if/when utilized outside the setting and fixed costs of a multidisciplinary pain treatment center. CDC guidelines also highlight evidence that less intense multidisciplinary rehabilitation can be as similarly effective as high intensity multidisciplinary rehabilitation (13,152); and consider combination of medications (such as 2 non-opioid medications with different mechanisms of action or a non-opioid with an opioid medication) as part of multidisciplinary management.

While reported short and intermediate outcomes of multidisciplinary care of chronic pain were certainly indicative of clinical effectiveness, third-party payor support for MPCs and integrative multimodal care of chronic pain patients all but disappeared by 2010, and the paucity of settings, programs and support for this approach has led to an absence of viable evaluations of long-term effects of coordinated multimodal care. Reflective of this, present evidence of long-term benefits of multidisciplinary pain management varies from small to none (152,154,220). This is reflected in a recent review (218) that reported insufficient evidence of multi- or interdisciplinary pain rehabilitation for lumbar radiculopathy (154). Similarly, a Cochrane review (220) also showed that pain, disability, and work outcomes among candidates for spinal fusion were similar at 2-years between those treated surgically and those treated with multi- or interdisciplinary pain rehabilitation.

6.0 Effectiveness of Interventional Techniques

Key Question 4. What is the effectiveness of interventional techniques in managing chronic pain?

Among the various modalities of available treatments, interventional techniques, which include various types of epidural injections, facet joint interventions, sacroiliac joint interventions, other types of nerve blocks, and multiple neuromodulation techniques have been utilized in managing subacute and chronic pain. Appropriate indications and medical necessities have been developed for most of the interventions using evidence-based principles. Multiple systematic reviews have been performed for epidural interventions, facet joint interventions, and neuromodulation techniques with guidelines developed based on evidence and consensus. Despite this, discordant conclusions exist that establish multiple challenges to the conduct of the RCTs of interventional methods, based on approach (e.g., for epidural, transforaminal, interlaminar or caudal), controlled design (e.g., active-controlled vs. placebo-controlled), technical performance (e.g., with or without fluoroscopy), alternative techniques, and outcome assessments ranging from absolute difference between 2 groups to minimally clinically important difference (MCID) with assessment of proportion of patients (23,26,28,53,123-126,221-253). Various authors (27,28,45,46,222-242,245-270) have described issues related to the discordant conclusions based on IOM guidelines, conflict and/or confluence of interest, confusion of verifiable facts with opinions, judgements based on beliefs, and conviction based on personal values, which ultimately lead to prejudicial perspectives and statements that, in the main, are based on insufficient or unexamined evidence.

While these concerns are noteworthy, it is important to emphasize that to date, there have been extensive evaluations, and systematic reviews that have been considered as the ethically-sound basis for establishing evidence informing and formulating guidelines. The guidelines utilizing appropriate methodology in evidence synthesis and development are included here (27,28).

Manchikanti et al (27) published evidence-based guidelines for epidural interventions, which included 47 systematic reviews and 43 RCTs covering all types of epidural procedures, inclusive of percutaneous adhesiolysis.

Manchikanti et al (28) published evidence-based guidelines for facet joint interventions in 2020 in which 7 systematic reviews, 35 RCTs, and 25 observational studies covering all types of facet joint interventions were included. In addition to the systematic reviews included in the aforementioned guidelines published in 2021, herein those systematic reviews and RCTs that have been published subsequently are also considered for current guideline formulation.

7.0 Prescription Opioids and Opioid Epidemic

7.1 Opioids in Chronic Pain

Over the years, multiple reviews have been performed in reference to opioid use, overuse, abuse, and a multitude of adverse consequences including opioid-related deaths (15,21,27-29,35,271-281). In reviewing the prescription trends in the United States, multiple reports over the years have captivated the country with most attention paid to the opioid epidemic, which changed in 2020 in the face of the COVID-19 pandemic (2,5,282-303). Patients with chronic pain and addiction have been affected by disruptions to life and healthcare during COVID. Choe et al (287) reviewed the impact of the COVID-19 pandemic on chronic pain and opioid use in marginalized populations. They included 25 articles, in the final analysis, with result showing the differential distribution of pain burden across marginalized groups and how it serves to heighten the existing marginalized groups and how it served to heighten the existing disparities. They described that service disruptions due to social distancing orders and infrastructural limitations prevented patients from receiving the care they needed, resulting in adverse psychological and physical health outcomes. Efforts to adapt to COVID-19 circumstances included modifications to opioid prescribing regulations and workflows and extended telemedicine services. However, at the end of the global emergency, as well as the emergency in the United States (304-306), the changes in multiple regulations related to opioid prescribing, as well as limited access to these prescriptions because of the restrictions of telemedicine services impacted and continues to impact not only the marginalized populations, but also the entire population of chronic pain.

Prescription opioid trends in the United States has been published by the IQVIA Institute (307-310) and adapted by all authorities (2,5,9,13,15,16,311,312). The use of prescription opioids, measured by MME dispensed, increased from 27 billion MME in 1992 to 246 billion MME in 2011, and has decreased since then to an estimated 100 billion MME in 2020 (311). The data also showed that the declines in opioid prescribing measured in MME per capita were largest in states that previously had the highest rates of opioid prescribing. From 2018 to 2019, every state experienced a decline in MME per capita (309). The data also shows that prescription opioid use segmented by MME per capita (309) demonstrated significant changes with a 70% decline in prescriptions of 90+ MME per day, 32% for prescriptions of 50 to 90 MME per day, 35% for prescriptions of 20 to 50 MME per day, and 11% for less than 20 MME per day from 2011 to 2019, as shown in Fig. 15 (309).

The data on opioid dispensing rates published by the CDC (312) also shows significant changes. CDC data is available from 2006 to 2020 based on overall prescriptions in the United States, state wise data per 100 persons, and based on county level data. The findings are as follows:

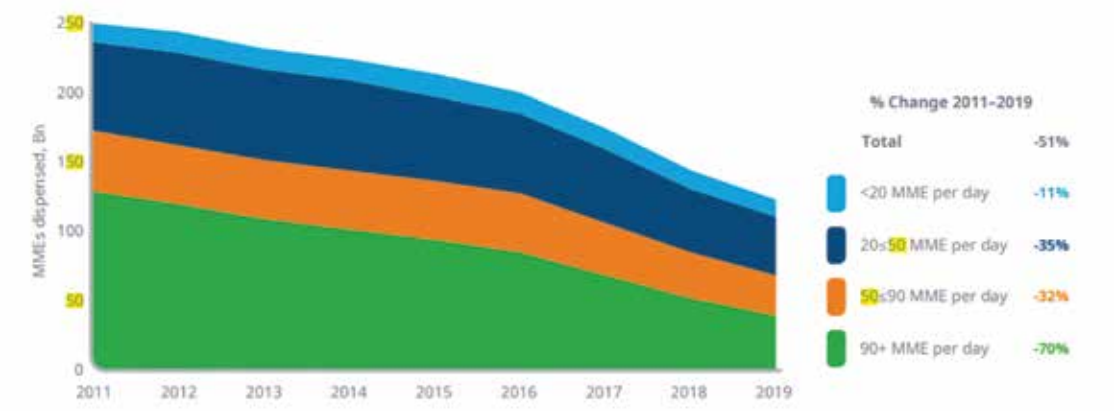


Fig. 15. *Prescription opioid use segmented by morphine milligram equivalents (MME) per day, 2011–2019.*

Source: IQVIA Xponent, Mar 2020; IQVIA Prescription Audit; IQVIA Institute, Nov 2020.

- After a steady increase in the overall national opioid dispensing rate starting in 2006, the total number of prescriptions dispensed peaked in 2012 at more than 255 million and a dispensing rate of 81.3 prescriptions per 100 persons.
- The overall national opioid dispensing rate declined from 2012 to 2020, and in 2020, the dispensing rate had fallen to the lowest in the 15 years, for which we have data at 43.3 prescriptions per 100 persons (total of more than 142 million opioid prescriptions).
- Nonetheless, in 2020, dispensing rates continued to remain very high in certain areas across the country.
- In 3.6% of U.S. counties, enough opioid prescriptions were dispensed for every person to have one.
- While the overall opioid dispensing rate in 2020 was 43.3 prescriptions per 100 people, some counties had rates that were nine times higher than that.

The total number of prescriptions changed from 216 million in 2006, increasing to 251 million in 2010, 255 million in 2012, and gradually declining from thereon to 143 million in 2020 (312). These rates of decline show that overall decrease from 2006 to 2020 of 33%, 2010 to 2020 of 43%, and from 2012 the highest levels of prescriptions to 2020 of 44%. The opioid dispensing rate per 100,000 persons also changed from 72.4 in 2006 to 81.2 in 2010 and decreased to 43.3 in 2020 with a decrease of 46.67% from 2010 to 2020.

Even though statistics highlight the overall decrease in prescriptions as well as MMEs, it is famously described that the United States remains the world's largest consumer of prescription opioids (311). A 2022 congressional report (311) stated that the amount of prescription opioids dispensed per million people per day in the United States is approximately 4 times the median for the member countries of the Organization for Economic Cooperation and Development (OECD). However, a country level observational study of global consumption of prescription opioid analgesics between 2009 to 2019 by Jayawardana et al (313) showed consumption was higher in the United Kingdom and Germany than the United States, followed by Canada and other countries as shown in Fig. 16. Thus, like all other data there is variability based on not only what is being studied, but also who is studying it. Further, this publication (313) showed decline of opioid rates from 216 to 152 MME per 1,000 persons between 2009 and 2019, with consumption declines in the United States and Germany. In addition, as reflected in this publication, substantial heterogeneity in opioid consumption not only in the United States, but globally reflects the challenges involved with providing adequate access to opioid treatment while avoiding potential misuse.

A publication studying opioid prescription patterns in Germany and the global opioid epidemic by Rosner et al (314) showed that there was an increase in the number of patients with opioid prescriptions and defined the daily doses of opioids per recipients in Germany over time. Further, most opioid prescriptions were for patients with non-cancer pain. Opioids were more common in older people and women in the North of Germany. Surprisingly enough, Fentanyl was shown to be the most prescribed strong opioid in outpatient settings. Even though patterns of opioid prescriptions followed trends in other developed countries, the authors felt that there were no signs of an opioid epidemic in Germany.

Overall, these decreases in volume and dosage along with redistribution among the populations have been driven by changes in clinical usage, regulatory and reimbursement policies, progressively more restrictive legislation enacted since 2012, and finally the guidelines from the CDC. A multitude of these legislations, including the National All Schedules Prescription Electronic Reporting (NASPER) Act, have resulted in PDMPs in all states and which facilitates decreases in inappropriate prescriptions (35,277,311,312,315-339).

7.2 Opioid Epidemic and Prescription Opioid Deaths

There has been substantial debate in relation to opioid overdoses and prescription opioid pain reliever relationships including the nomenclature (7,8). Thus, it is crucial to realize and report that all opioid overdose deaths are not related to prescription opioid overdose deaths and the illicit opioid epidemic is not a prescription drug epidemic. Josh Bloom (8) described issues related to inappropriate classification and changes in the wording. As per CDC terminology, natural opioids include codeine and morphine, whereas semisynthetic opioids include oxycodone and heroin. In addition, synthetic opioids, other than methadone, include fentanyl and tramadol. In contrast, the National Institute of Standards and Technology (NIST) (17), a subsidiary of the U.S. Department of Commerce, provided a separate classification based entirely on CDC data as shown in Fig. 17. In contrast to the CDC, they made some changes

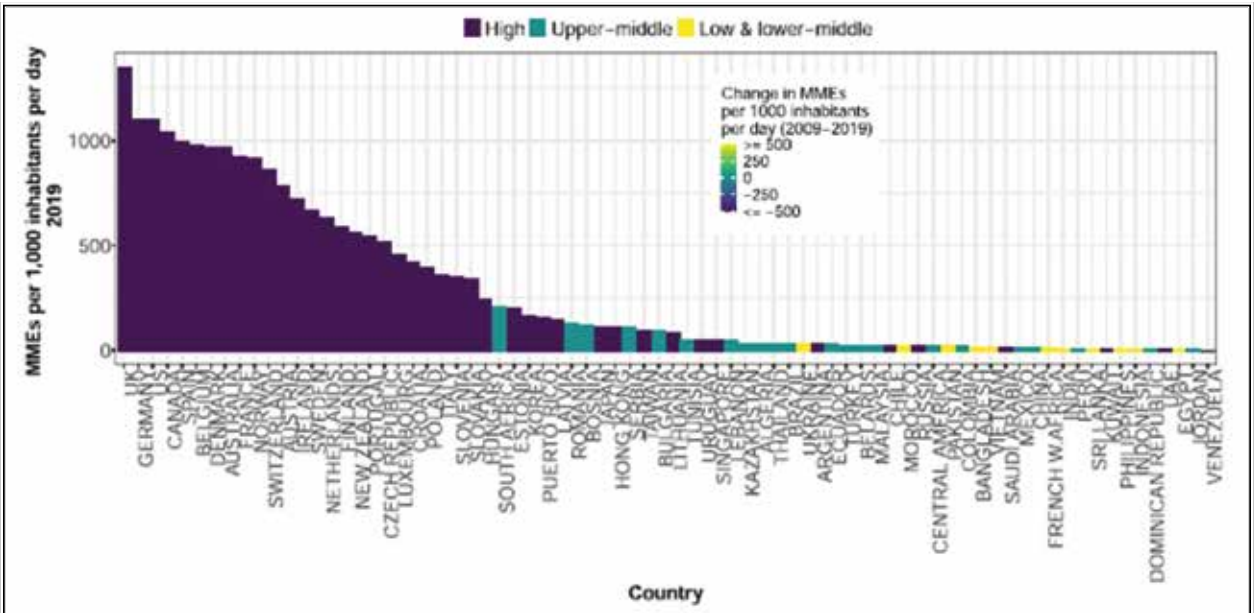


Fig. 16. *Global opioid consumption by country:2009-2019. (A) Change in the national opioid consumption rate between 2009 and 2019 in morphine milligram equivalents (MME) per 1,000 inhabitants per day. The color scale is continuous with darker shades indicating negative values and lighter shades indicating positive values. Countries with no data shaded in grey. (B) Opioid consumption rate by country for 2019 in MME per 1,000 inhabitants per day. Colors represent the 2014 World Bank income classification of high, upper-middle, and low- and lower-middle income countries.*

Adapted and modified from: Jayawardana S, Forman R, Johnston-Webber C, et al. Global consumption of prescription opioid analgesics between 2009-2019: A country-level observational study. *EClinicalMedicine* 2021; 42:101198 (313).

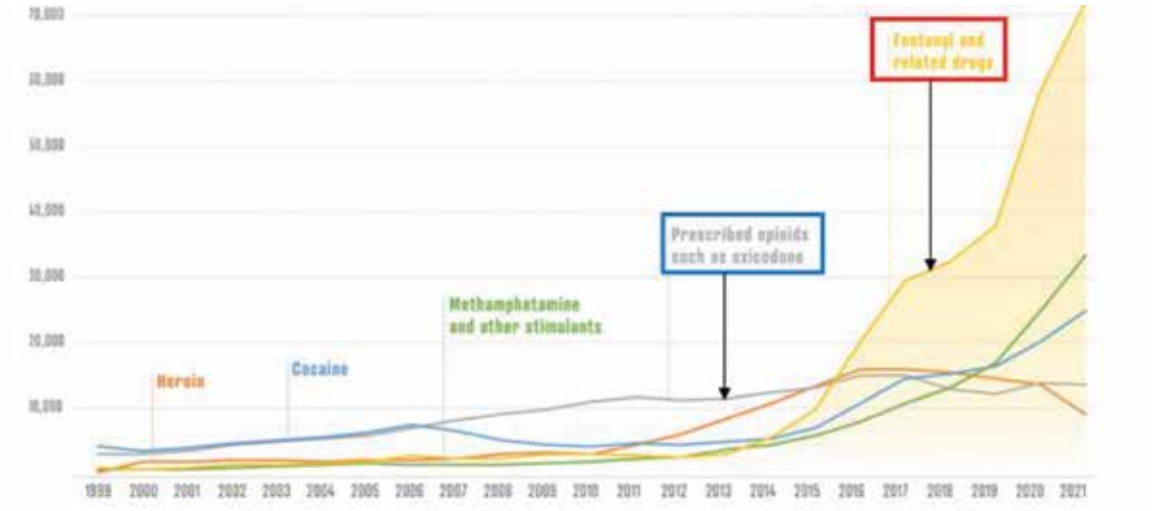


Fig. 17. *Overdose deaths by drug – clearly and accurately portrayed.*

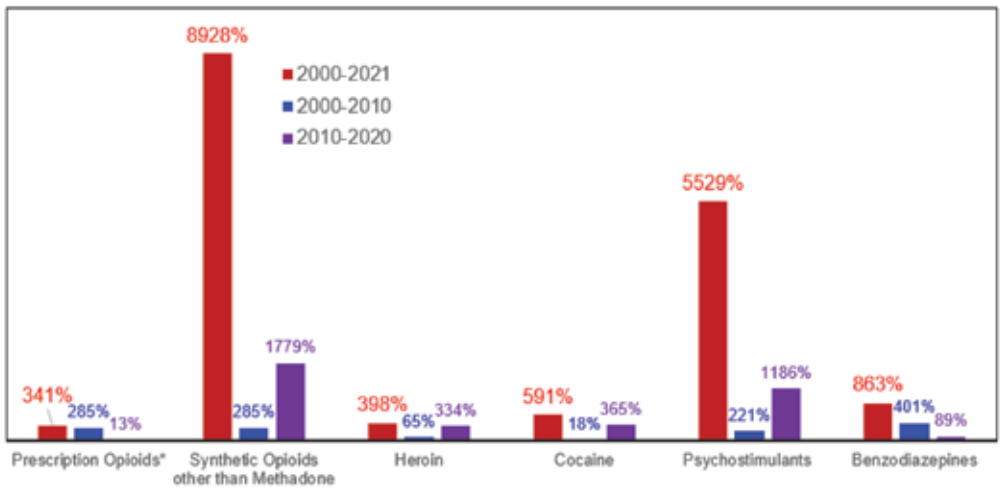
"Semi-synthetic opioids" has been replaced by "prescribed opioids, such as oxycodone [sic]. The category formerly titled "Synthetic opioids other than methadone" is now "fentanyl and related drugs." Quite a difference. Both of these categories are now clearly defined. Credit: B. Hayes/NIST (March 2021) based on data from the U.S. Centers for Disease Control and Prevention.

which identify as heroin, cocaine, methamphetamine, and other stimulants, prescription opioids such as oxycodone, fentanyl, and related drugs. Both graphs show exponential increases in fentanyl and its related drug deaths; however, there are subtle differences with prescription opioids such as oxycodone showing a clearer picture.

The evaluation of the relationship between opioid overdoses, OTAs, and prescription opioid pain reliever relationships in the United States has been described from 2010 to 2019 (7). As shown in Figs. 3 and 4, the relationships between total opioid doses, AOD, prescription opioid deaths, OTAs, and annual prescription sales, i.e., morphine milligram equivalents (MME) per capita Ire either nonexistent or significantly negative/inverse (20).

The analysis of quantification of opioid deaths showed a 13% increase from 2010 to 2021 and 16% from 2019 to 2020. In contrast, synthetic opioids other than methadone, primarily fentanyl increased 1,770% from 2010 to 2020, with an increase of 55% from 2019 to 2020. During the same period, psychostimulants with abuse potential (primarily methamphetamine) increased 1,186% from 2010 to 2020 and the rate was 47% higher in 2020 compared to 2019 (Fig. 18). During the same period, cocaine increased 365% from 2010 to 2020, whereas it increased 22% from 2019 to 2020. In contrast, deaths involving heroin increased 334% from 2010 to 2020, whereas they decreased 6% from 2019 to 2020.

The opioid paradox of overdose deaths in prescribing was also highlighted in a recent publication by Kharasch et al (330). They described an "opioid paradox" in that opioid overdose mortality has continued to increase despite steady reductions in opioid prescribing (Fig. 19) (277,278,331-333), similar to Aubry



	2000	2010	2017	2018	2019	2020	2021	Change 2000-2021	Change 2000-2010	Change 2010-2020	Change 2019-2020	Change 2020-2021
Prescription Opioids (natural & semi-synthetic opioids & methadone)	3,785	14,583	17,029	14,975	14,139	16,416	16,706	341%	285%	13%	16%	2%
Synthetic Opioids other than Methadone (primarily fentanyl)	782	3,007	28,466	31,335	36,359	56,516	70,601	8928%	285%	1779%	55%	25%
Heroin	1,842	3,036	15,482	14,996	14,019	13,165	9,173	398%	65%	334%	-6%	-30%
Cocaine	3,544	4,183	13,942	14,666	15,883	19,447	24,486	591%	18%	365%	22%	26%
Psychostimulants	578	1,854	10,333	12,676	16,167	23,837	32,537	5529%	221%	1186%	47%	36%
Benzodiazepines	1,298	6,497	11,537	10,724	9,711	12,290	12,499	863%	401%	89%	27%	2%

Fig. 18. *Quantification of opioid deaths 2000-2021.*

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 2/9/2023. Accessed on 5/3/2023 https://www.cdc.gov/nchs/products/databriefs/db428.htm

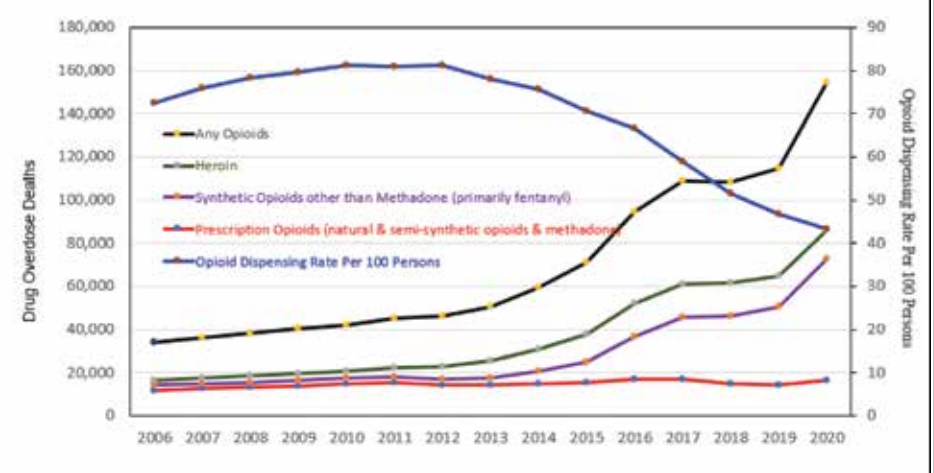


Fig. 19. *The opioid paradox. Opioid prescriptions are declining while opioid overdose deaths are increasing.*

Source: https://www.cdc.gov/nchs/products/databriefs/db428.htm
https://www.cdc.gov/drugoverdose/rxrate-maps/index.html
Accessed on 1/25/2022.

and Carr (7), as shown in Figs. 3 and 4. This is illustrated by an overall decrease in prescriptions both in numbers of patients exposed and average doses prescribed, but with a lack of decline of opioid overdose deaths, due to the increased rise of heroin and illicit fentanyl, and reversal of decline in 2020 of prescription opioid deaths.

Manchikanti et al (35) described various issues related to the opioid epidemic and pointed out the tragic failures of the current systems to control misuse. Thus, multiple factors propagated the epidemic, starting with the fifth vital sign pain movement together with a confluence of interest and a failure of oversight from the opioid industry, which was largely responsible for the epidemic. Multiple confluences of interests were reported, including promotion of opioids based on inadequate evidence with advocacy (334). Further fuel was added with the establishment of pain as the fifth vital sign, which was embraced by multiple organizations, and it was essentially forced on hospitals and other healthcare professionals in assessing pain relief and quality improvement (21,35). Further contributing issues were the medical boards themselves. Most of the guidelines, although allegedly written for appropriate opioid use, were essentially promoting excessive use and abuse patterns, as they were developed by the opioid industry with a confluence of interest. Further, multiple failures in the oversight of opioid manufacturing, distribution, diversion, and import, in addition to medical necessity and appropriate monitoring of opioid prescriptions fueled the epidemic (35).

It is difficult to point out the reasons for the explosion of the fentanyl epidemic, along with increases in the usage of heroin, as well as cocaine (35,271,276,277,280,281,335-338). The significant movement to control the opioid epidemic in the United States was initiated with PDMPs, state regulations curbing opioid prescriptions, and increasing the focus on education. Overall federal spending increased 128% from 2017 to 2018 with the major increases in federal spending due to treatment and recovery programs with costs ranging from approximately $599 million to $2.1 billion (315). Overall, total opioid spending increased from $3.3 billion in 2007 to $7.4 billion in 2018 in the United States (315).

Manchikanti et al (5) reviewed the fourth wave of opioid (illicit drug) overdose deaths and diminishing access to prescription opioids and interventional techniques to assess cause and effect relationship. They identified as the fourth wave originating in 2016 secondary to AHRQ and CDC guidelines, COVID-19 epidemic effects, reduced interventions, and flow of illicit drugs. They posited that the CDC guidelines and subsequent regulatory atmosphere have led to aggressive tapering up to and including, at times, the overall reduction or stoppage of opioid prescriptions. Forced tapering was linked to an increase of 69% for overdoses and 130% for mental health crisis. The data from the review suggested that the decrease in access to opioid prescriptions may be occurring simultaneously with an increase in illicit opioid use. They concluded that combined with CDC guidelines, the curbing of opioid prescriptions to medically needed individuals, among non-opioid treatments, interventional techniques have been affected with declining utilization rates and medical policies

reducing access to such modalities. They further described that wave four continues to escalate with an increasing number of deaths as a confluence of factors including the CDC guidelines, the COVID-19 pandemic, increased availability of illicit synthetic opioids, and the reduction of access to interventional techniques, which continues to lead patients to seek remedies on their own. The major focus on buprenorphine treatments for OUD and elimination of X-waiver do not appear to decrease illicit drug usage, despite promotions by advocates.

In addition, there is also an issue related to the onset of fourth wave. The report from the nonpartisan Congressional Budget Office (CBO), showed that a fourth wave was emerging, characterized by using illegally manufactured opioids in combination with psychostimulants such as cocaine and methamphetamine (311,339). Further, as described earlier, a multitude of other factors including CDC guidelines with significant decreases in opioid dosages resulting in increasing overdoses and deaths and continuing to facilitate illicit drug usage.

7.3 Opioid Epidemic and "Deaths of Despair"

In addition to the worsening illicit drug epidemic with the exacerbation related to the COVID-19 pandemic, "Deaths of Despair: The Unrecognized Tragedy of Working Class Immiseration" has been once again discussed frequently (340). The terms deaths and despair come from Case and Deaton, who published rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century (341). They showed that the fastest rising death rates among Americans were from drug overdoses, suicide, and alcoholic liver disease, increasing between 56% and 387%, depending on the age cohort, over the past 2 decades, averaging 70,000 per year. They described that these effects are largely the result of economic hardship or the loss of work or wages, lack of education or low education, resulting in insecurity, deprivation, the loss of possibilities, the lack of belonging, hopelessness, and social maladjustment leading to negative emotions including loneliness, unhappiness, worry, and stress that in turn led individuals to, in part, experience more pain and pain sensitivity, both physi-

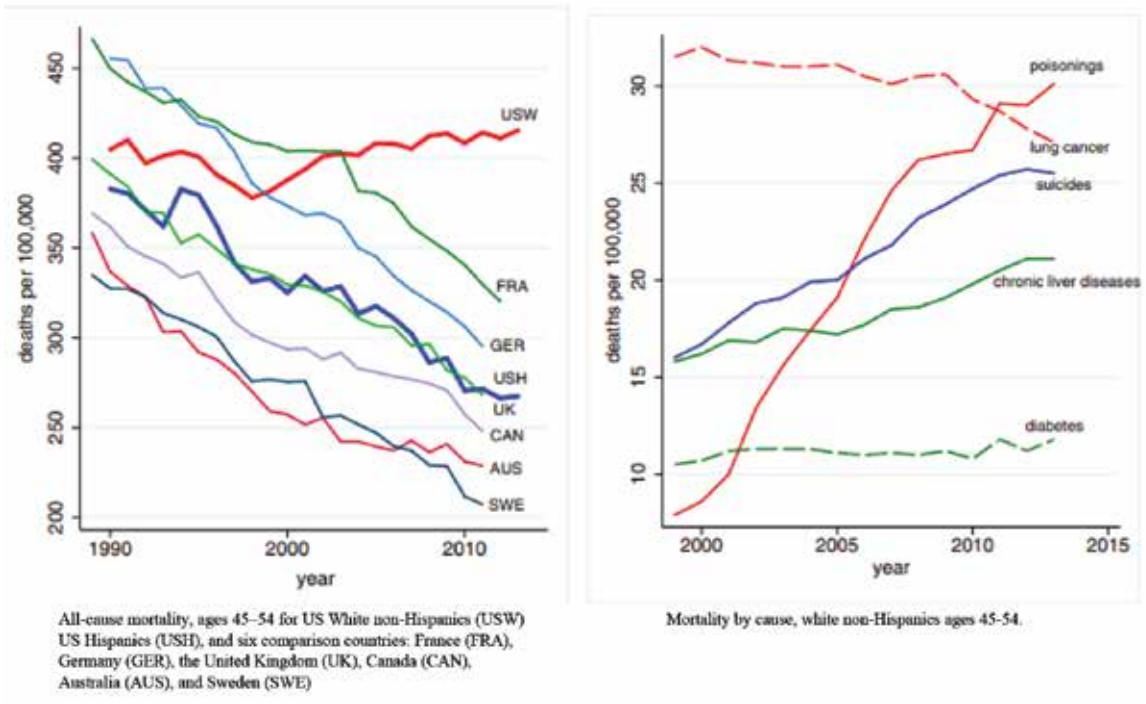


Fig. 20. *Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century.*

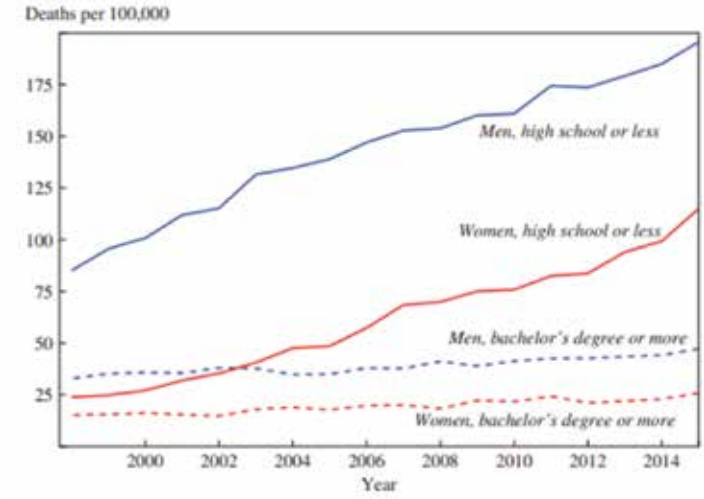


Fig. 21. *Deaths of despair for White Non-Hispanics age 50-54, by level of education, 1998-2015.*[a]
[a]Deaths of despair refer to deaths by drugs, alcohol, or suicide.

