

Narrative Review

 **Opioids in the Management of HIV-Related Pain**

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Background: Human Immunodeficiency Virus (HIV) patients have an increased rate of chronic pain, particularly peripheral neuropathy. This disease burden causes considerable disability and negatively affects quality of life. Pain is undertreated and more complex to manage in these patients for a number of reasons, including complex anti-retroviral drug regimens, higher risks of side effects, and higher rates of comorbid psychiatric illness and substance abuse. Pain management must take these factors into account and use all available modalities, including nonopioid pain relievers, adjuvant medications, and psychosocial therapies in addition to opioid analgesics. Here we review recent recommendations regarding acute and chronic opioid treatment of pain and the treatment of opioid dependence in HIV-infected patients, and provide suggestions regarding aberrant behavior in pain treatment.

Objectives: The objective of this comprehensive review is to assess and summarize the complicating factors involved in treating HIV patients' pain with opioid analgesics.

Study Design: This is a narrative review without a systematic quality assessment of the literature discussion.

Methods: A comprehensive review of the literature relating to pain and pain treatment in HIV patients. The literature was collected from electronic databases, textbooks, and other sources. The scientific literature reviewed includes randomized trials, observational studies, systematic reviews, guidelines, and government reports.

Results: This patient population is heterogeneous and diverse in their medical issues and comorbidities, but a systematic, stepwise approach to assessing and managing pain in HIV patients is described. Chronic opioid treatment has proven to be problematic and considerations and alternatives to this treatment are described. Management of pain in patients with opioid addiction, a frequent comorbidity of HIV infection, requires special awareness and different prescribing practices. Screening and identifying patients who are at special risk for developing medical or behavior complications of pain treatment is essential, and approaches to this, and common forms of aberrant behavior, are described.

Limitations: The scientific literature on opioid treatment in this population is limited. The population of HIV patients is heterogeneous and differs in significant ways based on ethnicity, national origin, and mode of transmission, making it difficult to generalize about pain treatment in such a diverse group.

Conclusions: Pain management in HIV patients must take these factors into account and use all available modalities for treatment, including nonopioid analgesics, adjuvant medications, and psychosocial therapies. Opioid analgesics should be prescribed with caution in accordance with current guidelines and after careful risk assessment.

Key words: HIV, Human Immunodeficiency Virus, acute pain, chronic pain, psychiatric comorbidity, opioid dependence, opioids, chronic opioid therapy, substance abuse.

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The treatment of Human Immunodeficiency Virus (HIV) infection has changed dramatically. With new treatments, HIV has become a chronic disease and HIV patients in developed countries have a nearly normal life expectancy when given access to adequate treatment(1). With this change has come a renewed focus on comorbidities and quality of life in HIV. Chronic pain is common in the general population and has increased incidence in HIV patients, with multiple HIV-related conditions raising risks of pain disorders. Estimates of the prevalence of pain in HIV-infected individuals vary from 30% to 90% with prevalence increasing in later stages of the illness. In 1997, Larue et al (2) found that 30% of outpatients and 62% of inpatients with HIV reported HIV-related pain, and that the severity of this pain was significantly underestimated by physicians providing HIV care. The largest nationwide study of HIV patients, the HIV Cost and Services Utilization Study (HCSUS), included pain as one subscale of the SF-36, a widely used instrument to assess health-related quality of life. Using this data, it was calculated that 67% of the sample reported experiencing at least some pain in the week prior to the survey (3). An Italian study of patients with HIV showed that 60.8% had pain complaints, the mean number of pains reported was 1.33, and that head pain was most common, followed by legs, abdominal, and chest pain (4). These findings correlate with a more recent HIV study done in India which showed that 66.7% of inpatients and 24.5% of outpatients complained of pain. This discrepancy may be related to the fact that many more of the inpatients were in Stage 3 or 4 of HIV (90% vs. 40%). The primary pain sites were listed as the head, legs, and back (5). In a study of pain in indigent HIV patients, fully 91.2% reported pain, with 53.7% rating their pain as severe (6). The most frequent locations for pain in this population were calves, legs, and lower back (6).

