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Managing Opioid Use Disorder in the Setting of a Terminal Disease: Opportunities and Challenges

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Abstract

Opioids have long been a mainstay of symptom management in palliative care (PC), allowing patients with terminal illnesses to have an improved quality of life. Unfortunately, these same medications have contributed to the explosion of the opioid epidemic. This article explores the case of a patient with opioid use disorder (OUD) and pancreatic cancer. We share our experience of managing his symptoms and treating OUD in the setting of an outpatient PC clinic. We explore the challenges and joys of this case while reflecting on the need for more research investigating best practices for individuals where opioids serve as both a pain reliever and contributor to further suffering from their OUD.

Keywords: opioid misuse; opioid use disorder; pain; palliative care; substance use disorders

Introduction

An estimated 7.8 million adults in the United States over the age of 26 years misused prescription pain relievers in the past year, and 886,000 individuals of all ages used heroin in 2017.[1] Of surveyed heroin users, ~80% reported using prescription pain medications before transitioning to heroin.[2,3] Although the majority of these individuals are younger, there are growing number of older adults who misuse opioid medications. A national survey found that of adults 65 years and older who misused opioids in the past month, nearly half (47.7%) obtained their opioids from a physician.[4] These figures point to the widespread nature of opioid misuse in the United States. In palliative care (PC), accurate measurements of opioid misuse and opioid use disorder (OUD) are difficult to find due to limited application of urine drug screens and existing screening tools simply assessing risk of misuse.[5,6] As medicine grapples with the current opioid crisis, greater attention is being paid to addressing OUD in serious illness and at end of life.[7,8] Early research likely underrepresented substance use disorders (SUDs) in patients with cancer[9] but individuals with serious illness remain at risk for OUD and nonmedical use of opioids.[10,11]

Despite this increased awareness, there remains a lack of understanding regarding the rates of SUDs in cancer patients and patients with other chronic illnesses seen by palliative providers.[12] Similarly, there is little in the way of outcomes-based research on how to manage opioid misuse in PC settings. Many of the existing guidelines are adapted from the chronic pain and psychiatric literature, with the CDC explicitly excluding PC and oncology patients from its own guidelines.[13] Despite the lack of guidelines, several groups have written about and advocated for the need to establish an attitude of ''universal precautions'' surrounding opioid prescribing in PC.[5] Still, approaches to management and screening typically differ from organization to organization or rely on the individual provider's level of comfort.[14] Disparities also exist in the training of PC physicians regarding opioid misuse and SUDs,[15] whereas a more recent survey of PC providers showed continued lack of confidence in managing SUDs.[16]

Case Description

A.P. was a middle-aged male who was diagnosed with locally advanced pancreatic adenocarcinoma found incidentally by imaging performed after a fall. An expedited workup was delayed several weeks due to his reluctance in coming to the hospital. During initial PC consultation, he described a 20-year history of OUD including remote history of IV heroin use, last use ~10 years prior. He long had struggled with OUD but had achieved several years of abstinence and was placed back on opioids by his primary care physician for the

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treatment of abdominal and back pain, now thought to be caused by his cancer. During this time, he began supplementing his prescribed opioids with illicit fentanyl. At our initial meeting, A.P. was receiving a 100 mcg fentanyl patch and as needed oxycodone initiated by his oncologist. He described adequate pain relief from this regimen. His pain and OUD were discussed frankly during these initial visits, and given his initial opioid requirements and severity of his cancer diagnosis, the decision was made to continue with full agonist opioid treatment rather than rotation to buprenorphine. Methadone maintenance was also considered, but with his upcoming treatment schedule and distance from cancer care, it was not felt to be feasible. Full agonist opioid treatment was continued while recognizing the risks of misuse, and these challenges were discussed frankly with the patient. At hospital discharge, he was receiving fentanyl 100 mcg patch and 30 mg PRN oxycodone every four hours.

To manage his pain as in the context of comorbid OUD, the PC team developed a treatment plan with the help of addiction psychiatry that included weekly appointments, prescription of naloxone, limits on opioid prescribing (e.g., no early opioid prescription fills), assessments for nonmedical use and cravings at each visit, regular urine drug screens, and recommend follow-up with a psychotherapist and participation in a recovery support program. Addiction psychiatry provided support for our clinicians during the case, and offered additional supports for A.P. We established with A.P. that the goal of pain treatment was to be able to return to work rather than lowering subjective pain intensity. Although A.P. continued to test positive for illicit opioids over the first six weeks, he gradually reduced the amount of opioid misuse. This period of misuse was followed by eight weeks during which nonmedical use of opioids ceased per his report, and urine toxicology showed only prescribed opioids. A.P. experienced improved relationships with his family and returned to work. Fentanyl was rotated to methadone 10 mg TID when pain began to increase and was initially effective. He was in regular contact with a peer support specialist recommended by addiction psychiatry and our clinical social worker.

In time A.P.'s cancer progressed. He began experiencing increased pain and emotional distress, coinciding with urine drug screens that were positive for nonprescribed opioids. Despite a trial escalation of his opioids, a celiac plexus block, and maximizing nonopioid adjuvants, he continued to test positive for nonprescribed opioids including fentanyl. He expressed increasing frustration and anger with the team, feeling that the focus was solely on his opioid use and not his suffering. The team had increasing concerns regarding the safety of continuing to prescribe opioids. Inpatient admission for symptom control was offered including consideration of rotation to buprenorphine. He refused admission, missed his last appointment with the team, and requested a hospice referral.

Discussion

Opioid risk assessment tools and urine drug screens are necessary but insufficient. PC as a field needs to incorporate evidence-based treatments for OUD into our routine management of pain and other symptoms

Although several original research and review articles have been written about the need to incorporate opioid risk assessment screening, urine drug testing, and universal opioid prescribing precautions into PC, there is less clarity on how to use these tools to inform clinical decisions. Effective management of pain and OUD should utilize evidence-based pharmacologic and behavioral interventions. For OUD, the only available FDA-approved treatments available are methadone, buprenorphine, and naltrexone.[17] To date, there are no studies exploring the effectiveness of these medications for OUD treatment in the context of PC. Despite this, there is growing interest in how to incorporate buprenorphine treatment into PC, with several concurrent sessions focused on its use at the 2019 Annual Assembly of Hospice and Palliative Medicine.[18–20] Despite the effectiveness of buprenorphine for pain and OUD, a minority of PC providers have the necessary Drug Enforcement Administration (DEA) certification to prescribe it for OUD.[16]

Rotation to buprenorphine was considered for our patient, both at the start of PC involvement and over the course of treatment. Given his high morphine equivalent daily dose (MEDD), our team and addiction psychiatry had concerns about achieving adequate pain control. Limited studies exist assessing pain relief in individuals with cancer rotated from full agonist to buprenorphine, and no studies exist examining buprenorphine use in individuals with cancer, OUD, and pain.[21] Several studies have been conducted in Europe utilizing formulations of buprenorphine not available in the United States. Insurance prior authorizations were also a concern as buprenorphine would be used for pain and OUD and an additional full agonist opioid may be prescribed for breakthrough pain. Providers may experience difficulties obtaining approval from insurance companies for higher doses of buprenorphine for patients with OUD.[22] Finally, our team worried about the induction process for an individual with cancer and a limited prognosis. Clearly, further research and practice guidelines for use of buprenorphine in individuals with serious illness, pain, and OUD are needed.

Increased monitoring: An opportunity and a burden

Although frequent visits were at times burdensome, they also represented an opportunity to provide high-quality PC. It allowed our team to take time to develop a deep level of trust with A.P., cultivate a greater understanding of his life, and understand the impact of his illness on him and his family. The frequent visits also allowed us to acutely manage the symptoms that emerged as his disease progressed and provide support for his significant other. Our team consisted of a palliative-boarded oncologist, licensed independent clinical social worker, and PC fellow who completed a psychiatric residency. This interdisciplinary approach is like other institutions and has demonstrated initial effectiveness in reducing aberrant behaviors of patients receiving opioid therapy.[23] The diversity in backgrounds allowed us to address the many sources of his suffering.

Although unintentional, the increased visit frequency further connected A.P. to the medical system and placed a significant burden on him and his family, from time, travel, and financial perspectives. SUDs disproportionately impact those from lower socioeconomic groups,[24–26] and increased scrutiny, regardless of its well-meaning underpinnings, may further burden a patient population already stigmatized by the

medical community. A.P. was seen weekly for nearly 6 months, with a typical appointment lasting 30 minutes to 1 hour. The frequent contact required to maintain safe opioid use was at times burdensome to the patient and may also be untenable for many PC outpatient practices.[27] Future research, guidelines, and policy decisions should consider both the provider and patient viewpoint. Individuals with OUD represent a marginalized population in health care and adding their voice to research is an important step that aligns with PC's goal of providing patient-directed family centered care.

The urine drug screen is positive, now what?

One of the challenging dilemmas encountered in this case was how to address recurrent drug screens positive for illicit opioids. We chose a harm reduction model focusing on the goal of reducing overall misuse and attempting to help guide A.P. toward meaningful recovery from OUD, something he identified as a goal at the start of treatment.[28–30] We also prescribed naloxone at the onset of treatment and counseled the patient and his spouse on its use. Given the relapsing–remitting nature of OUD, we did not implement a policy of positive urine drug screens triggering a reflexive change in prescribing. We felt that doing so would penalize the patient for expected findings that may occur during OUD.[31] With increased services, growing trust between patient and provider, and improved symptom control, the patient's pattern of illicit use decreased, leading to a two-month period without illicit use. This period was also one of personal growth for the patient, with a deepened connection to his family including reconnecting with several estranged relatives. Unfortunately, with increasing pain and overall distress, our patient began to test positive again for illicit opioids. Dose increases did not result in symptom improvement, and adjuvant therapies were met with only transient improvement. Continued positive urine screens led to further frustration from the patient, who described feeling singled out for his opioid use, and worry from providers due to safety concerns and risk for unintentional overdose.

Throughout caring for A.P., the PC team maintained close contact with addiction psychiatry. This relationship was helpful and allowed both sides to better understand the intricacies of managing pain and OUD in seriously ill patients. Frequent discussions with addiction psychiatry helped to provide support to our providers who felt distressed at both A.P.'s suffering and our own concern over opioid prescribing. This case demonstrated the need for continued collaboration. Few guidelines exist regarding when a psychiatry referral should be made for a PC patient, but we found that frequent discussions were helpful to best understand where the line between PC management and addiction psychiatry management lay. In certain instances, an inpatient PC unit admission may be indicated for a primary psychiatric reason.[32]

The current treatment paradigm of SUD treatment often centers on the creation of a better future, whereas PC aims to reduce suffering and provide support for the patient and family as life ends. Most PC patients suffer from a terminal and progressive disease. In contrast, SUDs are relapsing–remitting chronic diseases that may lead to death, but more frequently lead to remission, either naturally or with the help of treatment. By employing a harm reduction strategy, A.P. and the PC team worked together to achieve a period of remission in his OUD while his pancreatic cancer advanced. This provided the PC team an opportunity to reflect on the best methods to care compassionately for someone struggling to recover from one disease while limiting suffering from another. As a field, more research and expert guidelines are needed to increase the awareness of suffering at the end of life related to comorbid SUDs, as well as research to improve pain and symptom management in individuals with OUD.

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Author Disclosure Statement

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Craving Behavior from Opioid Addiction Controlled with Olanzapine in an Advanced Cancer Patient: A Case Report

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Abstract

Opioid addiction, although uncommon in cancer patients, can be a significant challenge for optimal pain management in certain patients. We present a case of a 59-year-old man with advanced colon cancer whose compulsive craving for the buccal tablet of fentanyl citrate (BTFC) was improved with the use of olanzapine. He was hospitalized for abdominal pain caused by disease progression. He had visited several times at outpatient follow-up to obtain a prescription for BTFC because he took all medications before the appointed times. After admission, intravenous infusion of oxycodone and opioid rotation were applied to the patient to control his pain. However, he complained that the pain was not relieved at all and persistently asked for only BTFC 7 to 15 times per day. With the diagnosis of opioid addiction, the transdermal buprenorphine patch was applied, but was ineffective for controlling the addictive behaviors. Finally, olanzapine (10 mg/day per os), a dopamine receptor antagonist, was given to control the craving behavior because psychological dependence is mediated by the dopaminergic system. Three days later, opioid craving was reduced from five to one on a 5-point Likert scale. The pain was well controlled to numeric rating scale 1 or 2 without cravings for BTFC. Craving behavior as a result of opioid addiction may be controlled with olanzapine. Further prospective studies on this issue are warranted.