Sources: National Vital Statistics System; authors' calculations.

cal and psychological. With the COVID-19 pandemic, the problem has been exacerbated as evidenced by the fact that 911 calls for opioid related use increased 250% between 2019 and early 2020 (340,341). Figures 20 and 21 show these factors with increasing mortality affecting mostly white middle-aged men. However, a multitude of these factors have been described to contribute to 5% to 15% of all drug deaths, 12% to 13% of illicit drug deaths, but virtually all the suicide and alcohol deaths.

8.0 Regulations Controlling Opioids

8.1 Controlled Substance Act and Drug Enforcement Administration

Key Question 5. What is the Controlled Substance Act (CSA) and its relation to opioid prescriptions?

The Federal Comprehensive Drug Abuse Prevention and Control Act of 1970, also known as the CSA (342), became effective on May 1, 1971. Congress enacted the CSA to facilitate the availability of controlled substances for authorized medical, scientific, research, and industrial purposes, while preventing these substances from being diverted out of legitimate channels for illegal purposes such as drug abuse and drug trafficking activities. To achieve this goal, the Drug Enforcement Administration (DEA), the agency charged with federal enforcement of the Act, relies primarily on a registration system. The Act requires persons who handle controlled substances (such as drug manufacturers, distributors, pharmacies, health care professionals and scientific researchers) to register with the DEA. In order to minimize theft and diversion and help the United States DEA monitor the flow of controlled substances in the United States, the CSA subjects registrants to strict requirements regarding recordkeeping, maintaining the security of their controlled substance inventories, and reporting certain information to the DEA. Registration and regulation of these entities results in the formation of a closed system from the creation to disposal of the substances.

The CSA provides civil and criminal penalties for any unlawful manufacturing, distribution, importation, exportation, or possession of controlled substances. Such violations may include: 1) "regulatory" offenses committed by registrants who do not adhere to their responsibilities under the CSA, thereby increasing the risk of diversion, and 2) illicit trafficking or possession crimes that occur outside the "closed system" that primarily involve non-registrants.

The CSA places all substances regulated under existing federal law into one of 5 schedules. A given drug's schedule is based on the substance use, potential for abuse, and safety or dependence liability. The five schedules are:

- Schedule 1
  - The drug or other substance has a high potential for abuse.
  - The drug or other substance has no currently accepted medical use in treatment in the United States.
  - There is a lack of accepted safety for the use of the drug or other substance under medical supervision.
- Schedule II
  - The drug or other substance has a high potential for abuse.
  - The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restriction.
  - Abuse of the drug or other substance may lead to severe psychological or physical dependence.
- Schedule III
  - The drug or other substances has less potential for abuse than the drugs or other substances in schedules I and II.
  - The drug or other substance has a currently accepted medical use in treatment in the United States.
  - Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.
- Schedule IV
  - The drug or other substance has a low potential for abuse relative to the drugs or other substances Schedule III.
  - The drug or other substance has a currently accepted medical use in treatment in the United States.
  - Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances and Schedule III.
- Schedule V
  - The drug or other substance has a low potential for abuse relative to the drugs or other substances and Schedule IV.
  - The drug or other substance has a currently accepted medical use in treatment in the United States.
  - Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances and Schedule IV.

8.1.1 The Federal Requirements for a Valid Controlled Substance Prescription

Under the CSA, a controlled substance prescription is valid only if it is issued: 1) for a legitimate medical purpose, by an individual practitioner who is 2) acting

in the usual course of professional practice (342). This is known as the "prescription requirement" under federal law. The U.S. Supreme Court has made clear: "… the prescription requirement … ensures patients use controlled substances under supervision of a doctor so as to prevent addiction and recreational abuse . . . [and] also bars doctors from peddling to patients who crave the drugs for those prohibited uses" (343).

The CSA does not specifically define "legitimate medical purpose". Instead, medical expert testimony is often used in administrative and criminal CSA cases to identify whether controlled substances were prescribed for a "legitimate medical purpose" and whether these efforts were memorialized in the prescriber's medical record documentation (344). The CSA does not establish a standard of care for controlled substance prescribing, as that term is referenced in medical practice.

Neither does the CSA establish rules or guidelines the same way that professional medical licensing boards do when it comes to controlled substance prescribing. In administrative and criminal cases involving an evaluation of a prescriber's compliance with the CSA, medical experts evaluate a prescriber's adherence to applicable state licensing board prescribing rules and guidelines pertaining to controlled substance prescribing, and those directed toward specific areas of medical practice such as pain management and treatment for SUD.

Prescribers charged with illegal prescription of scheduled drugs often advance the "good faith" defense which states that there should be no conviction where the prescriber "reasonably believed" or "subjectively" intended that the prescriptions fall within the usual course of professional practice. Prosecutors argue that a prescriber cannot have a good faith belief that his practices fall within the usual course of professional practice unless he makes an objectively reasonable "honest effort" to ascertain and adhere to professional medical boundaries, and that the "wholly subjective" views of the prescriber should not preclude conviction. On June 27, 2022, the United States Supreme Court ruled that once the defendant/prescriber proves his conduct was "authorized," the prosecution must prove beyond a reasonable doubt that the defendant/prescriber "knowingly and intentionally" acted in an unauthorized manner (345). A prescription for a controlled substance is only "authorized" when issued for a "legitimate medical purpose" by the prescriber acting in the usual course of his professional practice.

There are distinctions between how these requirements are applied and evaluated in administrative cases brought by the DEA against registrants and criminal cases brought by the federal government through its formal charging process and jury trials. Federal criminal cases involving allegations of illegal prescribing of controlled substances require the government to meet a tougher proof standard – beyond a reasonable doubt – and it must show the requisite intent of the defendant/prescriber to violate the CSA. A detailed discussion of the criminal standard and the use of medical expert testimony in criminal cases is beyond the scope of this guideline. Such a discussion must necessarily involve an examination of standards, misapplied standards, confusion of intent elements, and inconsistent application of medical expert testimony, among other things gleaned from a complex web of case law and trial testimony.

8.1.2 Suspension or Revocation of DEA Registration

The CSA grants the DEA the authority to suspend or revoke a DEA registration at any time. The Attorney General of the United States is required to consider the following factors when acting to suspend or revoke a DEA registration:

1. The recommendation of the appropriate State licensing board or professional disciplinary authority.
2. The registrant's experience in dispensing (prescribing) controlled substances.
3. The registrant's conviction record under Federal or local laws regarding controlled substances.
4. Compliance with applicable State, Federal, or local laws regarding controlled substances.
5. Such other conduct which may threaten the public health and safety.

The Government may consider these factors in the disjunctive so findings under a single factor may support revocation of a DEA registration.

A registrant facing suspension or revocation has appeal rights. The DEA begins the process by providing an order to show cause, which must set forth the reasons for the suspension or revocation. The registrant has thirty (30) days to request an administrative hearing or waive the hearing and provide a responsive written statement. The hearing is before an Administrative Law Judge, with the proceeding much like a trial in court including submitting evidence, calling witnesses, and cross-examining witnesses.

8.1.3 Compliance

To ensure full understanding of federal and state expectations surrounding the prescribing of controlled substances:

1. Read your licensing board rules and guidelines.
2. Read professional society guidance documents.
3. Map action directives based on the authorities discussed herein and measure your own practices against them.
4. Read DEA Administrative Cases to learn more about how medical experts approach review of patient files regarding a DEA Registrant's obligation to prescribe for a "legitimate medical purpose" while "acting in the usual course of professional practice."

Remember the emphasis that licensing boards and the DEA place on medical record documentation. Conscientious documentation is not just a ministerial act, but a key treatment tool and vital indicator to evaluate whether the physician's prescribing practices were within the usual course of professional practice. The DEA's ability to assess whether controlled substance registrations are consistent with the public interest is predicated upon the ability to consider the evidence and rationale of the practitioner at the time she prescribed a controlled substance – adequate documentation is critical to that assessment. By reading these materials and using the directives contained therein, along with making a concerted effort to meet applicable documentation requirements, the prescriber is better equipped to demonstrate adherence to federal law and professional licensing board standards and to minimize the risk of financial and legal losses associated with the violation of the same.

Federal law requires that licensed health care providers register with the DEA if they contemplate prescribing a controlled substance. It is very important that the registrant become well versed with the requirements and obligations of the CSA.

8.1.4 Medication Access and Training Expansion (MATE) Act

On March 28, 2023, the DEA issued guidance outlining requirements for a one-time, 8-hour training, on the treatment and management of patients with opioid or other SUDs. The Medication Access and Training Expansion (MATE) Act that was passed as part of the Consolidated Appropriations Act of 2023 PL117-328 requires all DEA registered providers to complete this training (346). There are multiple exemptions for those trained in addiction medicine, the following groups of practitioners are deemed to have satisfied this training:

1. Group 1: All practitioners that are board certified in addiction medicine or addiction psychiatry from the American Board of Medical Specialties, the American Board of Addiction Medicine, or the American Osteopathic Association.
2. Group 2: All practitioners that graduated in good standing from a medical (allopathic or osteopathic), dental, physician assistant, or advanced practice nursing school in the United States within five years of June 27, 2023, and successfully completed a comprehensive curriculum that included at least eight hours of training on:
    - Treating and managing patients with opioid or other SUDs, including the appropriate clinical use of all drugs approved by the FDA for the treatment of a SUD; or
    - Safe pharmacological management of dental pain and screening, brief intervention, and referral for appropriate treatment of patients with or at risk of developing opioid and other SUDs.

8.2 CDC Guidelines

Key Question 6. How were CDC guidelines developed and what is their impact on prescription opioids?

The CDC developed the CDC Guidelines for Prescribing Opioids for Chronic Pain as a response to the escalating opioid overdose epidemic targeting primary care clinicians treating adult patients in chronic pain in outpatient settings. The CDC engaged partners from ten federal agencies and a Stakeholder Review Group of eighteen organizations to provide comments. In addition, the National Center for Injury Prevention (NCIP) and Control Board of Scientific Counselors (BSC), a federal advisory committee provided input. All these observations and opinions were deliberated and considered. Meta-analysis was not attempted due to the limited number of studies, variability in study designs and clinical heterogeneity, and methodological shortcomings of studies.

These guidelines recommended practices for opioid use for treating chronic pain–excluding cancer treatment, palliative care, and end-of-life care–in patients aged 18 years and older in primary care settings (347-349). Compliance was designed as entirely volun-

tary. The CDC guidelines are broad reaching and have material impact on the care of chronic pain patients.

8.2.1 Problems/Challenges

The initial draft guidelines were met with sharp criticism from a number of medical organizations, including the American Academy of Pain Medicine (AAPM) and American Medical Association (AMA).

Despite benefits, these guidelines have been criticized by some for the unintended consequences related to their application, such as aggressive or abrupt tapering at times leading to utilization of illicit opioids resulting in overdose deaths, mental disorders, and suicide (5,350).

8.2.2 Effectiveness of CDC Opioid Guidelines

Among all providers, prior to the release of the CDC Guidelines, the rate of first-time opioid prescriptions with extended-release opioids decreased monthly to 5.84 in every 10,000 prescriptions. After the release of the CDC Guidelines, there was observed change in payer pharmacy coverage due to new prior authorizations with a reduction in first-time extended-release opioid prescription rates and other changes associated with an immediate reduction in level of first-time opioid prescriptions at doses of at least 50 MME per day across all specialties with an increased reduction over time among surgeons (351-353).

In addition, almost all specialties were influenced besides the initial target of primary care providers. Further, these Guidelines were also adapted by multiple state legislatures, licensing boards, multiple payer groups, and anyone with interests in controlled opioid prescriptions or focusing on opioid epidemic and tying it to prescription opioids. Further, these guidelines also restricted prescriptions of benzodiazepines (5,351-356).

8.2.3 2022 Revision of CDC Guidelines

An updated version of CDC guidelines was published in 2022 (13). These guidelines focused significantly on behavioral aspects of chronic pain with suicidal ideation and health disparities based on race, ethnicity, and gender. The guidelines described that a range of therapeutic options have historically been inaccessible to many patients because of the factors such as inadequate clinician education, training, and guidance; unconscious bias; a shortage of pain management specialist, insufficient access to treatment modalities such as behavioral therapy; siloed health systems; insurance coverage and reimbursement policy; and lack of clarity about the evidence supporting different pain treatments. Despite these arguments, in real life, these issues have not altered the application of the guidelines. While the guidelines make a statement that they do aim to provide flexibility, it may not be applicable in clinical settings as there are many other factors in managing chronic pain patients. Further, the guideline application has been widened to all specialties.

8.3 FDA Guidance

Key Question 7. Is there U.S. Food and Drug Administration (FDA) guidance on opioid prescriptions?

The FDA is the agency responsible for regulating opioid medications marketed in the United States, therefore playing a critical role in responding to the opioid crisis. Its decision making is guided by its goal to protect and advance public health, including enabling the availability of medical therapies and reducing harms associated with opioids, such as overdose and addiction (357).

Over the past 25 years opioid related misuse, abuse and deaths increased at an alarming rate sending the FDA and other federal agencies into a state of urgency to lead and combat these issues.

First, the trajectory of opioid-related deaths in the United States showed in 2015 each day 90 individuals overdosed with an opioid. This steep increase in annual opioid overdose deaths, which nearly tripled from 1999 (8,048) to 2011 (22,784), showed no sign of abating, while the prevalence of OUD continued to increase (358-360).

Second, concerns about the intertwining of use, misuse, and distribution of prescription opioids with the increasing use and distribution of illegal products, heroin, and fentanyl. Individuals who develop OUD from prescription opioids may eventually switch to one of these illegal narcotics. In one survey, about 80% of 125 000 individuals who recently initiated heroin use reported that their opioid use began with nonmedical use of prescription opioids (361).

8.3.1 Risk Evaluation and Mitigation Strategy (REMS)

To improve safety, effectiveness and enforce marketing regulations the REMS program was created. REMS was seen as a national effort by the FDA to address the Opioid epidemic, which had been recognized as a major public health problem. In April 2011, FDA announced the REMS program to ensure that the benefits of extended-release and long-acting (ER/LA)

opioid analgesics outweigh the risks. The stated goals by the FDA of the REMS program are:

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy
II. Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics
III. Managing Therapy with ER/LA Opioid Analgesics
IV. Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics
V. General Drug Information related to ER/LA Opioid Analgesic Products
VI. Specific Drug Information for ER/LA Opioid Analgesic Products

In addition, all ER/LA opioid analgesic companies are partners in this effort and must help to provide:

- Education for prescribers of these medications, which will be provided through accredited continuing education (CE) activities supported by independent educational grants from these ER/LA opioid analgesic companies.
- Information that prescribers can use when counseling patients about the risks and benefits of ER/LA opioid analgesic use.

The current oversight of REMS programs because the voluntary nature of the education component has not achieved even the modest aim of improving knowledge about the dangers of opioid overuse and diversion. We believe that the FDA should closely monitor the implementation of its post approval strategies to ensure those programs with disappointing outcomes can be quickly amended.

The FDA released its own action plan to address the opioid epidemic in response to CDC guidelines (362). The FDA's actions include:

- Expand the use of advisory committees with help from external experts and public input.
- Develop warnings and safety information for immediate-release (IR) opioid labeling.
- Strengthen post market requirements with better evidence on the risks of misuse and abuse associated with long-term use of opioids.
- Increase the number of prescribers who receive training on pain management and safe prescribing of opioid drugs to decrease inappropriate opioid prescribing.
- Expand access to abuse-deterrent formulations (ADFs) by increasing innovation and expanded use of generic ADFs.
- Broader access to overdose treatment with naloxone and new classes of pain medicines without the same risks as opioids.
- Reassess the risk-benefit approval framework for opioid use.

8.3.2 Abuse Deterrent Formulations (ADF)

Trying to be proactive and address misuse of prescription opioids, the FDA released guidance in 2015 for the development of ADF for narcotics. The purpose of ADFs is to create opioids with chemical properties that make it difficult for people who non-medically use prescription drugs to crush and dissolve opioid tablets, as well as by combining opioids with antagonists such as naloxone or naltrexone, which are released only when the dosage form has been manipulated or the drug is taken by a non-intended route (363).

8.3.3 Oversight and Education

In March 2017, the President's Commission on Combating Drug Addiction and the Opioid Crisis was formed and found as one of their conclusions, the opioid crisis was caused in part by "inadequate oversight by the Food and Drug Administration."

On May 23, 2017, the FDA Opioid Policy Steering Committee (OPSC) was established to explore and develop additional approaches or strategies FDA can use to combat the opioid crisis (364). The Committee is comprised of senior FDA leaders as designated by the Commissioner and resides in the Office of Medical Products and Tobacco (OMPT) in the Office of the Commissioner. The goals are:

1. Decrease exposure and prevent new addiction
2. Supporting the treatment with OUD
3. Fostering the development of novel pain treatment therapies
4. Improving enforcement and assessing benefit risk

In addition, the FDA sponsored a study in 2017 and asked The National Academies of Sciences, Engineering, and Medicine (NASEM) to provide independent, objective analysis and advice to help with the opioid epidemic.

The NASEM called on the FDA to overhaul its opioid policies:

- The FDA should complete a review of the safety and effectiveness of all approved opioids.
- States should convene a public-private partnership to implement drug take-back programs that

allow drugs to be returned to any pharmacy on any day, rather than relying on occasional take-back events.
- Public and private payers, including insurance companies, should develop reimbursement models that support evidence-based and cost-effective comprehensive pain management, including both drug and non-drug treatments for pain.
- HHS, in collaboration with state organizations, should conduct or sponsor research on how data from PDMPs can be better leveraged to track opioid prescribing and dispensing information; and
- The National Institutes of Health (NIH), the Substance Abuse and Mental Health Services Administration (SAMHSA), the U.S. Department of Veterans Affairs, and industry should invest in research that examines the nature of pain and OUD, as well as develop new non-addictive treatments for pain (365,366).

8.3.4 Role of Naloxone

Naloxone is used to treat those who have overdosed on opioids by family members, bystanders, and first responders. It can save lives. Both intramuscular and nasal formulations are available. Widespread, rapid availability of bystander and take-home naloxone rescue kits, coupled with enhanced education on naloxone's proper use, is essential, particularly in cases where higher doses of opioids are to be prescribed or there is evidence of underlying OUD, as emphasized by the Surgeon General of the U.S. Public Health Service (367-370).

8.3.5 Addressing Priority Areas and Developing New Treatments

As part of its mission, the FDA is committed to examining all facets of opioid abuse, misuse, addiction, overdose, and death in the United States. The agency is taking steps to address four priority areas to address the crisis: 1) decreasing exposure and preventing new addiction; 2) supporting the treatment of those with OUD; 3) fostering the development of novel non-opioid pain treatment therapies; and 4) improving enforcement and assessing benefit-risk.

Within the Center for Drug Evaluation and Research (CDER), an increase of $26.0 million above the FY 2021 enacted level will support development of opioid overdose reversal treatments and treatments for OUD. CDER will, among other things: assess feasibility to integrate the opioid Risk Evaluation and Mitigation Strategies (REMS) education into information technology (IT) health systems/electronic health records and explore use of health IT systems to support goals of this REMS, such as prescriber education; and continue to support opioid research efforts.

Meanwhile, CDER continues to work on evaluating potential opioid disposal and packaging requirements based on FDA authority under the SUPPORT (Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment) for the Patients and Communities Act. Other recent CDER actions to address the opioid crisis include the issuance of the final guidelines for OUD treatment endpoints; opioid label updates related to naloxone prescribing; and approval of naloxone products. The FDA maintains a list of medicines that can be disposed of by flushing when take-back options are not readily available (371,372).

Despite all these complaints, the FDA has attempted to continuously improve in all these areas and become more initiative taking to combat the epidemic looking for comments from different stakeholders.

9.0 Use of Illicit and Non-Prescription Drugs

9.1 Marijuana

Key Question 8. What are the utilization patterns, effectiveness, and adverse consequences of marijuana in the treatment of chronic pain?

Marijuana has long been considered a therapeutic herb that has been used to treat everything from arthropathies, to headaches, to muscle pain, and to assist those in pain with sleep. Studies are becoming more abundant, but there is still a mixed picture of marijuana's effectiveness as a therapeutic agent.

Although it has not been proven to be a pain adjunct, many believe it has helped with their pain and it is expected that providers of healthcare will be asked more regularly for this option as third or fourth tier in treating many painful disorders. The Tile National Academies' committee on the health effects of marijuana states "conclusive and substantial evidence" that it is a good treatment for chronic pain in adults. The concern is that in most cases the use of cannabis is accompanied with either alcohol or other polysubstance and so the answers are unclear.

The marijuana plant, cannabis, contains both the psychoactive ingredient delta-9-THC, and endocannabinoids. Endocannabinoids occur when injured tissues produce arachnoid derivatives and these endocannabinoids are felt to be anti-inflammatory in nature.

Pain is a subjective complaint, but more an experience affecting virtually every human, and is considered to be protective of the individual. Pain is propagated by the A-delta and C-fibers, to the spinothalamic tract from the dorsal horn and proceeds through the thalamus to sensory determinants in the brain. Nociceptive, neuropathic, or nonspecific pain is interpreted and the individual responds accordingly. The endocannabinoids modulate this neural conduction decreasing the potential for central sensitization of pain from significant activation of pain pathways. This decreases cellular inflammation. It is thought that cannabinoid receptors targeted by delta-9-THC play a role in this anti-inflammatory effect.

9.1.1 Cannabinoid Receptors (CB)

CB1 - Neurotransmitters of CB1 are released in the brain and spinal cord. They are responsible for nociceptive and non-nociceptive sensory pain at the dorsal root ganglion and the trigeminal ganglion as well. They're involved in defensive cells such as macrophages, mast cells, epidermal karyotype. This cannabinoid receptor is important in cellular inflammation.

9.1.2 Cannabinoid Type 2 (CB2)

This is of hemopoietic origin.

It is found in the brain, spinal cord, and the dorsal root ganglion. It is elevated when there is peripheral nerve damage, and it regulates neuro-immune interactions. This is likely going to interfere with hyperalgesia and other central inflammatory processes. This will inhibit pain. This may have a similar effect to alcohol or nicotine in tobacco abusers but is of different mechanisms than opioids that stimulate specific receptors such as the mu opioid. Therefore, the question as to whether it is a pain modulator persists when the potential psychoactive effects of marijuana predominate. Like many other agents, there is a minimum, moderate, and robust concentration of the drug that effects response. There appears to be a more important therapeutic window at the moderate level of dosing. Cannabis appears to have a role.

Chemicals such as endocannabinoids and anandamide produced in injured tissues are messengers to promote pain signals. Particularly with the CB2 receptor, peripherally, the anti-inflammatory effect could be considered useful (373-375).

9.1.3 Evidence of Effectiveness

The potential analgesic effect of cannabinoids, with the possible addition of tetrahydrocannabinol (THC), in humans has been experimentally suggested. The results are mixed and the effect for acute pain is limited. The route of administration by either vaporization, or oral did not yield significant differences. Marijuana did have more side effects than placebo. There is evidence that opioids and cannabis together decreased the opioid need or load, therefore would be associated with decreased deaths. Cannabis potentially is safer than opioids alone (373,374).

As the combination of cannabinoids and opioids is becoming more common in perioperative patients, an understanding of the effects on postoperative pain and risk of adverse events is essential. Comparing 2012 to 2017, cannabinoid use increased more than 60% while opioid use decreased approximately 30% (376).

Although there is some evidence to suggest that cannabinoid use has improved opioid-related adverse events and reduced overall use (377-382), there is a larger, more substantial body of evidence demonstrat-

ing that cannabinoids can worsen pain and increase postoperative opioid use. There is evidence of biphasic effects of THC with low doses reducing pain and high doses increasing pain, stressing the need for a better understanding of the relationship between THC consumption levels and pain (383). Moreover, inaccuracies in labelling between cannabidiol (CBD) and THC products can drastically alter patients' reported outcomes. For example, a 2017 study published in JAMA analyzed 84 commercially available CBD products from 31 companies and found that the amount of CBD on the label was often inaccurate; THC was detected in 18 of the 84 samples, and some of the products had levels of THC roughly equivalent to "a few deep puffs" on a joint (384). The implications of mislabeling are important to note given the paradoxical effects of cannabinoids; in low concentrations, THC may act as an analgesic; however, in higher concentrations and with more frequent use, THC is known to cause hyperalgesia. Where this distinction occurs and at what concentration and frequency of use is still not well delineated.

A prospective study on perioperative cannabis use compared 79 current cannabinoids users to 1,256 non-cannabinoid users undergoing elective surgery (385). The results of this study showed higher levels of pain, poorer QOL, and greater likelihood of using opioids or benzodiazepines in cannabinoid users compared to non-cannabinoid users prior to and 3 to 6 months following their surgery.

A systematic review (386) on the analgesic efficacy of cannabinoids for acute pain management after surgery and American Society of Regional Anesthesia (ASRA) Pain Medicine Consensus Guidelines (387) on the Management of Perioperative Patient on Cannabis and Cannabinoids have been published. Abdallah et al (386) in a systematic review and meta-analysis of 4,259 patients, demonstrated that patients receiving cannabinoids appeared to have an increased weighted mean difference of pain at 12 hours by 0.83 cm (p=0.04; 95% CI 0.04-1.63) but no differences in severity of rest pain at 24 hours.

Analgesic effects of cannabinoids are thought to be mediated through mechanisms in the frontolimbic structures in the CNS and contribute to pain perception via its dissociative effects. Dose-dependent effects of inhaled marijuana may contribute to hyperalgesia. While the mechanism for hyperalgesia is still unclear, it is postulated that it may be a phenomenon of long-term use and transient receptor potential vanilloid subtype 1 (TRPV1) modulation (373).

9.1.4 Adverse Consequences

There are several adverse consequences of utilizing marijuana, and do not necessarily show distinction between inhaled or oral use. Cannabis use disorder is characterized by only 2 of 11 prototypical symptoms in a 12-month period according to the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition. The typical overuse syndrome may result in a potential for withdrawal and craving, seeking behavior, and social impairment. It is estimated that one in eight will develop cannabis use disorder and withdrawal is similar to alcohol and tobacco with similar symptoms.

Also associated with cannabis use disorder is memory loss (388). This may be an association with brain-related chemicals, which could result in interruptions at the hypothalamus, or even decrease in brain-derived neurotrophic factor. As with many disease states from hypertension to diabetes to Alzheimer's, studies have shown us that the brain can decrease in mass. This is directly related to dendritic interconnection and decrease in brain-derived neurotrophic factor. Cannabis use disorder is particularly troubling in teens who utilize more marijuana now than the use of cigarettes. In early users, while the brain is developing structural and functional changes, THC use could affect young people and those susceptible to mental health issues with situational depression, anxiety, and those that are at risk for schizophrenia. Social anxiety is common, as is paranoia, particularly in chronic users.

Cardiac damage has also been related to chronic marijuana with tachycardia for up to two to four hours after using marijuana and those in chronic use patterns may experience progressive cardiac disease. Chronic use of marijuana is associated with lung disease and chronic cough as well (374). Lower IQ is observed in those that use marijuana chronically with less robust decision-making and may interfere with life goals and school life (388).

Chronic use disorder is also associated with decreased testosterone and sexual appetite and drive. Motor reaction is diminished, and drug driving now has surpassed driving under the influence of alcohol. With the ever-increasing recreational cannabis use this will become more and more of a problem for those that utilize vehicles. Due to lipophilic tendencies, and long-term detection it's going to be most difficult to determine recent use, and impairment tests will need to evolve overtime. The risk of involvement in an accident increases by a factor of two after recent use of marijuana. One nanogram per milliliter detects a

minimum level where three to seven times may be as likely to result in a motor vehicle accident. Those that ingest alcohol or progress to polypharmacy would be expected to have an even higher incidence.

Although marijuana is considered an appetite stimulant useful in cancer and human immunodeficiency virus (HIV), it also does diminish appetite in certain patient populations as well as changing eating patterns.

The question whether or not marijuana is a gateway drug that was popularly touted in the '70s and '80s is possibly true, particularly because of the developing brain's craving mixed at different levels. The craving for alcohol, marijuana, or opioids shares many characteristics and is a potential risk for polypharmacy abuse.

As we become more familiar with recreational and medicinal use of marijuana, we're going to learn about interactions and our most reasonable next steps. There are advocates for many sides of the debate and some believe that the pharmacotherapy of marijuana and its benefits outweigh its risks. The associated burden of another drug that could potentially be abused will increase as will the negative health consequences. As we learn more about the cannabinoid system in general, and its important role in the continuation and propagation of health as well as the attenuation of inflammation, applications could be formulated that are more specific to different conditions. The more cannabinoid present than THC decreases the likelihood of side effects, which promotes the use of cannabinoid over marijuana in its psychoactive delta-9 variant.

We are in a new age with an old drug from a plant used for thousands of years and a public belief that it is completely safe. As details emerge related to side effects and complications of use, positive outcome experiences could follow and be surprising.

9.2 Delta 8 Tetrahydrocannabinol (THC)

Another drug that is gaining popularity is the cousin of THC, the active psychoactive ingredient in cannabis, Delta-8 THC. Delta-8 THC is a non-FDA approved agent readily available and sold in stores, gas stations and online (389).