Pain conditions in HIV patients can be divided into 3 major categories, which frequently coexist: pain unrelated to HIV, such as discogenic back pain; pain related directly to HIV, such as HIV neuropathy, opportunistic infections, and Kaposi sarcoma; and pain secondary to HIV treatments, such as neuropathy due to antiretroviral therapy or chemotherapy. In a study from 1997, Hewitt et al (7) attempted to determine the etiology of pain complaints in ambulatory AIDS patients and found that 24% of the complaints resulted from unrelated pre-existing conditions, 30% resulted from HIV-related conditions, and 4% due to HIV treatments, while etiology was

unknown in 37% of pain complaints. A recent study by Merlin et al (8) showed that 61.9% of HIV patients in an academic medical center HIV clinic sample complained of pain. Pain was statistically more likely in patients with either substance abuse or psychiatric illness.

Pain can affect people with HIV at any point in the course of their illness, with more severe illness and poorer health being associated with more pain (3). Patients with more pain also utilized outpatient medical services more heavily (3). Further, people with HIV who have co-morbid substance abuse issues have increased pain symptoms (9). And even when these patients get pharmaceutical pain treatment, they are still likely to report persistently high levels of pain, suggesting that current pain management strategies are inadequate in this population (10).

Peripheral neuropathy in particular has been found to be prevalent in HIV patients and is associated with disability and lower quality of life (11). Peripheral neuropathy is the most common neurological complication of HIV infection. In a recent study of HIV patients in the USA and Puerto Rico, 44% of participants reported peripheral neuropathy symptoms (12). This syndrome commonly presents as slowly progressive numbness, tingling, and burning sensations which start symmetrically in the feet (13). It is important to distinguish neuropathic pain from other etiologies since neuropathic pain may respond better to adjuvant medications such as tricyclic antidepressants, gabapentin, pregabalin, or carbamazepine (14). Topical anesthetic or capsaicin patches have also been shown to be helpful in some patients (13). The mechanism of HIV neuropathy is complex, but is thought to include direct injury to peripheral nerves by the HIV virus, viral activation of perineural macrophages, and in some patients there is likely a component of medication-induced neuropathy from antiretroviral agents (ARVs) (15).

Other common pain syndromes include pain due to widespread Kaposi sarcoma, headache, abdominal pain, joint pain, and myofascial pain. The epidemiology of pain in HIV is complex, however pain is thought to be more common in women (16). While pain is reported to be less common and less severe in African-American HIV patients, (3) a recent study suggests that these patients are more likely to be suspected by health care providers of opioid misuse (17). It has been suggested that both women and non-White patients may be at higher risk for under-treatment of their pain (16,18).

Highly Active Antiretroviral Therapy (HAART) has revolutionized the treatment of HIV infection; howev-

er, it has also introduced a host of new complications to the medical management of these patients. ARV medications work best when taken on an absolutely regular schedule, thus preventing the development of drug resistance. These medications may require complex regimens of multiple dosing per day, and have numerous and complex interactions with each other and with other medications. As many HIV patients have co-morbid medical or psychiatric illnesses, they may be on long lists of medications with unpredictable interaction risks.

It is important to distinguish between the effects that ARVs have on pain medications and vice versa. Prescribing a medication which interferes with ARVs may have no visible effect, but lead to treatment failure; while interference with pain medicines may lower the effective dose, leaving the patient with untreated pain, or increase the blood levels, risking catastrophic side effects (19).

Opioids remain an essential element of pain treatment, but bring a complex set of issues and risks with them. Side effects such as nausea, vomiting, sedation or pruritus are common, but severe adverse effects were previously believed to be rare (20). However, according to the National Survey on Drug Use and Health in 2006 (21), medication misuse has increased steadily, particularly among young people aged 18-25, with more people over age 12 starting to misuse pain relievers than any other substance, including cannabis (22). The majority of these medications were obtained by a friend or relative from their physician (22). Medication overuse and misuse remain particularly prevalent among patients with a past substance abuse history (10); striking increases in morbidity and mortality were noted as being associated with opioid use. One study by Paulozzi (23) demonstrated a 91% increase in opioid poisonings from 1990 to 2002; it further documented that methadone-related deaths tracked an increase in the use of methadone as an analgesic, not as methadone maintenance. A follow-up report covering the years 2004-2008 that was based on data from the Drug Abuse Warning Network of emergency department reports, found that oxycodone, hydrocodone, and methadone continue to be highly implicated in overdoses (24). A history of mental health and substance abuse problems is a risk factor for starting and continuing opioid treatment (25).