Keywords: addictive; analgesics; behavior; neoplasms; olanzapine; opioid

Introduction

Advanced cancer patients suffer from diverse physical and psychological symptoms including pain, constipation, and depression.[1,2] Although opioids are an essential medication for cancer patients suffering from pain, the chronic use of opioids may result in addiction. There is growing evidence that chronic opioid use can result in these behaviors including in a palliative care setting.[3,4]

Addiction is associated with physical and psychological dependences. Although these terms are often confused by health providers, they are distinct phenomena. Physical dependence is considered a physiologic response with involvement of norepinephrine, and does not have a causal relationship with opioid addiction. In contrast, psychologically dependent patients exhibit one or more the characteristics of impaired control over drug use, continued use despite harm, compulsive use, and cravings.[5] Psychological dependence is mediated by the dopaminergic system. The dopamine D2 receptor availability and dopamine release are decreased in opioid-dependent subjects.[6,7] Recently, several dopamine gene variants are found to be associated with protection or risk for opioid dependence.[8]

Olanzapine is a second-generation atypical antipsychotic that antagonizes subtypes of D2/D4 receptors from the D2-like family. Olanzapine has been reported to reduce cravings and consumption in alcohol-addicted patients.[9] Given the common mechanism for opioid addiction, olanzapine may be a useful treatment for opioid-addicted cancer patients. However, previous studies on the efficacy of olanzapine have only indicated that it is effective in reducing the cravings of noncancer patients for alcohol,[10] heroin,[11] and cocaine.[12,13]

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There is no study on using olanzapine to treat opioid-addicted cancer patients.

In this study, we report a case of an opioid-addicted terminal cancer patient who had suffered from strong craving behavior that was controlled by olanzapine.

Case Description

A 59-year-old man with advanced colon cancer resistant to all conventional chemotherapy was hospitalized for abdominal pain and general weakness. The patient was a current smoker who had 20 pack-years of tobacco history and had moderate alcohol intake. He denied a history of illicit drugs such as marijuana, cocaine, and heroin. On the baseline mental status examination, he was slightly anxious and otherwise was normal with coherent thought process. His medical history revealed only medically controlled hypertension. The pain was dull aching in nature and was considered to be caused by metastatic lesions in the liver and abdominal lymph nodes. The pain intensity was severe and measured at a level of numeric rating scale (NRS) 8. He had received a low dose of opioid since a year ago. During the past 1 month, he had been on a fentanyl transdermal patch 75 μg/hour for background pain and on a buccal tablet of fentanyl citrate (BTFC; Fentora®; Cephalon, Inc., Frazer, PA) 400 μg for breakthrough pain episodes (morphine equivalent daily dose [MEDD] = 800 mg/day [150 mg/day for the background dose and 650 mg/day for the cumulative breakthrough dose]). During outpatient follow-up, he had visited several times to obtain a prescription for BTFC because of frequent breakthrough pain. He did not want to escalate the dose of fentanyl transdermal patch and took all BTFC before the appointed times.

After admission, continuous intravenous infusion of oxycodone (100 mg/day) was additionally prescribed for abdominal pain (MEDD = 1100 mg/day). However, he complained that his pain was not relieved at all even when he was given a dose of 200 mg/day of oxycodone the next day (MEDD = 1400 mg/day). Although the hyperalgesia syndrome from high-dose opioid use was considered, the characteristics and severity of pain were not changed while the dose of oxycodone rapidly increased. Subsequently, opioid rotation using intravenous morphine or fentanyl was attempted without success. He persistently asked for only BTFC 7 to 15 times per day, which was a similar dose before hospitalization. BTFC only lulled the craving for 2 to 3 hours. At this time, the MEDD was $\sim$1200 to 1600 mg/day.

The physician referred the patient to a psychiatrist for BTFC obsession, and the patient was diagnosed with opioid use disorder categorized as addiction. He was classified into the severe category by meeting 7 of the 11 checklist items: continued opioid use despite having social/interpersonal problems; tolerance (higher MEDD); used larger amounts (higher MEDD and frequent outpatient clinic visits for prescription of BTFC); much time spent using (frequent outpatient clinic visits for prescription of BTFC); continued opioid use despite knowledge of having physical/psychological problems; activities given up to use (his motivation had gone down while the dose of BTFC had increased); and craving.[14] The 20 μg/hour of transdermal buprenorphine patch (the only available form of buprenorphine in Korea) was applied and was ineffective for controlling the addictive behaviors. Finally, olanzapine (10 mg/day per os) was given to control the craving behavior and anxiety because, compared with other D2-receptor antagonists, its H1-blockade effect is stronger[15] and there is more evidence to support the role of olanzapine as a treatment for opioid craving.[9–12] Three days later, opioid craving was reduced from five to one on a 5-point Likert scale (It was difficult for me to forget about taking BTFC—1: not at all; 5: very much—not validated to assess the opioid craving). The opioid amount was reduced to MEDD 500 mg/day seven days after the initiation of olanzapine. The pain was well controlled to NRS 1 or 2 without cravings for BTFC and the level of consciousness was alert.

Since 1 week after hospitalization, the patient became depressed and felt his life is worthless. In addition, he complained of insomnia and decrease in appetite. Psychotic features and history of manic/hypomanic episodes were not observed. Under the diagnosis of major depressive disorder, duloxetine 30 mg/day was started and its dose was titrated up to 60 mg/day because it is known to be effective for anxiety and painful physical symptom as well as depression.[16,17] Depressed mood and physical activity then improved over time. However, the patient's craving for BTFC was not reduced at all until he was started on olanzapine.

He was discharged from the hospital four weeks after the initiation of olanzapine, with an average pain NRS of 2 and with MEDD of 520 mg/day. The patient died peacefully three months later due to cancer progression.

Discussion

To our knowledge, this is the first case of an opioid- addicted cancer patient whose craving behavior was successfully controlled by olanzapine. In patients with chronic nonmalignant pain, up to 11.5% of those were reported to have opioid addiction.[18] However, addiction to opioids is uncommon in patients with cancer pain. Although one study indicated that the prevalence of opioid addiction in cancer patients ranged from 0% to 7.7%, it included all problematic opioid uses such as addiction, dependence, improper medication, abuse, and misuse.[4] Schug et al. reported that addiction was a negligible problem, with only 1 observed case out of 550 cancer patients.[19] However, it was also reported that current smokers and alcoholics, as in our patient, were more likely to have a history of illicit drug use than never smokers and nonalcoholics.[20,21] Kwon et al. reported that $\sim$42% of CAGE (cut-down, annoyed, guilty, and eye-opener)-positive patients for alcohol were diagnosed as chemical copers, although this does not necessarily mean that they are addicts.[22]

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) diagnostic criteria, addiction is included in the categories of opioid use disorder.[23] Its severity was classified on the number of diagnostic criteria met by the patient. A minimum of 2 to 3 of the 11 criteria is considered mild, 4 to 5 is moderate, and 6 to 7 indicates severe opioid use disorder. Our patient was classified as severe opioid use disorder by these criteria. However, the DSM-5 diagnostic criteria may not be sufficient to distinguish addiction from other abuse or misuse disorders because physical dependence or pseudoaddiction may easily meet two or more of the criteria. The American Pain Society and the American Society of Addiction Medicine suggest four critical elements of opioid addiction: loss of self-control,

compulsiveness, persistent use despite harm, and craving. Our patient showed all four symptoms necessary for an addiction diagnosis.

Although both psychological and physical dependences on opioids contribute to addiction, their pathophysiological mechanisms are completely different. The mesolimbic system is believed to be an important mechanism in the development of psychological dependence on opioids. When people experience natural rewards, such as food, music, and sex, the neurons of the ventral tegmental area in the midbrain release dopamine into the nucleus accumbens and the prefrontal cortex, which plays a key role in the subjective feelings of pleasure.[24] Opioids induce a rush of dopamines in greater amount than under a normal stimulus and pathologically intercept the brain mechanisms of reward-related learning and memory.[25,26] Considering these pathophysiological mechanisms, olanzapine, a dopamine receptor antagonist, may play a role in managing psychological dependence.[27] The patient in this case was believed to respond to olanzapine through this mechanism. Chronic opioid use leads to neuroplastic changes in the brain of vulnerable individuals with drug-seeking behavior. Short-acting opioids including BTFC are more likely to cause a patient to develop misuse than are other long-acting opioid analgesics.[28] Another study suggested that the pharmacokinetic properties of morphine including the dosage and the rate of administration may affect the abuse liability of the drug.[29]

Physical dependence occurs by changing the cells and synapses in the brain into a hyperadrenergic state through high levels of norepinephrine coming from the locus coeruleus of the anterior pons, which is a physiological response to chronic opioid exposure. If opioids were abruptly stopped, the activated alpha2-adrenergic system dominated by norepinephrine can develop multiple symptoms from adrenergic hyperactivity, including abdominal pain, diarrhea, lacrimation, sweating, chill, yawning, sneezing, general weakness, and insomnia.[30,31] Our patient did not present with physically dependent symptoms.

Pseudoaddiction is defined as an iatrogenic syndrome where a patient displays aberrant behaviors that develop as a result of inadequate pain management. These behaviors are often mislabeled as chemical coping or even addiction. Only after adequate control of pain is achieved do these behaviors resolve and the opioid dose requirements stabilize and even decrease.[32] The patient was initially managed by opioid rotation and by dose escalation of other opioids based on the possibility of pseudoaddiction, but opioid craving was not improved at all. After olanzapine was administered, opioid craving and MEDD were markedly reduced although any anticancer treatment was not performed during this period. These findings may rule out the diagnosis of pseudoaddiction.

Depression is often associated with opioid addiction inpatients.[33] This phenomenon may be explained by the seeking behavior for euphoric agents, such as opioids, in depressed individuals, although an inverse causal relationship may still exist.[34] Our patient showed that the depressed mood was improved by the administration of an antidepressant. However, the patient's craving for BTFC was not reduced at all until he was started on olanzapine. This suggests that the patient's craving behavior may be explained by the opioid addiction rather than by the major depressive disorder.

In conclusion, we provide early evidence that olanzapine may inhibit craving behaviors associated with opioid addiction. There were several limitations to confirm this finding in our patient. Given that the usual therapeutic dose of sublingual buprenorphine to treat opioid addiction is 8 to 16 mg/day,[35] the dose of buprenorphine used in our patient (20 μg/hour of transdermal patch is $\sim$1 mg/day of sublingual type)[36] might be suboptimal. A previous report described that olanzapine was useful as an adjuvant analgesic in cancer patients with anxiety, which may have contributed to the beneficial effect on craving in this patient.[37] In addition, BTFC obsession seen in this patient might have been an attempt to manage his anxiety (chemical coping), which can be controlled by olanzapine. Therefore, further prospective studies are warranted to convince the role of olanzapine as a treatment for opioid addiction.

Author Disclosure Statement

No competing financial interests exist.

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Measurement of Chronic Pain and Opioid Use Evaluation in Community-Based Persons with Serious Illnesses

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Abstract

Background: Chronic pain associated with serious illnesses is having a major impact on population health in the United States. Accountability for high quality care for community-dwelling patients with serious illnesses requires selection of metrics that capture the burden of chronic pain whose treatment may be enhanced or complicated by opioid use.
Objective: Our aim was to evaluate options for assessing pain in seriously ill community dwelling adults, to discuss the use/abuse of opioids in individuals with chronic pain, and to suggest pain and opioid use metrics that can be considered for screening and evaluation of patient responses and quality care.
Design: Structured literature review.
Measurements: Evaluation of pain and opioid use assessment metrics and measures for their potential usefulness in the community.
Results: Several pain and opioid assessment instruments are available for consideration. Yet, no one pain instrument has been identified as ''the best'' to assess pain in seriously ill community-dwelling patients. Screening tools exist that are specific to the assessment of risk in opioid management. Opioid screening can assess risk based on substance use history, general risk taking, and reward-seeking behavior.
Conclusions: Accountability for high quality care for community-dwelling patients requires selection of metrics that will capture the burden of chronic pain and beneficial use or misuse of opioids. Future research is warranted to identify, modify, or develop instruments that contain important metrics, demonstrate a balance between sensitivity and specificity, and address patient preferences and quality outcomes.