Delta 8 THC is a mildly psychoactive drug close cousin to delta 9 THC, found in cannabis, derived from cannabis sativa. Marijuana derived from hemp, that contains more than 0.3% delta THC 9 is considered illegal in most states and is federally regulated: Delta 8 THC appeals to different groups because it is unregulated by the federal government and is not considered illegal. It does create a mild high but is considered weaker than delta 9 THC. It is manufactured from hemp-derived CBD. To date, Delta 8 has not been evaluated by the FDA, but is considered to potentially put patients at risk. Delta 8 THC shares many properties similar to delta 9 THC, including many of its side effects. This includes intention tremor, anxiety, euphoria, time distortion, dry mouth, paresthesia, and tinnitus.

Its mechanism of action is similar to delta 9 THC in the central nervous system, and has effects on the cardiovascular system, most commonly tachycardia. Cannabinoid receptors are abundant throughout various regions of the brain, and delta 8 THC mimics many delta 9 THCs' partial agonist activities at CB 1, and CB 2 cannabinoid receptors. The factor's potency, in delta 8 THC, apparently is about half as potent as delta 9 THC.

The pharmacokinetic profile is similar to delta 9 THC, and it is metabolized by the cytochrome P450 system through dual pathways CYP2C9, CYP384. Similar to delta 9 THC, it is a tricyclic terpenoid, and is synthesized by numerous different processes, and therefore considered synthetic. Not regulated by the FDA means that its potency and side effect profile from contaminants are unregulated. Considered "marijuana light," "diet weed," it is supplied in vapes, gummies, oils, edibles, and can also be smoked.

Side effects are similar to the isomer THC delta 9: increased heart rate, red eyes, dizziness, dry mouth, fatigue, sedation, visual images. Occasionally, mental health concerns are revealed, but among its positive effects Delta 8 does prevent nausea and vomiting in cancer therapy and can also boost appetite. On testing for THC, delta 8 will cause a positive test.

As with marijuana, hopes were that it would provide an answer to pain relief and assist a number of maladies. However, cannabis is considered one of the top 10 most addictive drugs, and delta 8 may be of significant risk as well, being a derivative.

Additional concerns have been raised by the American Chemical Society and the FDA, regarding the synthesis of this product. Delta-8-THC is found in very low concentrations in THC or CBD, therefore, this is a synthetic process, using the conversion of CBD to delta-8-THC involves refluxing CBD in an organic solvent, such as toluene or heptane, with p-Toluenesulfonic acid or another acid or heavy metal that serves as a catalyst. Many of the individuals manufacturing this compound are not chemists and merely follow directions found on Reddit or YouTube.

Although the FDA reports adverse events, they do not seem to be common, but as this drug becomes

more popular and available, we would expect to see this rise. Treatment would be supportive, as with the adverse effects from marijuana and delta THC 9.

Another particular concern is the developing brain, teenagers, and youth. The developing brain is particularly susceptible to the effects of THC psychoactive drugs, and in particular marijuana. The brain will undergo structural and functional changes. Teens are smoking more marijuana than cigarettes. A list of mental health concerns will likely follow and there is substantial evidence that IQ will be affected, as will learning and life experiences.

9.3 Cocaine

Key Question 9. What are the use patterns and adverse consequences of cocaine in chronic pain?

According to the 2020 National Survey on Drug Use and Health (NSDUH), 5.2 million people (1.9%) of the population 12 and older used cocaine in the last year (390). Moreover, cocaine accounts for nearly 1/3 of the 10.3 million people who misused CNS stimulants in 2020. Finally, in 2020, nearly 500,000 people 12 years of age or older used cocaine for the first time, with nearly 70% between the ages of 18 and 25 (390). Stimulants such as cocaine are often combined with opioids to create a dual effect on the CNS which intensifies the high while limiting the negative effects of each drug. This combination, known as "speed balling", can be administered typically via the intravenous route but intranasal is also used. Given the increased risk of death, as well as addiction, screening for cocaine is recommended as part of a comprehensive assessment and monitoring pain management plan.

9.4 Stimulants

Key Question 10. What are the utilization patterns and adverse consequences of various stimulants in chronic pain?

Stimulants are any medication and/or substance that excites any bodily function. Most pertinent in the fields of interest in the interventional pain domain is the CNS, including the brain and spinal cord and peripheral nervous system (PNS), including the sensory, motor, and autonomic components.

Annual prevalence rate of drug use in 2018 according to the United Nations Office of Drug and Crime (UNODC) (391).

- Amphetamines 3.30
- Ecstasy 1.20
- Cocaine 2.60
- Prescription stimulants 2.40

In the United States, in 2018, the top three etiologies for drug related deaths were opioids, cocaine and amphetamine type stimulants (391). In 2018, it was estimated that 27 million people used amphetamines and prescription stimulants, 21 million used ecstasy, 19 million used cocaine (391).

Around 27 million people worldwide (0.5 percent of the adult population) are estimated to have used amphetamines, including amphetamine, methamphetamine, and pharmaceutical stimulants, in the year 2018. The prevalence of the use of amphetamines is particularly high in North America (2.3% of the population aged 15-64). In North America, there were indications of an increase in methamphetamine use in 2018. In the United States, 1.9% of the population aged 12 and older, or 5.1 million people, reported the misuse of pharmaceutical stimulants, while 0.7% of the population aged 12 and older, or 1.9 million people, reported the use of methamphetamine in the year 2020 (391).

The mechanism of action is via direct and/or indirect stimulatory release or inhibited reuptake of neurotransmitters of specific monoaminergic neurotransmitters (i.e., norepinephrine, epinephrine, dopamine, serotonin, and histamine) within the CNS and elevating extracellular neurotransmitters including dopamine (DA), thus increasing the concentration of dopamine in the synaptic gap. The specific responses will depend on which stimulant is being consumed (392).

9.4.1 Types of Stimulants

Types of stimulants, their source, mode of use and consequences of use

A. Prescription: amphetamines, methylphenidate, diet aids
B. Illicit: methamphetamine, cocaine, bath salts (methcathinone, synthetic cathinones) (SC)
C. Over the counter (OTC) (licit): caffeine, tobacco, allergy, and cold medicine (ephedrine and pseudoephedrine)

9.4.1.1 Amphetamines

Amphetamine agents, also known as α-methylphenethylamine, were first discovered over 100 years ago (circa 1910) (393). The primary action of amphetamine is to increase synaptic concentrations

of monoamine neurotransmitters, thereby indirectly enhancing noradrenergic, and dopaminergic neurotransmission in the CNS (393). Oral therapy with amphetamine has been shown to increase cognitive abilities and improve psychological functioning and performance in children and adults with suspected attention deficit disorders (394,395).

Amphetamines are available in multiple forms for oral administration including capsules, tablets, oral solutions, and as extended-release and long-acting forms in concentrations varying from 2.5 to 54 mg in generic forms and under several brand names, including Adderall (dextroamphetamine and amphetamine), Dexedrine (dextroamphetamine), Vyvanse (lisdexamfetamine), Desoxyn (methamphetamine), and Benzedrine (amphetamine). Typical dosage in adults is 10 mg two or three times daily and average maintenance dosage is 40 to 60 mg daily. The dosage in children varies by formulation. Due to its risk of major abuse potential, they are listed as a Schedule II controlled substance (394).

Adverse effects of amphetamines include but are not limited to anorexia, weight loss, hepatotoxicity (at high doses), insomnia, nausea, vomiting, abdominal cramps, symptoms of anxiety, dry mouth, headaches, increases in blood pressure and heart rate and possibly also the exacerbation of motor tics (393,395,396). In a study by Volkow et al (397), it was found that addiction and abuse of stimulants was dependent on basal dopamine tone where people who have a higher number of dopamine D2 receptors found the stimulants resulted in an unpleasant response and therefore had less likelihood of abuse/addiction.

9.4.1.2 Methylphenidate

Methylphenidate was first synthesized in 1944 by the scientist Leandro Panizzon to treat his wife's hypotension (398). Its mechanisms of action work primarily to increase activity within the CNS via dopamine and norepinephrine transporter inhibition, to exert agonist activity at the serotonin type 1A receptor, and to redistribute the VMAT-2 (vesicular monoamine transporter -2) (399). These effects resulted in the discovery of its benefits for the treatment of attention deficit hyperactivity disorder (ADHD), weight loss and narcolepsy, off label use for bipolar disorder, major depressive disorder, and enhancing cognitive performance (399-401). The current commercially available brands are Ritalin, Concerta, Daytrana, Aptensio XR, Metadate CD, Methylin, Quillivant XR, Jornay PM, Adhansia XR, Cotempla.

Some of the most common adverse effects seen with use are appetite loss, dry mouth, anxiety, nausea and insomnia, abdominal pain, weight loss, tachycardia, and blurred vision. Due to the risk of major abuse potential, they are listed as Schedule II controlled substances.

9.4.1.3 Dietary Aids

Over two-thirds of the American population is overweight (36.2%) and obese (42.5%) across all adult age groups (402). From 1999-2000 through 2017-2018, obesity prevalence increased from 30.5% to 42.4%. This trend was also seen with the severe obese population which increased from 4.7% to 9.2% (402). Additionally, the prevalence of obesity in children and adolescents was 19.3% (403). With this increase in weight so has the increase for people to seek medical assistance in trying to lose this weight. There are many claims to weight loss with OTC medications regimes but unfortunately the majority are not FDA regulated and their claims lack unbiased studies. To date, a handful of medications for weight loss (orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide) have been approved by the FDA for long-term use for weight loss.

The mechanism of action is an indirect-acting sympathomimetic effect, by releasing noradrenaline and subsequent stimulation of beta2-adrenergic receptors. Some studies note that it also can inhibit neuropeptide Y, which is necessary for the induction of hunger. Its overall effects result in a continuous sympathetic response in which the body reduces the hunger signal and mobilizes stored energy for use (404).

Phentermine is a Schedule IV controlled substance. The average weight loss is about 5-8% of the initial weight of the patient (405,406). The most common adverse effects are chest pain, tachycardia, arrythmia, decreased ability to exercise, dizziness, headaches, weakness, and difficulty breathing.

9.4.1.4 Illicit Stimulants

Methamphetamine was developed in 1893, and further purified in 1919 by the Japanese pharmacologist, Nagayoshi Nagai, and the chemist, Akira Ogata, respectively (407). Its popularity for use has increased significantly over the past decade due to its relatively low cost and potent effects (408). Methamphetamine exists in two distinct forms (i.e., enantiomers) Dextromethamphetamine (which is used as an illicit recreational substance), and Levo-methamphetamine (which is the prescription-form of the compound, used in medical care). A handy mnemonic for recalling which

of these is the illicit variant is: "D" = Drug (illicit) and "L" = Legal.

Due to its high lipid solubility, it can cross the blood-brain barrier easily. The effect of methamphetamine works at multiple locations within the cerebrum via stimulation of specific neurotransmitter release (monoamines, GABA, glutamate). Methamphetamine structurally is very similar to the monoamine neurotransmitters class (serotonin, norepinephrine, dopamine and phenylethylamine) and thus can elicit their effects with both acute and chronic use/abuse (407,408). Monoaminergic neurons function increased arousal (cognitive and sexual), emotional/mood, reward, sleep, aggression, and memory.

Significant factors for cellular toxicity are oxidative stress reactions, including DA oxidation, excessive glutamate production, excess amount of reactive oxygen and nitrogen species, leading to mitochondrial dysfunction. Additionally, damage seen to the microglial cells leads to secondary inflammatory cytokines release. The neuroinflammation mediated by microglial cells also contributes to neuronal damage by attacking it with inflammatory cytokines. All the preceding insults contribute to cellular terminal degeneration or apoptosis (407,408).

Due to its stimulation of dopamine, monoamine oxidase release, and activation of mesolimbic dopamine neurons, arising from the cell bodies of the ventral tegmental area (VTA) and projecting to the nucleus accumbens, methamphetamine plays an important role in mediating the suppression of tonic pain.

SC, also known as "bath salts", have grown in popularity since the mid 2000's due to their hallucinogenic and psychostimulant effects that are commonly seen with the use/abuse of other common stimulants (i.e., cocaine, MDMA commonly known as ecstasy, and amphetamines) (409,410). The main difference is that these products are being sold over the counter and are intentionally mislabeled and marketed as bath salts, fertilizers, plant food. These "bath salts" are labeled "not for human consumption." Like other stimulants, SC are known to stimulate the release of monoamine concentrations (i.e., dopamine, norepinephrine, and serotonin). Low doses of SC cause euphoria and alertness; however, high doses or chronic use can cause serious adverse effects such as hallucination, psychosis, delirium, hyperthermia, tachycardia, renal failure, and ischemia. SCs are usually a white, amorphous, or crystalline powder, used by oral, rectal routes, injection, or inhalation/smoked (409-412).

9.4.1.5 Legal or Over-the-Counter Products

Caffeine is found in over 60 plants. Its most used product is found in coffee with an estimated 1.6 billion cups consumed daily worldwide (413,414). Other commonly used sources are found in tea, chocolate, cocoa beverages, soft drinks, and energy drinks. It takes about 30-60 minutes after consumption of caffeine to reach maximum plasma concentration. Its effects can be seen widely throughout the body, including crossing the blood-brain, blood-placenta, and blood-testis barriers. Caffeine's mechanism of action is noted to be 3-fold: 1) it antagonizes the adenosine receptors, specifically in the CNS thus leading to increased release of dopamine, noradrenalin, and glutamate and vasoconstriction of the blood vessels within the brain (thus is benefit seen in people who suffer from headaches) (415); 2) the mobilization of intracellular calcium storage via induced calcium release from the sarcoplasmic reticulum (place of Ca storage within striated muscle) which leads to the increased ability of contractility during submaximal contractions and impairs Ca reuptake thus perpetuating higher quantities. The higher quantities of Ca lead to secondary increases of nitric oxide via the activation of endothelial nitric oxide synthase (416-419); 3) the inhibition of phosphodiesterase degradation via cyclic adenosine monophosphate (cAMP) which stimulates lipolysis (via peroxidation) and reduced reactive oxygen species production (i.e., decreased oxidative stress and inflammation in the brain) and stimulation of the adrenaline cascade (420-422). Most people seek caffeine consumption due to its ability to increase alertness and reduce fatigue, leading to better performance in psychomotor tasks requiring fast reactions (421,423).

There have been numerous studies that looked at the possible treatment of neurodegenerative diseases (i.e., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and Machado-Joseph disease) (421-425). In epidemiological reports, regular/daily caffeine consumption was associated with a significantly lower risk of developing these devastating diseases.

Tobacco: In 2015, According to the World Health Organization (WHO) "tobacco is a legal drug" that kills many of its users when used as per instructions per manufacturers (426). In 2019, WHO released data stating that worldwide more than 8 million people die from tobacco related consumption each year (427). Many of these deaths are directly or indirectly caused by lung cancer, chronic obstructive pulmonary disease, or cardiovascular diseases. The major active

ingredients in tobacco are nicotine, hydrogen cyanide, formaldehyde, lead, and arsenic. Many of these are carcinogens.

Nicotine is an addictive ingredient found in tobacco. Its absorption is dependent on the pH of the body. The more basic the environment the more readily nicotine is absorbed through the oral, nasal, and pulmonary mucous membranes (428,429). Nicotine binds to nicotine acetylcholine receptors (nAChRs). These receptors are distributed throughout the CNS and the peripheral tissues (430). Nicotine activates the hypothalamic-pituitary-adrenocortical (HPA) axis and increases corticotrophin-releasing hormone, arginine, vasopressin, beta-endorphin, and cortisol levels (431). Additionally, activating the sympathetic–adrenal–medullary system, thus leading to an increase in blood pressure and heart rate, and ultimately an increase in cardiac output (432). Peripheral vascular disease (PVD) is a common complication that arises in chronic tobacco use secondary to endothelial dysfunction. Endothelial dysfunction is multifactorial due to increased production of reactive oxygen species (ROS) within the vascular wall, impaired nitric oxide synthase, thrombosis formation, impaired vascular tone, inflammation, and occlusion (428-433).

Allergy and Cold Medicine is most often found in OTC nasal decongestants (containing ephedrine and/or pseudoephedrine) but are used in the acute settings for treating hypotension. They are considered a nonspecific direct and indirect α- and β-adrenoceptor agonists; which leads to sustained or even increased heart rate due to norepinephrine release and inhibiting its reuptake, direct vasoconstricting action on the venous system, stimulation of receptors of smooth muscle within vasculature results in a rise in systemic vascular resistance resulting in increased both systolic and diastolic blood pressure and beta-2-adrenergic receptor stimulation in the lungs results in bronchodilation (434,435). Common adverse effects seen are palpitations, headache, dizziness, nausea, vomiting, restlessness, anxiety and arrhythmogenic (436).

9.5 Kratom

Key Question 11. What are the use patterns and adverse consequences and effectiveness of kratom?

Within the past decade, Kratom has gained popularity in the United States and the West in general. Although not an epidemic, it is an unscheduled drug with consequences, and potential for misuse, abuse, and unexpected complications.

There is poor awareness among healthcare professionals of the mechanism of its toxicity and the prevalence of this drug. This, with its unregulated processing and use, often leads to toxicity.

Kratom is from Southeast Asia, originating from a tree called M. Speciosa, which is indigenous to the region. It is similar to a coffee plant and has been utilized for centuries in that area with minimal side effects for its basic properties of a mild stimulant, and its opioid-like effects. Often utilized with diarrhea therapy, this would be akin to an opioid-like action. In Southeast Asia, dependence is not as prevalent as in the West where heavier use occurs. This is a public health concern that continues to emerge and is becoming more prevalent. It is not a benign drug, and is associated with many side effects, including death (437,438).

There are associations such as the American Kratom Association, Facebook groups, and multiple users estimated at about 1% of the U.S. population. The Poison Center receives multiple calls per year and case reports concerning Kratom's side effects and habituation continues to grow. Kratom users are often passionate and consider it both a therapeutic and a recreational drug, and is safe as a legal high, because of its plant origin. Attempts to schedule the drug by the DEA failed, and some states have criminalized it while others have decriminalized this agent.

It is widely available in the West, and as its opioid effects can be part of its seeking nature, it is a mild stimulant in low dose and sedating in high dose, with many characteristics of opium. During the pullback over the past few years of opioid prescriptions, this drug has remained an alternative to blunt the withdrawal effects and is widely available in head shops, gas stations, and vape stores. It is ingested multiple ways by tea, smoking or chewing, and over time develops dependence with known withdrawal at abrupt discontinuation. Some consider this an opioid replacement. Most do not, although the literature is not robust.

There appears to be two components that are most prominent in its activity, 7-OHmitragynine and mitragynine. The 7 variant is more potent, 13 times that of morphine, acting primarily on the mu and kappa receptors whereas mitragynine, on the mu and sigma receptor. Both have significantly different binding affinities, and act as simple agonists. They have a mild antagonist effect but are negligible.

Mitragynine has an activation at alpha 2 adrenergic synapse receptors, which promotes analgesic effects by the descending pathways. They both appear to block pain perception to a limited degree.

They both are metabolized by the P450 system at CYP3A4, and CYP2D6 with the half-life estimated at three hours. With higher dosing, cognitive impairment is evident and addiction potential has been demonstrated in animal models.

The toxicity of this drug is not disputed. In fact, the Mayo Clinic considers Kratom unsafe and ineffective. Concerning side effects include weight loss, dry mouth, nausea, vomiting, liver damage, and muscle pain. There is constipation, and that was one of the desirable side effects of the drug originally, particularly in Southeast Asia, where other options are limited. With the higher doses, drowsiness, hallucinations, delusion, respiratory impairment, and even seizures with coma and death have been reported. With its rapid onset of five to 10 minutes, this can overwhelm distribution processes. Infants of breastfeeding mothers have experienced withdrawal.

An important side effect that is not often discussed is the contamination effect, most troubling with salmonella and heavy metals. Mayo reports that in April 2018, 130 people in 38 states became ill. There is little chance of understanding its purity, potency, or origin when bought in an unregulated environment. Therefore, concentration of active Kratom varies widely, toxicity is dose dependent, and when dose is unknown, this adds further risk. Hepatitis, cardiotoxicity, and renal injury have been reported, with long-term effects. The CDC reports 152 deaths between 2016 and 2017. This is related to polysubstance abuse, which is another risk factor especially in those willing to take Kratom excessively. In Colorado, four deaths were attributed exclusively to Kratom (439,440).

Withdrawal symptoms are similar to opioids and are treated supportively. Kratom may require the use of a Buprenorphine detox if the patient has been using it regularly and in higher doses. Doses >40 g/day may need 12-16 mg of buprenorphine per day to stop withdrawal and initiate taper.

9.6 Psychedelics

Key Question 12. What are the use patterns and adverse consequences of psychedelics?

Two common psychedelics that are of emerging interest are old molecules that have been studied in different fields for depression, anxiety, and alcoholism. Lysergic acid diethylamide (LSD) is a prototypical stimulant. Renewed interest in LSD for treatment of depression has researchers considering micro dosing this drug at intermittent intervals for alcoholism and depression. People that are utilizing this drug in a research environment relate more energy, and side effects are few. The downside of LSD is its unpredictability. Some people develop depression and psychotic events, but it seems to be dose related.

Another psychedelic that is garnering attention is psilocybin for depression that is found in "magic mushrooms." There is a following for mushroom therapy and they believe that psychedelic assisted therapy is safe, if utilized in a supervised environment. Psilocybin is associated with euphoria, and at higher dose hallucinations and has been used for spiritual purposes. Research is underway for treating depression and researching potential for therapeutic option in mixed depressive disorder (441).

The side effects are delusions, drowsiness, headaches, nervousness, and paranoia, as well as psychosis. Panic has been described. It is a restricted agent, but there are numerous different forms of mushrooms and effects that are utilized in the community. The CSA places psilocybin as a Schedule I drug. Ongoing research is promising, but again, in micro doses.

9.7 Other Drugs

Key Question 13. What are the utilization patterns and adverse consequences and effectiveness of ketamine, designer drugs, and 3,4-methylenedioxy-methamphetamine (MDMA)?

9.7.1 Ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist, that has been utilized since it was synthesized in the late 60s and early 70s (442). It was an alternative to phencyclidine (PCP). PCP, its cousin, developed as an anesthetic, was found unsuitable for this purpose. The ideal anesthetic being minimal cardiovascular effect, rapid recovery, good analgesic capacity, and ketamine replaced PCP. Ketamine is a dissociative anesthetic that was utilized extensively in the 70s and 80s, fell to less favor, but the veterinary community adopted it and has been using it actively since. Ketamine is reemerging as an antidepressant and is showing significant promise. A nasal application has been approved by the FDA to treat depression, and intravenous preparations are also utilized.

The mechanism of action of ketamine is felt to be synaptogenic at the hypothalamus with elevated brain-derived neurotrophic factor (BDNF) and enhanced dendritic formation at the neuronal level. This increases brain activity, adds mass, and elevates mood. It is well-known that with chronic disease states such as diabetes, Alzheimer's, and depression, brain mass is diminished. This is rapidly enhanced with ketamine lending its advantage to treating depression rapidly and effectively. Oral agents typically take weeks, and with mixed depressive disorder is a response roughly 40% to oral agents. Ketamine has promised to exceed that, and ongoing studies and reports are promising. Ketamine has also been utilized in the treatment of neuropathic pain.

Ketamine side effects are dose dependent. Paranoia, agitation, anxiety, night terrors, and headaches have been reported, as has hypertension and tachycardia. These can be well-controlled, particularly in the intravenous administration under monitored conditions. The retention of results can be lasting but requires more than one treatment, and the intravenous form is not covered by insurance and is considered off-label by the FDA. The nasal application can be covered by insurance but is administered in the physician's office and requires familiarity and special training.

The future of ketamine is promising and a new tool to treat depression in certain patient populations.

9.7.2 Designer Drugs

Designer drugs are broad category and usually synthetic. They are designed to stimulate or create a euphoric state, and to avoid detection. They are common drugs of abuse, and frequently addictive (443,444).

The DEA classifies them in 7 categories: Cannabinoids, phenethylamines, PCPs, tryptamines, piperazines, pipradrols, n-ring systems (443,444).

They're usually designed to mimic other drugs, such as cocaine and cannabinoids. Their growth continues because many are unregulated and are commonly mixed for a combined or greater high. They tend to be expensive.

These drugs are usually made in laboratories and therefore not FDA regulated, and quality and contaminants cannot always be tracked or understood. If they are addictive, it is not clear. And in many cases, purity is unknown.

The desires to develop a psychoactive substance or an analog of a performance enhancing drug, such as steroids. Their duration is variable, and often the laboratories are of unknown origin. They have street value and are often found on the black market.

Their history goes back to the 1920s, and evolved to the 1980s when synthetic opioid drugs, such as methyl fentanyl was mostly on the fentanyl molecule and MDMA (ecstasy) was popular at rave parties. The DEA has difficulty keeping up with the ready availability, and the change in chemical characteristics.

The law is variable. The CSA has an intermittent record of trying to control these as Schedule I or II, with limited success. This is a large topic and so the most common designer drugs will be addressed.

Overdose is treated with support, and beta blockers for tachycardia. Also seen with this drug have been intracranial hemorrhage, severe hypertension, serotonin syndrome, and rhabdomyolysis.

Synthetic opioids are contributing to the opioid misuse and abuse in the United States. A particular concern is Isotonitazene, a synthetic opioid similar to fentanyl. There is concern that this drug will exceed fentanyl in its availability on the street. Synthesized in the 1950s, its popularity is increasing as a drug of abuse. It is a mu-opioid receptor agonist experiencing the same risk as others in that class. It is a Schedule I drug.

9.7.3 MDMA (Commonly Known as Ecstasy or Molly)

This drug was developed by the drug company Merck in the early 1900s. It was thought to be a psychotherapeutic drug but has shown little efficacy in that field. It is amphetamine in action, and stimulates serotonin, dopamine, and noradrenaline. It remains illegal but is common in rave parties where it is embraced for its emotional enhancing perception that is heightened and euphoria. MDMA alters the sense of time and decreases anxiety.

Some adverse side effects include insomnia, increased heart rate, bruxism, and diarrhea. Irritability and memory loss can be seen. Its long-term effects are not clear. It does seem to interfere with memory and sleep.

It is metabolized by the Cytochrome P450 system, 2D6. MDMA is rapidly absorbed and lasts over four hours. It is rising in recreational use, particularly at social gatherings and parties seen in the larger cities and urban areas.

Bath salts' history originates from khat leaves of the African regions, that were chewed, developing a stimulus similar to cocaine and methamphetamine.

Some of these bath salts are found at gas stations and head shops. Common reports of adverse effects include psychosis, combativeness, and aggressiveness.

They are often labeled for non-human consumption and resemble Epsom salts. Flakka, Spice/K2, and U-4770 are emerging highly potent synthetic drugs. Spice resembles THC and U-4770, a synthetic opioid. They are urged to be kept from young children and animals and are not recommended for humans at any level.

10.0 Effectiveness of Opioid Therapy in Chronic Pain

Key Question 14. What is the evidence for the therapeutic efficacy and/or effectiveness of opioids in managing chronic non-cancer pain?

Effectiveness of opioids for chronic non cancer pain has been defined by clinical consensus from multiple updated RCTs, guidelines, systematic reviews, and observational studies. Literature on long-term opioid therapy has traditionally suffered from study design, industry supported trials, methodology, duration, specific opioids reviewed, varying opioid strengths, dosing, administration, duration, co-administration with other substances including benzodiazepines/muscle relaxants and government restrictions- all of which challenge definitive conclusions. Endpoints that define long-term opioid therapy effectiveness are sustained reductions of pain and disability with the least serious harms such as death, aberrant drug behaviors, low dropout rates with sustained improvements in pain reduction and functionality greater than 6 months. Serious adverse events of long-term opioid therapy are well known to include physical, psychological, and affective risk which appear to increase with duration of use (445,446). Due to the extensive reviews and guidance published, no analysis of individual studies was performed. The evidence was derived from published guidelines and systematic reviews, along with the addition of updated trials, which were not included in the analysis (447-483).

The CDC opioid prescribing guidelines published in 2016 (9) were based on a systematic clinical evidence review sponsored by AHRQ on the effectiveness and risks of long-term opioid therapy for chronic pain (21,448,473), a CDC update on AHRQ-sponsored review, and additional contextual questions (9,474).

CDC guidelines published in 2022 (13) utilized the CDC funded AHRQ systematic reviews conducted in 2018 and 2019 (147,480-483). The AHRQ review of opioids for chronic pain updated and expanded the evidence. These systematic reviews included studies with short-term (one to less than 6 months, intermediate term (6 to less than 12 months), and long-term (> 12 months), outcomes of therapy involving opioids, effects of long opioid plus nonopioid combination therapy, effects of tramadol, effects of naloxone co-prescription, risks of co-prescribed benzodiazepines, risks of co-prescribed gabapentinoids, and effects of concurrent use of cannabis (480). They also assessed contextual questions on clinician and patient values and preferences, costs and cost effectiveness of opioid therapy, and risk and mitigation strategies (480). In addition, the CDC also considered 4 new complementary AHRQ reviews on the benefits and harms of nonpharmacological treatments for chronic pain (481), nonopioid pharmacologic treatment for chronic pain (147), treatment for acute episodic migraine (483), and treatment for acute non-migraine pain (482).

Canadian guidelines for opioid therapy for chronic noncancer pain (38) published in 2017 summarized the evidence as follows: there was low quality evidence that opioids may have similar effects on relief as NSAIDs, TCAs, or nabilone (synthetic cannabinoid) and similar improvements in physical function as NSAIDs, anticonvulsants, TCAs, or nabilone. High quality evidence shows that opioids increase the rate of gastrointestinal adverse events compared with NSAIDs, and low-quality evidence shows that they may increase the rate of gastrointestinal adverse events compared with anticonvulsants and TCAs.

Busse et al (481) also described a trial of opioids, dosing, tapering, and implementation of the guidelines. In fact, a survey of perceptions and impact of Canadian guidelines for opioid therapy of Canadian physicians showed that there was high awareness of the opioid guideline among respondents, and preliminary evidence that recommendations have changed practice to better align with the evidence. This contrasts with CDC guidelines which faced substantial criticism including from ASIPP even though they are widely promulgated.