METHODS

We conducted an electronic literature search using the PubMed and Medline databases to identify articles published during the 10-year period between 2000 and

2010 using the following keywords: "HIV and opioid therapy," "HIV-related pain and opioids," and ancillary search terms including "pain management," "pain treatment," and "aberrant behavior." The search also included the terms "opioids and pain therapy" with the name of each condition requiring chronic treatment. Articles were included if they pertained to chronic or acute pain in the setting of HIV infection. Using this process, we selected over 1,000 articles for abstract review, of which 324 merited further review. Additional articles were found from the references in these reviewed articles and from a review of the Cochrane Review and the UpToDate database. We selected a smaller subset of articles that not only discussed the complexities of pain treatment in this population, but also presented evidence in support of specific treatment approaches.

Interactions between ARVs and Opioids

Opioids and ARVs can interact to cause changes in either ARV or opioid blood levels, potentially affecting efficacy and toxicity. These interactions are complex and have been summarized below (Table 1). Opiates (opioids derived from opium poppies, including heroin, morphine, and codeine), are unlikely to cause changes in ARV blood levels (19). Heroin is converted by esterases in the plasma to morphine, and both morphine and codeine are metabolized by glucuronidation. Ritonavir, which can stimulate glucuronidation, can cause acute drops in morphine levels and provoke withdrawal (26). However, synthetic opioids, which are generally metabolized using the P450 enzyme system, carry higher risks. For example, oxycodone, used in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen and in long-acting formulations such as Oxycontin, is metabolized by CYP2D6. Therefore, its effective blood level may change when a CYP2D6 inhibitor such as ritonavir is added or stopped. Hydrocodone, also commonly used for pain, is metabolized by both CYP2D6 and CYP3A4. There is a theoretical risk of CYP2D6 inhibition triggering withdrawal symptoms, but has not been reported clinically.

Methadone is commonly used as a long-acting pain medication for chronic pain and has a role in treating opioid dependence. It is a long-acting μ -opioid receptor agonist. Methadone has a nonlinear dose-response curve and complex interactions, and should generally be managed by experienced clinicians. Methadone is metabolized via CYP 3A4, CYP2B6 and CYP2C19 as well as CYP2D6. Methadone levels can be influenced

Table 4. Analgesic medications and clinically significant interactions with ARVs.

| Medication | Level Affected | Effect on ARV | Management |
|-------------------|--|--|---|
| Nonopioids | | | |
| Acetaminophen | | Increased doses of atazanavir and rilpivarin | No adjustment needed |
| NSAIDs | | | Avoid piroxicam with ritonavir or indinavir |
| Celecoxib | | May increase efavirenz level | May raise risk of renal injury with tenofovir |
| Amitriptyline | Increased by ritonavir | | Use decreased dose of amitriptyline, monitor for side effects |
| Cannabis | | Decreases atazanavir levels | Monitor clinical response |
| Lamotrigine | Decreased by lopinavir/ritonavir | | May need to increase lamotrigine dosage |
| Gabapentin | No direct interaction, but antacid in didanosine decreases gabapentin absorption | | Stagger didanosine and gabapentin dosing |
| Pregabalin | | | |
| Opioids | | | |
| Tramadol | Metabolized to active drug by 2D6, hence less effective when given with ritonavir | | Use alternate medication |
| Codeine | | | |
| Morphine | May be decreased by ritonavir, indinavir | | Monitor for signs of withdrawal |
| Oxycodone | May be increased by ritonavir | | |
| Hydrocodone | May be decreased by ritonavir | | Monitor for withdrawal, rarely seen clinically |
| Buprenorphine | Mild decrease with efavirenz | | |
| | Ritonavir, indinavir and iquinavir: potential increase (3A4 inhibition) | | Monitor for sedation |
| | Increase with atazanavir, delavirdine | | Monitor for sedation |
| Methadone | Efavirenz and nevirapine can lower levels by 50% | | Monitor for withdrawal |
| | Etravirine causes minor decrease in methadone level | | |
| | Lopinavir/ritonavir and darunavir/ritonavir cause decrease in level with 2 week lag time | | |
| | | Stavudine: decreased absorption | |
| | | Zidovudine: increased levels | |
| | | Didanosine: decreased levels | |

by numerous ARVs, particularly those in the nonnucleoside reverse transcriptase inhibitor class, including efavirenz, nevirapine, and etravirine (27). Efavirenz and nevirapine can reduce the area under the curve (AUC) for methadone by over 50%, resulting in acute opioid withdrawal and the need for increased dosing. Etravirine causes a measurable decrease in methadone activity that is not usually clinically significant.