Keywords: accountability; chronic pain; opioid use; serious illness; symptom assessment; symptom control

Introduction

Approximately 100 million adults in the United States, or from 11% to 40%, report chronic pain.[1,2] The estimated economic cost is from $560 to $635 billion for necessary healthcare and lower worker productivity.[3,4] Chronic pain is often associated with serious illnesses: conditions associated with a high risk of mortality, impaired quality of life, restricted function, high symptom and/or treatment burden, and caregiver stress.[5] Using pain assessment information, treatment decisions are made, preferably within the context of the patient's associated illnesses, functional status, and quality-of-life goals.

One standard analgesic treatment for moderate-to-severe pain is use of opioids. While opioids are often successful in minimizing pain, it is incumbent upon treating health

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professionals to be concerned about their potentially serious adverse consequences such as injury, dependence, addiction, and death. Indeed, the current opioid epidemic and associated increased death rates have highlighted these concerns.[2] Consideration of opioid use risk is an essential element for determining accountability for high-quality care delivery to community-dwelling patients with serious illnesses. This article has three aims: (1) to present options for assessing pain in seriously ill community dwelling adults according to their ability to communicate by proposing pain metrics that are effective representations of the patient's condition; (2) to discuss the use of opioids, as appropriate, and their intended and unintended consequences, in patients with serious illnesses; and, (3) to suggest accountability measures for use during pain treatment that can promote quality care and minimize adverse consequences in seriously ill patients.

Assessing and Recording Chronic Pain Metrics

Defining and classifying chronic pain through use of pain metrics

Metrics that define and classify chronic pain provide a focus for professional interventions and evaluation of quality of care. Selecting quality pain metrics requires answers to these questions: (1) what pain metrics are necessary for a screening examination to identify pain? (2) will the patient have the capacity to provide information about the pain metrics, or will input from a patient's family member, surrogate, or health professional be necessary? (3) if a screening examination is positive for chronic pain, what pain metrics are necessary to capture the dimensions, burdens, and impact of pain on the seriously ill patient and response to treatment?

The definition of pain has evolved over the years but still retains the characteristic of being a distressing experience associated with actual or potential tissue damage. (See Table 1 for a glossary of terms.) Pain is recognized as having sensory, emotional, cognitive, and social components, the latter making pain a shared experience. Chronic pain, when described by a time frame, is that which persists past the normal time of healing or lasting at least three months.[6] When chronic, or persistent, pain is associated with substantial restriction of participation in work, social, and self-care activities for six months or more, it is identified as high impact chronic pain.[7] However, looking beyond a time framework for classifying chronic pain, consideration must be given to the mechanisms and burden of pain[8] and recognize that pain classification can evolve over time and new discoveries.[9] Indeed, a new classification is currently under development.[10]

Table 1. Glossary of Terms

Definition
Serious illness: ''Serious illness'' is a condition that carries a high risk of mortality, negatively impacts quality of life and daily function, and/or is burdensome in symptoms, treatments, or caregiver stress.[5]
Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[41]
Pain (updated): An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.[42]
Pain (suggested modification): Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components.[43]
Chronic pain, when described by a time frame, is that which persists past the normal time of healing or lasting at least three months.[6]
High impact chronic pain: persistent pain with substantial restriction of participation in work, social, and self-care activities for six months or more.[1]
Nociceptive pain: Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.[42]
Neuropathic pain: Pain resulting from a lesion or dysfunction of the peripheral or central nervous systems.[42]
Pain behaviors: Various actions observed in an individual by others that may indicate that pain is present. These may include language, vocalizations, facial expression, body posture, and escape or avoidance actions.[23]
Medication abuse is self-administration of medications to alter or enhance one's state of consciousness.[37,44] This is an intentional maladaptive pattern of use of a medication (whether legitimately prescribed or not) leading to significant impairment or distress.
Medication misuse is defined as not taking a medication exactly as prescribed, for example, being prescribed an opioid for pain after ankle surgery but using it for headaches well after the surgical healing period.[45,46]
Medication addiction is defined as a primary chronic disease of brain reward, motivation, memory, and related circuitry.[47] Dysfunction in these circuits leads to characteristic biological, psychological, social, and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

Pain metrics

The important characteristics and domains of pain are identified by instruments and systems with specific pain metrics. (See Table 2 which outlines the relationship among pain domains, metrics, and instruments.) Pain domains as targets for assessment can include pain's sensory and affective qualities, its temporal characteristics, its location and bodily distribution, pain behaviors, and psychological impact on function.[1,11,12] Ascertaining the details of a patient's pain relies on a patient's ability to reliably communicate their pain experience and to access individuals and systems that capture pain information. A comprehensive pain assessment would optimally include use of metrics for each domain, while a screening pain assessment would be more focused. Providers are required to gather ''enough information'' to make treatment decisions and evaluate outcomes for which they are

Table 2. Clinimetrics for Chronic Pain Assessment

Tools with specific metrics	*Pain domain measured*[a]									*Comments*
	Sensory[a]	*Temporality*[a]	*Relief*[a]	*Location*[a]	*Interference/ functional impact*[a]	*Affective*	*Evaluative*	*Psychosocial impact*	*Behavioral*[b]	
VAS, NRS, VRS	x					x				Separate scales used for each dimension, sensory, and affect
BPI-SF	x		x		x					
MPQ-SF	x			x		x	x			
PEG	x				x			[a]		Pain intensity, enjoyment of life, interference with general activity
PROMIS					x (6 items)				x (7 items)	
PD-Q	x	x		x radiating						7 questions on sensations; 4 on course patterns; 1 on radiating
PAINAD									x	
PACSLAC									x	
DOLOPLUS-2									x	
MOBID									x	
NATIONAL HEALTH INTERVIEW SURVEY	x	x		x	x					Interference with life and work activities
PROMIS	x				x				x	Other nonpain items can be added such as depression and sleep
RAI	x				x				x	

[a]The first five domains on left represent those deemed most important, in order of importance, by Palliative Care clinician experts.[28]

[b]Behaviors for nonself-reporting patients.

BPI-SF, Brief Pain Inventory-Short Form; DOLOPLUS-2, Abbreviation for a French-language scale; MOBID, Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale; MPQ-SF, McGill Pain Questionnaire-Short Form; NRS, numeric rating scale; PACSLAC, Pain Assessment Checklist for Seniors with Limited Ability to Communicate; PAINAD, Pain Assessment in Advanced Dementia Scale; PD-Q, painDETECT questionnaire; PEG, Pain Intensity, Enjoyment, General Activity; PROMIS, Patient-Reported Outcomes Measurement Information System; RAI, Resident Assessment Instrument; VAS, visual analog scale; VRS, verbal rating scale.

accountable. Gathering pain data from community dwelling individuals with serious illnesses may require a triaging process that begins with more simple interrogations.

Unidimensional pain measures and short questionnaires

Simple interrogations generate data from use of unidimensional measures and brief questionnaires by patients who can self-report and/or self-record. Well validated unidimensional numeric rating scale (NRS) and visual analog scale (VAS) are often used to quantify degree of pain intensity and, less often, degree of pain distress.[13] However, simply focusing on a pain intensity number provided by patients with chronic pain can be problematic since one number does not reflect the total burden of chronic pain. A decrease in a number may not serve as a metric of treatment outcome success[14]; nor can chronic pain treatment be unsuccessful even when a pain intensity number does not change.[15]

There are a number of brief questionnaires that focus on multidimensional domains of pain: the Brief Pain Inventory (BPI), the Short Form-McGill Pain Questionnaire (SF-MPQ), the PEG, and the painDETECT. The BPI is a short self-administered questionnaire that assesses pain severity, as well as its impact on function.[16] The BPI-Short Form (BPI-SF) has been used to identify characteristics of breakthrough pain in patients with cancer-related pain in remission.[17] The SF-MPQ is also a self-administered questionnaire that addresses sensory, affective, and cognitive (evaluative) domains of pain[18] and correlates highly with the well validated Long Form-MPQ.[19] The PEG is a 3-item scale that measures pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G).[20] It has been tested against the BPI for reliability and content validity and has been shown responsivity to clinical interventions.[21] Recent Center for Disease Control (CDC) Guidelines[2] offer the PEG as one example of an instrument to assess treatment outcomes. Finally, the painDETECT questionnaire (PD-Q) evaluates symptoms associated with neuropathic versus nociceptive pain. Since patients with neuropathic pain often suffer more severely than patients with nociceptive pain,[22] a tool such as the PD-Q may help with better diagnosis and treatment.

Behavioral pain measures

Some patients with serious illnesses are unable to self-report their pain due to impaired cognitive capacity associated with delirium, dementia, and/or somnolence. Assessing behavioral indices as proxy measures of pain can help to identify people with chronic pain and make them more likely to receive therapeutic interventions.

Pain behaviors noted by healthcare workers in patient medical records in a palliative care center included patient vocalizations such as moans or groans or crying out; facial expressions such as grimaces and winces; and actions such as holding a body part and clenching fists.[23] Recognition of these behaviors in a palliative care population may assist with development and validation of a pain behavior tool for seriously ill patients in those and other settings. One such tool is the MOBID scale (Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale).[24] The MOBID has been tested in nondelirious, nonpsychotic nursing home patients with dementia suspected to have chronic pain of >3 on a 0–10 NRS intensity scale. Researchers identified the following: pain behaviors were more frequently observed during mobility than rest; observer-generated NRS pain intensity scores and number of behaviors observed were positively correlated; and the best agreement between the testers was for pain noises, although facial expression was demonstrated most frequently. Observation and recording of behaviors by family members or health professionals that may indicate pain deserve careful consideration as a metric-generating activity in seriously ill community-based patients unable to reliably self-report.

Several other pain behavior scales have been developed for older persons with severe cognitive impairment, such as the PAINAD, PACSLAC, and the DOLOPLUS-2 (see footnote of Table 2 for full name of scales). Psychometric properties of these three scales were tested in Dutch nursing home residents.[25] The PACSLAC had better psychometric attributes and was found to be more ''user friendly'' to raters than the other two scales. However, the testing paradigm was acute (vaccination) pain rather than chronic pain. Items on the PACSLAC and PAINAD could be examined for their applicability to a newly constructed behavioral assessment scale that may reflect chronic pain in persons with serious illnesses.

Use of electronic healthcare data to assess pain and its impact on the person

von Korff et al.[1] pilot tested a 25-item electronic pain survey in a sample of patients in a large group health plan in Washington, with most items derived from established questionnaires. Answers to three specific questions allowed for categorization of respondents as persons with high-impact chronic pain (14% of 365 respondents) versus those with moderate-impact chronic pain (19% of respondents.) There were clear differences between the two groups in responses to survey questions regarding frequency of healthcare use, level of pain intensity, level of life interference, and higher number of painful body sites. This led to researcher confidence that responding to questions on an electronic health survey would be feasible and beneficial in identifying primary care, population-based patients with moderate-to-high impact chronic pain.

A second electronic database, Patient-Reported Outcomes Measurement Information System (PROMIS),[26] was developed by academic scientists, primarily for research purposes, from several institutions and the NIH as a computerized bank of measures of patient symptoms, functional status, and quality of life. There is a pain intensity question as part of a global health scale, and there are two pain measures, pain behavior (a 7-item short form) and pain interference (a 6-item short form), that showed good reliability and validity. The PROMIS short form was a less sensitive measure of pain interference than the BPI or the PEG when used with patients with moderate musculoskeletal pain.[21] Nevertheless, PROMIS has shown to be efficient, flexible, and precise; its item bank is available for public use and items can be made part of an Internet survey platform.[26]

A third large electronic database is one used in nursing homes certified by Medicare and Medicaid to assess residents' strengths and needs through comprehensive

assessments to help ensure that a resident's quality of life is maintained or improved through quality care. The Long-Term Care Facility Resident Assessment Instrument (RAI) 3.0[27] contains one section, ''Section J, Health Conditions in the Minimum Data Set,'' which includes questions about pain that require self-report by the resident: pain presence, intensity, frequency, and effect on function. When residents are unable to self-report, staff complete questions about behavioral indicators of pain or possible pain. These data are used to identify interventions to meet the resident's individual needs and to monitor the quality of care provided. However, these metrics are specific to pain that the resident experienced over a previous five-day period of assessment, not necessarily chronic pain.

A palliative care perspective on assessing pain

Pain metrics deemed important to assess in patients with advanced cancer receiving palliative care were identified during a systematic search of pain assessment literature.[28] Six pain and palliative care physician experts ranked pain dimensions for relevance and importance. The first five of a list of 10 in order of deemed importance were the following: pain intensity, temporal pattern, treatment and exacerbating/relieving factors, location, and interference. In an update to this work,[29] 11 new tools were identified in the literature, but none was found to be inclusive. Experts ($n = 32$) again ranked the five most relevant dimensions of pain to be assessed within a 24 hour time window, with the substitution of pain quality for interference (No. 6 on this list).