Among the various reviews of opioids for chronic noncancer pain, Busse et al (449), in a systematic review and meta-analysis, included 96 RCTs including 26,169 participants. Of the included studies, there were 25 trials of neuropathic pain, 32 trials of nociceptive pain, 33 trials of central sensitization pain present in the absence of tissue damage, and 6 trials of mixed types of pain. The results showed that compared with placebo, opioid use was associated with reduced pain on a 10 cm Visual Analog Scale (VAS) for pain, moderate risk difference for achieving the minimally important difference (MID), improved physical functioning and increased vomiting compared with placebo for trials that excluded patients with adverse events during a run-in period. In addition, low to moderate quality evidence suggested similar associations of opioids with improvements in pain and physical function compared with NSAIDs, TCAs, and anticonvulsants. They concluded that in this meta-analysis of RCTs of patients with chronic noncancer pain, evidence from high quality studies showed that opioid use was associated

with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo. Further, comparisons of opioids with nonopioid alternative suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality.

Surveillance Report 3 of Systematic Review on Opioid Treatments for Chronic Pain (484) with literature update from December 2021 to March 16, 2022, focused on the use of opioids in adults for chronic pain management and addressed effectiveness and comparative effectiveness of opioids, risks of opioid therapy, and accuracy of instruments for predicting risks for opioid overdose, addiction, abuse, or misuse. In this analysis, overall, they included 176 studies with 78 studies evaluating opioids vs. placebo, 17 studies evaluating effectiveness in subgroups, 13 studies evaluating opioids vs. nonopioids, and 10 studies evaluating opioids plus nonopioids vs. opioids or nonopioid alone. A summary of conclusions and assessments informed by new evidence from the surveillance reports was as follows:

- Opioids vs. placebo, short-term pain: Opioids were associated with small improvement in short-term pain with no change in conclusions from earlier reports of 2020.
- Opioids vs. placebo, short-term function: Opioids were associated with small improvement in short-term function with no change in conclusions from previous assessment of 2020.
- Opioids vs. no opioids, long-term pain, and function: Opioids were associated with decreased likelihood of improvement in pain and no difference in function at one year and without any difference on either outcome at 2 years with no change in conclusion. This is an important aspect of opioid preparation guidelines and was used as a basis in the CDC guidelines.
- Opioids vs. placebo, short-term harms: Opioids were associated with increased risk of withdrawal due to adverse events, nausea, vomiting, constipation, dizziness, somnolence, pruritis.
- Opioids vs. no opioids, long-term harms (all-cause mortality and cardiovascular events): Opioids were associated with increased risk of all-cause mortality and cardiovascular events, myocardial infarction, or cardiovascular mortality.
- Harms by dose or duration: Opioids associated with increased risk of overdose and one observational study found higher dose of opioids associated with increased risk of mortality.
- Dose tapering vs. no tapering and long-term pain and function: Based on one cohort study with 290 patients, there were no differences between involuntary or voluntary opioid tapering vs. no tapering in pain intensity or function but was rated poor quality.
- Dose tapering strategies: Slower tapering was associated with decreased risk of opioid-related emergency department visit or hospitalization.
- Treatment of OUD, buprenorphine/naloxone vs. methadone: There was no difference between buprenorphine/naloxone vs. methadone in likelihood of study retention, pain, function, or likelihood of positive urine drug test.

The German guidelines of long-term opioid therapy for chronic non-cancer pain were updated in 2020 (454). In preparation of these guidelines and evidence-based recommendations, the panel utilized respective meta-analysis for chronic low back pain (479), osteoarthritis pain (453), and neuropathic pain (467) and open-label extension studies of these RCTs (447,453). They also utilized >50% pain relief as primary outcomes, along with patient global impression to be much or very much improved, disability, dropout rates to adverse events, tolerability frequency of serious adverse events and death. Secondary outcomes were pain relief of > 30%, mean pain intensity, sleep problems, withdrawal symptoms and abuse or dependence of prescribed opioids.

Table 4 shows the summary of evidence of effectiveness and adverse events of opioid therapy in various conditions of chronic pain.

Table 4. *Summary of evidence and adverse effects of opioid therapy.*

Disease Process/Pain Syndrome	Source	Study type	Summary/ Recommendation
Chronic noncancer pain, disease process or pain syndrome	Dowell et al (13)	Guidelines based on systematic reviews sponsored by AHRQ.	Insufficient evidence to determine long-term benefit of opioid therapy for chronic pain and an increased risk for serious harms related to long-term term opioid therapy that appears to be dose dependent.
Chronic noncancer pain, disease process or pain syndrome	Chou et al (484)	Systematic review on opioid guidelines for chronic pain AHRQ surveillance report.	Opioids were associated with decreased likelihood of improvement and pain and no difference in function at one year; no difference on either outcome at 2 years. Long-term opioid therapy was also associated with increased risk of all-cause mortality and cardiovascular events, including myocardial infarction or cardiovascular mortality.
Opioids for chronic non cancer pain	Busse et al (449)	A systematic review and meta-analysis of 96 RCTs including 26,169 participants.	The meta-analysis of RCTs of patients with chronic noncancer pain in this review showed that opioid use was associated with statistically significant but small improvement in pain and physical functioning, and increased risk of vomiting compared to placebo, evidence based on high quality studies.
Opioids for chronic non cancer pain	Petzke et al (454)	Second update of the German guidelines for long-term opioid therapy for chronic noncancer pain.	Opioids are one drug-based treatment option for short (4-12 weeks), intermediate (13-26 weeks), and long-term (over 26 weeks) therapy of chronic pain in osteoarthritis, diabetic polyneuropathy, post herpetic neuralgia and low back pain.
Opioids for chronic non cancer pain	National Opioids Use Guideline Group (NOUGG) (38)	Canadian guideline for opioid therapy and chronic noncancer pain guidelines	• There was low quality evidence that opioids may have similar effects on pain relief as NSAIDs, tricyclic antidepressants, or nabilone, a synthetic cannabinoid, and similar improvements in physical function as NSAIDs, anticonvulsants, tricyclic antidepressants, or nabilone. • High-quality evidence shows that opioids increase the rate of gastrointestinal adverse events with NSAIDs and low-quality shows that they may increase the rate of gastrointestinal adverse events compared with anticonvulsants and tricyclic antidepressants.
Low back, osteoarthritis, and neuropathic pain	Bialas et al (447)	Review article, 3,590 participants of a total of 15 studies	Quality of evidence- low. Review article did not address different types of CNCP; however, based on very low quality of evidence, those who completed an RCT and entered the open label extension phase, reported a sustained reduction of pain and disability. Opioids in this group appear well tolerated and safe.
Neuropathic Pain: DPN, HIV, radicular pain, peripheral neuropathy	Erosa et al (460)	Systematic meta-analysis: 1619 articles retrieved; 10 studies included	Level 3 evidence. The efficacy of Tapentadol ER, buprenorphine TD, and levorphanol IR for neuropathic pain still requires future RCT
Neuropathic Pain: PHN, DPN, spinal cord injury, or polyneuropathy.	Duehmke et al (465)	Systematic meta-analysis: 6 studies with 438 patients, duration 4-6 weeks	Level 3 evidence. The benefit from tramadol 100-400 mg /day in neuropathic pain was of low or very low quality because of small study size, few actual events, and the limited duration of the studies.
Neuropathic Pain: PHN and diverse neuropathic pain syndromes	McNicol et al (466)	Systematic meta-analysis: included 3 studies, ranged from 20 days to 8 weeks. Oral methadone 10-80 mg daily	Level 3 evidence. No conclusion was made in efficacy or safety between methadone versus placebo, other opioids, or other treatments. Comparators were primarily placebo
Persistent Pain (Trauma/ Orthopedic surgery)	Côté et al (472)	Systemic review and meta-analysis	Moderate to High Level Minimum effective dose, no dose escalation, use for short time possible

Table 4 cont. *Summary of evidence and adverse effects of opioid therapy.*

Disease Process/Pain Syndrome	Source	Study type	Summary/ Recommendation
DPN	Azmi et al (458)	Systemic review: Morphine, Tramadol, Tapentadol	Level 3 evidence. Tapentadol ER is FDA-approved for DPN pain but not a disease-modifying therapy
DPN	Schwartz et al (459)	Pooled analysis	Level 2 evidence. Tapentadol ER was effective in DPN pain
PHN	Xing et al (462)	Retrospective study, 134 patients aged 50 or older	Level 3 evidence. supplemental pain medicine earlier in moderate to severe acute herpetic pain versus delayed over 14 days
PHN	Huang et al (463)	RCT, 201 patients, treatment course lasted 2 weeks, follow up for 12 weeks	Level 2 evidence. NRS score, IV PCA hydromorphone with oral pregabalin provided superior pain relief than pregabalin alone evaluated at 1, 4, and 12 weeks.
PHN	Song et al (464)	Systematic meta-analysis	Level 3 evidence. Topical therapies, antiepileptics, analgesics, and antidepressants exhibited better pain relief versus placebo
PHN, DPN and other peripheral neuropathies	Sommer et al (467)	Systematic review and Meta-analysis for treatment 4-12 weeks, 16 studies included.	Level 2 evidence. Buprenorphine, hydromorphone, morphine, oxycodone, tramadol, Tapentadol provided substantial pain relief compared to placebo
HIV Neuropathic Pain	Canneti et al (468)	RCT: 40 advanced AIDs patients, used neuropathic pain scale, 0-10 VAS.	Level 3 evidence. Transdermal Fentanyl & buprenorphine both reduced neuropathic pain with stable immunological parameters reports with high efficacy, tolerability and patient compliance.
Spine surgery	Cook et al (470)	Retrospective review	Level 3 evidence, Opioid naïve patients use less post-operative opioids and for a short period of time. 15-18% of these patients become long term opioid users after surgery.

AHRQ, Agency for Healthcare Research and Quality; RCT, randomized controlled trial; NSAIDs, nonsteroidal anti-inflammatory drugs; CNCP, chronic noncancer pain; DPN, diabetic peripheral neuropathy; HIV, human immunodeficiency virus; ER, extended release; TD, transdermal; IR, immediate release; PHN, postherpetic neuralgia; FDA, U.S. Food and Drug Administration; Visual Analog Scale (VAS); NRS, numeric rating scale; IV PCA, intravenous patient-controlled analgesia; AIDs, Acquired immunodeficiency syndrome

11.0 Adverse Consequences of Opioid Therapy

Key Question 15. What are the burdens, risks, adverse consequences, and harms of chronic opioid therapy?

Long-term effects of opioids may result in several reinforcement disorders, such as tolerance, addiction, physical dependence, vomiting, drowsiness, nausea, itching, respiratory depression, increased sensitivity to pain, work disruption, reduced level of attention, hypothermia, hallucinations, urticaria, dizziness, urinary retention, delirium, headache, muscle rigidity, hypotension, and bradycardia (485-487).

11.1 Tolerance, Physical Dependence, Addiction and Death

Opioid tolerance, dependence, addiction, and death are significant potential adverse effects for physicians to consider when writing opioid prescriptions. These effects are caused by a combination of molecular and behavioral changes that can affect patients of all educational and socioeconomic backgrounds. Opioid tolerance has been defined as a diminished response to repeated opioid use and may result in dose escalation to achieve analgesic effects (485,488,489). Patients who are opioid-tolerant are more likely to experience withdrawal symptoms with abrupt discontinuation. These withdrawal symptoms including stomach cramps, diarrhea, rhinorrhea, sweating, irritability, dysphoria, hyperalgesia, and insomnia can occur with abrupt cessation or a substantial decrease in dosage. This syndrome can occur within 24 hours and persist from 7-10 days (488).

Opioid use disorder also referred to as "opioid addiction" is the desire to seek and use opioids despite clinically significant distress or impairment, as defined by the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition, Text Revision (DSM-V-TR). As of

2018, OUD affected over 2.1 million individuals in the United States and over 16 million people globally (490). Approximately 8-12% of patients being prescribed opioids for chronic pain syndromes develop OUD. Additionally, 80% of heroin users misused prescription opioids (491).

Opioid overdose is the most concerning potential adverse effect of opioid use. Unsurprisingly, higher doses of opioids increase the risk of overdose (492). Per 2019 CDC statistics, an average of 38 people died each day from overdoses. Over the last few years, an increase in the availability and recreational use of potent, synthetic opioids has fueled an increase in overdose deaths. New data from the CDC suggests that a major spike in opioid-related deaths during the COVID-19 pandemic was likely due to synthetic opioid deaths increasing by 38.4%. From an economic perspective, in 2017, costs in the United States for OUD and fatal opioid overdose were estimated at over $1 trillion (493).

The effects on the CNS are multiple and varied and may not occur in all users. Sedation and psychomotor impairment can be seen in a dose-dependent manner, although tolerance to this side effect develops quickly (494). Sleep may be negatively affected, as morphine has been shown to decrease rapid eye movement (REM) sleep (495). Cognition may also be mildly decreased (489,496). Delirium, hallucinations, and nightmares have been known to occur, likely due to anticholinergic effects in the cortical and subcortical regions of the brain (489). Lastly, in rare episodes, patients may experience direct opioid-induced neurotoxicity, manifested as myoclonus and seizures (489). Although the mechanism of opioid-induced neurotoxicity remains unclear, glutaminergic upregulation of the NMDA receptor-caspase pathway is thought to play a major role.

11.2 Cardiovascular Effects

The effects of opioids on the cardiovascular system have been growing interest in recent years. Opioids demonstrate several effects on the cardiovascular system that can be visualized with the help of an electrocardiogram (497). The changes are displayed in terms of progression and regression of the QT interval (489). The QT interval refers to the time between the beginning of the Q wave and the end of the T wave, which depicts ECG repolarization and ventricular depolarization electrical presentation (498). QT interval prolongation shows slow electrical conduction of the ventricle (499). Thus, QT changes the heart rate. QTC interval in females is greater than 470 ms, whereas in males, it is greater than 450 ms. These changes may lead to torsade de pointes (TdP) which is self-limited, but it mostly turns into ventricular fibrillation, a life-threatening condition that can lead to death unexpectedly (500). However, there may be fundamental states that can lead to QT prolongation, such as HIV infection, cardiac disease, and female gender (501). Several drugs lead to QT interval prolongation and a greater level of prolongation including antiretroviral protease inhibitors (indinavir, ritonavir, and atazanavir), macrolide antibiotics (roxithromycin, erythromycin, dirithromycin, and clarithromycin) antifungal azole agents (itraconazole, ketoconazole, and fluconazole), buprenorphine metabolizing enzyme, and methadone (502). Finally, the effects of opioids are dependent upon the type of opioid that has been taken into consideration (448). Among various drugs, buprenorphine is considered as a safe drug in reference to cardiac changes based on multiple studies and does not appear to cause clinically significant QT interval prolongation or arrythmia when used at typical doses (503,504). On the other hand, methadone has a greater issue with QT-prolonging impact, which can result in TdP as a potentially fatal arrythmia, in addition to certain major adverse effects, such as hypotension and oedema (502). Morphine has not shown significant effect on QT interval, whereas fentanyl has shown QT interval prolongation, even though there are no reports of arrhythmia occurring after taking fentanyl (486,505).

11.3 Respiratory Effects

Opioid-related deaths are mostly caused by respiratory arrest and often occur during sleep where ventilation is primarily regulated by autonomic neurochemical control (506-509). Since 2000, a significant association with chronic opioid use and central sleep apnea has been identified (499,510-513). Central sleep apnea due to drug and substance was officially recognized in the 2005 edition of International Classification of Sleep Disorders (ICSD) (514). Two systematic reviews published in 2015 and 2016 confirmed that 24% of chronic opioid users had central sleep apnea that was dose-related (513). However, apart from central sleep apnea, obstructive sleep apnea (OSA) is also a major issue (515). central sleep apnea indicates a cessation of airflow without respiratory effort -- defined during polysomnographic (PSG) studies as a pause of breathing for > 10 seconds in nasal flow, chest, and abdomen movement channels (516). In contrast, OSA is characterized by episodes of complete collapse of the airway or partial collapse with

an associated decrease in oxygen saturation or arousal from sleep, resulting in fragmented, nonrestorative sleep. Opioids may exacerbate central sleep apnea or OSA, concomitant use of benzodiazepines and hypnotics and sedatives, also elevate the risk and exacerbate symptomatology and complications (517).

11.4 Immune Effects

Many opioid analgesics are associated with immunosuppressive effects. Animal studies indicate that fentanyl, morphine, methadone, oxycodone, and buprenorphine suppress innate immunity, (i.e., macrophages, neutrophils, mast cells, Natural Killer cells and dendritic cells) and have mixed effects on adaptive immunity (B and T cell response) (518,519).

Morphine suppresses key cells of innate immunity and is associated with greater risk of infection. In the surgical and critical care setting, opioid analgesic use is associated with greater risk of secondary infections and mortality. A retrospective case–control trial reported a 2-fold greater risk of mortality among people using opioids > 1 month. In cancer pain, there are concerns that opioids may promote tumor growth or metastasis due to their ability to suppress anti-cancer immunity. Tramadol has been reported to preserve or promote the immune response, including natural killer cell activity, and may therefore be preferred to other opioids in cancer patients.

When prescribing opioids, research indicates the need to optimize management to mitigate against the risk of infection in high-risk settings. Clinicians need to identify and avoid opioid treatments that have adverse effects on immune system parameters and clinical outcomes (518). Efforts are needed to achieve adequate analgesia while avoiding suppression of innate immunity especially in the immediate postoperative period, particularly in cancer surgery.

11.5 Endocrine Effects

Long term opioid therapy directly suppresses the hypothalamic-pituitary axis leading to a gamut of endocrine related changes (519-521). In a meta-analysis done by de Vries et al (520), showed that among male patients on chronic opioids, hypogonadism is present among 63% of patients while hypocortisolism is present in 15%-24% of patients of both genders. The decrease in cortisol level may precipitate Addisonian crisis and life-threatening adrenal insufficiency if unrecognized. Hyperprolactinemia was also a common feature. These inhibitory effects of opioids have been found to be reversible when doses are tapered or when opioid therapy is abrogated (519-521).

11.6 Gastrointestinal Effects

Opioids are associated with gastrointestinal discomfort, malfunction, and intolerance, exemplified by opioid-induced constipation and enteral feeding intolerance. Δ-, κ-, and μ-opioid receptors are present throughout the central and enteric nervous system (myenteric and submucosal plexus). Opioid interaction with μ-opioid receptors reduces acetylcholine release in smooth muscles of the gastrointestinal tract. This leads to inhibition of gastric emptying through inhibition of propulsive gastric contractility and stimulation of distal resistance at the antrum and pylorus as well as decreased gastrointestinal fluid secretion (522,523).

Growing evidence from animal and human studies show that opioids also have a major impact on the composition and function of gut microbiota. This leads to disruption in gut permeability and altered microbial metabolites, driving both systemic and neuroinflammation, which in turn impacts CNS homeostasis (524). Recently, this "opioid-induced dysbiosis" (OID) has been linked to antinociceptive tolerance development in preclinical models and may therefore provide new opioid-sparing strategies (525). Targeting the gut microbiome during opioid use through prebiotics, probiotics, antibiotics, and fecal microbial transplantation holds promise for novel treatments for opioid abuse (524,525).

Constipation is the most reported opioid-induced side effect and affects 50–80% of patients. Increased fiber intake and physical activity are encouraged, while laxatives are often co-administered as first-line therapy. An alternative approach is the use of the opioid Tapentadol which has a dual mode of action, both as an agonist of the μ-opioid receptor and as a norepinephrine reuptake inhibitor that affects descending mechanisms and inhibits pain impulses. Tapentadol has similar analgesic effects as oxycodone in equipotent doses and may be more tolerable with fewer gastrointestinal side effects (526).

11.7 Opioid Induced Hyperalgesia

Opioid-induced hyperalgesia (OIH) is defined as an enhanced response to painful stimuli, caused by exposure to opioids. It may manifest as hyperalgesia or allodynia, and it may present, in the clinical setting, as a worsening of pain despite an increase in the dose of pain medication, unlike tolerance which improves with

increased dosage opioids. Clinically, OIH is a worsening of pain that cannot be explained by progression of the original condition diffuse pain or pain at anatomically different sites occurs. Animal studies have reported a decrease in nociceptive threshold from baseline after the administration of opioids.

OIH can be observed immediately and persists for several days after single or repeated administrations of opioids. It occurs with various opioids, delivered by different routes of administration, such as intravenous, intrathecal, and oral. After an initial phase of analgesia, OIH appears to be dose dependent (527).

As prevention of OIH may serve as the best treatment, patient risk factors, opioid mitigation, and both pharmacologic and non-pharmacologic strategies are important (528). Pharmacologic strategies include opioid rotation, opioid cessation, and the use of adjuvant pharmacotherapies such as infusions of ketamine, dexmedetomidine, parecoxib and low dose naltrexone. The decrease in pain is achieved by 8 days, on average. Ketamine and dexmedetomidine are the most widely used adjuvant drugs (527).

Although the mechanisms of OIH are thought to primarily involve medullary descending pathways, it is likely multifactorial with several relevant therapeutic targets (528). Previous studies have suggested that activation of astrocytes in the spinal dorsal horn is essential for the development and maintenance of OIH. Recent animal data indicate that suppression of astrocyte activation does not ameliorate mechanical hyperalgesia in mouse OIH models (529). The descending serotonergic pain-facilitatory pathway in the spinal dorsal horn appears to be crucial in OIH, and that inhibition of this pathway with 5HT3 antagonists holds promise to decrease OIH (530).

11.8 Patient's Perception of Opioid Risk

There is considerable disparity regarding the perception of opioid risk between patients who never took opioids and those on chronic opioid therapy. In a cross-sectional observational study by Lavergne et al (531) showed that most people perceived the risk of OUD secondary to opioid analgesic medication use, with 65% believing that the consumption of these drugs can likely or very likely lead to OUD. In contrast, a significant majority of those who had used opioid pain medication in the past 2 years were little or non-concerned about the risk of OUD when using them. This paradox creates a stigma that surrounds patients on chronic opioid use (531). The complexity and subjective nature of human perception made patients think that clinics' monitoring policies are in response to other patients' opioid misuse and are means to protect clinicians. This also demonstrates that current opioid policies may not foster optimal patient-clinician communication about relative benefits versus risks of opioid use. Patients with recent use of illicit substances viewed clinicians' decisions to discontinue opioids as a response to medico-legal concerns, as opposed to concerns about patient safety. Such perspectival differences may lead to disparity in providing appropriate care to low-income individuals and minorities. Establishment of a positive physician-patient relationship can be useful toward mitigating such dissonances and disparities (532).

11.9 Medicolegal and Emotional Risks to Prescribers

The pervasive use of opioids in clinical practice has become a public health hazard due to the inherent risk to individual patients and providers. Besides knowing clinical indications for opioid use, prescribers also have ethical and legal responsibility to employ opioids (and other controlled substances) aptly and soundly within the scope of clinical practice. Physicians can be subjected to professional disciplinary and legal actions if found to be non-compliant with regulations defining prescribing, dispensing, reporting, and consumption of controlled substances. Extant gaps in knowledge and awareness of state legislation and regulation of opioids only serve to fortify medicolegal risk. In Canada, 151 medico-legal cases involving allegations of patient harm related to opioid prescribing between 2010 and 2015 (533). A review of 32 opioid prescribing related disciplinary decisions in Australia and all the providers had conditions placed on their practice, and some were suspended or de-registered. Sanctions ranged from a caution to a reprimand. The decisions all involved failure to keep adequate records and mostly involved inappropriate prescribing to multiple patients (534). Yet, it is important to note that such risk of punitive response might discourage pain practitioners from prescribing opioids - even when necessary. Such "defensive practice" essentially represents an under-treatment of pain, and as such transgresses the pain clinicians' ethical act of profession. However, it cannot be ignored that many clinicians' inherent concern is that they could be found liable for the deaths of patients or community members who overdosed on opioids that they had prescribed (532). Comer et al (535) undertook an institutional

ethnography of social organization of opioid policies and their implications for both patients with chronic pain and clinicians. They assessed Ontario's Narcotics Monitoring System and the 2017 Guidelines for Opioids for Chronic Non-Cancer Pain and concluded that these policies intended to mitigate opioid related harms by reducing the number of opioids prescribed, but indeed had repercussions for people with chronic pain, as well as practitioners. Based upon these conclusions, the authors explicated an urgent need to investigate the unintended and unanticipated impacts of drug policies, which may only be revealed through exploration of people's everyday lives and experiences.

Similarly, Braithwaite et al (536) reviewed federal and state guidelines and their effects on orthopedic practices. They concluded that orthopedic surgeons' prescribing patterns have certainly contributed to the opioid crisis, in concert with inconsistent state and/or federal regulations. It was also noted that while the opioid crisis remains a difficult challenge to overcome, steps must be undertaken at state and federal levels to standardize practices involving opioid management, and prescribers must reflect on, review, and aptly revise their prescribing styles, so as to take proactive lead in efforts to mitigate their contribution to the crisis.

11.10 Co-Administration with Other Drugs

A vast majority of non-cancer pain patients on medically directed opioid therapy have pre-existing comorbidities requiring maintenance medications to treat anxiety, depression, and mental illness. Understanding that concomitant use of opioids with certain medications may cause inadvertent harm such as over sedation and drug overdose due to synergistic effect and alteration of drug metabolism. Boon et al (537) analyzed the effect of benzodiazepine and opioid and found that these drugs in combination negatively affect respiration and patients are more prone to hypoxemia and hypercarbia. In a retrospective cohort study of Medicare part D claims data from 71,248 patients showed that during the first 90 days, concurrent benzodiazepine use is associated with a 5-fold increase in the risk of opioid-related overdose (538). In patients who are chronic opioid abusers and on maintenance therapy with buprenorphine and methadone, showed high risk of overdose and does not imply tolerance to respiratory depression for benzodiazepines. It is also a false reassurance to clinicians expecting their patients on opioid replacement therapy to require larger doses of sedatives to obtain an adequate treatment effect (537). The use of gabapentinoids (gabapentin and pregabalin) can potentiate the respiratory depressant effects of opioid including overdose, compared with pain management strategies that did not involve gabapentinoids. The overall occurrence of outcomes was very low, with overdoses occurring in less than 0.1% of patients (539). A similar retrospective study done by Minhaj et al (540) in 295 patients found that use of gabapentinoids increases the risk of opioid related adverse effects. The same study concluded that patients taking opioids who were 65 years or older, female, had orthopedic surgery, certain comorbid conditions (diabetes, pulmonary, kidney, or liver diseases), or received patient-controlled analgesia (PCA) opioids were more likely to require reversal with naloxone.

12.0 Prevalence of Opioid Use Disorder in Patients With Chronic Non-Cancer Pain and Management Options

Key Question 16. What is the prevalence of opioid use disorder in chronic non-cancer pain patients and what are the management options for such co-morbidity?

12.1 The Disease of Addiction

In September 2019, the American Society of Addiction Medicine (ASAM) defined addiction as a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with disease of addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

Essential features of addiction: A cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems (DSM-V-TR) (541,542).

Exception to the diagnosis can be found in patients with chronic pain: Tolerance and Physical Dependence (DSM-V-TR – Opioid Use Disorder). Unlike tolerance and physical dependence, addiction is not a predictable result of opioid prescribing. Addiction occurs in only a small percentage of persons who are exposed to opioids — even among those with preexisting vulnerabilities (543).

12.2 Prevalence of Opioid Use Disorder in the Population and in Chronic Pain Patients

The most recent data from the NSDUH reveals that 28.6 % of people 18 years or older have had some use of prescription pain relievers. Misuse in 2020 among the total population is 3.5%. The prevalence rate of OUD in patients prescribed pain relievers is reported as 12.3% (544).

There is wide variation regarding rates of OUD in the literature. Five systematic reviews estimated the rates of prescription opioids or other opioid use in chronic pain populations with substantial variation in results (0.05% to 81%), likely due to widely varying definitions of dependence, SUD, misuse, addiction, and abuse (545).

Boscarino et al (546) in a large interview survey of a clinic population, reported a lifetime prevalence of mild OUD [2–3 DSM-V symptoms] of 28.1%, moderate OUD (4–5 symptoms) of 9.7%, and severe OUD (6+ symptoms) of 3.5%. Illicit drug use has been reported in 14% to 34% of patients in chronic pain management settings (547). Meta-analysis of 784 studies estimated the prevalence of problematic use of opioids in adults with chronic noncancer pains was 36.3% (548).

Hser et al (549) using an electronic health record database from 2006–2015, assessed 5,307 adult patients with OUD in a large healthcare system; 35.6% had no pain issue, 9.7% had OUD first, 14.9% had both at the same time, and 39.8% had pain first.

12.3 Managing Opioid Addiction in the Chronic Pain Patient

The rewarding effects of opioids play a major role in the risks of opioid diversion, overdose, and addiction. However, the likelihood and severity of these risks are largely independent and governed by different factors. All these risks are present to some degree with all opioids and with all pain diagnoses. This means that no single or simple change in prescribing behavior can be expected to alleviate all risks while properly managing pain.

There are common strategies, however, that can help mitigate all risks, including limiting the prescribed opioid to the lowest effective dose for the shortest effective duration (543), and following the recommended screening for addiction within all patients. Using the PDMP and monitoring for diversion is critical (550,551). All prescribers of opioids for pain management should expand the use of naloxone to prevent overdoses (552).

Most patients with chronic non-cancer pain do not have the disease of addiction. However, most patients with addiction will have an issue with acute or chronic pain at some point in their lives. There are three scenarios in which physicians may need to provide pain treatment in patients with the disease of addiction:

1. Patients with an untreated and active OUD; may have been newly diagnosed within the pain practice
2. Patients under Medication Assisted Therapy (MAT) treatment with opioid agonists.
3. Patients under MAT treatment with naltrexone (553).

12.3.1 Medication Assisted Therapy (MAT)

The use of MAT in managing opioid addiction among patients with co-occurring pain significantly improves outcomes (554). With implementation of MATE that was passed as part of the Consolidated Appropria-

tions Act of 2023, DATA-waiver requirement has been eliminated (346). The curriculum now for renewal of DEA license includes at least 8 hours of training which includes treating and managing patients with opioid or other SUDs. Healthcare providers should consider learning more about using buprenorphine products to treat patients who have chronic pain requiring the use of opioids and addiction.

12.4 ASAM National Practice Guideline for the Treatment of Opioid Use Disorder

It is important to understand and treat opioid use disorder appropriately (553).