Protease inhibitor (PI) ARVs are known to act as inhibitors of CYP3A4 in vitro, but have been found to decrease methadone levels in vivo. Both the combinations of lopinavir/ritonavir and of darunavir/ritonavir have been shown to significantly reduce the AUC of methadone and cause withdrawal symptoms (28,29). As this response is not consistently predictable, and usually takes 2-3 weeks to manifest since P450 enzymes

must be synthesized, it is usually recommended to wait for clinical changes before adjusting methadone doses. However, if the inducing agent is stopped suddenly, the patient is at risk of overdose with methadone since blood levels may rise precipitously. Methadone can also affect blood levels of some old ARVs, such as the nucleoside analog reverse transcriptase inhibitor (NRTI) stavudine, by impairing absorption through the gastrointestinal tract, and the NRTI zidovudine by inhibiting its glucuronidation, causing possible toxicity (30).

Buprenorphine is a μ -opioid partial agonist with strong affinity for opioid receptors. It has been used for acute pain for many years in inpatients, especially in obstetrics, and more recently has been approved for treatment of opioid dependence in a special tamper-resistant form, which is combined with naloxone. It is metabolized via CYP3A4 to an active metabolite and also by CYP2C8. Both the drug and its metabolite are also metabolized by glucuronidation, which reduces the risk of clinically significant medication interaction (27). Thus, ARVs have so far shown much less risk of interaction with buprenorphine. Efavirenz has been shown to decrease the AUC of buprenorphine, but this has not been clinically significant. However, the PI atazanavir, with or without ritonavir, has been shown to increase plasma concentrations of buprenorphine, causing significant drowsiness and confusion in some patients (31).

Tramadol is a μ -opioid agonist as well as a reuptake inhibitor of norepinephrine and serotonin. It is metabolized by CYP2D6 to a highly potent metabolite, O-desmethyl-tramadol, as well as several other P450 enzymes and glucuronidation. Drugs that inhibit CYP2D6 can therefore cause decreased pain relief. Tramadol also has a potential for drug interactions with antidepressants such as selective serotonin reuptake inhibitors and monamine oxidase inhibitors (32).

Adjunctive therapy

Adjunctive medications can prove helpful in treating HIV pain and should generally be given adequate trials before escalating to opioids. Even when not totally effective, these medications may improve function and reduce opioid requirements. In myofascial or musculoskeletal pain, analgesics may be reinforced by the use of centrally acting muscle relaxants. The main side effects of these medications are sedation and dizziness, and they may interact with other central nervous system (CNS) depressants, alcohol, opioids, and antiepileptic medications. Carisoprodol and benzodiazepines, such as diazepam, are habit-forming and have high

abuse potential. Benzodiazepines should be considered highly risky in combination with opioids and are increasingly present in cases of fatal opioid poisonings in the United States (33).

NSAIDs, especially in the elderly, should be used cautiously given the risk of gastritis, renal impairment, and bone marrow suppression. COX-2 inhibitors such as celecoxib carry a slightly increased risk of cardiovascular disease but a decreased risk of renal disease and have recently been investigated for possible immunity-enhancing effects in AIDS (34).

Antidepressants are commonly described as "pain blockers" rather than "pain killers" as they are thought to decrease nociceptive transmission in the spinothalamic tract. Tricyclic antidepressants, such as nortriptyline and amitriptyline, can reduce pain and also reduce the need for other pain medications. Protease inhibitors such as ritonavir can raise blood levels of these medications, which can have prominent side effects of orthostatic hypotension and dry mouth and be dangerous in overdose (35). Serotonin-norepinephrine reuptake inhibitors such as venlafaxine (in doses up to 300mg/d) and duloxetine (in doses up to 60-100mg/d) may also have a beneficial effect on pain, but evidence of efficacy in HIV-related pain is limited.