Despite the work described above, no one pain instrument has been identified as ''the best'' to assess pain in seriously ill patients. However, consideration of the ''right metrics'' for capturing a seriously ill individual's experience of chronic pain is based on an understanding of the possibilities. These data may lead the healthcare provider to conduct a more comprehensive assessment to consider factors that may be influencing current and proposed pain treatment.

Treatment of Chronic Pain Through Use of Opioids

One important avenue of exploration is the role of opioid therapy for seriously ill patients with chronic pain. It is essential to consider that all pains are not equal; there are some conditions that are opioid responsive; some that may be; and others for which opioids are not indicated. Recent CDC Guidelines[2] recommend that prescribers reconsider the use of opioids for chronic noncancer pain, leading to an increased awareness of patients of the dangers of opioids. However, they fall short in providing guidance for use in patients with cancer or other serious illnesses. In addition, Baker[30] warns that care should be taken in establishing new standards, as is being done by The Joint Commission, to avoid the risk of moving the care pendulum away from good pain management. Decreased opioid prescribing may leave a subset of patients, such as those who are seriously ill, with no effective options to manage their unique chronic pain. For this reason, it is important that we continue to gather evidence to determine condition-specific guidelines for pain management. According to recent Clinical Practice Guidelines from the American Society of Clinical Oncology,[31] consideration

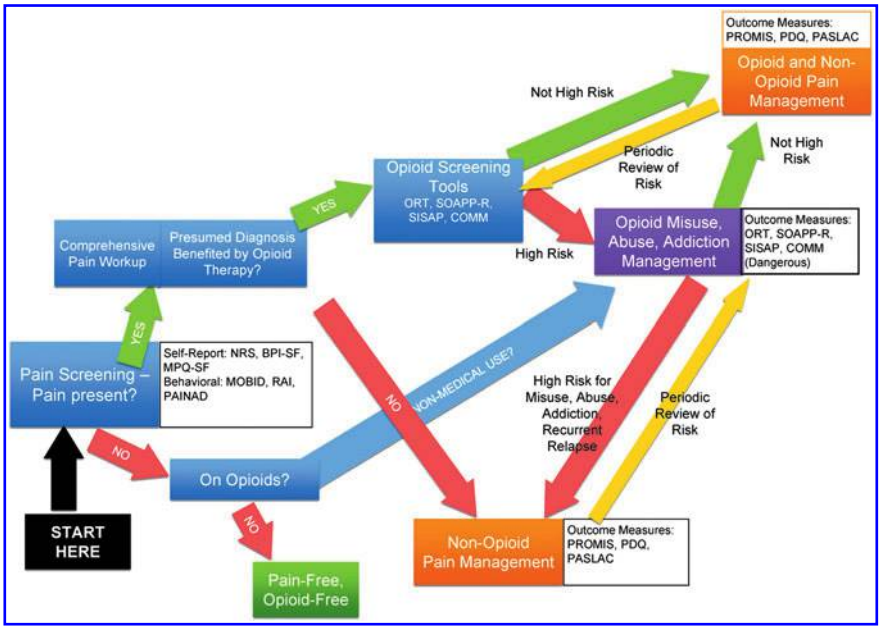

FIG. 1. Algorithm for pain screening metrics in the setting of Potential Opioid Misuse, Abuse, and Addiction. In this figure, we present a decision tree highlighting the interplay among pain assessment, pain management, opioid risk assessment, opioid benefit, and opioid management for community-based care. BPI-SF, Brief Pain Inventory-Short Form; COMM, Current Opioid Misuse Measure; MOBID, Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale; MPQ-SF, McGill Pain Questionnaire-Short Form; NRS, numeric rating scale; ORT, Opioid Risk Tool; PAINAD, Pain Assessment in Advanced Dementia Scale; PACSLAC, Pain Assessment Checklist for Seniors with Limited Ability to Communicate; PD-Q, painDETECT questionnaire ; PROMIS, Patient-Reported Outcomes Measurement Information System; RAI, Resident Assessment Instrument; SISAP, Screening Instrument for Substance Abuse Potential; SOAPP-R, Screener and Opioid Assessment for Patients with Pain—Revised.

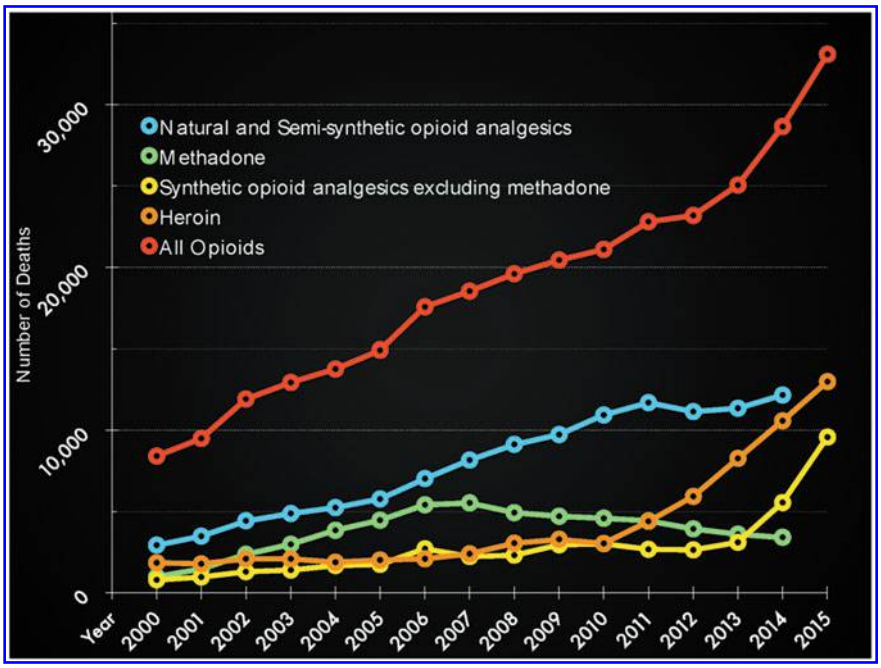

FIG. 2. Number of deaths related to opioids per year in the United States 2000–2015. CDC Wonder Data. Stratification based on opioid type: Natural and Semi-Synthetics (e.g., morphine, hydromorphone), Methadone, Synthetics excluding Methadone (e.g., fentanyl, carfentanil), Heroin, and All Opioids. CDC, Center for Disease Control.

should be given to the use of nonopioid and adjuvant analgesics for chronic pain in patients with cancer. The Guidelines note that, for patients who do not respond to these more conservative measures and have continued distress and impairment of function, a trial of opioids can be considered. While they are not effective for many conditions,[32] there is evidence to identify when opioids should and should not be used, even within the context of serious illness.[33] It is essential to consider metrics to evaluate the effectiveness of opioids, as well as the risks of their use, especially considering the current opioid epidemic.

Balancing the use and misuse of opioids

Determining if an opioid is effective and if a patient is using an opioid appropriately requires considerable vigilance and time.[34,35] While opioids can diminish suffering for those in pain, their abuse, misuse, and addiction potential (see Table 1 for definitions) can impact community and population health. Figure 1 provides an algorithm for a screening or a comprehensive assessment of pain and opioid use. The CDC has demonstrated that opioid-related deaths have been increasing over the past 10 years (Fig. 2) with much of the increase attributable to increasing opioid prescriptions. Currently, the estimation is that 3–20% of patients prescribed an opioid will be addicted.[2,36] However, rather than stigmatizing individuals who are susceptible to opioid addiction, monitoring and instituting a shared plan for aiding individuals who do become addicted is necessary.

Assessing the risk/benefit ratio of treating pain with opioids

Provider education of patients regarding the myriad risks of opioids is time consuming. The patient–provider relationship in American medicine has been affected by multiple forces, including managed care, medicine as a business, and shortened physician visits leading to quick decision making. Yet a shared decision-making model of medicine is paramount when it comes to the complex issue of opioid management. Assessing risk for opioid misuse can help providers understand how their patients may fare with potentially abusive and addictive substances. Guidelines suggest that clinicians take a ''universal precautions'' approach to minimize adverse consequences of opioid use[31] (p. 3339). The beneficial effects of opioids are important to note: improved function in activities of daily living, decreased pain severity, decreased pain interference, and improved quality of life. Clinicians must also recognize the risks of opioid therapy with an individual patient. Table 3 provides a checklist of opioid therapy risks. In addition, clinicians can use specific opioid risk screening tools to assess risk based on substance use history, general risk taking, and reward-seeking behavior. There are several screening tools specific to the assessment of risk in opioid management that can be incorporated into a community-based assessment of chronic pain and opioid use[37–39] (Table 4). Research is still needed on continued psychometric evaluation of these existing and newly developed instruments and the effects of their use in evaluating clinical outcomes.[40]

Determining Accountability for Quality Care: Selecting Pain and Opioid Metrics

Determining accountability for quality care of patients with serious illness who have chronic pain is complex. Selection of pain metrics is a context-dependent process depending on the patient's ability to report their pain; whether patients are in primary care, managed care, or residential care and; what type of data is required by health systems and

Table 3. Screening Tools for Opioid Misuse

Opioid Risk Tool.[48]	ORT	Brief self-assessment for patients with chronic pain being considered for opioid therapy. Tested on new patients treated in a pain clinic. Ten weighted risk items. Good sensitivity and specificity.
Screener and Opioid Assessment for Patients with Pain—Revised.[49]	SOAPP-R	Revised, shorter version of original (decreased from 142 to 24 items.) Intended for use with persons with chronic pain. Screens risk for aberrant medication-related behavior. Good reliability and validity.
Screening Instrument for Substance Abuse Potential.[50]	SISAP	Assesses risk of opioid dependency in those with substance abuse history. Contains five items. Good sensitivity and specificity. Used by primary care providers. Not validated by pain patients.
Current Opioid Misuse Measure.[51]	COMM	For pain patients already on long-term opioid therapy. Used to assess adherence to opioid prescribing. Tested on 277 patients with chronic noncancer pain. 17 items. Adequately measures aberrant behavior, excellent internal consistency, and test-retest reliability.

funding agencies to address their outcomes of interest. Quality outcomes of interest would include whether pain was identified through proper screening and comprehensive assessments and that the patient's relief from pain and their quality of life and functional capacity are improved with pain treatment.[31] Table 2 provides a grid of pain instruments that can be considered according to whether pain self-report is an option or whether proxy observation of patients' behaviors is required. Quality outcomes would include assessment of the appropriateness of pain treatment and treatment results. Ineffective or adverse results from treatment require accountability.

Table 4. Risks of Opioid Therapy (Check All That Apply)

- ☐ Worse Pain over time (Hyperalgesia)
- ☐ Respiratory Depression
- ☐ Risk of Death with Obstructive and/or Central Sleep Apnea
- ☐ Nausea
- ☐ Vomiting
- ☐ Constipation
- ☐ Hives (Urticaria)
- ☐ Tremors
- ☐ Potential Harm to Unborn or Newborn Baby (if breastfeeding)
- ☐ Itching (Pruritus)
- ☐ Impairment while Driving or Operating Heavy Machinery
- ☐ Drowsiness (Sedation)
- ☐ Sweating
- ☐ Weight gain
- ☐ Depressed mood
- ☐ Seizures
- ☐ Low Testosterone
- ☐ Irregular/Absent Menstruation
- ☐ Decreased Bone Density
- ☐ Withdrawals
- ☐ Potential for Addiction
- ☐ Potential for Abuse
- ☐ Inability to Control Pain with Increasing Doses of Opioid (Tolerance)
- ☐ Altered Mental Status (Delirium)
- ☐ Risk of others Using/Stealing your drugs
- ☐ Arrhythmia (specific opioids)
- ☐ Combination of Opioids with Other Sedating Medications (Benzodiazepines or Muscle Relaxants) or Alcohol increases other risks listed
- ☐ Sudden Death

Measures of accountability regarding the use and effectiveness of opioids must take the particular patient's situation in mind. Clinician concern about the use of opioids can sometimes depend on their estimates of the patient's life expectancy, being less concerned with patients in hospice settings and more concerned with patients who have a longer course of treatment. Nevertheless, clinicians' decision making regarding opioid use, especially with their attendant risks and ongoing monitoring of the balance of their effectiveness and risks, should be transparent. Table 4 suggests opioid risk tools that can be used on an ongoing basis for patients with chronic pain receiving opioids, to identify special needs. Identifying, intervening, and evaluating intervention results can improve accountability and quality care. Figure 1 offers an algorithm for screening patients' pain and opioid use while identifying instruments for consideration.