1. Alternative treatments including nonopioid medications, behavioral approaches, physical therapy, and procedural approaches (e.g., regional anesthesia) should be considered before prescribing opioid medications for pain.
3. For patients with pain who have an active OUD but are not on MAT, methadone or buprenorphine should be considered. The patient's OUD and pain should be stabilized and managed concurrently.
4. For patients taking methadone or buprenorphine, temporarily increasing the dose or dosing frequency (i.e., split dosing to maximize the analgesic properties of these medications) may be effective for managing pain.
5. For patients taking methadone for OUD, with acute pain refractory to other treatments, adding a short acting full agonist opioid to their regular dose of methadone can be considered to manage moderate to severe acute pain. The dose of a full agonist opioid is anticipated to be higher than the typical dose necessary to achieve adequate analgesia in opioid-I individuals.
6. Patients receiving buprenorphine for OUD, with moderate to severe acute pain refractory to other treatments may benefit from the addition of as needed doses of buprenorphine. The addition of a short acting full agonist is not recommended outside of a supervised hospital setting (554).
8. Discontinuation of methadone or buprenorphine before surgery is not required. Higher potency intravenous full agonists opioids can be used perioperatively for analgesia.
11. Patients on naltrexone may not respond to opioid analgesics in the usual manner. Therefore, it is recommended that mild pain be treated with nonopioid analgesics, and moderate to severe pain be treated with higher potency NSAIDs (e.g., ketorolac) on a short-term basis.
12. Oral naltrexone should be discontinued 72 hours before surgery and extended-release injectable naltrexone should be discontinued 30 days before an anticipated surgery.
13. Naltrexone's blockade of the mu-opioid receptor can often be overcome, when necessary, with high potency full agonist opioids. In these instances, patients should be closely monitored in an emergency department or hospital setting (555).
14. After discontinuation of naltrexone therapy an increased susceptibility to overdose may occur. Physicians need to be vigilant and inform the patients of this increased risk of opioid sensitivity after using an opioid antagonist (556).

In addition, there is a concern about a potentially higher overdose risk following discontinuation of XR-NTX due to a loss of tolerance that is not present for those discontinuing opioid agonists such as buprenorphine (557). The medication guide for XR-NTX, explicitly warns about this "rebound risk" of overdose but does not describe a particular period of risk (558). This risk may also be present for oral naltrexone, which is cleared from the system after just 24 h and may leave patients with low opioid tolerance.

Due to known hepatotoxicity in high doses, liver enzymes should be monitored before initiation and cautiously monitored throughout therapy. Thus, Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be five-fold or less. VIVITROL does not appear to be a hepatotoxin at the recommended doses. However, these warnings may not apply in low dose treatment with naltrexone, specifically for neuropathic pain.

13.0 Guidance for Responsible Opioid Prescribing for Chronic Non-Cancer Pain

Key Question 17. What constitutes responsible opioid prescribing and what is the management strategy is safest and most effective for long-term opioid therapy in managing chronic non-cancer pain?

Over the years, multiple guidelines have described various steps for long term opioid therapy in chronic non-cancer pain. Recent manuscripts, including the HHS recommendations from the Pain Management Best Practices Inter-Agency Task Force (23), the updated CDC guidelines (13), interagency guidelines (37), VA/DOD guidelines (36), and Canadian guidelines (38) have contributed to this body of knowledge. ASIPP also has provided steps for advising appropriate practice patterns for utilizing chronic opioid therapy. Since publication of the ASIPP guidelines (21) and the CDC guidelines in 2016, numerous publications have brought to light issues related to reducing opioid prescriptions. The multiplicity of these publications has generated a number of opinions and perspectives, which has tended to create ambiguity in establishment of a common positional stance.

The Pain Management Best Practices Interagency Task Force's final report published in May 2019 delineated updates, gaps, inconsistencies, and recommendations, and outlined the need for true multidisciplinary approaches to the treatment of chronic (23). In contrast, the updated CDC clinical practice guidelines (13) have maintained their approach, which has supported elimination of many clinically and cost-effective interventions. Several studies have also reported associations of patient perceptions of improvement in physical and functional status and the ability to improve their quality of life (21,23,559). There has also been substantial misunderstanding regarding prescription opioid usage and its contribution to overdose deaths. To a great extent, this has been demystified by recent publications showing the absence of relationship, or negative relationship between opioid doses, AOD, POD, OTAs, and annual prescription opioid sales MME per capita, as distinctly shown in Figs. 3 and 4 (7,20). Still, it has been difficult to assess the effect of any published guidelines. In fact, many continue to believe that the recently published CDC guidelines will continue to hinder access to patient care, despite certain changes; and thus, many physician and patient groups continue to oppose the CDC guidelines.

Despite significant advancements in understanding opioid overdose deaths, definitions of medical necessity criteria for opioid treatment, availability of addiction treatment and enhanced monitoring techniques, and numerous reported adverse consequences of CDC guidelines published in 2016 (9), the CDC clinical practice guidelines updated in 2022 (13) have remained largely unchanged, and have continued to focus on the behavioral aspects of chronic pain (with suicidal ideation and health disparities based on race, ethnicity, and gender). These guidelines also continued to offer multiple therapeutic options, some of which have been historically inaccessible or rarely used due to inadequate clinician education, training, and guidance; unconscious bias; a shortage of pain management specialists; insufficient access to treatment such as behavioral therapy; siloed health systems; insurance coverage and reimbursement policies; and lack of clarity about the evidence supporting different pain treatments. As we have long-maintained, if improbities, ineptitudes, and negative social effects of opioid misuse are to be mitigated, it will require a more pragmatic and ethically prudent approach to guiding physicians' and patients' utilization of prescription opioids, a more salient bridging of research, clinical, and socio-legal data and practices will be necessary.

The VA/DOD guidelines for opioid therapy in chronic non-cancer pain essentially followed the same philosophy as CDC guidelines (13), and overlooked issues related to inadequate management and rapid tapering of opioids. Further, the VA/DOD guidelines were similarly formatted, with 3 modules and 20 evidence-based recommendations including determination of appropriateness of care; initiation of treatment with opioids; and maintaining, tapering, discontinuing, or switching from full agonist opioids (14).

Dowell et al (9,13) provided 12 recommendations, from initiation to discontinuation of opioid therapy in chronic pain. These recommendations included determining when to initiate or continue opioids for chronic pain; determining opioid selection, dosage, duration, follow-up, and discontinuation; and for assessing risks and addressing harms of opioid use. Sullivan and Ballantyne (560) questioned the right to pain relief and its role in the opioid epidemic. They discriminate pain as a legitimate focus of medical treatment from pain as an associated symptom of an underlying disease. They described how pain intensity had become the metric used to determine the need for, and success of treatment. Sullivan and Ballantyne asserted that to prevent

future opioid epidemics we need to abandon clinical outpatient use of pain intensity scores and redefine the medical necessity of pain treatment to be less about the reduction of pain intensity and more about the capacity to pursue personally valued activities. Taken together, extant guidelines, and commentaries about guideline value and real-world patterns – and problems – of opioid utilization (i.e., clinician prescribing and patient need and use), establish a working overview of relative capabilities, inadequacies, and resultant gaps in current palette of opioid guidance.

In this light, and based upon experience with ASIPP's 2017 guidelines (21), herein is provided comprehensive consensus and evidence-based guidelines for prescription of opioids for chronic noncancer pain, as described by a 4-step process:

1. Initial steps of opioid therapy
2. Assessment of effectiveness of long-term opioid therapy
3. Monitoring adherence and side effects
4. Final phase of continuation or discontinuation of therapy

13.1 Initial Steps of Opioid Therapy

13.1.1 Comprehensive Assessment

Comprehensive assessment is mandatory for any chronic pain patient, specifically in managing the patients with opioid therapy.

13.1.1.1 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 that increase or exacerbate the pain, and those conditions that lead to diminution of pain must be documented (9,13,21,27-29,561-569). 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, a combination of these, widespread, or localized. The presence and extent of emotional pain also needs to be considered.

13.1.1.2 General Medical History

General medical history includes questions about general physical health, emotional health, and medication usage. Chronic pain patients tend to have multiple medical comorbid conditions, which may increase the pain levels, decrease functional status, or interact with drug therapy.

13.1.1.3 Previous Treatments

As a complement to the general medical history and pain condition, information about previous pain treatments is invaluable as it provides additional diagnostic benefits and helps direct future therapies. In particular, a history of previous treatments includes the patient's use of non-pharmacologic (lifestyle modifications and alternative treatments), pharmacologic (medications), psychological (cognitive behavioral therapy, talk therapy, counseling, behavioral modification, etc.), procedural (injection-based therapies or neurostimulation therapies), and surgical interventions. Along with each previous treatment, their associated analgesic and functional benefits and side effects should be documented. This paradigm allows for pain physicians to incorporate a comprehensive and multidisciplinary pain management strategy for their patients' pain treatment plans.

13.1.1.4 Psychosocial History and Evaluation

A comprehensive psychosocial history and evaluation can help establish the patient's social background and makeup, both of which heavily influence the patient's capacity for safe opioid use (570-582). Moreover, understanding this psychosocial context can provide insight into risk factors or protective factors for aberrant behaviors. A comprehensive psychosocial history includes understanding the patient's upbringing, family and support system, faith, occupation, hobbies, and interests. Moreover, it is important for physicians to understand the patient's perspectives on the use of alcohol, tobacco, and drugs. Psychosocial history complements psychiatric history, which can include personality, mood, and psychotic disorders.

Psychosocial history provides valuable insight into factors such as emotional stability and mood regulation. These factors suggest how patients' coping mechanisms for chronic pain may be compromised and/or lead or opioid misuse. Additionally, these factors can provide insight in treatment response with opioid medications. Symptoms of depression and anxiety have been shown to correlate with poorer health outcomes as well as

reduced treatment responses. Given these correlations, evidence also suggests benefits with behavioral and psychological therapies in treating chronic pain. Similarly, patients with other comorbidities including posttraumatic stress disorder and schizophrenia require psychiatric evaluation and optimization.

13.1.1.5 Substance Use History and Addiction Screening

Given the well evidenced addictive properties of medications, gathering a substance use history and addiction screening is necessary to characterize the addiction risk behaviors that a patient may possess. A comprehensive clinical assessment must include inquiry into both substances abused in the past along with documented SUDs using DSM-V-TR criteria. Screening includes personal and family history of addiction and SUDs with substances that include alcohol, tobacco, prescription medications (including opioids and benzodiazepines), and illicit substances (including but not limited to marijuana, heroin, cocaine, and psychoactive substances) (583,584). Given likely challenges with honest or complete data acquisition from the patient and family, clinicians must survey PDMP data, urine toxicology records, and medical records. There exists a plethora of validating screening tools that can be utilized depending on the patient's age (adult vs. adolescent), suspected substance (alcohol or drugs), or administration type (self vs. clinician administered). In those patients with a history of substance abuse disorders and treatment, compliance issues should be investigated.

13.1.1.6 Sleep Patterns

Sleep hygiene is a central component of physiological homeostasis. The prevalence of sleep disturbance has been well recognized within the chronic pain population (585-587). Consequently, measures to appropriately diagnose and characterize sleep disturbances can help to identify and treat associated daytime fatigue, lethargy, insomnia, and even cognitive dysfunction that may be present in vulnerable persons. Main risk factors for sleep disorders include congestive heart failure, OSA, central sleep apnea, older age, and obesity. Given the risk for opioid induced sedation, persons with these risk factors require close monitoring and judicious dose escalation (585-588). A sleep assessment in the clinic encounter can include questions regarding average sleep length, nighttime awakening, daytime fatigue, and sleep length. Validated risk tools such as the STOP-Bang (Snoring, Tired, Observed, Pressure, Body mass index more than 35 kg/m^2, Age older than 50, Neck size large, and Gender-male) can help diagnose OSA using a quick questionnaire (589-591). Persons with high suspicion of OSA or central sleep apnea should be referred to a formal sleep study that can help clearly elucidate the character of sleep disturbance and provide a formal diagnosis. Careful monitoring and judicious opioid escalation are warranted in persons at risk of excessive opioid sedation. Persons with a high risk for sedation or severe OSA may not be appropriate candidates for chronic opioid therapy (585-591). Furthermore, the concomitant use of opioid therapy with other CNS depressants or psychoactive medications may induce or exacerbate sleep disturbances. In particular, the concomitant use of opioids with benzodiazepines can lead to drastically elevated risks for sedation and respiratory depression.

13.1.1.7 Functional Assessment

Chronic pain invariably affects functional status including a reduced capacity for self-care, activities of daily living, mobility, employment, and social engagement. Many patients with chronic pain are known to suffer with significant disability and are often unemployed (61,63,592-594). Furthermore, persons with chronic pain and severe disability are thought to be refractory to numerous treatment modalities, including opioids (9,21,593,594). Given the limited capacity for pain severity assessments, monitoring functional status is thought to be a more important surrogate of treatment response in patients with chronic non-cancer pain, and those without painful debilitating diseases such as multiple sclerosis, Parkinson's disease, and acquired immunodeficiency syndrome (AIDS), in whom an expectation of functional improvement may not be reasonable (595). Functional assessment tools, including but not limited to the Oswestry Disability Index (ODI) and Neck Disability Index (NDI), have been validated in the chronic pain population.

13.1.1.8 Consultations

Multidisciplinary management of patients with chronic opioid therapy can help ensure that all their clinical needs are addressed. This is best achieved with targeted consultations with clear indications and objectives (9,21,41). Consultations are largely categorized as referrals to social services, rehabilitation therapists, mental health specialists, and physicians. Social services like social workers and case managers

can help navigate social barriers and obtain access to healthcare resources. Rehabilitation therapists such as physical and occupational therapists can help to optimize patients' functional status and physical wellness. Mental health specialists including psychologists and psychotherapists can provide additional care and recommendations for the treatment of patients with SUDs, and various other psychiatric comorbidities that may predispose them to medication misuse and preclude the safe use of chronic opioid therapy. Lastly, consultations to other physicians are based on underlying co-morbidities and may include referrals to sleep medicine, physiatry, psychiatry, addiction medicine, endocrinology, and pulmonology.

13.1.1.9 Prescription Drug Monitoring Programs (PDMP)

Electronic PDMPs are an established and essential component for documentation and management of opioid prescribing. The PDMP is an electronic database that tracks and collects state-wide data regarding controlled substances. A patient's PDMP should be reviewed prior to initiating opioids or other controlled substances, periodically during chronic therapy, and used as part of a compliance monitoring program. The appropriate use of the PDMP has been extensively debated and reviewed (21,596-599). The CDC states that "PDMP's continue to be among the most promising state-level interventions to improve opioid prescribing, inform clinical practice and protect patients at risk" (596). All fifty states, the District of Columbia, and Guam have implemented PDMPs.

Issues of concern with the PDPM include inadequate collection of some information in various states, lack of effective utilization of provided data into clinical practice, lag times in updating data, absence of tools for data analysis, limited interstate data sharing, and in some states, limited use by regulatory agencies (597). There is some evidence that an unintended consequence of PDMP is an association with higher rates of heroin-related deaths, potentially due to decreases in prescription opioid availability (600). Although the evidence basis for the positive impact of state-wide PDMPs remains mixed, they have become a part of the required medical record when managing patients with controlled substances, including opioids (21,596,601-605).

In multiple states, including California, Kentucky, New York, Ohio and in others, state law requires a mandatory evaluation of the State database. These requirements became part of state health and safety codes, as specified, and failure to comply is considered unprofessional conduct and actionable by the medical boards. Based on the regulations and evidence, it is recommended that when prescribing opioid therapy, and periodically during opioid therapy, clinicians should review the patient's history of controlled substance prescriptions using the state PDMP to determine whether the patient is receiving opioid dosages or combinations appropriately.

13.1.1.10 Risk Stratification

Patient evaluation and risk stratification is essential prior to initiating opioid or controlled substance therapy and throughout the term of treatment. Risk stratification is one of the most important strategies a physician can implement to mitigate potentially adverse consequences of chronic opioid use (9,13,21,605-613). In fact, the United States Department of Veterans Affairs has proposed a Stratification Tool for Opioid Risk Mitigation (STORM) as a clinical decision support tool to improve opioid safety in response to the opioid crisis. This is a predictive model that utilizes data from Veterans Health Administration (VHA) medical records to estimate patient risk of overdose and suicide. It helps identify patients at a high-risk for opioid-related adverse events and lists potential risk mitigation strategies. This web-based dashboard is available to all VHA physicians and providers (610). In addition, LCDs, medical policies, medical board regulations, and numerous practice guidelines mandate the use of risk assessment strategies (13,21,23,606-621).

Table 5 shows Opioid Risk Tool (ORT) (621), a brief, self-report screening tool designed for use with adult patients in primary care settings to assess risk for opioid abuse among individuals prescribed opioids for treatment of chronic pain (619,620). Based on the available literature, patients characterized as high-risk are at increased likelihood of future abusive drug-related behavior (40). The ORT has been validated in both male and female patients; however, not in non-pain populations. A score of 3 or lower indicates low risk for future opioid abuse, a score of 4 to 7 indicates moderate risk for opioid abuse, and a score of 8 or higher indicates a high risk for opioid abuse (619,621).

Table 6 shows SOAPP Version 1.0-14Q. To score the SOAPP Version 1.0-14Q, the ratings of all the questions are simply added. A score of 7 or higher is considered positive. The specificity increases as the scores increase to 9 or above, increasing from sensitivity of 0.91 and

Table 5. *Opioid risk tool*.

Mark each box that applies	Female	Male
Family history of substance abuse		
Alcohol	1	3
Illegal drugs	2	3
Rx drugs	4	4
Personal history of substance abuse		
Alcohol	3	3
Illegal drugs	4	4
Rx drugs	5	5
Age between 16 - 45 years	1	1
History of preadolescent sexual abuse	3	0
Psychological disease		
ADD, OCD, bipolar, schizophrenia	2	2
Depression	1	1
Scoring totals		
Risk classification: ≥ 8 high risk 4-7 moderate risk ≤ 3 low risk		

Questionnaire developed by Lynn R. Webster, MD to assess risk of opioid addiction. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the opioid risk tool. *Pain Med* 2005; 6:432-442 (621).

specificity of 0.69 with positive predictive value of 0.71 at score of 7 to 0.77 sensitivity and specificity of 0.8 with a positive predictive value of 0.77 with a score of 9 or above (622-624).

Even though LCDs, medical policies, and guidelines strongly recommend risk stratification, effectiveness and utility have been debated. In fact, the CDC recognizes the inaccuracy of opioid risk prediction instruments. This was consistent with the 2014 AHRQ report that described inconsistent estimates of diagnostic accuracy, methodological limitations, and few studies of risk assessment instruments other than the ORT, and Screening and Opioid Assessment for Patient with Pain-Revised (SOAPP-R) instrument. Evidence on the effectiveness of risk mitigation strategies remains limited. Even then, it is recommended to administer either ORT or SOAPP, or alternate instruments to patients upon an initial visit prior to beginning opioid therapy for pain management and periodically thereafter to meet published requirements.

13.1.1.11 Recommendations:

1. Comprehensive evaluation of pain history, medical

Table 6. *Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R)*.

Please answer the questions as honestly as possible below using the following scale: 0=Never, 1=Seldom, 2=Sometimes, 3=Often, 4=Very Often						
		Never	Seldom	Sometimes	Often	Very Often
		0	1	2	3	4
1	How often do you have mood swings?	❍	❍	❍	❍	❍
2	How often do you smoke a cigarette within an hour after you wake up?	❍	❍	❍	❍	❍
3	How often have any of your family members, including parents and grandparents, had a problem with alcohol or drugs?	❍	❍	❍	❍	❍
4	How often have any of your close friends had a problem with alcohol or drugs?	❍	❍	❍	❍	❍
5	How often have others suggested that you have a drug or alcohol problem?	❍	❍	❍	❍	❍
6	How often have you attended an AA or NA meeting?	❍	❍	❍	❍	❍
7	How often have you taken medication other than the way that it was prescribed?	❍	❍	❍	❍	❍
8	How often have you been treated for an alcohol or drug problem?	❍	❍	❍	❍	❍
9	How often have your medications been lost or stolen?	❍	❍	❍	❍	❍
10	How often have other expressed concern over your use of medication?	❍	❍	❍	❍	❍
11	How often have you felt a craving for medication?	❍	❍	❍	❍	❍
12	How often have you been asked to give a urine screen for substance abuse?	❍	❍	❍	❍	❍
13	How often have you used illegal drugs (for example, marijuana, cocaine, etc.) in the past five years?	❍	❍	❍	❍	❍
14	How often, in your lifetime, have you had legal problems or been arrested?	❍	❍	❍	❍	❍
Risk classification: < 7 low risk > 7 high risk						

history, psychosocial history, functional assessment, and appropriate consultations are recommended prior to initiation of opioid therapy.
Evidence Level: Strong; Strength of Recommendation: Strong

2. Review of Prescription Drug Monitoring Program (PDMP) data prior to initiating any/all controlled substance prescriptions and periodically or as mandated by regulations during treatment in order to provide information on patterns of prescribing from all providers registered with the system.
Evidence Level: Moderate to strong; Strength of Recommendation: Strong
3. Risk stratification as part of patient management is essential for opioid and controlled substance medication management.
Evidence Level: Limited; Strength of Recommendation: Moderate

13.1.2 Urine Drug Testing

Urine drug testing (UDT) serves as a valuable resource for healthcare providers, offering them timely, objective, and actionable insights. It aids clinicians in their decision-making process by confirming the presence or absence of potentially abused substances within a patient's body. This information is crucial for guiding treatment choices (606,607).

Two types of testing are available for monitoring compliance with controlled substance use: qualitative (presumptive) and quantitative (definitive) testing. These methods encompass urine drug monitoring (UDM), examination of biological fluids (such as sweat or saliva), and toxicology analysis (using blood samples). Qualitative testing identifies the existence of drug classes (e.g., opioids, benzodiazepines), illicit drugs, or specific drugs, while quantitative testing pinpoints individual medications within a class, illicit substances, drug metabolites, and quantifies drug and metabolite concentrations.

Numerous organizations have formulated guidelines outlining the medical necessity and indications for UDT. However, clinicians are strongly advised to adhere to the guidelines set forth by the Medicare Administrative Contractors (MACs), which maintain consistent contracts nationwide (606). It is imperative for clinicians to possess a thorough understanding of pharmacology, pharmacodynamics, drug interactions, and the correct interpretation of laboratory findings. A wealth of literature on UDM is available, encompassing clinical, forensic, and regulatory sources (13,21,605-627).

The policies established provide definitions for fundamental UDT forms (606):

1. Presumptive/Qualitative Drug Testing: This is medically necessary for promptly determining the presence or absence of drugs or drug classes in a urine sample. Results of presumptive drug testing are expressed as either negative or positive or as numeric values. This category includes competitive immunoassays and thin-layer chromatography (608).
2. Definitive/Quantitative/Confirmatory Testing: Clinically indicated and medically justifiable according to LCD, this method is used to identify specific medications, illicit substances, and metabolites. Test results typically report analyte presence or absence, often in concentrations measured in ng/mL. Definitive methods encompass Gas Chromatography coupled with Mass Spectrometry (GC-MS) and Liquid Chromatography coupled with Mass Spectrometry (LC-MS/MS) testing exclusively (608).

13.1.2.1 Presumptive Testing Methods

13.1.2.1.1 Presumptive UDT

A presumptive urine drug test (UDT) employs diverse platforms like cards, dipsticks, cassettes, and cups, all of which rely on qualitative competitive immunoassay methodology and include one or more analytes in the test. In the case of a presumptive immunoassay test, it serves to identify the presence of a drug or substance in urine above a predetermined "cut-off" value and can be interpreted through direct visual examination or with the aid of optical observation instruments (606).

A positive test result is recorded when the drug concentration surpasses the specified cutoff point, whereas a negative result is documented when the drug concentration falls below the cutoff value. It's important to note that positive test results are indicative but not conclusively definitive, as they may be subject to limitations stemming from sensitivity and cross-reactivity issues (605,606,609). Conversely, negative test results do not necessarily guarantee the absence of a drug or substance in the urine sample (605). The accuracy of presumptive UDT results hinges on factors such as the testing environment, the type of test employed, the specific drug under scrutiny, and the proficiency of the person conducting the test. This kind of test should exclusively be employed when immediate results are imperative.

13.1.2.1.2 Presumptive UDT by Instrumented Chemistry Analyzers

Chemistry analyzers equipped with immunoassay UDT technology find utility in both office and clinical laboratory settings. However, it's essential to note that this testing method does not yield immediate results. It's important to emphasize that immunoassay technology in chemistry analyzers is never considered confirmatory (definitive) testing (606).

A presumptive positive immunoassay test identifies the presence of a drug or substance in urine at or above the specified "cut-off" value. Conversely, if the drug concentration falls below the cut-off, the result is recorded as negative. Nevertheless, it's crucial to understand that presumptive positive test outcomes aren't always unequivocally accurate due to inherent limitations such as sensitivity, specificity, and potential cross-reactivity issues. Negative test results should not automatically be interpreted as the absence of a drug or substance in the urine specimen (605).

In the marketplace, one can find test platforms that are approved or cleared by the FDA, as well as laboratory-developed tests (LDTs). These LDTs may encompass modified FDA-approved/cleared platforms and non-FDA approved/cleared platforms and/or reagents. Typically, LDTs have been adapted to detect substances at lower cutoff values, as opposed to the higher cutoffs used in FDA-labeled tests. For instance, while an FDA-labeled cutoff may be set at 300 ng/mL, the LDT cutoff for the same drug might be as low as 100 ng/mL (605,606).

Presumptive UDT can be conducted at any validated cutoff concentration. Lowering the cutoff concentration leads to stricter criteria for detecting illicit drugs. LDTs may encompass non-FDA cleared tests that are not available in Clinical Laboratory Improvement Amendments (CLIA)-waived or moderately complex tests, examples of which include tramadol, tapentadol, carisoprodol, fentanyl, and zolpidem. Reducing the cutoff value enhances the likelihood of detecting a drug when the test has been modified from the manufacturer's specifications.

13.1.2.1.3 Limitations of Presumptive UDT

Presumptive UDT has several limitations that need to be considered:

1. Lack of Specificity: Presumptive UDT primarily categorizes drugs into classes rather than pinpointing specific substances. Consequently, when a positive result is obtained, it may not clarify which drug within that class is responsible, leading to uncertainty (606).
2. Potential for Errors: These tests may yield inaccurate results due to cross-reactivity with other compounds or may fail to detect all drugs within a given class (606,613).
3. Incomplete Testing: Some prescription medications and synthetic drugs may not be detectable through presumptive tests, leaving doubt about the presence of certain substances (606,613).
4. High Cut-off Values: The cut-off values employed in presumptive testing may be set too high to detect the presence of certain drugs, further limiting their effectiveness (606,613).

These limitations underscore the inadequacy of presumptive testing for specific clinical needs. immunoassay technology which employs antibodies that react primarily with the target drug and have minimal cross-reactivity with others in the same class, may provide more accurate results. However, even immunoassay has shortcomings, particularly in detecting prescription drugs such as opiates, barbiturates, benzodiazepines, and opioids.

For example, opiate IA, often derived from morphine, exhibits varying cross-reactivity with different opioids, potentially leading to false positives or negatives. Semisynthetic opioids like hydromorphone and hydrocodone may trigger positive immunoassay results, while oxycodone and oxymorphone are typically undetected, even with a 300 ng/mL cutoff. Synthetic opioids such as fentanyl, meperidine, and methadone generally escape detection via opiate immunoassay testing. Therefore, a positive opiate result by immunoassay necessitates further identification of the specific substances involved, and a negative result does not necessarily rule out the absence of opiates or opioids (606,614).

Similarly, presumptive UDT for benzodiazepines, formulated for oxazepam and older benzodiazepines like diazepam and chlordiazepoxide, may yield false negatives for newer benzodiazepines like clonazepam and lorazepam. This can require more specialized testing to confirm the absence or presence of these drugs (606).

Synthetic and designer drugs, designed to evade detection, demand definitive testing for identification. Most commercially available immunoassay reagents are ill-suited for detecting designer drugs, including psychedelic phenethylamines, even at high concentrations.

In summary, given the available evidence, clinicians are advised to opt for definitive UDT when presumptive tests yield negative results for the following reasons:

- Particularly within drug classes such as amphetamines, barbiturates, benzodiazepines, TCAs, and opiates/opioids.
- Low cross-reactivity or non-reactivity in drugs like buprenorphine, amphetamines, benzodiazepines, and cocaine/heroin may lead to false negative immunoassay results.
- Certain drugs, such as fentanyl, carisoprodol, tramadol, tapentadol, and synthetic designer drugs, are undetectable through presumptive immunoassay testing (606,607,610).

13.1.2.1.4 Definitive UDT

GC-MS and LC-MS/MS represent intricate technologies that combine the separation capabilities of gaseous or liquid chromatography with the analytical power of mass spectrometry.

The utilization of quantitative drug data holds significance for various reasons, particularly in the context of patient assessment. For instance, when a patient prescribed a single opioid exhibits the presence of multiple opioids in their urine, quantification plays a pivotal role in aiding the clinician's decision-making process. It allows them to discern whether the additional opioids are consistent with the metabolic byproducts of the prescribed opioid, potential contamination during manufacturing, or the use of more than one drug within the same class.

It's important to note that quantification is not suitable for determining adherence to a specific dosage or dosing schedule of a pain medication or illicit drug for clinical purposes. Instead, it primarily serves as a tool for providing insights, especially in cases of illicit drug use. Sequential creatinine-corrected quantitative values can be valuable in the ongoing assessment of drug usage or cessation of drug intake with continued excretion (606,607).

The LCD (606) further elaborates on these aspects.

13.1.2.1.5 Purpose of UDT

Presumptive UDT is typically requested by a clinician caring for a patient when there is a need for swift access to results that can be promptly integrated into the clinical evaluation and treatment decisions.

Definitive UDT is considered justifiable and essential when the clinical context provides strong support for the need for comprehensive testing. This includes situations where:

- There's a requirement to identify a specific substance or metabolite not adequately detected by a presumptive UDT screen.
- The necessity arises to definitively pinpoint specific drugs within a broad drug category.
- Certain substances or metabolites, such as fentanyl, meperidine, synthetic cannabinoids, and other synthetic or analog drugs, need to be identified, which aren't typically detected by presumptive UDT.
- Precise drug concentrations are needed to guide patient management (e.g., discontinuing THC use as part of a treatment plan).
- A presumptive UDT result contradicts a patient's self-report, clinical presentation, medical history, or current prescribed pain medication plan, necessitating confirmation or negation.
- There's a need to eliminate the possibility of an error as the cause of a presumptive UDT result.
- Non-prescribed medication or illicit substance use needs to be identified for the safe ongoing prescription of controlled substances.
- Definitive UDT is essential for conducting a thorough assessment of medication effectiveness, side effects, or potential drug interactions.