Antiepileptic drugs are also helpful, particularly in neuropathic pain related to HIV. Gabapentin is thought to work by decreasing calcium influx into neurons in the CNS and is generally well tolerated and fairly effective at higher doses (up to 3600mg/d) (36). Lamotrigine acts on voltage-gated sodium ion channels; it has also been shown to be effective, but requires slow titration up to 2 months in duration to reduce the risk of CNS side effects and serious toxicity such as Stevens-Johnson Syndrome (37).

Topical medications offer the promise of analgesic effect with minimal systemic absorption, but effectiveness is unclear. Capsaicin, which depletes Substance P from nerve terminals, may be effective in the higher 8% concentration (38). Lidocaine transdermal patches have not proven effective for this condition (39).

Finally, medical cannabis has been extensively studied in HIV for various conditions and has been shown to be beneficial in polyneuropathy pain in HIV. A recent study performed at an HIV clinic associated with the University of Washington showed that HIV patients accessing medical cannabis for pain commonly suffered from multiple pain diagnoses, of which the most common were myofascial pain syndromes, polyneuropathy, discogenic back pain and osteoarthritis (40).

Acute Pain Management

The management of acute pain in patients with chronic medical problems and pre-existing pain conditions poses special challenges. Particularly in immunocompromised patients, the differential for pain is large and it is essential to have a specific pain diagnosis for any acute pain that is being treated. The specific evaluation and testing required for this goes beyond the subject matter of this article. The World Health Organization (WHO) has developed a ladder for cancer pain treatment which has found general use in pain management (41). The ladder recommends starting with nonopioid treatment and progressing to codeine or tramadol, either alone or in combination with acetaminophen (Table 2).

The treatment of acute pain should be symptom-focused and time-limited. As the acute pain resolves, the opioids should be rapidly tapered and discontinued. Clearly communicating the expectation of this will often decrease conflict and prevent aberrant behaviors. Keeping opioid treatment as low-dose and short-term as possible will be helpful. It is necessary to note that both the dosage and the time to wean will be greater in patients who are already opioid tolerant. The provider should also assess other issues that may be worsening the perception or tolerance of pain, such as anxiety or depression, and should make full use of adjunctive pain treatments (42).

For more severe pain, morphine is highly effective in tablet, oral liquid form, or intramuscularly/intravenously, but may cause constipation and nausea. In opioid-tolerant patients, the dose may need to be raised and the frequency of administration increased. Synthetic opioids such as oxycodone and hydromorphone are also highly effective but should be used cautiously in the opioid naïve population; these medications are also highly addictive and have high street value. In particularly fraught psychosocial situations, such as homelessness or suspected substance abuse, more frequent prescriptions and evaluations may reduce the risk of diversion or misuse.

Table 2. *WHO Pain Ladder for cancer pain.* (75)

| |
|--|
| Nonopioids (NSAIDs, acetaminophen +/- adjuvants) |
| Weaker opioid: (tramadol, codeine, etc.) +/- non-opioids +/- adjuvant |
| Strong opioids (morphine, oxycodone, etc.) +/- non-opioids +/- adjuvants |

Chronic Pain Management

Managing chronic pain in HIV patients can be complex and challenging. Patients presenting with chronic pain should be fully assessed prior to symptomatic treatment, as there are many potential etiologies and definitive treatment is usually preferable to symptomatic treatment whenever possible. The HC-SUS data mentioned previously show that drug abuse (not including marijuana) had a prevalence of 25.6% and drug dependence had a prevalence of 12.5%. It is noteworthy that this figure does not include patients whose substance abuse history is older than 12 months, although they are likely still at higher risk for opioid misuse (43). The same study identified 36% of the sample screening positive for major depression, 26.5% for dysthymia, 15.8% for generalized anxiety disorder, and 10.5% for panic attacks. In the study by Merlin et al, patients with psychiatric illness were 40% more likely to have pain (8). Patients with both psychiatric illness and substance abuse histories scored higher on symptoms assessment and global distress scales. Thus, a care provider treating pain in the setting of HIV is working with a patient population with elevated rates of psychiatric and substance use disorders, and must routinely screen for these conditions, assess them when present, and adjust the treatment approach as necessary.