Conclusion

Accountability for high quality care for community-dwelling patients with serious illnesses requires selection of metrics that will capture the burden of chronic pain whose treatment may be enhanced or complicated by opioid use. Community-based care will need to be accountable through selection of, and attention to, appropriate pain and opioid metrics. Future research is warranted to identify, modify, or develop instruments that contain important metrics, demonstrate a balance between sensitivity and specificity, and, importantly, speak to the preferences of patients with serious illnesses.

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Original Article

Screening for Opioid Misuse in the Nonhospitalized Seriously Ill Patient

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Abstract

Background: Responding to an epidemic of opioid-related deaths, guidelines and laws have been implemented to promote safe opioid prescribing practices.
Objective: This study evaluates differences in screening practices and knowledge of laws between oncologists and cardiologists who prescribe opiates.
Design: Surveys regarding screening practices and knowledge of opioid prescribing laws were distributed in March 2017 to oncology and congestive heart failure (CHF) clinicians at the University of Virginia. Chi-square and Wilcoxon rank sum tests were used.
Results: Forty-six of 129 (35.6%) oncology providers and 7 of 14 (50%) CHF providers reported prescribing opiates in their clinic with usable survey results. The majority of oncology (65.22%) and cardiology (85.71%) providers report screening for substance abuse ''when indicated'' ($p = 0.053$). Only 19.6% of oncologists reported always using the prescription monitoring program (PMP), while 71.43% of cardiologists reported using it always ($p = 0.014$). Of the oncology providers, 66.67% report never using the urine drug screen (UDS), while 86.7% of cardiologists reported using it ''when indicated'' ($p = 0.0086$). Up to 34.78% of the oncologists and 57.14% of the cardiologists reported of never screening the family members for misuse ($p = 0.317$). Knowledge of laws was similar between groups, with 14.29% of cardiology and 17.39% of oncology providers reporting no knowledge of opioid prescribing laws ($p = 0.2869$).
Conclusions: Routine screening for substance misuse risk was uncommon for both groups, but cardiology providers were more likely to use the PMP or UDS. Knowledge gaps regarding Virginia laws were noted in both groups. Improved education regarding best practices and laws, as well as programs to promote screening, is needed for all providers.

Keywords: cardiology; misuse; oncology; opioid; screening

Introduction

In 2015, there were 33,091 deaths in the United States due to opioid-related drug overdoses, and opioid overdoses have quadrupled since 1999.[1] In 2016, 11.5 million people aged 12 or older misused prescription pain medications within the last year (4.3% of this age group), and an estimated 1.8 million had a prescription pain reliever use disorder. The most common reason for misuse was to relieve physical pain, reported in 62.3% of misusers.[2]

In response to this crisis, there have been increasing efforts to regulate opioid prescribing at the state and national level. These regulations generally include mandating the use of prescription drug monitoring programs, screening tools, and urine drug screens (UDSs) for at-risk populations. Almost all of them are focused on patients with chronic nonmalignant pain and actively exclude the cancer population from current laws. Pain, however, is one of the most common symptoms associated with cancer,[3] and the use of prescription opioids is the foundation of treatment for malignant pain.[4,5] Cancer patients are not exempt from opioid misuse and diversion behaviors, and this has been shown in prior studies.[6–8]

This study aims to show the differences in screening habits and knowledge of current laws and regulations between two university-based specialty prescriber groups—one that treats malignant pain and one that treats nonmalignant pain.

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Materials and Methods

We developed a survey to assess screening practices and knowledge of current laws for substance abuse and diversion in patients and their family members in an adult heart failure cardiology clinic as well as an adult oncology clinic (Appendix A1). These populations have relevance to the palliative care clinician given the life limiting nature of their diagnoses. At the University of Virginia, each of these clinics has imbedded palliative care presence.

The survey was designed and adapted with permission from a study by Blackhall et al.[9] Institutional Review Board (IRB) approval was obtained from the IRB for Behavioral Sciences, University of Virginia. Surveys were sent via SurveyMonkey to all physicians, nurse practitioners, physician assistants, and registered nurses associated with the University of Virginia Emily Couric Clinical Cancer Center clinics and Adult Heart Failure and Transplant clinic in March 2017. All physicians, nurse practitioners, and physician assistants surveyed have opioid prescribing privileges in their respective clinics. Two separate follow-up e-mail reminders were sent at 5- and 10-day intervals to those who had not yet completed the survey.

The survey's initial question identified whether opioids were prescribed within the providers' clinic. If respondents answered ''no,'' they were instructed not to continue participating in the survey. We then aimed to identify how often staff members screened for substance abuse or a history of drug diversion in either patients or their family/caregivers, including the use of urine drug tests or the Virginia Prescription Monitoring Program (PMP). We further ascertained whether providers could identify current legislation regarding prescription opioids, if staff received any mandatory training regarding substance abuse or prescription drug diversion, and if providers felt that substance abuse and/or prescription drug diversion is a problem in their clinic. Questions pertaining to screening use or frequency were answered ''never,'' ''when indicated/when provider feels it is appropriate,'' or ''routinely, all are screened.'' Those questions addressing the particular Virginia laws allowed respondents to choose one of two correct statements derived directly from the legislation, ''all of the above,'' ''none of the above,'' or ''I don't know the current laws.'' Respondents answered ''yes'' or ''no'' in response to whether staff members receive any mandatory training related to substance abuse or diversion, and via Likert scale (''strongly agree,'' ''somewhat agree,'' ''neither agree nor disagree,'' ''somewhat disagree,'' and ''strongly disagree'') to describe whether they felt that prescription drug abuse and/or diversion was a problem in their clinic.

At the time of this survey, the Commonwealth of Virginia mandated that every provider assess patients' risk for addiction and substance abuse, as well as document personal and family history of addiction, substance abuse, and diversion. Prescribers were required to obtain a UDS at initiation of opioid treatment, every three months for the first year, and at least every six months thereafter for the duration of treatment. The PMP was to be reviewed at least every three months while prescribing opioids. Written opioid contracts were also mandated. The aforementioned provisions were not required, however, if the opioids were prescribed to a patient receiving hospice or palliative care.[10]

Statistical analysis

To analyze the survey, we looked at responses stratified by oncology versus cardiology providers. We used chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. For all tests, differences were considered statistically significant at $p < 0.05$. Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

An invitation to participate in the survey was sent to 129 physicians, nurse practitioners, physician assistants, and registered nurses associated with the University of Virginia Emily Couric Clinical Cancer Center clinics (oncology), and 14 providers of the same disciplines associated with the University of Virginia Heart Failure and Transplant clinic (cardiology). These teams were chosen due to their regular contact with patients facing serious illness with a high likelihood of symptom burden, including pain.

Sixty-two of the 129 oncology providers responded, 5 indicated that their clinic did not prescribe opiates, while 11 were omitted because the respondent did not complete the survey, leaving 46 responses with completed surveys (35.6%). Of the 14 cardiology providers contacted, we received 11 responses; 3 providers indicated that opioids were

Table 1. Questions Addressing Screening for Opioid Abuse and Diversion in Patients

Question	*Response*	*Cardiology (%)*	*Oncology (%)*	p
How often does your staff screen for substance abuse in patients?	Never	0	6.5	0.5269
	When indicated	85.7	65.2	
	Routinely	14.3	28.3	
How often does your staff screen for diversion history in patients?	Never	16.7	15.6	0.9696
	When indicated	66.7	71.1	
	Routinely	16.7	13.3	
Do your patients routinely undergo UDS?	Never	14.3	66.7	0.0086
	When indicated	85.7	33.3	
	All patients	0	0	
Do you or someone in your clinic use the Virginia PMP?	Never	0	13.0	0.0138
	When indicated	28.6	67.4	
	Always	71.4	19.6	

PMP, prescription monitoring program; UDS, urine drug screen.

Table 2. Questions Addressing Screening for Opioid Abuse and Diversion in Family and/or Caregivers

Question	*Response*	*Cardiology (%)*	*Oncology (%)*	p
How often does your staff screen for substance abuse in family/caregivers?	Never	57.1	34.8	0.3170
	When indicated	28.6	58.7	
	Routinely	14.3	6.5	
How often does your staff screen for a history of prescription drug diversion in family/caregivers?	Never	28.6	43.5	0.5942
	When indicated	71.4	52.2	
	Routinely	0	4.4	

not prescribed, and 1 survey was omitted due to incompletion, leaving 7 responses total (50%).

Screening patients (questions 2, 4, 6, 7)

Only one-third (28.3%) of oncology providers whose clinics prescribe opiates routinely screen for substance abuse in patients, and 6.5% report never screening for substance abuse in patients at all (Table 1). Sixty-seven percent (66.7%) of oncology respondents report that they never use UDSs and 13.0% say they never check the Virginia PMP. A majority of oncology providers report screening for abuse (65.2%), diversion (71.1%), and use the PMP (67.4%) only ''when indicated'' or when the provider feels it is appropriate.

Seventy-three percent (72.7%) of cardiology providers reported prescribing opioids in their clinic. In contrast to the oncology group, there were no cardiology providers who never screen patients for abuse or never use the PMP. However, similar to oncologists, most cardiology providers (85.71%) report screening patients ''when indicated.'' Of all, 71.4% of cardiology providers reported using the PMP routinely for every patient, while most oncologists used it when indicated ($p=0.0138$). Most reported using the UDS ''when indicated'' or when the provider felt it appropriate, in contrast to the oncology group where most report never using it ($p=0.0086$).

Screening family/caregivers (questions 3, 5)

Screening for concerning behaviors in family members of patients was infrequent in both groups (Table 2). Over half of all cardiology providers (57.4%) and more than one-third of oncology providers (34.8%) reported never screening family/caregivers for substance abuse behaviors ($p=0.3170$). Similarly, close to one-third of cardiology providers (28.6%) and almost half of oncology providers (43.5%) reported never screening for diversion in family members or caregivers; the majority reported completing this only ''when indicated'' or the provider feels it necessary ($p=0.5942$).

Feelings toward drug abuse and diversion, knowledge of current laws, and frequency of mandatory training (questions 8, 9, 10)

On average, there was no difference between cardiology providers and oncology providers in the perception that substance abuse is a problem in their respective clinics ($p=0.0765$, with both groups tending to be in the neither agree nor disagree range on a Likert scale (Table 3). Knowledge of laws was similar between groups, with 14.3% of cardiology and 17.4% of oncology providers reporting no knowledge of opioid prescribing laws ($p=0.84$). However, only 34.8% of oncology providers were able to identify current laws correctly. Despite significant numbers reporting a lack of knowledge, 71% of cardiology and 61% of cancer providers reported no mandatory training in this area ($p=0.5913$).

Discussion

At our institution, almost all oncologists prescribe opioid medications for their patients. Despite their familiarity with opioid prescribing, these clinicians were less likely than cardiologists to screen for substance abuse and diversion, and less likely to use the PMP or UDS. Our data are consistent with other studies showing that UDS are used infrequently in cancer clinics.[6,11] Both UDS[12] and PMP[13] have been shown to be effective at mitigating trends toward rising opioid misuse and abuse. In addition, a recent study highlighted the effective application of UDS in cancer patients, indicating that 85% of those at high risk for opioid misuse had either a positive or inappropriately negative UDS.[14] Another study showed that UDS can be useful in patients with serious illness.[15]

One explanation for this difference in practice between oncology and cardiology providers is that the heart failure patient population falls into the category of nonmalignant pain, at which current laws and regulations for opiate prescribing are directed. However, after the completion of our data collection, the National Comprehensive Cancer Network published clinical practice guidelines for adult cancer pain.[16] They recommend including routine assessment of risk factors for aberrant use of pain medications at every initial patient evaluation with the use of screening tools such as the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) and Opioid Risk Tool (ORT), monitor for aberrant drug-taking behaviors, or evidence of diversion throughout the relationship with the patient, and to periodically review prescription drug monitoring program databases. While this is a pertinent step forward to protect patients with cancer, there must be laws put into effect that follow these important guidelines.

Table 3. Knowledge of Virginia Laws Surrounding Opioid Prescribing (Question 8)

Question	*Response*	*Cardiology (%)*	*Oncology (%)*	p
What are the Virginia laws surrounding the use of the Virginia PMP?	Incorrect answer or did not know	28.6	65.2	0.0765
	Correct answer	71.4	34.8	

Our results indicate that most providers rely on ''feeling it is appropriate'' to screen, but this practice is not well defined. Usually, if a provider feels it necessary to screen a patient or family member for abuse behavior or diversion, a suspicious incident has already taken place, and abuse or diversion events have likely already occurred. A universal approach to identifying patients with abuse risk and aberrant behaviors has been shown effective in nonmalignant chronic pain, and many have postulated that this is also effective in those with serious illness and chronic pain.[8] We agree that those treating malignant pain should consistently screen every patient at his or her initial visit to improve the safety of patients and their family members.