The decision to opt for definitive UDT should be guided by patient-specific considerations, including their past drug usage, response to medications, and clinical evaluation, all of which are crucial when precise and reliable results are essential for making informed clinical decisions (606,607).

To demonstrate the reasonableness and necessity of a specific test, the clinician's rationale for ordering definitive UDT and the chosen tests must be documented in the patient's medical record.

13.1.2.2 Drug Testing Panels

13.1.2.2.1 Presumptive UDT Panels

Presumptive UDT typically includes the screening of multiple substances, with the selection of analytes determined by the beneficiary's individual clinical history and risk assessment. This information should be well-documented in the patient's medical record. These tests may be ordered as a panel and billed as a "Per Patient encounter," regardless of the number of analytes included in the screening.

13.1.2.2.2 Definitive UDT Panels

Physician-directed definitive profile testing is reasonable and necessary when ordered for a particular patient based upon historical use, clinical findings, and community trends. However, the same physician-defined profile is not reasonable and necessary for every patient in a physician's practice. Definitive UDT orders should be individualized based on clinical history and risk assessment and must be documented in the medical record.

13.1.2.3 Specimen Type

Urine or oral fluid is the preferred biologic specimen for testing because of the ease of collection, storage, and cost-effectiveness (606,607). UDT cannot detect the dosage of drug ingested/used, the time of use, or the means of delivery (intravenous vs. oral vs. inhaled). Detection time of a substance in urine is typically 1-3 days depending on the drug, rate of metabolism, and rate of excretion. Lipid-soluble drugs, such as marijuana, may remain in body fat and be detected upwards of a week or more.

The LCD does not discuss Ethanol. Ethanol is a known drug of abuse, but is routinely tested in blood, not urine. In addition, the Drug Enforcement Agency (DEA) resource guide (615) states that alcohol is exempt from control by the Controlled Substance Act.

13.1.2.4 Covered Indications for UDT

There are multiple covered indications for UDT including symptomatic patients with multiple drug ingestion and/or patients with unreliable history, diagnosis and treatment for substance abuse or dependence, and, finally, treatment for patients on chronic opioid therapy.

- A physician prescribing controlled substances to treat chronic pain can manage a patient better if the physician knows whether the patient is consuming another medication or substance, which could suggest the possibility of SUD or lead to drug-to-drug interactions.
- UDT may help the physician monitor medication adherence, diversion, efficacy, side effects, and patient safety in general (606,616).

A broad cross section of the general population will develop either cancer pain syndrome or non-cancer pain which will require prolonged or chronic opioid therapy for management with normal risk of addiction inherent to the substance(s) exposed (606,617).

13.1.2.4.1 Chronic Opioid Therapy UDT Testing Objectives

1. Identifies absence of prescribed medication and potential for abuse, misuse, and diversion.
2. Identifies undisclosed substances, unsanctioned prescription medication, or illicit substances.
3. Identifies substances that contribute to adverse events or drug-drug interactions.
4. Provides objectivity to the treatment plan (616).
5. Reinforces therapeutic compliance with the patient.
6. Provides additional documentation demonstrating compliance with patient evaluation and monitoring (618).
7. Provides diagnostic information to help assess individual patient response to medications (e.g., metabolism, side effects, drug-drug interaction, etc.) over time for ongoing management of prescribed medications.

13.1.2.4.2 Medical Necessity Guidance

The establishment of medical necessity for UDT should rely on patient-specific factors identified during the clinical evaluation, and it should be documented by the clinician in the patient's medical record. At a minimum, these elements should include the following (40,606):

1. Patient history, including a thorough review of their medical history, physical examination findings, and previous laboratory test results.
2. The current treatment plan for the patient.
3. A list of prescribed medication(s) the patient is currently taking.
4. A risk assessment plan, which evaluates the patient's potential for substance misuse or abuse.

It's important to note that organizations such as ASIPP, as well as various pain organizations, physician societies, and the Federation of State Medical Boards (619), advocate for a practical approach to managing definitive UDT for patients on chronic opioid therapy.

The frequency of UDTs conducted beyond the initial presumptive UDT should be determined based on the specific needs of each individual patient, supported by thorough documentation in the patient's medical record.

Recommendations for ordering presumptive and definitive UDT for patients on chronic opioid therapy are listed in LCDs.

13.1.2.4.3 Chronic Opioid Therapy Baseline Testing

The choice of initial presumptive and/or definitive

testing for patients on chronic opioid therapy may vary according to the patient's individual situation. These tests may encompass a range of substances such as amphetamine/methamphetamine, barbiturates, benzodiazepines, cocaine, methadone, oxycodone, TCAs, THC, opioids, opiates, heroin, as well as synthetic or analog drugs, often referred to as "designer" drugs (620).

13.1.2.4.4 Chronic Opioid Therapy Monitoring Testing

1. Ongoing testing may be medically reasonable and necessary based on the patient history; clinical assessment, including medication side effects or inefficacy; suspicious behaviors; self-escalation of dose; doctor-shopping; indications/symptoms of illegal drug use; evidence of diversion, or other clinician documented change in affect or behavioral pattern (620).
   - As part of the clinical evaluation of the patient, the provider should inquire about prescription compliance and potential issues of abuse or diversion such as: lost prescriptions; early refill requests, or requests for escalating dose of medication (620).
   - The number of UDTs billed over time must be based on the individual's risk potential (606,607). Appropriate number of UDTs billed over time based on risk is listed in Table 7 (40,606).
2. The clinician should perform random UDT at random intervals to properly monitor a patient (606).
   - UDT testing does not have to be associated with an office visit.
3. Patients with specific symptoms of medication aberrant behavior or misuse may be tested in accordance with this document's guidance for monitoring patient adherence and compliance during active treatment (< 90 days) for substance use or dependence.
4. Testing must be based on clinician's documented medical necessity and reviewed by the clinician in the management of prescribing/renewing a controlled substance for every risk group outlined below.
5. Any additional definitive UDT beyond recommendations above must be justified by the clinician in the medical situations in which changes in prescribed medications may be needed, such as:
   - Patient response to prescribed medication suddenly changes.
   - Patient side effect profile changes.
   - To assess for possible drug-drug interactions.
   - Change in patient's medical condition or behavior.
   - Patient admits to use of illicit or non-prescribed controlled substance.

The proportion of patients receiving opioids in interventional pain management settings is variable ranging from a very low proportion in physiatry settings, mostly dealing with acute or subacute pain problems, whereas in patients with chronic pain problems with much longer duration of symptomatology and suffering, it may be high. As a result, assessment of opioid risk is crucial in interventional pain management settings. The most frequently recommended instruments for assessing the risk of opioid misuse before initiating long-term opioid therapy include the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) (624) or ORT (621). The SOAPP-R and ORT are patient self-administered instruments. The ORT and SOAPP Version 1.0 are quick and easy to use questionnaires designed to help providers to evaluate the patient's relative risk for developing problems when placed on long-term opioid therapy. An alternate instrument in addition to SOAPP is being evaluated at Pain Management Centers of America (Table 8).

Table 7. *UDT frequency based on risk assessment and stratification*.*

Risk Group	Baseline	Frequency of Testing
Low Risk	Prior to Initiation of chronic opioid therapy	Presumptive and definitive UDT not to exceed 2 times each in a rolling 365 days for prescribed medications, non- prescribed medications that may pose a safety risk if taken with prescribed medications, and illicit substances based on patient history, clinical presentation, and/or community usage.
Moderate Risk	Prior to Initiation of chronic opioid therapy	Presumptive and definitive UDT not to exceed 2 times each in a rolling 180 days for prescription medications, non- prescribed medication that may pose a safety risk if taken with prescribed medications, and illicit substances, based on patient history, clinical presentation, and/or community usage.
High Risk	Prior to Initiation of chronic opioid therapy	Presumptive and definitive UDT not to exceed 3 times each in a rolling 90 days for prescribed medications, non-prescribed medications that may pose a safety risk if mixed with prescribed and illicit substances based on patient history, clinical presentation and/or community usage.

UDT = Urine drug testing

Table 8. *Patient risk assessment: Risk stratification explanation for scoring.*

1. Smoking (1-4) Current within last 6 months 1 Rare - once or twice a week or e-cigarette 2 ½ PPD or 10 cigarettes within the past year 3 1 PPD or 20 cigarettes within the past year 4 > 1 PPD or more than 20 cigarettes within the past year	11. Methadone (2-4) 2 Methadone 30 mg/day 4 Methadone > 30 mg/day
2. ADD/ADHD, OCD, bipolar, schizophrenia (1-6) 1 ADD/ADHD 1 OCD 2 Bipolar 2 Schizophrenia Add combinations	12. Doctor Shopping (2-8) 1 Rare 2 Occasional 3 Frequent 4 Very frequent
3. Depression (1-4) 1 Mild - no treatment 2 Moderate - treat 3 Severe - treat 4 Very severe - treat	13. Drug Overdose (5) 5 Multiply for multiple amounts
4. Anxiety (1-4) 1 Mild - no treatment 2 Moderate - treat with antidepressants/or BuSpar/or no treatment 3 Severe - treat with Benzodiazepines/psychotherapy or no treatment 4 Very severe - Benzodiazepines + psychotherapy or no treatment	14. Soma (2-4) 1 < 750 mg daily 2 > 750 mg daily
5. Somatization Disorder (3)	15. Dealing in Drugs (5) 5 Multiply for multiple dealings
6. PTSD (1-4) 1 Mild - no effect 2 Moderate 3 Severe 4 Very severe	16. Suicide Attempts (5) 5 Multiply for multiple attempts
7. Sex Abuse (3-6) ↑ for multiple abuses	17. Sleep Apnea Syndrome (2)
8. More Medication (1-4) 1 Mild - request 2 Moderate - request somewhat infrequently 3 Significant - demanding, manipulative, repetitive 4 Extensive - involving abuse patterns	18. Fibromyalgia (1)
9. High Dose Opioids (2-4) 1 <= 90 MMEQ 2 91-120 MMEQ 3 121-240 MMEQ 4 > 240 MMEQ	19. Prescription Drugs from Street or Others (5)
10. Benzodiazepines (1-4) 1 Mild - prn, low dose/infrequent 2 Moderate - ≤ 10 mg diazepam daily or equivalents 3 High - 11- 29 mg diazepam daily or equivalents 4 Very high - > 30 mg diazepam daily or equivalents	20. Illicit Drugs from Streets (5)

13.1.2.5 Recommendation

4. Urine drug monitoring (UDM) should be implemented at the initiation of opioid therapy and conducted periodically for monitoring therapeutic compliance as per available guidance referential to mode and frequency of testing.
   Evidence Level: Moderate; Strength of Recommendation: Strong

13.1.3 Establishing Medical Necessity

To establish medical necessity for opioid therapy, it is essential to perform a complete medical evaluation and document a physical diagnosis along with previous treatments (including benefit and side effects) with non-pharmacologic (lifestyle modifications and alternative treatments), pharmacologic (medications), psychological (cognitive behavioral therapy, talk therapy, counseling, behavioral modification, etc.), procedural (injection-based therapies or neurostimulation therapies), and surgical interventions.

The CDC recommends that clinicians should consider non-opioid therapies are preferred (13). Clinicians should discuss with patients known risks and benefits of opioid therapy, establish treatment goals for pain and function, and consider how opioid therapy will be discontinued if benefits do not outweigh risks (13).

Opioid therapy is only one part of a multidisciplinary and multimodality treatment program. Response to treatment demonstrating reduction in pain along with improvements in function and QOL should support medical necessity and be clearly documented to support medical necessity for continued treatment (13,21,23).

It is important to establish medical necessity prior to initiation or maintenance of opioid therapy for acute, subacute, or chronic pain. Opioid therapy should only be considered if benefits are anticipated to outweigh risks to the patient. Benefits include reduction in pain and improvement in function and QOL. Response to treatment goals must be documented to maintain medical necessity and continued treatment.

13.1.3.1 Recommendation

5. Prior to starting opioid therapy, clinicians should discuss the realistic benefits, and known risks with patients; should establish clear treatment goals for pain and/or function and should consider – and discuss - how opioid therapy will be discontinued if benefits do not outweigh risks.
   Evidence Level: Strong; Strength of Recommendation: Strong

13.1.4 Establishing Treatment Goals

It is essential to establish treatment goals both prior to and across the duration of chronic opioid therapy. Treatment goals should include pain reduction along with improvements in function and QOL with minimal or no adverse effects. The risks and benefits of opioid therapy are established prior to initiating opioid therapy and assessed at regular intervals for clinical improvement. Such intervals may be weekly, monthly, or scheduled as appropriate based on risk factors for a given patient. At a minimum, patients should be assessed at least every three months. The periodic assessment may include UDM, PDMP screen, review of pain management metrics of function, assessment of activities of daily living (ADLs) and other QOL scores, and a measurement of pain reduction (13,21,23,611).

Outcomes assessments may include numeric rating pain scale (0-10), functional assessment using the ODI (0-50 scale) or similar functional status metrics, employment status, and restrictions at work or with activities of daily living. The minimum change in scores to achieve meaningful improvement has been considered to be a 2–3-point improvement on the numeric rating scale. This corresponds with a 30% pain reduction that is perceived by patients to be significant. Pain reduction, improvement in functional capabilities, and improvement in QOL are measured at each assessment. Opioid therapy with interventional techniques, exercise program, etc., meaningful pain reductions (≥ 50%), along with associated functional benefits (≥ 30%), will be considered to warrant continued treatment. Clinical context remains important when assessing all three parameters of response.

Prior to initiating opioid analgesic therapy, it is important to have a comprehensive discussion with the patient about risks and benefits of therapy and a discussion about realistic outcomes. If, for example, a patient with chronic pain desires complete (100%) pain relief, one may deem this treatment goal to be unrealistic. Therefore, setting realistic expectations consistent with overall clinical experience in similar patients is appropriate. These goals include pain reduction, functional improvement, and improvement in QOL. Setting realistic expectations prior to therapy is essential in achieving treatment goals.

13.1.4.1 Recommendation

6. It is essential to establish goals of opioid therapy related to pain relief, improvement in function if and as possible, improvement in quality of life,

and a plan for opioid tapering and cessation if and when meaningful, realistic improvement is not achieved from opioid therapy.

Evidence Level: Strong; Strength of Recommendation: Strong

13.1.5 Informed Decision Making

The treatment plan and goals should be established prior to initiation of treatment and can be revisited regularly to provide clear and individualized objectives to guide the choice of therapies. The treatment plan should contain information supporting the selection of therapies, inclusive of both pharmacologic (including medications other than opioids) and nonpharmacologic approaches. It also should specify measurable goals and objectives that will be used to evaluate treatment progress, such as relief of pain and improved physical and psychological function (13,21,611).

The plan should document any further diagnostic evaluations, consultations, referrals, or additional therapies that have been considered. The treatment plan should also discuss discontinuation of opioid therapy in the event the tapering or termination of opioid therapy becomes necessary (611).

Patient consent should include an active (bidirectionally affirmed) discussion of the benefits, burdens and risks of the treatment plan, in which there is explicit acknowledgment of comprehension by the patient, or with persons designated (as responsible medico-legal representatives) by the patient. If opioids are prescribed, the patient and possibly family members, if appropriate, should be counseled on safe ways to store and dispose of medications. For convenience, the patient consent and a pain management agreement can be combined into a single document that is formalized by a third-party witness. Patient consent typically addresses many risks well known to potentially occur with medication management, particularly opioids (13,21,611).

A pain management agreement has become a mandatory document that clearly specifies expectations and joint responsibilities for the patient and the treating physician, or health care team. This agreement typically includes the physician's prescribing policies and expectations, including the number and frequency of prescription refills, as well as the physician's policy on early refills and replacement of lost or stolen medications; specific reason for which drug therapy may be changed or discontinued (including violation of the policies and agreements written in the treatment agreement);the patient's responsibility for safe medication use, taking the medications as prescribed and not in combination with alcohol or other illicit substances; storing medications in a secure location; and safe disposal of any unused medication to prevent misuse by other household members; the patient's agreement to share information with family members and other close contacts on how to recognize and respond to an opioid overdose, including administering an opioid antagonist such as naloxone, if necessary; the patient's responsibility to obtain prescribed opioids from one physician or practice and one pharmacy; the patient's agreement to periodic drug testing (urine, blood, hair, or saliva); the physicians responsibility to be available or to have a covering physician available to care for unforeseen problems and to prescribe scheduled refills, if appropriate and in accordance with the patients pain management agreement (13,21,610,611,628,629).

13.1.5.1 Recommendation

7. A controlled substance agreement that is detailed with each item, including safe storage and disposal, and initialed and signed by the patient is essential prior to initiating therapy.

   Evidence Level: Strong; Strength of Recommendation: Strong

13.2 Initiation and Assessment of Opioid Therapy

13.2.1 Initiation with Low-Dose Opioid Therapy

A physician should follow the principles of prescribing as low an opioid dose as reasonably achievable or ALARA (as low as reasonably achievable), similar to radiation exposure guidelines to provide therapeutic effect without major side effects.

Low dose therapy can be effective, with a reduction in the rate of complications, side effects, and adverse effects and specifically when opioid therapy is combined with other modalities, including interventional techniques (9,21,630,631). Consideration of higher dosage is individualized and requires careful reassessment of pain and the risk of overdose and continued monitoring with evidence of improved patient care. Abuse-deterrent opioid formulations have been developed in order to decrease abuse, overuse, and overdose fatalities. This is one of the many strategies that has been available but not maximally utilized due to various barriers such as cost and awareness (632).

Reasonable, first line opioid choices for mild pain often include tramadol, codeine, Tapentadol, or hydrocodone. For second line mild to moderate pain therapy, clinicians can start with hydrocodone or oxycodone. For severe pain, first line therapy may begin with hydrocodone, oxycodone, hydromorphone, or morphine, second line therapy with fentanyl and third line therapy for severe pain with methadone (633). Buprenorphine should be considered as a viable alternative to strong opioids in moderate to severe chronic pain therapy (553-555). The literature suggests that codeine and tramadol may confer a lower abuse risk than more potent opioids (634,635).

Methadone has not been shown to be more effective than other opioids and in most cases has been associated with multiple adverse consequences including death (40,636-642). Methadone is also dispensed in methadone clinics for prescription opioid or heroin abuse with many regulations and variable supervision. Given its unique risk profile, the CDC recommends that methadone not be used as a first line long-acting opioid formulation and that it should be prescribed by clinicians familiar with methadone's unique risk profile. Thus, methadone is recommended for use after failure of other opioid therapies, only after EKG and evaluation of QT intervals and drug interactions, and only by clinicians with specific training in its risks and uses. Methadone has torsadogenic potential in itself, and specifically when added to other medications with QT prolongation activity. TdP is associated with QTc prolongation and is often the result of drug interactions, electrolyte abnormalities, and even genetic and gender related causation (640-642). The FDA recommends methadone dosage not to exceed 30 mg per day. Low methadone may be started in doses as low as 2.5 mg, twice a day, and slowly titrated to achieve appropriate pain relief, titrated on a weekly basis to achieve appropriate pain relief. Methadone withdrawal and substitution with buprenorphine has been met with significant difficulties (637-642).

If methadone is prescribed, an electrocardiogram shall be obtained prior to initiation, at 30 days, with dose adjustments with concomitant medication that may affect QTc interval, and 6 to 12 months thereafter.

Meperidine is not recommended for chronic pain treatment, due to the risk of adverse neurological events resulting in confusion and seizures. This is secondary to the accumulation of the toxic metabolite normeperidine. The adverse events with meperidine are also increased with long-term use, renal insufficiency, and concurrent benzodiazepine use.

Opioid medications should be started at low doses and titrated gradually to higher levels if necessary. All attempts must be made to maintain patients on the lowest clinically effective dose bearing in mind that patients differ in their response to the analgesic and adverse effects of a specific opioid. Doses of other CNS depressant medications should be adjusted, if possible, as well. Combinations of short- and long-acting opioids, and higher doses of long-acting opioids should be prescribed with caution, weighing the benefits of pain relief with the risks of overdose.

13.2.1.1 Recommendations

8. Once medical necessity is established, opioid therapy may be initiated using low doses and short-acting drugs, with appropriate monitoring to provide effective relief and avoid side effects.
   Evidence Level: Moderate; Strength of Recommendation: Moderate to Strong
9. Long-acting opioids should not be utilized for the initiation of opioid therapy.
   Evidence Level: Strong; Strength of Recommendation: Strong
10. Methadone is recommended for use after failure of other opioid therapies only if EKG and evaluation of QT intervals and drug interactions have been conducted and evaluated; commencing with low doses, with dose adjustments with repeat EKG performed at least 6-12 months thereafter. Only clinicians with specific training in methadone prescribing, use, and risk management should offer this agent for treatment of noncancer pain that is resistant to effect(s) of other opioids.
    Evidence Level: Strong; Strength of Recommendation: Strong

13.2.2 Assessment of Effectiveness of Opioid Therapy

Multiple publications, systematic and comprehensive reviews, and guidelines have been published evaluating the effectiveness and safety of opioids (13,23,40,41,447,449,454,458-460,462-468,470,484,631,637,643-650). The clinical evidence based on RCTs shows insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and shows an increased risk for serious adverse consequences related to long-term opioid therapy that appears to be dose dependent and may be related to the combination of opioids with benzodiazepines and other drugs. However, the majority of the trials were of short-

term duration. Consequently, there are no studies assessing the effectiveness of opioids on a long-term basis.

Kollas et al (645) published outcomes of long-term opioid therapy for chronic pain in an outpatient palliative medicine clinic. This study included 97 patients with 4-year follow-up with measurements of pain intensity, performance scores, and overall overdose risk scores. The results showed a stable treatment-related reduction in pain intensity of 4.9 out of 10 points over 4 years. They concluded that the evidence supported outpatient palliative care longitudinally over 4 years.

The lack of randomized trials or even observational studies does not preclude the effectiveness of long-term opioid therapy. Chronic opioid therapy in appropriately selected patients may be beneficial. Thus, opioids provide effective pain control for a significant proportion of patients in combination with other therapies or in some patients as a standalone treatment; however, they are not effective for all patients. Furthermore, as with other pharmacologic therapies, opioids can be associated with multiple adverse consequences. Lower doses may also have similar, but less serious consequences.

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

- Analgesia
- Activity
- Aberrant behavior
- Adverse effects

Periodic assessments should survey and document the presence of at least 30% improvement in pain and function, without adverse consequences.

Chronic opioid therapy in older adults may be associated with multiple adverse effects related to reduced hepatic and renal function, increased susceptibility to accumulation of opioids with a small therapeutic window, exacerbation of cognitive impairment, increased risk of medication errors, risk of falls, and finally, multiple comorbidities related to medical conditions and other drug therapies. While opioid therapy can improve the QOL in this population, it is essential to exercise additional caution in older adults when providing chronic opioid therapy.

Older patients deserve special mention with regards to chronic opioid therapy. They can suffer from complex multi generator pain that is often ignored, misdiagnosed, or undertreated. Pharmacological titration must be carefully adjusted in this population due to declining organ function, presence of concurrent diseases, and polypharmacy (646).

Patients with mental health conditions may require therapy of comorbidities with anti-anxiety medications as well as antidepressants. In particular, patients taking benzodiazepines for anxiety should be warned of the elevated risks for respiratory depression with concomitant opioid use. Physicians should be judicious with opioid initiation and monitoring in these patients. Consideration of psychological conditions and treatment thereof may improve overall pain treatment outcomes; however, due to established risks with the combination of opioids and benzodiazepines and psychiatric instability including suicide risk, clinicians should cautiously provide chronic opioid therapy with or without benzodiazepines and antidepressant therapy in this group. Clinicians should consider behavioral health consultations, specifically in those with uncontrolled psychological disorders and suicide risk.

Cognitive behavioral therapy has been shown to be useful in patients on long term opioid therapy to reduce opioid exposure and associated risks to patients, families, and communities while offering patients an alternative for managing pain (647).

Pregnant women may be at increased risk of adverse consequences to both the mother and fetus. Some studies have shown stillbirth, poor fetal growth, preterm delivery, birth defects, and, more importantly, neonatal opioid withdrawal syndrome in association with chronic opioid therapy. The effectiveness of opioid therapy in patients with a previous history of nonfatal overdoses has not been assessed. In patients with a nonfatal overdose, clinicians should carefully assess the risks, as well as educate and manage the patients about reduced opioid dosage and discontinuing opioids when possible. A good understanding of the indications for ongoing opioid use in pregnancy is essential as well as clarification about the differences between opioid dependence and OUD. This is crucial for appropriate diagnosis, screening for common concurrent conditions, adequate counseling about individualized maternal and perinatal risks, and accurate documentation of diagnoses and medical decision-making (648).

The issue of chronic opioid therapy with long-acting/sustained release opioids compared to short-acting opioids has been discussed with proponents and opponents using equally emotional arguments (5,21,41,628,630). The present evidence shows the lack of superiority of long-acting opioid therapy compared to short-acting opioid therapy (13,21,41,628,629,649). However, long-acting opioids are associated with higher risk than short-acting opioids (13,21,41,628,630,649). In

fact, in 2014 the FDA modified the labeling of extended release or long-acting opioid pain medications, noting the potential for serious risks and recommending that these medications be reserved for "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment" (650). Dowell et al (9), in preparation of the CDC guidelines were unable to find evidence that long-acting opioids were more effective or safer than intermittent use of immediate release opioids, or that long-acting opioids reduced the risks for opioid misuse or addiction. Overall, long-acting opioid use is associated with greater total average daily opioid dosage compared with short-acting opioids that are provided on an as needed basis.

The evidence basis for breakthrough pain phenomena in chronic pain contexts is unclear and remains somewhat controversial. Hence, there is lack of evidence for the use of short-acting opioids in conjunction with long-acting opioids to treat pain exacerbations (21,41,651). Opponents (41,651-653) argue that immediate release opioids are typically offered several times a day, whereas long-acting opioids are offered once or twice a day. In addition, there may be multiple practical issues related to long-acting opioids such as access to abuse deterrent formulations, reduced tolerability, and the cost of the medications.

The recent data on more limited efficacy of long-term opioid therapy and the risk of complications have led to more frequent opioid tapering and discontinuation, which in turn has led to worsening pain, declining function, and clinical instability. This has led to increasing recognition of the utility of complex persistent opioid dependence, a clinically distinct but biologically similar state compared with OUD as explained by Manhapra et al (654). They review the clinical definition, mechanism, and treatment of complex persistent opioid dependence and recommend further clarification through research and policy development.

13.2.2.1 Recommendations

11. Physicians should evaluate meaningful benefit (i.e., least 30% benefit in pain and/or function) produced by opioid treatment and should ensure that opioid therapy does not incur aberrant behaviors and/or adverse effects.
    Evidence Level: Moderate; Strength of Recommendation: Moderate
12. Clinicians must understand the effectiveness, viability, limitations, adverse consequences, and relative value (versus burden/risk) of long-term opioid therapy in chronic non-cancer pain.
    Evidence Level: Strong; Strength of Recommendation: Strong
13. The evidence of effectiveness is similar for short-acting and long-acting opioids, with increased incidence and prevalence of adverse consequences evidenced with the use of long-acting opioids.
    Evidence Level: Moderate; Strength of recommendation: Moderate
14. The administration of high doses of long-acting opioids is recommended in limited circumstances wherein severe intractable pain is not responsive or mitigated by short-acting opioids or moderate doses of long-acting opioids.
    Evidence Level: Moderate; Strength of Recommendation: Moderate

13.2.3 Dose Descriptions

With overwhelming evidence for the risk of misuse, abuse, and limited efficacy of chronic opioid therapy, the rationale for high-dose opioids continues to be limited and absolute MME cut offs remain inconsistent (9,13,21,40,41,630,649-660). Generally, it is believed that patients who do not respond to low or medium opioid doses are unlikely to respond to higher doses, although individual patient circumstances also exist. In 2007, and then updated in 2010 (609), the State of Washington issued interagency guidelines that include guidance that the daily dose of opioids should not exceed 120 mg of MME. The guidelines by American Pain Society (APS) and AAPM in 2009 defined "high doses" as 100 mg MME (40). CDC guidelines (9,13) recommended a limit of 50 – 90 mg MME. ASIPP guidelines (21) designated a low dose as 40 MME. The Canadian Guidelines in 2010 identified a 200 MME dose as a "watchful dose" (38). Bohnert et al (661) concluded that the risk of opioid overdose increased when the opioid dose was equivalent to 50 MME or higher. Dunn et al (662), in a population from a health maintenance organization (HMO) in Washington State, reported a 9-fold increase in opioid overdoses in patients receiving higher doses of opioids (> 100 MME) when compared to those receiving lower doses (< 20 MME). Paulozzi et al (504) found that, compared to patients receiving lower to no opioids doses, the risk of overdose was greater if daily opioid doses were above 40 MME. Gomes et al (660) found that patients receiving higher doses (200 – 400 MME) and very high doses (> 400 MME) had a much higher overdose death rate than those getting

moderate doses (< 200 MME), with an overdose rate of 7.92 (9.94 per 1,000 population). Braden et al (663) showed that patients receiving > 120 MME per day were more likely to have drug-related encounters than those getting lower doses. Franklin et al (664) showed that appropriate guidelines that considered 120 MME as a 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 > 120 MME per day. Moreover, the number of deaths was reduced by 50% from 2009 to 2010. Rome et al (665), in a report of the outcomes at discharge of a chronic non-cancer pain rehabilitation program, showed that patients taking higher doses reported significantly greater catastrophizing and greater pain severity than the nonopioid group. Adverse events were also reported more commonly at higher daily doses (660,666).

Pascual et al (666) showed an increasing frequency of adverse effects of high dose tramadol (> 400 mg) compared with lower doses, with 2 patients experiencing seizures. Other studies (485,512,667) have shown that there was a dose-dependent relationship between chronic opioid use, specifically with high doses and sleep disorders. Ballantyne and Mao (485) in 2003, indicated that doses > 100 MME per day have not been validated in clinical trials and should be considered excessive.