The patient should have an adequate trial of nonopioid pain relievers and other treatment modalities before opioids are considered. In current practice, many patients receive opioid analgesics; in the previously mentioned study of indigent HIV patients, over half were actively being treated with short- or long-acting opioids (6). In a recently published analysis of data from the Consolidated Standards of Reporting Trials (CONSORT) study, the prevalence of long-term opioid use in HIV patients remains higher than in the general population, but has remained stable, without the growth seen in the general population (44). Opioid use was more prevalent in women and in those with comorbid substance abuse or other diagnoses.

It is essential to obtain a full substance use history, since HIV patients have rates of substance abuse greater than those of the population at large. In one large study in the United States, illicit drug use was found in 37% of HIV-positive patients followed at 7 primary care sites (45). Clinical experience suggests that active substance abuse within the past 6 months is the most significant risk factor for aberrant behavior during pain treatment (42). Finally, establishing whether the patient is receiving treatment for their chronic pain from

other providers is necessary to prevent “doctor shopping” and polypharmacy. In many states, a prescription monitoring program is in place to track how many controlled substance prescriptions a patient is receiving, and from whom.

The treatment of non-cancer pain with long-term opioid medications has increased significantly since 1990. Initial studies suggested that chronic opioid therapy (COT) for chronic pain was safe and associated with low rates of opioid abuse and dependence, but these findings have not proven valid outside of carefully screened populations that have very low substance abuse and psychiatric risk (46). A study of a large group practice in Washington State suggests that chronic pain patients are heterogeneous, and identified subgroups of patients that demonstrate either addictive or pain-related dysfunction; in either case using much higher amounts of opioids than the other pain patients (47). The CONSORT study followed treatment patterns of patients in 2 very large group practices in California and Washington State, and found that long-term use of opioids doubled between 1997 and 2005, with almost a third of these patients also receiving sedative-hypnotics (48). COT was found in this large study to be more common, and at higher doses, in depressed patients (49). Finally, patients with a prior substance abuse disorder also received higher doses, more long-acting opioids, and were more likely to also get sedative-hypnotics prescribed at the same time (50). Together, these studies suggest that the current practice of COT involves prescribing opioids to patients who are very different, and much riskier, than the patient population in which COT was originally shown to be effective. This prescribing pattern is associated with an increase in opioid-related morbidity and mortality. Overdose is more common in patients prescribed higher doses of opioids (51), as are fractures among the elderly (52), risk of opioid misuse (53), alcohol and drug-related emergency department visits (54), and opioid use disorder diagnoses (55). In addition, high dose opioids have been shown to cause hyperalgesia, which is not quickly reversed (56).

Prior to the first prescription, a pain treatment agreement between patient and provider should be established, setting ground rules, goals, and prohibitions associated with treatment. Regular follow-up with monitoring of prescriptions and urine drug testing is advised, as this will help detect drugs of abuse as well as drug diversion. Regular reassessment of both pain levels and functional impairment will help guide treatment.

When the decision has been made to start or continue a patient on opioid therapy, the choice of medication and schedule must be made. Some patients will have difficulty tolerating a slow titration of long-acting opioids, as there may be a period of inadequate pain relief. Short-acting opioids may be used to help cover this pain temporarily or to treat acute pain exacerbations. This short-acting medication may be of the same type, in the case of oxycodone or morphine, or different, as in the case of methadone. It has been clinically suggested that meperidine be avoided due to short activity, limited analgesic effect, toxic metabolites, and addictive potential (42). Mixed agonist-antagonist opioids such as buprenorphine, nalbuphine, or pentazocine are likely to provoke withdrawal symptoms and render the long-acting opioid medication ineffective. A cautious approach towards dose escalation is best, as the risks of opioid therapy increase at higher doses but outcomes are not necessarily improved. High dose opioid therapy is concentrated among a relatively small group of patients, which in one study accounted for nearly 70% of total dosage despite only being 5% of the patient population.(57)

Definitive studies are still pending, but preliminary recommendations are to take a stepwise approach to pain treatment, attempting to make full use of nonopioid pain medications, and to limit the dosage of opioids for chronic pain. A stepped approach which minimizes opioid use and makes specific recommendations for conditions including fibromyalgia, low back pain, neuropathy, and osteoarthritis was presented by Kroenke et al (58). Another set of guidelines for chronic opioid treatment of non-cancer pain was published recently which covers all aspects of opioid prescribing in considerable detail.(59)