According to the most recent data from the National Survey on Drug Use and Health (NSDUH) published in 2017, more than half (53%) of opioid misusers obtained their pain medications from a friend or relative; specifically, 40.4% obtained them from a friend or relative for free, 8.9% bought them from a friend or relative, and 3.7% took them from a friend or relative without asking.[2] Most commonly, the friend or relative of the misuser obtained their medications from one health care provider.[17] In addition, the next largest group of misusers (37.5%) obtained pain medications via prescription from one health care provider, and only 6% of misusers reported buying pain relievers from a drug dealer.[2]

Cancer patients may have problems with substance abuse and may have friends or family members prone to misuse. At our institution, $\sim$45% of all opioids stronger than tramadol prescribed for more than two weeks were prescribed in the cancer center (unpublished data). Failure to institute safety measures for the use of opioids in this patient population may contribute to the opioid epidemic in this country.

While there are no existing statewide regulations surrounding opiate prescribing in patients with cancer or who are at the end of life, potential guidelines have been described.[6,8,14,16,18–20] We advocate for initiation of these practices in oncology clinics as well as supportive care and palliative care clinics across the country.

Nothing discussed in this article should be construed to suggest that oncologists or palliative care physicians should not prescribe opioids to patients with cancer-related pain. In this setting, appropriate use of opioids has been shown to reduce pain and improve quality of life, and failure to address cancer-related pain is and has been an important public health issue. However, if clinicians providing care for cancer patients do not develop and implement strategies for addressing substance abuse in the cancer population, we may find ourselves saddled with regulations not appropriate for this setting.

There are multiple limitations to our study. First, the cardiology group has a low number of participants, and therefore may not be generalized to the greater population. Heart failure specialist groups are usually a small subset of university-based cardiology departments, however, so our results are suggestive of trends in this expert faction. Second, our response rate in the oncology group is low at 35.6%. In addition, respondents may not always provide accurate answers and may overestimate the screening they provide. However, this means that the data we collected showing a low level of universal screening is likely an upper limit; the already low level of reported screening may be even lower than reported.

Those who treat chronic nonmalignant pain in patients with serious illness, who are also under the scrutiny of laws and regulations surrounding opioid prescribing, are more likely to understand the regulations and adhere to them, improving the safety of their patients. It is evident that we need more attention to the safe use of opioids in patients with cancer and others who are facing the end of life.

Author Disclosure Statement

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Appendix A1. Opiate Prescribing Survey

1. Does your clinic prescribe opiates to patients?
   Yes
   No—no need to continue this survey
2. How often does your staff screen for substance abuse (including alcohol) in patients?
   Routinely, all are screened
   When indicated/when provider feels it is appropriate
   Never
3. How often does your staff screen for substance abuse (including alcohol) in family/caregivers?
   Routinely, all are screened
   When indicated/when provider feels it is appropriate
   Never
4. How often does your staff screen for a history of prescription drug diversion in patients?
   Routinely, all are screened
   When indicated/when provider feels it is appropriate
   Never
5. How often does your staff screen for a history of prescription drug diversion in family/caregivers?
   Routinely, all are screened
   When indicated/when provider feels it is appropriate
   Never
6. Do your patients routinely undergo urine drug tests?
   Yes, all patients undergo routine urine drug tests
   When indicated/when provider feels it is appropriate
   No
7. Do you or someone in your clinic use the Virginia Prescription Monitoring Program (PMP)?
   Yes, PMP is used for all patients
   When indicated/when provider feels it is appropriate
   No
8. What are the Virginia laws surrounding use of the Virginia PMP?
   Any prescriber who is licensed in the Commonwealth to treat human patients and is authorized to prescribe controlled substances should be registered with the Virginia PMP.
   At the time of initiating a new course of treatment to a human patient that includes the prescribing of opioids anticipated at the onset of treatment to last more than 14 consecutive days, request information from the Director for the purpose of determining what, if any, other controlled substances are currently prescribed to the patient.
   All of the above
   None of the above
   I don't know the current laws
9. Does your staff receive any mandatory training regarding issues related to substance abuse and/or prescription drug diversion?
   Yes
   No
10. Substance abuse and/or prescription drug diversion is a problem in our clinic.
    Strongly agree
    Somewhat agree
    Neither agree nor disagree
    Somewhat disagree
    Strongly disagree

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Original Articles

Opioid Screening Practices in the Cancer Pain Patient

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Abstract

Background: Despite the growing use of opioids to treat cancer pain and the probability of opioid aberrancy in the cancer setting, clinical practice guidelines (CPGs) or recommendations for active screening and monitoring of opioid compliance are lacking.
Objectives: To evaluate the current practices and attitudes clinicians have toward monitoring and prescribing opioids in patients with cancer; to describe the current practice of screening and monitoring opioid compliance in the cancer setting; to provide insight into the role that CPGs may have in addressing opioid aberrancy in the oncologic population.
Hypothesis: Clinicians adopt diverse clinical practices and attitudes toward opioid screening and monitoring based on cancer status.
Design: A 24-question survey that evaluated the practices and attitudes that clinicians have when screening, monitoring, and prescribing opioids in patients with active cancer and history of cancer was completed by 105 pain management physicians. A comprehensive literature review was completed, evaluating the current state of available literature regarding opioid aberrancy and opioid risk in the cancer setting and CPGs for opioid monitor compliance in the cancer setting.
Setting: Multicenter, survey-based study to clinicians regarding pain management strategies in patients with active cancer, patients with a history of cancer, and patients with no history of cancer.
Results: Cancer status plays a role in the clinician's decision to screen and monitor opioid compliance in the oncologic population. For patients with active cancer, clinicians are more likely to prescribe opioids despite patient refusal for toxicology screen as well as history of substance abuse. For patients with no history of cancer, clinicians are more likely to refuse a prescription refill and eliminate opioids from treatment regimen.
Conclusions: Based upon the results of our study and evidence from current literature provided, the authors advocate for further investigation and development of CPGs to ensure the safe and prudent screening, monitoring, and prescribing of opioids in the oncologic population.

Keywords: cancer pain; clinical practice guidelines; compliance monitoring; opioid misuse, urine drug screening

Introduction

Pain is one of the most common symptoms reported in patients with cancer,[1] prevalent in ~50% of cancer patients undergoing chronic treatment and ~70% of cancer patients with advanced disease.[2] While cancer pain can vary significantly based on the primary site of the disease and the stage of disease,[2] most patients with cancer will require the use of opioids on a regular schedule to treat moderate and severe pain.[1,3,4] Debilitating treatment-related sequelae can necessitate the long-term use of opioid therapy for cancer survivors,[3] and even in cancer survivors who are 10 or more years past their cancer diagnosis, opioid prescribing is higher than in individuals with chronic, noncancer pain.[5] With the significant improvement in cancer remission rates during the past two decades,[6] the number of cancer survivors who are maintained on chronic opioid therapy has increased. Although many patients are initially managed by their primary care physician or oncologist, patients with more severe pain or those who require higher opioid doses are often referred to pain management specialists.[7]

Some cancer patients who report severe pain request increasing doses of opioids to cope with their psychological distress rather than their physical pain.[8] A recent review published by Carmichael et al. concluded that at least one in five patients with cancer may be at risk for an opioid-use

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disorder, and that the prevalence of opioid use-disorder risk is substantially higher among patients with cancer as compared with patients with no history of cancer.[9] Other studies have revealed that despite the use of screening tools to assess for risk of aberrant behavior before initiating opioids for treatment of cancer pain, opioid aberrancy still exists in the oncologic population.[10–15] A study published by Rauenzahn et al. reported that urine drug screening (UDS) aberrancies were common in ambulatory patients with cancer, and almost half of the patients tested were positive for nonprescribed opioids or potent illicit substances.[16]

The complexity of opioid use and misuse in the cancer setting is vast and encompasses medical, legal, psychological, financial, and ethical components. Clinicians have a dual obligation to ensure patients with cancer pain have access to opioid therapy and to guard from the public health risk that opioids can pose. Clinicians have been warned about the opioid epidemic, but at the same time, cancer pain remains undertreated in ~75% of patients with advanced cancer who experience moderate-to-severe pain.[17] This balance often requires a multidisciplinary approach consisting of primary care, oncologic, palliative, and pain management physicians who can ensure that the cancer-related pain is appropriately and adequately managed, while the risk of opioid misuse is judiciously and meticulously monitored and prevented.[3] This multidisciplinary approach is also effective in preventing burnout in individual clinicians who attempt to address the complexity of opioid management in the cancer setting alone.[3]

In recent years, international authorities, such as the National Institutes of Health (NIH), the National Cancer Institute (NCI), and the World Health Organization (WHO) have emphasized the importance of vigilant pain management strategies to ensure the proper use of opioids in patients with chronic pain,[18] but few guidelines and policies exist regarding the standardization of screening, monitoring, and prescribing opioids in the cancer setting. While the use of UDS as a diagnostic tool to guide pain management physicians' therapeutic decisions has been described in chronic noncancer pain, the use of UDS in patients with cancer pain has not been appropriately discussed. Similarly, while clinical practice guidelines (CPGs) exist on how to escalate opioid treatment in patients with cancer pain, these guidelines do not offer specific recommendations on how to actively screen and monitor opioid compliance for cancer patients and cancer survivors.

The authors hypothesize that clinicians adopt diverse clinical practices and attitudes toward opioid screening and monitoring based on cancer status due to the lack of CPGs that exist in the cancer setting. The aim of this study is to describe the current practice of screening and monitoring opioid compliance in the cancer setting, and to provide insight into the role that CPGs may have in addressing opioid aberrancy in the oncologic population.

Methods

This study was approved by the Memorial Sloan Kettering Cancer Center (MSKCC) Institutional Review Board and supported by MSKCC Support Grant (P30 Core Grant) as well as the Department of Anesthesiology & Critical Care.

A literature review was conducted using the Peer Review of Electronic Search Strategies (PRESS) 2015 guidelines to evaluate the current state of available literature regarding physicians' practices and attitudes in employing urine toxicology screens in patients with cancer and noncancer etiologies as well as opioid aberrancy and opioid risk in the cancer setting. Data were obtained from PubMed and EMBASE databases from inception to October 31, 2018 using MeSH terms: analgesics, opioid; cancer pain; substance abuse detection; practice guideline; and substance-related disorders. In addition, Google Scholar search engine was utilized to find gray literature. The quality of study, focusing on methodology and evidence, was evaluated by two reviewers using the GRADE system. Risk of bias, inconsistency, indirectness, imprecision, and publication bias were all used to guide reviewers. Any disagreements were resolved by consensus from a third independent reviewer.

A survey consisting of 24 questions was developed by investigators (see Supplementary Appendix A; Supplementary Data are available online at www.liebertpub.com/jpm) using a literature review and focus group to design the survey questions. The focus group was comprised of 12 pain management physicians who manage cancer pain. The clinicians were informed of the aims of the study and then divided into two groups and asked to review, modify, and/or challenge survey questions previously written by the authors. After a group discussion and consensus on survey questions, participants were also asked to form additional survey questions that they believed would help achieve the aims of the study.

All survey questions and answer choices were subsequently reviewed systematically by the authors so that the survey only included standard terms that are considered unambiguous to pain management physicians. Any term that may have been considered ambiguous was defined in the survey instrument. All survey questions were designed to collect data on three patient populations of interest: patients with active cancer, patients with a history of cancer, and patients with no history of cancer.

The survey included two sections; part one of the survey was created to better understand how pain management physicians employ urine toxicology screening in the three patient cohorts; part two of the survey was created to understand how pain management physicians prescribe opioids to the same three cohorts.

Numerical and/or ordinal scales were created with the goal of covering the full continuum of possible answer choices for each question. For questions in which more than one answer choice response was anticipated, respondents were given the option to include multiple answer choices. For questions in which alternative, nonlisted answers were anticipated, respondents were given the option to answer in a corresponding text box. A definition or reference frame was included in the question stem for all questions that required specific clarification.