The above evidence illustrates the dose-related effects at 40 MME (504), 50 MME (661,662), 120 MME (668,669), and 200 MME (660). Thus far, it appears that all the available literature correlates increasing mortality with increasing doses. Figure 22 shows the proportion of patients with drug overdoses, based on risk group (670).

Several studies have demonstrated that for patients with severe pain on high opioid doses, tapering resulted in reduced pain and improved mood (665). However, recent evidence has identified the opioid tapering practices leading to overdoses, as well as mental health crisis among patients prescribed long-term opioids (671-679). Overall, the evidence has been overwhelming with adverse effects of guidelines in the United States with reduced prescribing patterns and adverse events related to rapid tapering. Consequently, tapering is recommended at a slow pace of reduction of 10-25% of the dosage per month.

13.2.3.1 Recommendation

15. Tapering or weaning processes must be initiated slowly after appropriate criteria have been met and should entail slow tapering of the dosage across a specified period of time. Reinstitution of opioid therapy can be considered when such treatment is deemed medically necessary if the patient's behavior and pattern of drug use are shown to be stable, and if results of at least two consistent urine drug tests are negative (for opioids and/or illicit drugs).

Evidence Level: Moderate; Strength of Recommendation: Moderate

13.3 Monitoring Adherence and Side Effects

13.3.1 Adherence Monitoring

As described earlier in the document on patient assessment, risk stratification, and urinary drug testing, adherence monitoring is not only based on evidence, but also upon regulation(s) and recommendations.

Lack of adherence, aberrant behavior, and/or abnormal drug testing will necessitate that the patient may be tapered off the medication and ultimately discharged from the services, unless they are willing to undergo treatment(s) without opioid therapy.

Figures 23 and 24 show algorithmic approaches to adherence monitoring and tapering process with appropriate drug testing based on the risk stratification and results of the drug testing. Once the abnormality is identified, the patient is provided with a single chance for illicit drugs and two chances for THC prior to initiating tapering process with monthly drug testing. Appropriate history is important as patients may

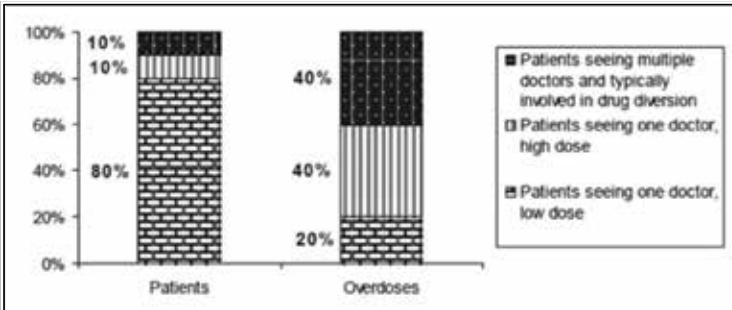


Fig. 22. *Percentage of patients and prescription drug overdoses, by risk group – United States.*

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 (670).

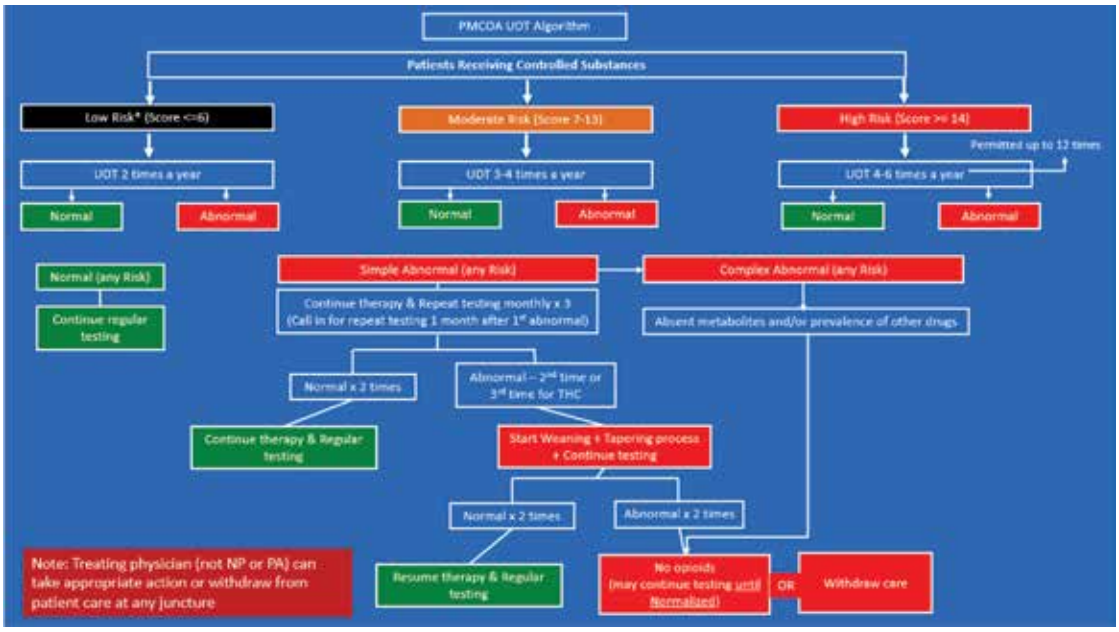


Fig. 23. *Steps to adherence monitoring.*

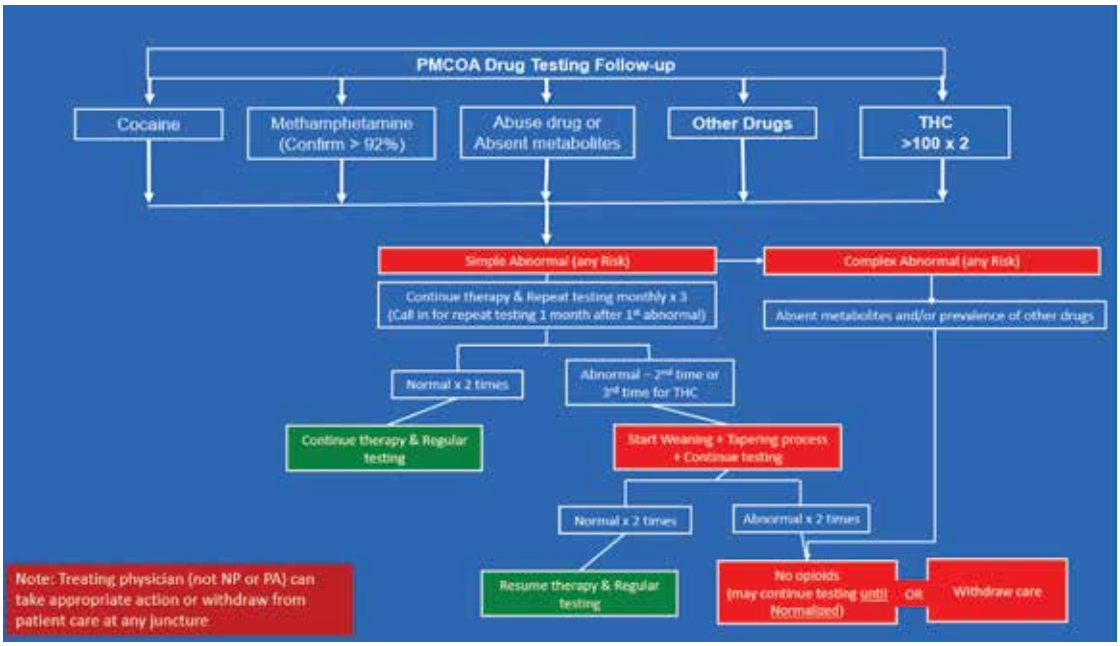


Fig. 24. *Adherence monitoring, tapering process, and withdraw of care.*

receive medications for other issues and may be using products with CBD, which also may contain varying levels of THCs. Physicians must develop a policy to avoid unnecessary discharges allowing 100 nanograms or less per mL for THC to be abnormal. Once the process of tapering and monthly drug testing is started, the patient may return to normal behavior and return to therapy may occur after two normal drug tests. However, if this does not occur, all opioids may be stopped with continuation of interventional techniques if the patient desires and, finally, chronic opioid therapy may be reconsidered at a later date.

13.3.1.1 Recommendations

16. Adherence monitoring to assess and sustain appropriate use must be instituted at proper intervals, as based on risk stratification and indication(s) of other issues that may be regarded as negatively influencing therapeutic compliance.
    Evidence Level: Moderate; Strength of recommendation: Moderate

13.3.2 Monitoring and Managing Side Effects

In older and other vulnerable patients, constipation may prove to be more frequent and problematic. Consequently, a physician should consider the initiation of a prophylactic bowel regimen. Even though the evidence for bowel regimen is mostly anecdotal, the use of increased fluid and fiber intake, stool softeners, and laxatives are often simple and effective. Multiple publications have evaluated opioid antagonists in the treatment of opioid-induced bowel dysfunction (658), but the evidence is insufficient to recommend such antagonists to prevent bowel dysfunction.

During dosage titration of opioid therapy, it is important to advise the patient to avoid engaging in dangerous activities, such as driving a motor vehicle or using heavy machinery until a stable dosage is established and it is certain that the opioid dose does not cause sedation. Similarly, patients should be warned about the greatly increased risks for sedation and respiratory depression when opioids are taken in combination with alcohol, benzodiazepines, or other sedating drugs (633). 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 (633).

13.3.2.1 Recommendations

17. It is essential to monitor and manage side effects appropriately; such management may include discontinuation of opioids if indicated.
    Evidence Level: Strong; Strength of Recommendation: Strong
18. Bowel function must be closely monitored to assess opioid-induced constipation, and a bowel regimen should be initiated as soon as deemed necessary.
    Evidence Level: Strong; Strength of Recommendation: Strong

13.4 Final Phase

13.4.1 Continuation and Maintenance of Therapy

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

If the patient continues to present with persistent pain or there is new pain, a comprehensive evaluation can be repeated, or a referral may be made to a specialist. Similarly, if there is any indication of abuse, misuse, lack of analgesia, lack of activity, adverse effects, or aberrant behavior, the physician may consider tapering or discontinuing the drug therapy after conducting a careful assessment of the circumstances behind the symptoms or behavior. Alternative modalities can be pursued if tapering or discontinuation occurs.

Opioid therapy is continued if appropriate analgesia and functional status is achieved and maintained, either with opioid therapy alone or in conjunction with other modalities. Per prior CDC recommendations, physicians should evaluate for a 30% benefit in pain and function with opioid treatment along with ensuring that there is no misuse/abuse, or major adverse effects. If treatment is successful, one may consider intermittent dose reduction after discussion with the patient to determine whether a lower dose can achieve the same degree of relief and improvement. If necessary to continue, close patient monitoring is imperative.

13.4.1.1 Recommendations

19. Chronic opioid therapy may be maintained, with continuous adherence monitoring, and modified at any time during this phase, in conjunction with - or after failure of - other modalities of pain care, for those patients demonstrating reasonable improvement in physical and functional status, and minimal adverse effects.

Evidence Level: Moderate; Strength of Recommendation: Moderate

20. Chronic opioid therapy should be monitored for (burdensome and adverse) side effects, and these side effects should be managed appropriately.
Evidence Level: Strong; Strength of Recommendation: Strong

13.4.2 Discontinuation of Therapy

In patients with OUD, office-based opioid dependence treatment may be helpful. In a narrative review, Colson et al (680) described that office-based opioid dependence treatment is a viable alternative to methadone treatment or rehabilitation programs. Thus, for physicians providing opioid management of pain, the use of buprenorphine/naloxone (suboxone) is an important tool to consider for OUD which may arise when treating chronic pain. Farmer et al engaged an expert panel process that rated 90 candidate guideline statements across 8 domains, and advocated an updated and expanded set of buprenorphine treatment guidelines that may increase credentialed physicians' comfort with prescribing buprenorphine to patients with OUD (681).

If needed, tapering or discontinuation of opioid therapy should occur. Tapering may be slowly articulated with a decrease of 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 adverse effects 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. Nausea can be managed with antinausea medications. Patients should be monitored 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 or abusing them, then tapering is going to be unsuccessful, and patients should be referred to inpatient facilities. In conclusion, careful and meticulous downward tapering along with close monitoring is warranted when weaning patients off high doses of opioids (659).

Symptoms of mild opioid withdrawal occasionally persist for 6 months after opioids have been discontinued. The physician may 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. Opioid deprescribing is perceived as a complex and challenging practice and thus evidence-based opioid deprescribing guidelines may be a valuable resource for clinicians to support clinical decision-making and reduce suboptimal opioid use (656).

The patient may be referred for counseling or other psychological support during the tapering period if there are significant cognitive-emotional and/or 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 medicine may refer their patients in need of opioid tapering to pain management specialists or if complex to addictionologists.

13.5 Documentation

13.5.1 Appropriate Documentation and Establishing Medical Necessity

13.5.1.1 History

The history includes:

- Chief complaint
- History of present illness
- Review of systems
- Past, family, and/or social history.

The extent of history obtained and documented depends on the clinical judgment of the physician and the nature of the medical decision making (MDM) relevant to the problem. Nevertheless, the required documentation is progressively detailed, and complex based on the level of complexity:

- 99202 Straightforward
- 99203 Low level
- 99204 Moderate
- 99205 High level

13.5.1.2 Chief Complaint

The chief complaint is a concise statement describing the symptom, problem, condition, diagnosis, physician-recommended return, or other factor that

is the reason for the encounter, usually stated in the patient's words. This should be clearly documented in the medical record. The chief complaint should always be the first thing in the initial evaluation, history and physical, and progress note.

13.5.1.3 History of Present Illness

History of present illness is a chronological description of the development of the patient's present illness from the first sign or symptom or from the previous encounter to the present. It includes the following elements:

- Location: Describing the area of the body (neck, low back, head, abdomen, etc.).
- Quality: Characteristic of chief complaint — pain character (deep, throbbing, cramping, aching, sharp, shooting, etc.).
- Severity: Satisfied by pain-rating scale, either visual analog, verbal, or numerical scale describing the level of pain.
- Duration: Symptom duration from onset to the present encounter.
- Timing: Description of the pain pattern — continuous, intermittent, in the evening or afternoon, etc.
- Context: Specific circumstances, conditions, and activities surrounding the present condition.
- Modifying factors: Measures taken to relieve symptoms or discomfort, such as physical therapy, surgery, injection therapy, drug therapy, and the like, and results with these measures.
- Associated signs and symptoms: Numbness, weakness, blurred vision, disturbed sleep pattern, difficulty with activities of daily living, etc.

Brief and extended histories of the present illness are distinguished by the amount of detail needed to characterize the clinical problem accurately. A straightforward and low-level history of the present illness requires documentation of one to 3 elements of the present illness, whereas moderate and high levels of history of present illness requires documentation of at least 4 elements of the history of the present illness.

13.5.1.4 Review of Systems

Review of systems is an inventory of body systems obtained through a series of questions seeking to identify signs or symptoms (or both) that the patient may be experiencing or has experienced relevant to medical decision making.

13.5.1.5 Past, Family, and Social History

The past, family, and social history relevant to MDM is required.

- A review of a patient's history including experiences, illnesses, operations, injuries, and treatments.
- Family history, including a review of medical events in the patient's family, hereditary diseases, and other factors.
- Social history should be appropriate for age reflecting past and current activities.

13.5.1.6 Physical Examination

The type and extent of physical examination is dependent on medical decision making.

The requirements prior to 2021 are no longer applicable. However, a physical examination is essential to meet the criteria of medical decision making. The elements and bullets have been eliminated.

13.5.2 Medical Decision Making (MDM)

Documentation of the complexity of MDM involves 4 types of engagement so as to accommodate all levels of evaluation and management (E/M) services (682-691). The 4 types of MDM options include:

- Straightforward (CPT 99202, 99212)
- Low (CPT 99203, 99213)
- Moderate (CPT 99204, 99214)
- High (CPT 99205, 99215)
- The most significant changes include:
- MDM has always been part of the algorithm for choosing a level of service but will now be the sole determinant of level of service (unless the provider intends to bill based on time).
- From 2021, MDM is based on:
- Number and complexity of problem(s) addressed.

* Including status (e.g., uncomplicated, exacerbation) and timeline (e.g., acute, chronic)

- Amount and/or complexity of data reviewed and analyzed.

* This category attempts to quantify the amount of data, efforts to gather data, and communications utilized to evaluate a patient. Collection of more data leads to a higher level of MDM.

- Risk of complications and/or morbidity or mortality.

13.5.2.1 Selecting a Level of Service

Effective January 1, 2021, the appropriate level of service for office or other outpatient E/M services is based on the following:

- The level of the MDM as defined for each service.

- Number and complexity of problem(s) addressed at the encounter.
- Amount and/or complexity of data to be reviewed and analyzed.
- Risk of complications and/or morbidity or mortality of patient management.
- The total time on the date of the encounter.
- Includes total time on the date of the encounter.
- May be used to select a code level whether or not a counseling and/or coordination of care dominates the service.
- Includes physician/other qualified health professional face-to-face and non-face-to-face time.
- Count only one person per minute when more than one clinician is addressed.

The activities involved in total time for physicians and qualified health professionals are shown in Table 9.

13.5.2.2 Number and Complexity of the Problem(s)

One element in the level of code selection for an office or other outpatient service is the number and complexity of the problem(s) that are addressed at an encounter.

- Symptoms may cluster around a specific diagnosis and each symptom is not necessarily a unique condition.
- Low back and leg pain
- Neck pain with headache and arm pain

Table 9. *Total time: Physicians and qualified health professional.*

Physician/other qualified health professional time includes the following activities (when performed):
• Preparing to see the patient (e.g., review of tests)
• Obtaining and/or reviewing separately obtained history
• Performing a medically necessary appropriate examination and/or evaluation
• Counseling and educating the patient/family/caregiver
• Ordering medications, tests, or procedures
• Referring and communicating with other health care professionals (when not reported separately)
• Documenting clinical information in the electronic or other health record
• Independently interpreting results (not reported separately) and communicating results to the patient/family/caregiver
• Care coordination (not reported separately)
DO NOT COUNT time spent on separately reported services

Noting chronic conditions that another specialist manages in the patient's medical record does not alone qualify as being problem-addressed (688).

13.5.3 Conditions: Acute, Uncomplicated, Stable or Chronic Illness

13.5.3.1 Acute Uncomplicated Illness or Injury

A recent or new short-term problem with low risk of morbidity for which treatment is considered.

- There is little to no risk of mortality with treatment, and full recovery without functional impairment is expected.
- A problem that is normally self-limited or minor but is not resolving, consistent with a definite and prescribed course is an acute uncomplicated illness. Examples may include:
  - Cervical, lumbar strain
  - Twisting of ankle.

13.5.3.2 Stable Chronic Illness

- Conditions are treated as chronic whether or not stage or severity changes.
- Controlled or uncontrolled pain condition
- Chronic low back pain
- Chronic neck pain
- Stable
- Defined by the specific treatment goals for an individual patient.
- Not at treatment goal is not stable, if the condition does not change.
- The risk of morbidity (return of pain and dysfunction without treatment is crucial).

13.5.4 MDM: Risk of Complications and/or Morbidity or Mortality of Patient Management

13.5.4.1 MDM Risk

AMA defines risk as:

- The probability and/or consequences of an event.
- The assessment of the level of risk is affected by the nature of the event under consideration.
- The risk of patient management criteria applies to the patient management decisions made by the reporting physician or other qualified health care professional as part of the reported encounter.
- A low probability of death may be high risk, whereas a high chance of a minor, self-limited adverse effect of treatment may be low risk.
- For the purposes of medical decision making,

level of risk is based upon consequences of the problem(s) addressed at the clinical encounter when appropriately treated.
- Risk also includes MDM related to the need to initiate or forego further testing, treatment and/or hospitalization.
- Major or minor risk, and not a major or minor procedure.
- The provider needs to assess and clearly document the patient's individual risk factors along with the procedure's risk factors to determine the overall risk.
- The risk determination is also based upon the "usual behavior" of a physician or qualified health professional within that specialty.

13.5.4.2 MDM Risk of Complications and/or Morbidity or Mortality of Patient Management
- Straightforward
- Minimal risk from treatment (including no treatment) or testing (most would consider this effectively as no risk).
- Low
- Low risk (i.e., very low risk of anything bad), minimal consent/discussion
- Moderate
- Would typically review with patient/surrogate, obtain consent and monitor, or there are complex social factors in management.
- High
- Need to discuss some significant adverse things that could happen for which physician or other qualified health care professional will watch or monitor.

13.5.4.3 Prescription Drug Management
- It is essential to clarify that prescription drug management in the moderate row of the MDM chart does NOT include refills or continuation of current medications.
- Consequently, prescription drug management would only include increasing or decreasing medication or adding a new medication.
- Only documenting "reviewed" on the medication list does not support prescribing drug management.
- A refill or a continued current medication without a refill being needed at that visit may or may not be considered as prescription drug management.
- Importantly:
- Prescription drug management includes:
- If the provider is addressing a problem that includes continuing a prescription drug (or refill) in their education and MDM to manage the diagnosis, then it may be included in prescription drug management.
- The provider may choose to use qualifying factors of total time when choosing the E/M level of service.

13.5.4.4 Identification of MDM in Interventional Pain Management
- Straightforward (CPT 99202, 99212) as shown in Table 10.
  - One self-limited or minor problem (cervical strain, shoulder strain, lumbar strain).
  - Minimal or no diagnostic procedures ordered.
  - Risk of complications and/or morbidity or mortality of patient management.
    - Minimal risk of morbidity from additional diagnostic testing or treatment.
- Low (CPT 99203, 99213) as shown in Table 10.
  - 2 or more self-limited or minor problems, or one stable chronic illness, or one acute, uncomplicated illness or injury.
  - 2 minor problems or one acute, uncomplicated illness or injury (cervical strain, lumbar strain, knee strain, shoulder strain).
  - One stable chronic illness (chronic low back pain, chronic neck pain, chronic hip pain).
  - Amount and/or complexity of data to be reviewed and analyzed This includes meeting of at least one out of the 2 criteria from the following categories.
    - Category 1: Tests and documents or
    - Assessment requiring an independent historian(s)
- Risk of complications and/or morbidity or mortality of patient management
  - Low risk of morbidity from additional diagnostic testing or treatment:
    - Exercise program
    - Physical therapy
    - NSAIDs
    - Ordering x-rays
    - Referral
- Moderate (CPT 99204, 99214) as shown in Table 11.
  - One or more chronic illnesses with mild exacerbation, progression, or side effects of treatment:
    - Chronic low back pain with exacerbation or worsening, or

- ◦ 2 or more stable chronic illnesses (chronic low back pain, chronic neck pain, chronic chest wall pain), or
- ◦ One undiagnosed new problem with uncertain prognosis (low back pain, neck pain, headache, abdominal pain), or
- ◦ One acute illness with systemic symptoms or one acute complicated injury (vertebral fracture, spinal cord injury).

- The amount and/or complexity of data to be reviewed and analyzed is somewhat complicated and difficult for interventional pain management practices to meet. This includes meeting of at least one out of the 3 criteria from the following categories.
  - Category 1: Tests, documents, or independent historian(s) or
  - Category 2: Independent interpretation of tests or
  - Category 3: Discussion of management or test interpretation with external physician
- Risk of complications and/or morbidity or mortality of patient management
  - Moderate risk of morbidity from additional diagnostic testing or treatment:
    - ◦ Prescription drug management.
    - ◦ Decision regarding minor surgery with identified patient or procedure risk factors.
    - ◦ Decision regarding elective major surgery without identified patient or procedure risk factors.
    - ◦ Diagnosis or treatment is significantly limited by social determinants of health.
- High (CPT 99205, 99215) as shown in Table 12.

Table 10. *Elements of medical decision making (MDM) for Level 2 and 3 or straightforward or low complexity services.*

Code	Level of MDM (Based on 2 out of 3 elements of MDM)	Elements of Medical Decision Making		
		Number and Complexity of Problems Addressed at the Encounter	**Amount and/or Complexity of Data to be Reviewed and Analyzed *Each unique test, order, or document contributes to the combination of 2 or combination of 3 in Category 1 below.**	**Risk of Complications and/or Morbidity or Mortality of Patient Management**
99202 99212	Straightforward	Minimal • 1 self-limited or minor problem • Cervical strain • Shoulder strain • Lumbar strain	Minimal or none	Minimal risk of morbidity from additional diagnostic testing or treatment

99203
99213
	Low	Low
		• 2 or more self-limited or minor problems, or one stable chronic illness, or one acute, uncomplicated illness or injury
		or
		• 2 minor problems or one acute, uncomplicated illness or injury
		  • Cervical strain
		  • Lumbar strain
		  • Knee strain
		  • Shoulder strain
		  or
		• 1 stable chronic illness;
		  • Chronic low back pain
		  • Chronic neck pain
		  • Chronic hip pain
			Limited
			(Must meet the requirements of at least 1 of the 2 categories)
			Category 1: Tests and documents
			• Any combination of 2 from the following:
			  • Review of prior external note(s) from each unique source*;
			  • review of the result(s) of each unique test*;
			  • ordering of each unique test*
			  or
			Category 2: Assessment requiring an independent historian(s)
			(For the categories of independent interpretation of tests and discussion of management or test interpretation, see moderate or high)
				Low risk of morbidity from additional diagnostic testing or treatment
				• Exercise program
				• Physical therapy
				• NSAIDs
				• Ordering X-Rays
				• Referral

Adapted and modified from:
Hollman P, Jagmin C, Levy B. Evaluation and Management (E/M) Office Visits – 2021. American Medical Association. Accessed 03/10/2023. https://www.ama-assn.org/system/files/2020-04/e-m-office-visit-changes.pdf (682).
American Medical Association. CPT Evaluation and Management (E/M) Code and Guideline Changes, effective January 1, 2023. Accessed 04/11/2023. https://www.ama-assn.org/system/files/2023-e-m-descriptors-guidelines.pdf (683).

Table 11. *Elements of medical decision making (MDM) for Level 4 or moderate complexity services.*

Code	Level of MDM (Based on 2 out of 3 elements of MDM)	Elements of Medical Decision Making		
		Number and Complexity of Problems Addressed at the Encounter	**Amount and/or Complexity of Data to be Reviewed and Analyzed *Each unique test, order, or document contributes to the combination of 2 or combination of 3 in Category 1 below.**	**Risk of Complications and/or Morbidity or Mortality of Patient Management**
99204 99214	Moderate	Moderate • 1 or more chronic illnesses with mild exacerbation, progression, or side effects of treatment; • Chronic low back pain with exacerbation or worsening or • 2 or more stable chronic illnesses; ◦ Chronic low back pain ◦ Chronic neck pain ◦ Chronic chest wall pain or • 1 undiagnosed new problem with uncertain prognosis ◦ Low back pain ◦ Neck pain ◦ Headache ◦ Abdominal pain or • 1 acute illness with systemic symptoms; or • 1 acute complicated injury ◦ Vertebral fracture ◦ Spinal cord injury	Moderate (Must meet the requirements of at least 1 out of 3 categories) Category 1: Tests, documents, or independent historian(s) • Any combination of 3 from the following: • Review of prior external note(s) from each unique source*; - ER, MD • Review of the result(s) of each unique test*; - Imaging, UDI • Ordering of each unique test*; - MRI, UDI • Assessment requiring an independent historian(s) or Category 2: Independent interpretation of tests • Independent interpretation of a test performed by another physician/other qualified health care professional (not separately reported); or Category 3: Discussion of management or test interpretation • Discussion of management or test interpretation with external physician/other qualified health care professional/appropriate source (not separately reported)	Moderate risk of morbidity from additional diagnostic testing or treatment Examples only: • Prescription drug management ◦ Opioids ◦ Adherence mentoring ◦ Referral • Decision regarding minor surgery with identified patient or procedure risk factors • Decision regarding elective major surgery without identified patient or procedure risk factors • Diagnosis or treatment significantly limited by social determinants of health ◦ Housing, transportation, income, racism, discrimination etc.

- One or more chronic illnesses with severe exacerbation, progression, or side effects of treatment or one acute or chronic illness or injury that poses a threat to life or bodily function (acute disc herniation, cauda equina syndrome, spinal cord injury, epidural abscess, discitis).
- One acute or chronic illness or injury that poses a threat to life or bodily function (spinal cord injury, epidural abscess, epidural hematoma, discitis)
- The amount and/or complexity of data to be reviewed and analyzed is difficult for interventional pain management practices to meet. Extensive data must meet the requirements of at least 2 out of the 3 criteria from the following categories.
  - Category 1: Tests, documents, or independent historian(s) or
  - Category 2: Independent interpretation of tests or
  - Category 3: Discussion of management or test interpretation with external physician.
- Risk of complications and/or morbidity or mortality of patient management
  - High risk of morbidity from additional diagnostic testing or treatment:
    - Drug therapy requiring intensive monitoring for toxicity.
    - Decision regarding elective major surgery with identified patient.
    - Procedure risk factors, decision regarding emergency major surgery.

Table 12. *Elements of medical decision making (MDM) for Level 5 or high complexity services.*

Code	Level of MDM (Based on 2 out of 3 elements of MDM)	Elements of Medical Decision Making		
		Number and Complexity of Problems Addressed at the Encounter	Amount and/or Complexity of Data to be Reviewed and Analyzed *Each unique test, order, or document contributes to the combination of 2 or combination of 3 in Category 1 below.	Risk of Complications and/or Morbidity or Mortality of Patient Management

99205
99215
	High	High
		• 1 or more chronic illnesses with severe exacerbation, progression, or side effects of treatment;
		  • Acute disc herniation
		  • Cauda equina syndrome
		  • Spinal cord injury
		  • Epidural abscess
		or
		• 1 acute or chronic illness or injury that poses a threat to life or bodily function
		  • Spinal cord injury
		  • Epidural abscess
		  • Epidural hematoma
			Extensive
			(Must meet the requirements of at least 2 out of 3 categories)
			
			Category 1: Tests, documents, or independent historian(s)
			• Any combination of 3 from the following:
			  • Review of prior external note(s) from each unique source*;
			  • Review of the result(s) of each unique test*;
			  • Ordering of each unique test*;
			  • Assessment requiring an independent historian(s)
			or
			Category 2: Independent interpretation of tests
			• Independent interpretation of a test performed by another physician/other qualified health care professional (not separately reported);
			or
			Category 3: Discussion of management or test interpretation
			• Discussion of management or test interpretation with external physician/other qualified health care professional/appropriate source (not separately reported)
				High risk of morbidity from additional diagnostic testing or treatment:
				
				Examples only:
				• Drug therapy requiring intensive monitoring for toxicity
				  • Concurrent opioid therapy
				  • Methadone
				  • High Doses
				  • Intrathecal fusion systems
				• Decision regarding elective major surgery (SCS) with identified patient or procedure risk factors
				• Decision regarding emergency major surgery
				  • Epidural hematoma
				  • Epidural abscess
				  • Discitis
				  • Cauda equina syndrome

Table 13. *Time range and starting point: Reporting prolonged clinical staff time (99415, 99416) with E/M office or other outpatient codes (99202-99205, 99211-99215).*

Office or Other Outpatient Code and Typical Clinical Staff Time (Minutes)	Prolonged Service Codes	
	99415 Time Range (Minutes)	99416 Starting Point
99202 (29)	59-103	104
99203 (34)	64-108	109
99204 (41)	71-115	116
99205 (46)	76-120	121
99211 (16)	46-90	91
99212 (24)	54-98	99
99213 (27)	57-101	102
99214 (40)	70-114	115
99215 (45)	75-119	120

Source: American Medical Association. *CPT E/M Companion* 2023.