Psychosocial Treatments of Chronic Pain

Multiple psychosocial treatments have been shown to be helpful in chronic pain to reduce perceived pain, pain behavior, and restore function. The details and indications for these treatments are beyond the scope of this article, however it should be noted that these interventions often require a significant level of cooperation, psychological insight, and cognitive function for full effect. Hypnotherapy has been used to modify and diffuse the perception of pain, which in low back pain decreases both pain behavior and pain ratings (60). Biofeedback teaches the patient to modify their physiologic state using visual or audio cues, and has been shown to be helpful in conditions including tension-type head-

ache, migraine, temporomandibular joint syndrome, and fibromyalgia (61). Many chronic pain patients have increased muscle tension related to soreness, guarding, and physical expression of stress (62). Relaxation training can reverse this and decrease autonomic arousal, increase the patient's sense of self-efficacy and decrease their avoidance of activity (61). Cognitive behavioral therapy helps patients identify and change maladaptive thoughts and behaviors regarding their health and pain problems, and has been shown to decrease catastrophization and helplessness and improve coping and function in some chronic pain patients (61). This has been shown to be an affective treatment for HIV patients suffering peripheral neuropathy, although one study also demonstrated difficulties with retaining patients until completion of treatment (63). Psychotherapy is also frequently offered to couples or to families of patients suffering pain (64).

Harm Reduction and Behavioral Management

Precise definitions of prescription drug abuse and misuse have been somewhat elusive, with contrasting definitions offered by the National Institute of Drug Abuse, the Diagnostic and Statistical Manual, Fourth Edition, Text Revision, and expert panels. In the setting of opioid treatment of chronic pain, the identification is particularly blurred since patients on chronic opioids are likely to have physiological dependence (65). For the purposes of this article, behavior that transgresses or obstructs standard opioid prescription policies in pain clinics, known as aberrant behavior, will be the focus of attention. HIV patients may have increased incidences of aberrant and problematic behavior regarding opioid treatment, particularly given that intravenous drug abuse is a primary vector for HIV infection in the United States. HIV patients with a past history of substance abuse are at higher risk for

aberrant behavior than cancer patients or HIV patients without such a history (66).

The range of aberrant behavior is wide and is detailed in Table 3. HIV patients with histories of problematic drug use experience more pain and show greater and more persistent aberrant use of opioids than HIV patients without such histories (10). In an open label study, Kaplan (67) found that HIV patients with a drug history required almost twice the dose of morphine for HIV-related pain as patients without such histories (67). Specifically assessing the patient's potential for aberrant behavior prior to initiation of treatment using structured clinical interviews and tests such as the Screener and Opioid Assessment for Patients in Pain and Opioid Risk Test may be helpful to identify patients likely to have problematic behaviors with treatment, allowing extra care and monitoring to be done (68). Urine toxicology testing can be used both prior to opioid prescribing and periodically during opioid therapy to identify the risk of complications and untreated addiction problems.

There is a lengthy differential diagnosis for aberrant behavior, which ranges beyond addiction and is important to assess in HIV patients (Table 4) (66). To properly assess this, it may be helpful to seek the input of a psychiatrist or other mental health specialist. There is evidence that pain in HIV patients is significantly undertreated, which raises the risk of "pseudoaddiction" presenting as a cause of aberrant behavior (10). Opioid dose escalation in response to aberrant behaviors is not recommended, but such behaviors may be a cue to increase monitoring for addiction and add adjunctive and nonpharmacological pain treatments.

While it is important to have a pain treatment agreement and establish expectations for prescribing, it is also necessary to have further contingency plans if

Table 3. *Elements of aberrant behavior with opioid treatment*

| |
|---|
| • "Lost prescriptions |
| • Early refill requests |
| • Abuse of other substances or alcohol |
| • Functional impairment |
| • Doctor shopping |
| • Diversion of medications |
| • Failure to comply with treatment plan and treatment agreement |

Table 4. *Differential of Aberrant Behavior*

| |
|--|
| Substance Dependence/ Addiction |
| Pseudoaddiction due to inadequate pain relief |
| Confusion due to Encephalopathy/Delirium |
| Disorganization due to HIV Dementia or other infectious process |
| Major Mental Disorder, for example Major Depression or Schizophrenia |
| Personality Disorder |
| Psychosocial Stressors: victimization, crisis |

the patient is unable to comply with this plan. In some cases the patient may be able to use these medications appropriately with adequate psychosocial support and structure; for example, having a partner assist with administering medications or dispensing medications only a week at a time. Discontinuation of opioids when an adequate trial does not improve pain and function or when aberrant behaviors persist is crucial to avoid prolonged side effects and reduce risk. If patients demonstrate evidence of addiction or escalate their behavior to acting out or suicidal threats, it is important to obtain input from addiction treatment providers or psychiatric consultation whenever possible.