The survey was delivered through electronic mail to 195 pain management physicians who were identified using a third-party service between July and August 2017. Physicians were identified through an electronic mailing list in which they self-identified as pain management specialists, and were invited to participate in the anonymous survey. Survey filters were used to further refine the study population so that only physicians who manage cancer pain were included. The inclusion criteria included physicians who currently specialize in pain management in the United States and actively manage

cancer-related pain. No limitations were placed on the length of time the physician has practiced cancer pain management or the type of training in pain management. An introduction and consent were included in the initial correspondence, which requested voluntary participation.

Statistics

Data were collected using online survey cloud-based software, and was analyzed by the investigators. Frequency distributions were calculated for all survey questions. For each question, chi-squared tests or Fisher's exact tests were used to test differences in rates of endorsement of answer choices regarding patients with active cancer, history of cancer, and no history of cancer. A p-value <0.05 was considered statistically significant. Analysis was performed in SAS version 9.4.

Results

Demographics

A total of 105 pain management physicians completed the survey (54.4% response rate). 72.1% of the responders were male, and 80.2% of responders noted formal training in cancer pain management. All 105 respondents had managed cancer pain as a part of their clinical practice, and a majority of responders were either <5 years or >20 years in practice. The average time to complete the survey was ~10 minutes (Table 1).

Screening practices

The clinicians who responded to the survey demonstrated variability in toxicology screening practices based on cancer status. Clinicians are three times less likely to require a toxicology screen for patients who have active cancer as compared with patients with a history of cancer and patients with no history of cancer (8.6% vs. 2.9% vs. 0%; p-value 0.004). All 105 physicians report using at least one type of toxicology screen for patient with no history of cancer; however, the same cannot be said for patients with active cancer and cancer survivors. Of the types of toxicology screens used, 93% of clinicians employ urine screens in their practice (vs. saliva or blood). For physicians who use more than one type of screen, cancer status does not play a role in their decision to use multiple types of screens.

Table 1. Physician Demographics (N=105)

Gender	
Male	72.1%
Female	27.9%
Years in pain management practice	
1–4 years	27.9%
5–9 years	18.6%
10–19 years:	20.9%
20+ years	32.6%
Have you had formal training in treating cancer pain?	
Yes	80.2%
No	19.8%
How frequently do you treat cancer pain?	
0% of patients	0%
Approximately 1–9% of patients	51.1%
Approximately 10–19% of patients	23.3%
Approximately 20–49% of patients	11.6%
50% or more of patients	14.0%

Before initiating opioid therapy, baseline toxicology screens are more often required in patients with no history of cancer and cancer survivors than in patients with active cancer (64.1% vs. 61.5% vs. 44.2%; p-value 0.043). Similarly, twice as many clinicians report ''never'' using a baseline screen in patients with active cancer as compared with patients with no history of cancer (9.6% vs. 4.9%; p-value 0.043).

For patients who refuse a toxicology screen, clinicians are almost twice more likely to refill a prescription without a completed screen for patients with active cancer than for cancer survivors or patients with no history of cancer (18.5% vs. 9.7% vs. 5.8%; p-value <0.0001). Similarly, while 92.2% of physicians endorsed that they would not refill an opioid prescription until the urine toxicology screen is completed for patients with no history of cancer, 68.0% of physicians noted that they would refill the prescription for patients with active cancer (p-value <0.001). Several clinicians noted (through free text boxes) that stage of cancer as well as the clinical scenario are also considered when deciding whether to refill the prescription.

Pain management physicians overall report feeling very comfortable managing pain caused by cancer and noncancer etiologies, although more clinicians report ''very comfortable'' if the patient's pain etiology is not due to cancer (85.9% vs. 79.8%; p-value <0.001). For patients with a history of substance abuse, clinicians are over four times more likely to report ''not comfortable'' in their treatment strategy if the pain is due to a noncancer etiology (21.5% vs. 5.3%; p-value <0.001). Of the physicians surveyed, more report ''doctor shopping'' on internet prescription monitoring programs in patients who have no history of cancer than in cancer survivors and patients with active cancer (65.7% vs. 38.1%; p-value 0.0003).

Prescribing practices

For patients who fail a toxicology screen, clinicians are twice more likely to prescribe a refill of opioid after a discussion about the importance of urine toxicology screen if the patient has active cancer as compared with if the patient has no history of cancer or is a cancer survivor (54.3% vs. 23.8% vs. 28.6%; p-value <0.0001). Similarly, physicians are nearly two times less likely to eliminate opioids from the treatment regimen if the patient has active cancer (26.7% vs. 48.6% vs. 50.5%; p-value 0.0005). One hundred percent of the physicians reported a reason to order a toxicology screen for patients with no history of cancer or patients who are cancer survivors, while the same cannot be said for clinicians caring for patients with active cancer.

While 83.9% of clinicians endorse that they would prescribe opioids to patients who have a history of substance abuse if they had active cancer, only 49.5% and 40.9% of clinicians endorses the same practice if the patient was a cancer survivor or had no history of cancer (p-value <0.0001). The same physicians surveyed are almost five times more likely to prescribe opioids to patients with active substance abuse if the patient has active cancer than if the patient is a cancer survivor or has no history of cancer (25.5% vs. 5.3% vs. 4.3%; p-value <0.0001).

Clinicians are more likely to prescribe sublingual tablets, sublingual spray, oral transmucosal lozenges, buccal tablets,

Table 2. Survey Questions with Significant Differences Regarding Patients with Active Cancer, History of Cancer, and No History of Cancer

Q2. Which toxicology screen do you use in your practice?
Urine; saliva; blood; more than 1
p-values >0.05
None
Active cancer: 9 (8.6%)
Cancer survivor: 3 (2.9%)
No history of cancer: 0 (0.0%)
p-value = 0.004

Q4. Do you require a baseline toxicology screen before initiating opioids?
Always
Active cancer: 46 (44.2%)
Cancer survivor: 64 (61.5%)
No history of cancer: 66 (64.1%)
Sometimes
Active cancer: 35 (33.7%)
Cancer survivor: 28 (26.9%)
No history of cancer: 28 (27.2%)
Rarely
Active cancer: 13 (12.5%)
Cancer survivor: 6 (5.8%)
No history of cancer: 4 (3.9%)
Never
Active cancer: 10 (9.6%)
Cancer survivor: 6 (5.8%)
No history of cancer: 5 (4.9%)
p-value = 0.043

Q11. For patients who refuse a toxicology screen, I:
Discuss the importance of a urine toxicology screen and prescribe refill without a completed screen
Active cancer: 19 (18.5%)
Cancer survivor: 10 (9.7%)
No history of cancer: 6 (5.8%)
Do not refill prescription until the urine toxicology screen is completed
Active cancer: 70 (68.0%)
Cancer survivor: 90 (87.4%)
No history of cancer: 95 (92.2%)
p-value <0.0001

Q12. For patients who fail a toxicology screen, I:*
Discuss importance of urine toxicology screen and prescribe refill
Active cancer: 57 (54.3%)
Cancer survivor: 30 (28.6%)
No history of cancer: 25 (23.8%)
p-value <0.0001
Eliminate opioids from treatment regimen
Active cancer: 28 (26.7%)
Cancer survivor: 53 (50.5%)
No history of cancer: 41 (48.6%)
p-value = 0.0005
Do not refill future prescriptions; Dismiss patient from practice; Refer patient to addiction medicine
p-values >0.05
**A toxicology screen is failed if the patient either (a) tested negative for the prescribed opioid, (b) tested positive for an opioid that was not prescribed, or (c) tested positive for other illicit substance(s)*

Q15. What is your reasoning for ordering toxicology screening?
It is a practice standard; Due to concerns about potential abuse; Due to concerns about potential diversion
p-values >0.05
Not sure
Active cancer: 5 (4.8%)
Cancer survivor: 0 (0.0%)
No history of cancer: 0 (0.0%)
p-value = 0.006

Q16. Do you prescribe opioids to patients who have a history of substance abuse?
Yes
Active cancer: 78 (83.9%)
Cancer survivor: 46 (49.5%)
No history of cancer: 38 (40.9%)
No
Active cancer: 15 (16.1%)
Cancer survivor: 47 (50.5%)
No history of cancer: 55 (59.1%)
p-value <0.0001

Q17. Do you prescribe opioids to patients who are active substance users?
Yes
Active cancer: 24 (25.5%)
Cancer survivor: 5 (5.3%)
No history of cancer: 4 (4.3%)
No
Active cancer: 70 (74.5%)
Cancer survivor: 89 (94.7%)
No history of cancer: 90 (95.7%)
p-value <0.0001

Q18. How would you describe your comfort level in treating pain caused by:
Cancer
Very comfortable: 75 (79.8%)
Somewhat comfortable: 17 (18.1%)
Not comfortable: 2 (2.1%)
Noncancer etiology
Very comfortable: 79 (85.9)
Not comfortable: 2 (2.2%)
Cancer in patient with history of substance abuse
Very comfortable: 44 (46.8%)
Somewhat comfortable: 45 (47.9%)
Not comfortable: 4 (5.3%)
Noncancer etiology in patient with history of substance abuse
Very comfortable: 45 (48.4%)
Somewhat comfortable: 28 (30.1%)
Not comfortable: 20 (21.5%)
p-value <0.0001

Q19. Do you prescribe Transmucosal Immediate-Release Fentanyl to your patients?
Sublingual tablet
Active cancer: 15 (14.3%)
Cancer survivor: 5 (4.8%)
No history of cancer: 3 (2.9%)
p-value = 0.003
Sublingual spray
Active cancer: 13 (12.4%)
Cancer survivor: 5 (4.8%)
No history of cancer: 2 (1.9%)
p-value = 0.006
Oral transmucosal lozenge
Active cancer: 23 (21.9%)
Cancer survivor: 6 (5.7%)

(*continued*)

TABLE 2. (CONTINUED)

No history of cancer: 4 (3.8%)
p-value <0.0001
Buccal tablet
Active cancer: 18 (17.1%)
Cancer survivor: 7 (6.7%)
No history of cancer: 3 (2.9%)
p-value = 0.0008
Buccal soluble film
Active cancer: 11 (10.5%)
Cancer survivor: 5 (4.8%)
No history of cancer: 2 (1.9%)
p-value = 0.024
Nasal spray
Active cancer: 11 (10.5%)
Cancer survivor: 4 (3.8%)
No history of cancer: 1 (1.0%)
p-value = 0.006
None
Active cancer: 62 (59.1%)
Cancer survivor: 83 (79.1%)
No history of cancer: 87 (82.9%)
p-value = 0.0001

Q20. Have you experienced any of the following situations of misconduct with your patients?
Abnormal toxicity screen
Active cancer: 71 (67.6%)
Cancer survivor: 77 (73.3%)
No history of cancer: 89 (84.8%)
p-value = 0.014
Doctor shopping on I-STOP
Active cancer: 40 (38.1%)
Cancer survivor: 58 (55.2%)
No history of cancer: 69 (65.7%)
p-value = 0.0003
Opioid hyperalgesia; difficulty weaning opioid once in cancer remission
p-value >0.05

Q22. Are the following treatments/therapies offered to treat pain?
Opioids
Active cancer: 92 (87.6%)
Cancer survivor: 83 (79.1%)
No history of cancer: 77 (73.3%)
p-value = 0.034
Implantable devices (i.e., spinal cord stimulator)
Active cancer: 66 (62.9%)
Cancer survivor: 82 (78.1%)
No history of cancer: 86 (81.9%)
p-value = 0.004
NSAIDs and/or acetaminophen; antiepileptics; antidepressants; intrathecal infusion therapy; alternative, nonpharmacologic therapies (i.e., acupuncture, physical therapy, massage therapy)
p-value >0.05

NSAID, nonsteroidal anti-inflammatory drug.

buccal soluble film, and nasal spray to patients with active cancer than to patients with a history of cancer or no history of cancer. In addition, clinicians are more likely to offer opioids in the treatment plan to patients with active cancer than to patients with a history of cancer or patients with no history of cancer (87.6% vs. 79.1% vs. 73.3%; *p*-value 0.034). Interestingly, physicians are more likely to offer implantable devices such as spinal cord stimulators to patients with no history of cancer than to patients with a history of cancer and patients with active cancer (81.9% vs. 78.1% vs. 62.9%; *p*-value 0.004) (Tables 2 and 3).

Discussion

The current study sought to build upon previous works that have investigated opioid aberrancy and opioid risk in the cancer setting, as well as CPGs for opioid monitoring compliance in the cancer setting. Data from this study provide evidence that there is variability among clinicians' clinical practice and attitudes toward opioid screening, monitoring, and prescribing based upon cancer status. Our results demonstrate that cancer survivors were managed differently than patients with active cancer; patients who are cured of cancer have different opioid monitoring, screening, and prescribing strategies than those patients who are currently living with incurable cancer or advanced cancer. While life expectancy was not examined as a possible factor in clinicians' decision making, this may also play a role in daily clinical practice.