Tables 10 to 12 show various components of MDM from straightforward to high levels of risk.

Prolonged services code changes effective January 1, 2023, are shown in Table 13 (692).

- A new code has been created (99418) to align with the new prolonged inpatient E/M services.
- Codes 99354-99357 have been deleted.
- Code 99418 should be reported for prolonged services on the date of an inpatient, observation, or nursing facility service.
- Significant revisions have been made to the guidelines to direct users regarding the appropriate use of these codes. Codes 99358 and 99359 are still reported for prolonged services conducted on a date other than the date of the face-to-face E/M service.
- The E/M guidelines have been revised to reflect

the now-uniform structure and additional clarifications or modifications pertinent to these services. It is essential to review the official E/M guidelines in full to ensure complete understanding of all the changes.

13.5.5 Algorithmic Approach to Documentation: E/M Services

An algorithmic approach is designed to promote the efficient use of E/M services based on the guidelines, which may not be applicable for each and every patient. The purpose of the algorithmic approach is to provide disciplined use of documentation to avoid unnecessary care, poor documentation practices, fraud, abuse, and increase compliance. Table 14 shows an algorithmic approach to the documentation of E/M services which shows documentation based on symptomatology or history of present illness, which includes number of problems and complexity, medical necessity, and risk assessment.

13.5.6 Documentation of Pain Scores

The most commonly utilized pain scores are based on the 11-point Numeric Rating Scale (NRS) scale on scale 0-10 with 0 as no pain, 1-3 as mild, 4-6 as moderate, and 7-10 as severe. Table 15 shows NRS.

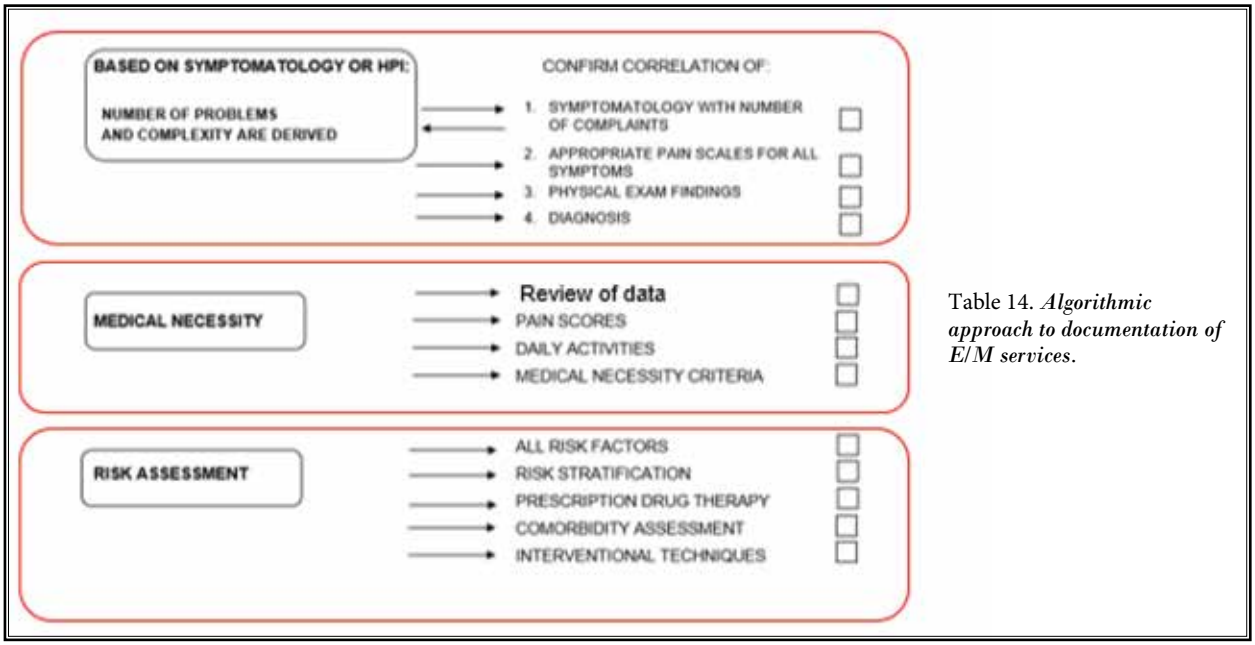


Table 14. *Algorithmic approach to documentation of E/M services.*

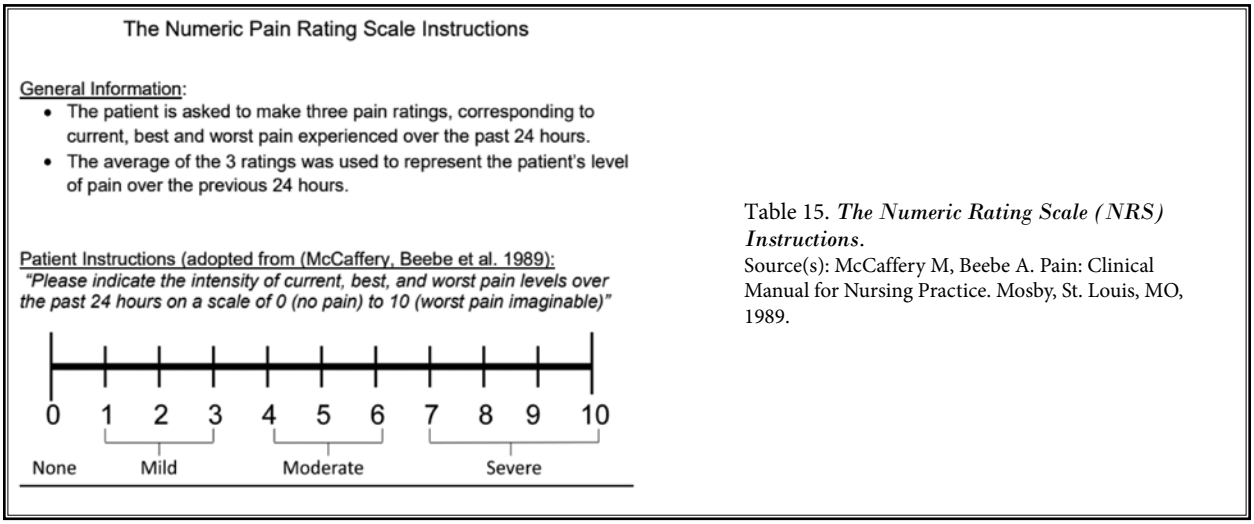


Table 15. *The Numeric Rating Scale (NRS) Instructions.*
Source(s): McCaffery M, Beebe A. Pain: Clinical Manual for Nursing Practice. Mosby, St. Louis, MO, 1989.

Table 16. *Pain relief documentation with interventional techniques.*

Pain Status			
Cervical Epidural Injections:			
•80% relief for 11 weeks with neck pain with cervical epidural injection on 06/15/2022 •50% relief for 1½ weeks with neck pain with cervical epidural injection on 06/15/2022			
Lumbar Radiofrequency Thermoneurolysis:			
•80% relief for 4 months with low back pain with lumbar radiofrequency thermoneurolysis on 02/02/2022 •60% relief for 1½ months with low back pain with lumbar radiofrequency thermoneurolysis on 02/02/2022 •50% relief for 1½ months with low back pain with lumbar radiofrequency thermoneurolysis on 02/02/2022			
Medical Management:			
•70% relief with medical management with knee and abdominal pain			
Structured Exercise Program:			
•Cervical Exercise Program – continued since 06/15/2022 •Lumbar Exercise Program – continued since 02/02/2022			
Numeric Pain Score:			
	Baseline	**Average**	**Today's**
Cervical	9	3	4
Lumbar	10	4	7
Abdomen	9	3	3
Bilateral knee	8	3	3

Pain relief documentation must be performed for all patients scheduled for interventional techniques, as well as medical therapy. Table 16 shows pain relief documentation with interventional techniques and medical management; however, this may be either for interventional techniques, medical management, or combination of both.

13.5.7 Functional Status

Multiple tests have been recommended for functional disability testing. These include ODI, Neck Disability Index (NDI) scored on 0-5 for each item with total scores of 50, and many others as shown in Tables 17 (693,694) and 18 (695). These instruments are essential to elucidate that the patient has moderate to severe disability for various types of interventional techniques. A score of:

- 0-4 no disability
- 5-14 – mild disability
- 15-24 – moderate disability
- 25-34 – severe disability
- 35-50 – completely disabled.

The follow-up at each appointment with these tests may become cumbersome and time consuming. Consequently, a simpler form has been developed to demonstrate changes from the baseline; without treatment; or if the treatments were to be stopped as compared to the functional status following the treatment on the date of observation or follow-up (Table 19).

As shown in Table 19, this assessment provides information on status while working, sitting, standing, walking, climbing stairs, lifting, carrying, or ability to perform overhead activities and drive.

13.5.8 Activities of Daily Living (ADLs)

There are various tests available for ADLs. None of the more commonly utilized, comprehensive, and easy to administer is the Katz Index of Independence in Activities of Daily Living, which has been well validated as shown in Table 20.

13.5.9 Opioid Risk Assessment

Opioid risk assessment has been described in UDT.

Table 17. *Oswestry Low Back Disability Questionnaire.*

Oswestry Disability Index (ODI)

Patent Name: _____

Date: _____

1. Pain Intensity	
☐ I have no pain at the moment	+0
☐ The pain is very mild at the moment	+1
☐ The pain is moderate at the moment	+2
☐ The pain is fairly severe at the moment	+3
☐ The pain is very severe at the moment	+4
☐ The pain is the worst imaginable at the moment	+5

2. Personal Care (Washing, Dressing, Etc.)	
☐ I can look after myself normally without causing extra pain	+0
☐ I can look after myself normally but it causes extra pain	+1
☐ It is painful to look after myself and I am slow and careful	+2
☐ I need some help but can manage most of my personal care	+3
☐ I need help every day in most aspects of self-care	+4
☐ I do not get dressed, I wash with difficulty and stay in bed	+5

3. Lifting	
☐ I can lift heavy weights without extra pain	+0
☐ I can lift heavy weights but it gives extra pain	+1
☐ Pain prevents me lifting heavy weights off the floor, but I can manage if they are conveniently placed, for example, on a table	+2
☐ Pain prevents me from lifting heavy weights but I can manage light to medium weights if they are conveniently positioned	+3
☐ I can only lift very light weights	+4
☐ I cannot lift or carry anything at all	+5

4. Walking	
☐ Pain does not prevent me walking any distance	+0
☐ Pain prevents me from walking more than 1 mile	+1
☐ Pain prevents me from walking more than ½ mile	+2
☐ Pain prevents me from walking more than 100 yards	+3
☐ I can only walk using a stick or crutches	+4
☐ I am in bed most of the time	+5

5. Sitting	
☐ I can sit in any chair as long as I like	+0
☐ I can only sit in my favorite chair as long as I like	+1
☐ Pain prevents me sitting more than 1 hour	+2
☐ Pain prevents me from sitting more than 30 minutes	+3
☐ Pain prevents me from sitting more than 10 minutes	+4
☐ Pain prevents me from sitting at all	+5

6. Standing	
☐ I can stand as long as I want without extra pain	+0
☐ I can stand as long as I want but it gives me extra pain	+1
☐ Pain prevents me from standing more than 1 hour	+2
☐ Pain prevents me from standing more than 30 minutes	+3
☐ Pain prevents me from standing more than 10 minutes	+4
☐ Pain prevents me from standing at all	+5

7. Sleeping	
☐ My sleep is never disturbed by pain	+0
☐ My sleep is occasionally disturbed by pain	+1
☐ Because of pain, I have less than 6 hours of sleep	+2
☐ Because of pain, I have less than 4 hours of sleep	+3
☐ Because of pain, I have less than 2 hours of sleep	+4
☐ Pain prevents me from sleeping at all	+5

8. Sex life (if applicable)	
☐ My sex life is normal and causes no extra pain	+0
☐ My sex life is normal but causes some extra pain	+1
☐ My sex life is nearly normal but is very painful	+2
☐ My sex life is severely restricted by pain	+3
☐ My sex life is nearly absent because of pain	+4
☐ Pain prevents any sex life at all	+5

9. Social Life	
☐ My social life is normal and gives me no extra pain	+0
☐ My social life is normal but increases the degree of pain	+1
☐ Pain has no significant effect on my social life apart from limiting my more energetic interests, for example, sports	+2
☐ Pain has restricted my social life and I do not go out as often	+3
☐ Pain has restricted my social life to my home	+4
☐ I have no social life because of pain	+5

10. Travelling	
☐ I can travel anywhere without pain	+0
☐ I can travel anywhere but it gives me extra pain	+1
☐ Pain is bad but I manage journeys over two hours	+2
☐ Pain restricts me to journeys of less than 1 hour	+3
☐ Pain restricts me to short necessary journeys under 30 minutes	+4
☐ Pain prevents me from traveling except to receive treatment	+5

Total Score: 50

Source(s): Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa 1976)* 2000; 25:2940-2952 (693).
Fairbank JC, Couper J, Davies JB. The Oswestry Low Back Pain Questionnaire. *Physiotherapy* 1980; 66:271-273 (694).

Table 18. *Neck Disability Index*.

Neck Disability Index

Patent Name: _____

Date: _____

1. Pain Intensity	
☐ I have no pain at the moment	+0
☐ The pain is very mild at the moment	+1
☐ The pain is moderate at the moment	+2
☐ The pain is fairly severe at the moment	+3
☐ The pain is very severe at the moment	+4
☐ The pain is the worst imaginable at the moment	+5

2. Personal Care (Washing, Dressing, Etc.)	
☐ I can look after myself normally without causing extra pain	+0
☐ I can look after myself normally but it causes extra pain	+1
☐ It is painful to look after myself and I am slow and careful	+2
☐ I need some help but can manage most of my personal care	+3
☐ I need help every day in most aspects of self-care	+4
☐ I do not get dressed, I wash with difficulty and stay in bed	+5

3. Lifting	
☐ I can lift heavy weights without extra pain	+0
☐ I can lift heavy weights but it gives extra pain	+1
☐ Pain prevents me lifting heavy weights off the floor, but I can manage if they are conveniently placed, for example, on a table	+2
☐ Pain prevents me from lifting heavy weights but I can manage light to medium weights if they are conveniently positioned	+3
☐ I can only lift very light weights	+4
☐ I cannot lift or carry anything at all	+5

4. Reading	
☐ I can read as much as I want to with no pain in my neck	+0
☐ I can read as much as I want to with slight pain in my neck	+1
☐ I can read as much as I want with moderate pain in my neck	+2
☐ I can't read as much as I want because of moderate pain in my neck	+3
☐ I can't hardly read at all because of severe pain in my neck	+4
☐ I cannot read at all	+5

5. Headaches	
☐ I have no headaches at all	+0
☐ I have slight headaches, which come infrequently	+1
☐ I have moderate headaches, which come infrequently	+2
☐ I have moderate headaches, which come frequently	+3
☐ I have severe headaches, which come frequently	+4
☐ I have headaches almost all the time	+5

6. Concentration	
☐ I can concentrate fully when I want to with no difficulty	+0
☐ I can concentrate fully when I want to with slight difficulty	+1
☐ I have a fair degree of difficulty in concentrating when I want to	+2
☐ I have a lot of difficulty in concentrating when I want to	+3
☐ I have a great deal of difficulty in concentrating when I want to	+4
☐ I cannot concentrate at all	+5

7. Work	
☐ I can do as much work as I want to	+0
☐ I can only do my usual work, but no more	+1
☐ I can do most of my usual work, but no more	+2
☐ I can't do my usual work	+3
☐ I can hardly do any work at all	+4
☐ I can't do any work at all	+5

8. Driving	
☐ I can drive my car without any neck pain	+0
☐ I can drive my car as long as I want with slight pain in my neck	+1
☐ I can drive my car as long as I want with moderate pain in my neck	+2
☐ I can't drive my car as long as I want because of moderate pain in my neck	+3
☐ I can hardly drive at all because of severe pain in my neck	+4
☐ I cannot drive my car at all	+5

9. Sleeping	
☐ I have trouble sleeping	+0
☐ My sleep is slightly disturbed (less than 1 hr sleepless)	+1
☐ My sleep is mildly disturbed (1-2 hrs sleepless)	+2
☐ My sleep is moderately disturbed (2-3 hrs sleepless)	+3
☐ My sleep is greatly disturbed (3-5 hrs sleepless)	+4
☐ My sleep is completely disturbed (5-7 hrs sleepless)	+5

10. Recreation	
☐ I am able to engage in all recreational activities with no neck pain at all	+0
☐ I am able to engage in all my recreational activities with some pain in my neck	+1
☐ I am able to engage in most but not all of my usual recreational activities because of pain in my neck	+2
☐ I am able to engage in a few of my usual recreational activities because of pain in my neck	+3
☐ I can hardly do any recreational activities because of pain in my neck	+4
☐ I can't do any recreational activities at all	+5

Total Score: 50

Source: Vernon H, Mior S. The Neck Disability Index: A study of reliability and validity. J Manipulative Physiol Ther 1991; 14:409-415 (695).

Table 19. *Functional status.*

	Baseline or Without Treatment	Average After Treatment or Since Last Visit
Working status	☐ Full-time ☐ Part-time ☐ Self-employed ☐ Unemployed ☐ Homemaker ☐ Retired ☐ Disabled	☐ Full-time ☐ Part-time ☐ Self-employed ☐ Unemployed ☐ Homemaker ☐ Retired ☐ Disabled
Sitting	At a time _____ minutes Total _____ hours	At a time _____ minutes Total _____ hours
Standing	At a time _____ minutes Total _____ hours	At a time _____ minutes Total _____ hours
Walking – feet, blocks or miles	At a time _____ Total _____	At a time _____ Total _____
Climbing stairs (at a time)	_____ flights	_____ flights
Lifting	_____ lbs.	_____ lbs.
Carrying	_____ lbs.	_____ lbs.
Overhead Activities	☐ Normal ☐ Very difficult ☐ Moderately difficult ☐ Unable	☐ Normal ☐ Very difficult ☐ Moderately difficult ☐ Unable
Driving	☐ Normal ☐ Very difficult ☐ Moderately difficult ☐ Unable	☐ Normal ☐ Very difficult ☐ Moderately difficult ☐ Unable

Table 20. *KATZ index of independence in activities of daily living.*

Activities Points (1 or 0)	Baseline or without treatment	Average after treatment or since last visit
BATHING Independence: Bathes self completely or needs help in bathing only a single part of the body. Dependence: Need help with bathing more than one part of the body	☐ 1 - Independence ☐ 0 - Dependence	☐ 1 - Independence ☐ 0 - Dependence
DRESSING Independence: Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. Dependence: Needs help with dressing	☐ 1 - Independence ☐ 0 - Dependence	☐ 1 - Independence ☐ 0 - Dependence
TOILETING Independence: Goes to toilet independently Dependence: Needs help	☐ 1 - Independence ☐ 0 - Dependence	☐ 1 - Independence ☐ 0 - Dependence
TRANSFERRING Independence: Moves in and out of bed or chair unassisted Dependence: Needs help	☐ 1 - Independence ☐ 0 - Dependence	☐ 1 - Independence ☐ 0 - Dependence
CONTINENCE Independence: Exercises complete self-control over urination and defecation. Dependence: Is partially or totally incontinent of bowel or bladder	☐ 1 - Independence ☐ 0 - Dependence	☐ 1 - Independence ☐ 0 - Dependence
FEEDING Independence: Gets food from plate into mouth without help Dependence: Needs partial or total help feeding	☐ 1 - Independence ☐ 0 - Dependence	☐ 1 - Independence ☐ 0 - Dependence
TOTAL POINTS - SCORING: 6 = High (patient independent) 0 = Low (patient very dependent)		

14.0 Summary of Steps for Chronic Opioid Therapy

This evidence synthesis and guidance preparation provides the following recommendations with 4 steps to opioid therapy:

14.1 Initial Steps of Opioid Therapy

1. Comprehensive evaluation of pain history, medical history, psychosocial history, functional assessment, and appropriate consultations are recommended prior to initiation of opioid therapy.
   Evidence Level: Strong; Strength of Recommendation: Strong
2. Review of Prescription Drug Monitoring Program (PDMP) data prior to initiating any/all controlled substance prescriptions and periodically or as mandated by regulations during treatment in order to provide information on patterns of prescribing from all providers registered with the system.
   Evidence Level: Moderate to strong; Strength of Recommendation: Strong
3. Risk stratification as part of patient management is essential for opioid and controlled substance medication management.
   Evidence Level: Limited; Strength of Recommendation: Moderate
4. Urine drug monitoring (UDM) should be implemented at the initiation of opioid therapy and conducted periodically for monitoring therapeutic compliance as per available guidance referential to mode and frequency of testing.
   Evidence Level: Moderate; Strength of Recommendation: Strong
5. Prior to starting opioid therapy, clinicians should discuss the realistic benefits, and known risks with patients; should establish clear treatment goals for pain and/or function, and should consider – and discuss - how opioid therapy will be discontinued if benefits do not outweigh risks.
   Evidence Level: Strong; Strength of Recommendation: Strong
6. It is essential to establish goals of opioid therapy related to pain relief, improvement in function if and as possible, improvement in quality of life, and a plan for opioid tapering and cessation if and when meaningful, realistic improvement is not achieved from opioid therapy.
   Evidence Level: Strong; Strength of Recommendation: Strong
7. A controlled substance agreement that is detailed with each item, including safe storage and disposal, and initialed and signed by the patient is essential prior to initiating therapy.
   Evidence Level: Strong; Strength of Recommendation: Strong
8. Once medical necessity is established, opioid therapy may be initiated using low doses and short-acting drugs, with appropriate monitoring to provide effective relief and avoid side effects.
   Evidence Level: Moderate; Strength of Recommendation: Moderate to Strong
9. Long-acting opioids should not be utilized for the initiation of opioid therapy.
   Evidence Level: Strong; Strength of Recommendation: Strong
10. Methadone is recommended for use after failure of other opioid therapies only if EKG and evaluation of QT intervals and drug interactions have been conducted and evaluated; commencing with low doses, with dose adjustments with repeat EKG performed at least 6-12 months thereafter. Only clinicians with specific training in methadone prescribing, use, and risk management should offer this agent for treatment of noncancer pain that is resistant to effect(s) of other opioids.
    Evidence Level: Strong; Strength of Recommendation: Strong

14.2 Assessment of Effectiveness of Opioid Therapy

11. Physicians should evaluate meaningful benefit (i.e., least 30% benefit in pain and/or function) produced by opioid treatment and should ensure that opioid therapy does not incur aberrant behaviors and/or adverse effects.
    Evidence Level: Moderate; Strength of Recommendation: Moderate
12. Clinicians must understand the effectiveness, viability, limitations, adverse consequences, and relative value (versus burden/risk) of long-term opioid therapy in chronic non-cancer pain.
    Evidence Level: Strong; Strength of Recommendation: Strong
13. The evidence of effectiveness is similar for short-acting and long-acting opioids, with increased incidence and prevalence of adverse consequences evidenced with the use of long-acting opioids.
    Evidence Level: Moderate; Strength of recommendation: Moderate

14. The administration of high doses of long-acting opioids is recommended in limited circumstances wherein severe intractable pain is not responsive or mitigated by short-acting opioids or moderate doses of long-acting opioids.
    Evidence Level: Moderate; Strength of recommendation: Moderate
15. Tapering or weaning processes must be initiated slowly after appropriate criteria have been met and should entail slow tapering of the dosage across a specified period of time. Reinstitution of opioid therapy can be considered when such treatment is deemed medically necessary if the patient's behavior and pattern of drug use are shown to be stable, and if results of at least two consistent urine drug tests are negative (for opioids and/or illicit drugs).
    Evidence Level: Moderate; Strength of Recommendation: Moderate

14.3 Monitoring Adherence and Side Effects

16. Adherence monitoring to assess and sustain appropriate use must be instituted at proper intervals, as based on risk stratification and indication(s) of other issues that may be regarded as negatively influencing therapeutic compliance.
    Evidence Level: Moderate; Strength of recommendation: Moderate
17. It is essential to monitor and manage side effects appropriately; such management may include discontinuation of opioids if indicated.
    Evidence Level: Strong; Strength of Recommendation: Strong
18. Bowel function must be closely monitored to assess opioid-induced constipation, and a bowel regimen should be initiated as soon as deemed necessary.
    Evidence Level: Strong; Strength of Recommendation: Strong

14.4 Final Phase

19. Chronic opioid therapy may be maintained, with continuous adherence monitoring, and modified at any time during this phase, in conjunction with - or after failure of - other modalities of pain care, for those patients demonstrating reasonable improvement in physical and functional status, and minimal adverse effects.
    Evidence Level: Moderate; Strength of Recommendation: Moderate
20. Chronic opioid therapy should be monitored for (burdensome and adverse) side effects, and these side effects should be managed appropriately.
    Evidence Level: Strong; Strength of Recommendation: Strong

15.0 Conclusion

Comprehensive, evidence-based, consensus guidelines for prescription of opioids for treatment of chronic non-cancer pain from the ASIPP were developed by a panel of multidisciplinary experts, so as to provide a clear explanation of the logical relationships of medical use and abuse, and multiple care options with outcomes, as based upon systematic review of both clinical and epidemiological quality of evidence and the strength of recommendations. The publication of a CDC document with characterization of the rise in opioid overdose deaths as a triple wave epidemic, with description of 3 distinct waves (4), has been extended in this analysis by the inclusion of a fourth wave. This the fourth wave is described as beginning in 2016 and progressively increasing since then due to multiple factors related to the misapplication of the 2016 CDC guidelines, increased availability of illicit drugs, the COVID-19 pandemic, and policies reducing access to interventional procedures (5). Despite the focus on prescription opioids, overdose deaths have reached record levels mainly due to the use of illicit fentanyl. A study by Aubry and Carr (7) of overdoses, OTAs, and prescription opioid pain relief relationships in the United States from 2010 to 2019, showed there is no direct correlation between these aspects as shown in Figs. 3 and 4 (20). In fact, there was a significant negative relationship of prescription opioids with TOD versus MME per capita, AOD with MME and a non-significant relationship with prescription opioids (Fig. 4).

The evidence supporting the effectiveness of use of opioids as a treatment for chronic non-cancer pain is limited. And while patient-based surveys and physician surveys provide somewhat contradictory findings, a general synopsis is that prudent use of opioids can result in significant improvement in patients who are deemed to have medical necessity and indication for the use of such agents. Indeed, emerging evidence shows the need for opioid (low or moderate dose) therapy in patients with proven medical necessity and stability with improvement in pain and function, independently or in conjunction with other modalities of treatments. Thus, opioids for treatment of chronic non-cancer pain should be reserved for select patients with moderate or severe pain that significantly affects function or QOL.

With comprehensive review of the literature and consensus based on evidence, the guidelines afford multiple recommendations for responsible opioid prescribing, inclusive of initial steps of opioid therapy, assessment of the effectiveness of opioid therapy, monitoring adherence and side effects, and the final phase to continue or discontinue opioid therapy on a long-term basis. Overall, 20 recommendations have been provided, with accompanying evidence level and strength of recommendation.

In conclusion, the goal of these updated guidelines continues to be to objectively integrate evidence, consensus and practice patterns to mitigate opioid abuse, misuse, and overuse, while concomitantly enabling maintained access to, and ethico-legally sound prescription of opioids for those patients in demonstrated need.

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Conflicts of Interest

Dr. Dennis received consulting fees from Abbott for physician and device representative education.

Dr. Soin is the founder and CEO of Soin Therapeutics. Soin Therapeutics has patents for low dose naltrexone for treatment of CRPS.

Dr. Limerick receives grants or contracts from Blaustein Pain Endowment for Research and Education.
Dr. Hirsch is a consultant for Medtronic, Relievant, and Sanofi. He is a grant supported Senior Affiliate Research Fellow at the Neiman Policy Institute.

Dr. Slavin receives research grants to home institution from Medtronic, Abbott, Neuros, Stryker; receives consulting fees from Abbott, Biotronik, Integer, Saluda, Synergia, Epiminder, Varian, WISE, and is President, World Society for Stereotactic and Functional Neurosurgery (WSSFN), President-Elect, International Neuromodulation Society (INS).

Dr. Harned received an education grant made to UK from Medtronic and receives payment or honoraria for Pikeville Medical Center lecture and payment for expert testimony for medical malpractice.

Dr. Justiz is Vice President of Oklahoma Pain Society

Dr. Shah receives grants or contracts from National Institutes of health and consulting fees from Allergan, Inc; SPR Therapeutics.

Dr. Helm receives payment for expert testimonies and support for attending meetings and/or travel.

Dr. Blank received payment or honoraria from ASIPP Lectures Controlled Substance, DEA MATE Course, Georgia Podiatric

Medical Conference Lecture and Tennessee Podiatric Medical Conference Lecture, payment for expert testimonies for State of Georgia vs Opioid Manufacturers, et al and State of Alabama vs Opioid Manufacturers, et al, is GSAM President of Chapter (unpaid) and is a member of Skyland Trail – Professional advisory Board (umpaid) and Medical Association of Georgia -Chair Think About it Campagne and is the owner of Atlanta Healing Center and Susan K. Blank, MD, LLC.

Dr. Grami is a participant on the Pennsylvania Contractor Advisory Committee (CAC).

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