Opioid Dependence, Opioid Replacement, and Pain Management

Patients with a past history of opioid dependence may need larger doses of opioids to treat acute pain, as they often have increased tolerance, even when currently abstinent (69,70). It is important to note that it is illegal under current law in the United States to treat opioid dependence with opioids unless the patient is properly enrolled with a methadone clinic or buprenorphine prescriber; however, there is no legal restriction on treating pain with opioids, regardless of dependency history.

Methadone is an effective treatment for chronic pain, where it is frequently dosed 3 times daily. However, because the effective duration of analgesia is only 6 to 8 hours, much shorter than the half-life of 12 to 16 hours which can also be as great as 130 hours, prescribers must be wary of accumulating methadone levels and sedation (71). It is also widely used for opioid dependence as a once-daily medication because its long activity prevents acute withdrawal without producing excessive euphoria.

Patients already treated with chronic methadone or buprenorphine for opioid dependence may continue this treatment while hospitalized. However, increased methadone dosing to cover pain may result in excessively high doses with side effects such as sedation, nausea, and prolongation of the QT interval. Current recommendations call for continuing methadone at its usual dose and adding short-acting opioids as necessary to cover acute pain.(72)

Buprenorphine maintenance is a safe and effective outpatient treatment for opioid dependence; however, it can be problematic in acute pain management, since buprenorphine has both high receptor binding affinity for the μ -opioid receptor as well as a pronounced "ceiling effect" due to its partial agonist status (73).

Alford (72) described 3 approaches to this problem: increasing the buprenorphine dosage and the frequency of dosing up to 3 times a day, but not more than 32 mg/d; adding a short-acting full agonist with high receptor affinity (such as hydromorphone) to improve pain relief; and finally, converting the patient from buprenorphine to a full agonist long-acting opioid (72). The conversion strategy requires several weeks lead time to allow opioid receptors to turn over. This is a challenging management problem and ideally should be done with the input of a pain specialist. The provider prescribing also needs to be involved in treatment planning. If the patient is using buprenorphine-naltrexone to treat opioid dependence, the risk of triggering relapse of opioid abuse should be discussed frankly with the patient as well.

CONCLUSION

HIV patients are at risk for pain syndromes, both from HIV infection directly and from associated factors. They are less likely to get adequate pain treatment, yet pain, which influences health-related quality of life, may play a role in survival(74). Pain management needs to be highly individualized in these patients. In particular, it is important to identify specific pain syndromes that may respond better to nonopioid treatment, such as neuropathies. When the decision has been made to start opioid treatment, it is necessary to gather a complete history from the patient, especially covering their medication history and any psychiatric and substance history they may have. It is advisable to develop clear communication between the pain management prescriber and the provider treating the HIV and related conditions, as HIV regimens are both complex and subject to change. Careful prescribing is needed, taking multiple potential drug-drug interactions into account. It is clear that patients with a history of substance abuse are much more likely to develop aberrant pain treatment behaviors than those without, but risks can be reduced by following best practices. Opiates such as codeine or morphine may be less likely to interact with antiretroviral medications. Long-acting opioids should never be used for acute pain or in opioid-naïve patients. Methadone is complex in its interactions and dosing and should be prescribed by experienced providers.

Regarding practice strategies, it is worthwhile (and legally required, in some states) to discuss and document the rationale and expectations associated with opioid treatment prior to starting, and to discuss the

circumstances under which opioid treatment will be discontinued. Screening for substance abuse and psychiatric illness is recommended. In addition, limiting the amount of medication prescribed and requiring patients to have secure storage for opioid medications

may help decrease diversion and misuse.

Finally, it is important to note that opioid replacement therapy is very helpful for opioid-dependent patients with HIV, but needs to be taken into account when treating their pain conditions.

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