The variability in clinical practice is likely a result of the lack of CPGs that exist when screening and monitoring opioids in the oncologic population.[16] Before establishing CPGs for the safe and prudent screening and monitoring of opioids in the cancer population, it is important to acknowledge previous key studies that have investigated opioid aberrancy and opioid risk in the cancer setting. By better understanding the risk factors for opioid aberrancy in the oncologic population, we can more effectively develop guidelines that can be used in clinical practice.

Opioid aberrancy and opioid risk in the cancer setting

In 2016, Carmichael et al. published a review that evaluated the current state of literature regarding opioid abuse and misuse in patients with cancer.[9] Thirty-four case studies, case series, retrospective observational studies, and narrative reviews were included in the review. The authors concluded that at least one in five patients with cancer may be at risk for an opioid-use disorder, and that the prevalence of opioid-use disorder risk is substantially higher among patients with cancer.[9] In addition, patients with specific cancer types that are related to tobacco and alcohol abuse, such as lung, esophageal, and head and neck cancers, are at even greater risk for opioid-use disorders.[19] While policies for screening patients for opioid misuse and abuse are routinely absent,[9] current evidence supports the need for assessing opioid risk in cancer patients. Of note, only 3 of the 34 clinical studies discussed the use of UDS in cancer patients.[11,20,21]

Three studies investigated the associated risk factors for opioid aberrancy in cancer patients. Kwon et al. completed a prospective, observational study to determine the risk predictors of opioid-related ''chemical coping'' among patients with advanced cancer.[10] The authors concluded that ~18% of the patients used opioids or other medications in a nonprescribed way to cope with various illness-related stresses. Interestingly, <25% of the patients found to be ''chemical coping'' had documentation of such aberrant behavior in their medical record. CAGE-positivity and younger age,

among other factors, were associated with a higher likelihood of chemical coping. Similarly, Arthur et al. completed a retrospective chart review to determine the factors associated with UDS test ordering in patients with cancer.[22] The authors observed that only 6% of patients underwent urine drug testing, and that younger age and CAGE positivity were considered significant predictors of urine drug testing ordering. A 2014 retrospective chart review by Barclay et al. examined the frequency in which risk factors for opioid aberrancy—such as substance abuse, diversion, and abnormal drug screens—exist in the cancer setting.[11] The authors noted that while opioids can be effective treatments for cancer-related pain, there is substantial risk for opioid abuse in the cancer population and, therefore, screening tools such as the Opioid Risk Tool (ORT) should be used to balance risk mitigation and treatment strategies.

Risk screening tools

The ORT and the Screener and Opioid Assessment for Patients (SOAP) tool are two self-reporting screening tools that can help clinicians assess for risk of aberrant behavior before initiating opioid therapy for cancer pain. Several studies exist that utilize these opioid risk screening tools to assess risk of opioid aberrancy in cancer patients. Koyyalagunta et al. utilized the SOAP tool to risk stratify opioid misuse among patients with cancer pain.[12] After reviewing over 500 patient charts, the authors concluded that patients classified as high risk by SOAP were generally younger, had comorbid depression and anxiety, and had higher morphine equivalent daily doses. Similarly, a retrospective analysis by Ma et al. made use of the ORT to risk stratify opioid misuse in cancer patients; the most common patient risk factors associated with opioid misuse were a history of depression and family history of alcohol abuse.[13]

Substance abuse and opioid risk

As seen in the studies by Koyyalagunta et al. and by Ma et al., comorbid psychiatric illness can play a significant role on the risk of opioid aberrancy in cancer patients. Comorbid substance abuse has also been studied as a risk factor for opioid misuse and abuse. Parsons et al. analyzed 665 patient charts to investigate the frequency of patients who screen positive for alcoholism in a palliative care outpatient clinic.[14] The authors concluded that patients who were CAGE positive were more likely to be on opioid therapy. Bruera et al. showed a similar finding in their retrospective study, noting that alcoholism is highly prevalent and underdiagnosed among terminally ill cancer patients.[15]

CPGs for opioid monitor compliance in the cancer setting

CPGs for the safe initiation and escalation of opioids in managing cancer pain have been published by various international societies and organizations. In 1986, the WHO created an analgesic ladder for cancer pain that provided clinicians with a step-wise approach to opioid prescribing, and in 1996 the WHO updated their prescribing guidelines.[23,24] Despite offering detailed recommendations regarding opioid prescribing practices, both the 1986 and 1996 guidelines drafted by the WHO lacked recommendation on opioid compliance monitoring.

Table 3. Survey Questions with No Significant Differences Regarding Patients with Active Cancer, History of Cancer, and No History of Cancer ($N = 106$)

Q1. Do you require a toxicology screen to monitor opioid compliance?
Q3. Does the toxicology screen you employ test only for the opioid you prescribe or does it also include other opioids and illicit drugs?
Q5. For a patient with NO history of substance or chronic opioid use, how frequently do you have the patient complete a toxicology screen to monitor compliance?
Q6. For a patient with a history of substance or chronic opioid use, how frequently do you have the patient complete a toxicology screen to monitor compliance?
Q7. When monitoring a patient's compliance with a toxicology screen, do you schedule it (patient is given advanced notice) or is it random (patient is not given advanced notice)?
Q8. What method do you use to decide when to screen your patient?
Q9. Are patients directly observed as they urinate for the urine toxicology screen?
Q10. Do you require a toxicology screen before every opioid refill?
Q13. For patients who fail a toxicology screen due to nonmedical cannabis use, I (do not refill future prescriptions; discuss importance of urine toxicology screen and prescribe opioid refill; dismiss patient from practice; eliminate opioids from treatment regimen; refer patient to addiction medicine)
Q14. Do you use a psychometric screening tool to risk stratify a patient's potential for opioid abuse?
Q21. Before prescribing opioids, are concerns about treatment side effects, dependence or tolerance discussed with your patients?

In 2012, guidelines introduced by the European Society for Medical Oncology (ESMO) outlined recommendations on cancer pain assessment, opioid escalation, and opioid side effect management.[25,26] This CPG, like earlier ones set forth by the WHO, did not define specific recommendation on opioid compliance monitoring in the cancer setting. In the same year, the European Association for Palliative Care (EAPC) updated their consensus guidelines regarding the use of opioids to treat cancer pain.[27] These guidelines, comprised of 16 evidence-based recommendations, provided guidance on initiating and titrating opioids for the treatment of cancer pain, but did not address the subject of opioid screening and monitoring.

In 2016, both the American Society of Clinical Oncology (ASCO) and the Centers of Disease Control (CDC) published CPGs regarding opioid treatment strategies. ASCO's guidelines centered on the use of opioids to manage chronic pain in adult cancer survivors.[28] This CPG noted that ''clinicians should incorporate a universal precautions approach to minimize abuse, addiction, and adverse consequences of opioid use'' and that tools such as urine drug testing are available and may mitigate risk. The CDC's ''Guideline for Prescribing Opioids for Chronic Pain'' also provided recommendations surrounding opioid prescribing practices for the treatment of chronic pain, but noted that their recommendations set forth

were not intended for patients who are in active cancer treatment, palliative care, or end-of-life care.[29] Both 2016 CPGs were not meant for patients with active cancer, and both omitted information regarding opioid compliance monitoring.

The National Comprehensive Cancer Network's 2017 ''Guidelines for Adult Cancer Pain'' advocated for the routine monitoring of abnormal patterns of opioid use that may suggest misuse or abuse.[30] While the NCCN guidelines recommend that prescribers make use of state prescription drug monitoring programs if available and consider the use of urine drug testing to document opioid adherence and screen for aberrant behavior, the guidelines lack specific instruction on exactly when and for which patients it would be appropriate to consider screening. The guidelines also note that prescribers should utilize risk factor screening tools, such as SOAP and ORT, and that the Food & Drug Administration is currently responding to the public health crisis of addiction, misuse, abuse, overdose, and death by establishing Risk Evaluation and Mitigation Strategy (REMS) programs for all patients receiving opioids analgesics.

To date, CPGs that identify specific recommendations for the active screening and monitoring of opioid compliance in the cancer setting do not exist.

Integral and interdependent strategies to mitigate opioid misuse in the cancer setting

UDS plays an integral role in monitoring for opioid aberrancy and is an important method to apply in clinical practice. If opioid misuse is diagnosed, clinicians can make informed decisions regarding possible alterations of pain management strategies and can enlist the guidance of an addiction specialist. However, drug screening is not the only solution to this complex problem and there are other interdependent strategies physicians can use to mitigate opioid misuse in the cancer setting. As in chronic, noncancer pain, universal screening through risk assessment tools and a thorough patient history that includes the use of a prescription-monitoring database is vital. Opioid management plans, opioid contracts, and comprehensive patient education on the risks and benefits of opioid use can also mitigate the risk opioid misuse. Close follow-up with continual vigilance and reassessment for aberrant behaviors is critical. If opioid aberrancy occurs, prompt referral to an addiction specialist is essential. A multidisciplinary approach consisting of primary care, palliative care, and psychiatric physicians can provide support to the patient and guide further management plans.

Limitations

A limitation in this study is the population of the survey that includes physicians who self-identify as pain management specialists but does not include other clinicians, such as primary care physicians, palliative care physicians, oncologists, and surgeons, who often initially manage cancer pain. Similarly, the type of formal training—whether fellowship-trained or otherwise—was not specified by the respondents. The aim of the study, to establish if there exists standard practice when screening and monitoring opioids in the cancer setting, did reach statistical significance even among pain management specialists trained in managing cancer pain. The authors believe that the results are generalizable and valuable to clinicians who do not have specialized training in pain management as the general principles of opioid screening are applicable to all physicians. In the future, the authors would like to extend the survey to primary care physicians, palliative care physicians, oncologists, and surgeons to investigate how these specialists screen and monitor opioid compliance in treating cancer pain.

Another study limitation is the 54.4% response rate, which may increase the likelihood of nonresponse bias, or error resulting from differences between those who respond to a survey and those who do not respond to a survey. However, this response rate is likely underestimated, as many physicians who received the survey do not manage cancer pain and did not complete the survey as they self-identified themselves as unsuitable candidates for the survey. In total, 105 of the 195 physicians completed the survey, allowing statistical significance to be assessed for all survey questions. Similarly, while the sample of 195 physicians is relatively small in comparison to the total number of pain physicians practicing in the United States, the sample size was large enough to detect statistically significant differences in responses regarding the three cohorts of patients.

Future directions

Based upon the results of our study as well as evidence from current literature, the authors advocate for the development of CPGs to help guide clinicians' therapeutic decisions when treating cancer pain. Certain populations, such as cancer patients with advanced disease and comorbid opioid use disorder, may require specific opioid monitoring guidelines. Investigation into the clinical practices and attitudes that primary care physicians and oncologists have when screening and monitoring opioids may provide further insight into the role that CPGs have in addressing opioid aberrancy in the oncologic population.

To better understand the complexity of opioid use and misuse in the cancer setting, further research into the potential barriers of implementing strategies to mitigate opioid misuse is needed. Considering that a multidisciplinary approach can be beneficial to both the patient and the clinician managing the cancer pain, further insight into the obstacles of instituting this multidisciplinary approach is warranted. In particular, research that can further elucidate specific practices clinicians can employ to confront opioid misuse can help clinicians cultivate and maintain safe opioid prescribing and monitoring techniques in clinical practice.

In the future, the authors would also like to investigate how clinicians employ urine drug testing when deescalating opioid therapy in cancer survivors. This information is critically needed, as remission rates continue to improve and increasingly more patients who once required opioids to control their pain are being titrated off chronic therapy. The authors are currently investigating international regional differences in opioid monitoring practices in the cancer setting to gain better insight into how regional and cultural differences may affect compliance monitoring. Future research into the cost effectiveness of different types of UDS may also help guide physicians on which screening tools to use in their practice.

Conclusion

For patients with active cancer, clinicians are more likely to prescribe opioids despite patient refusal for toxicology screen

and history of substance abuse. For patients with no history of cancer, clinicians are more likely to refuse a prescription refill and eliminate opioids from treatment regimen. The authors advocate for further investigation and development of CPGs to ensure the safe and prudent screening, monitoring, and prescribing of opioids in the oncologic population.

Author Disclosure Statement

No competing financial interests exist.

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