Clark MR, Treisman GJ (eds): Pain and Depression. An Interdisciplinary Patient-Centered Approach. Adv Psychosom Med. Basel, Karger, 2004, vol 25, pp 123–137

Opioid Effectiveness, Addiction, and Depression in Chronic Pain

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Abstract

Opioids are a viable treatment for chronic pain, but their use requires individualization, specified treatment goals, and patient education. Opioid responsiveness is influenced by patient-centered characteristics, including a predisposition to opioid side effects, psychological distress, and opioid use history; pain-centered characteristics, which involve the temporal pattern, rapidity of onset, severity, and type of pain; and drug-centered characteristics relating to the impact of specific types of opioids on specific patients. Thus, opioid doses should be titrated to achieve a favorable balance between analgesia and adverse effects. Opioid therapy can be enhanced through the adjunct administration of agents such as NMDA antagonists, calcium channel blockers, clonidine, and even low-dose opioid antagonists. Controversy exists over 1) the long-term use of opioids for non-cancer pain, and patients receiving opioids for long periods must be monitored carefully for signs of addictive and aberrant behavior, 2) the impact of opioid therapy on emotional depression in patients with chronic pain, and 3) whether opioid therapy causes cognitive impairment in the elderly. Our ability to determine the validity of such assertions and the exact role of opioids in the treatment of chronic pain will benefit from further study.

Introduction

One third of the United States population will experience chronic pain. In fact, chronic pain is the most common cause of long-term disability in the United States and partially or totally disables nearly 50 million people [1]. Among the therapeutic options for treatment of chronic pain, the use of opioids remains a viable choice. Research into opioid pharmacology over the past

20 years has expanded our knowledge of the mechanism of action of opioids [2]. Many studies on patients with cancer pain have provided insight into the clinical pharmacology of opioids. Research findings support the idea that the pharmacokinetic and pharmacodynamic principles of opioids in cancer patients with pain hold true in patients with chronic, nonmalignant pain [3].

While the use of opioids for chronic cancer pain is widely accepted, the efficacy and role of opioids in the management of chronic noncancer pain has been intensely debated. Opponents argue that there is no place for opioids in the treatment of chronic benign pain and opine that narcotics are a major impediment to the successful treatment of chronic pain. This view is largely based on concerns regarding tolerance, physical dependence, addiction, and adverse affective and cognitive side effects. Supporters, in contrast, state that some types of pains, e.g., nociceptive pains, are opioid responsive, while others such as neuropathic pain might be less responsive, but not resistant. Much of this debate has occurred till recent years in the absence of randomized clinical trials. Although several recent studies have demonstrated that chronic pain, including neuropathic pain states such as postherpetic neuralgia, is responsive to opioids, these studies have followed patients for relatively short periods of 2 months or less. More careful studies of the long-term efficacy of opioids are needed to determine if tolerance to the analgesic effects of opioids limits its usefulness for long-term therapy.

Opioid Effectiveness

The appropriate use of opioids in the management of chronic pain demands individualization [4]. That is, one opioid does not 'fit all' patients with a certain type of pain. In addition, we lack a mechanistic approach that would guide the management of chronic pain states with specific opioids. The goal in the management of a patient's pain with opioids is to achieve an optimal balance between the drug's analgesic effects and any associated adverse effects.

In 1990, Portenoy et al. [5] advanced a strategy for conceptualizing opioid effectiveness in managing patients with chronic pain. According to this strategy, the rational use of opioids should focus on achieving maximum analgesic efficacy while limiting toxicity. The success of this approach requires gradual titration of the opioid to the point at which a favorable balance between analgesia and side effects is achieved. Finding this acceptable balance between analgesia and side effects requires frequent interactions between the clinician and patient.

Several factors can influence opioid responsiveness in managing chronic pain: specifically, patient-centered characteristics, pain-centered characteristics, and drug-centered characteristics.

Patient-Centered Characteristics

Patient-centered characteristics, such as a predisposition to opioid side effects, reduce opioid responsiveness, irrespective of pain syndrome type [5]. This predisposition may derive from higher than normal plasma levels of opioid following a single dose (pharmacokinetic) or even from an exaggerated response to modest levels of plasma opioid (pharmacodynamic). Therefore, side effects after a given dose or doses of opioid are difficult to predict but will prevent the patient from achieving a balance between analgesia and adverse effects. Further, concurrent use of other medications with additive side effects will increase the risk of intolerable opioid side effects at doses that are inadequate for analgesia.

If patients are experiencing psychological distress, they may respond less favorably to opioid therapy [6]. Among the cancer population, patients who receive psychological interventions or psychotropic medication achieve better analgesia with the same opioid and dose than do patients receiving no psychological assistance. Similarly, poor opioid responses by addicted individuals may result from affective disturbances such as depression and anxiety.

Those patients who have recently consumed large doses or escalating doses of opioids also may respond poorly to current opioid therapy. This outcome may result from disease progression among the cancer or noncancer population or may result from tolerance. It is important to remember that patients consuming high doses of an opioid at baseline will require large incremental doses to achieve analgesia.

Finally, genetic determinants may influence opioid effectiveness in patients by altering the density or proportion of opioid receptors or by changing the expression of opioid isoforms.

Pain-Centered Characteristics

Pain-centered characteristics can influence patient responsiveness to opioids. For instance, the temporal patterns of pain exert a strong influence on opioid effectiveness [7]. If pain is of rapid onset, the opioid tends to be ineffective, perhaps due to our inability to deliver the drug fast enough. Furthermore, intermittent and severe pain often require large or quickly escalating opioid doses for pain control, but such doses often cause intolerable side effects [8].

Neuropathic pain is another pain-focused characteristic that influences opioid effectiveness. In the past, clinical observations and studies described neuropathic pain as unresponsive to opioids [9, 10]. Yet, data from clinical surveys supported a revised notion that opioids can relieve neuropathic pain

[11, 12], and controlled studies provided convincing evidence that this is true [13, 14]. Further, a randomized, placebo-controlled trial comparing the use of opioids with that of tricyclic antidepressants to treat postherpetic neuralgia found that the opioids provided superior analgesic efficacy with minimal cognitive effects [15]. In short, the evidence supports the rational use of long-term opioid treatment in patients with nonmalignant painful neuropathies and/or cancer pain. Clinically, patients with neuropathic pain probably display a reduced response to opioids compared with patients with nociceptive pain. Work by Cherny et al. [16] suggests that neuropathic pain responds to standard opioid doses, but less analgesia is achieved than for nociceptive pain, and the efficacy/side effect balance is more difficult to accomplish. Other studies add to the growing clinical concept that neuropathic mechanisms merely reduce opioid response without imparting opioid resistance [17–19].

Drug-Centered Characteristics

Opioid responsiveness can differ according to drug-specific effects. That is, patients may experience better analgesia and fewer associated side effects with one opioid yet fail to achieve adequate analgesia with another opioid that also induces unmanageable side effects [5, 20]. The results of animal studies indicate the possibility that a relationship exists between a physiological pain mechanism (visceral vs. cutaneous) and the opioid receptor subtypes that produce analgesia. Specifically, work by Sengupta et al. [21], using experimental models of visceral pain, suggests a role for peripheral kappa receptors and not mu or delta receptors in the modulation of visceral pain. The mechanistic process may relate to the sensitivity or density of receptor subtypes or isoforms and/or to the specific binding properties of the opioids to these subtypes and isoforms.

Tolerance to the analgesic effects of opioid occurs even after a single dose of the drug in experimental animals. However, the extent to which this is a problem in the clinical use of opioids for chronic pain management is less clear. It is generally considered to be less of an issue in clinical pain states as patients can often be maintained on stable doses for prolonged periods of time [7].

Enhancing Opioid Therapy by Adding N-Methyl-D-Aspartate Antagonists, Calcium Channel Blockers, Clonidine, and Opioids Plus Low-Dose Opioid Antagonists

Insights into the process of neuroplasticity indicate that adding N-methyl-*D*-aspartate (NMDA) antagonists may help treat types of pain that are not optimally responsive to opioids (neuropathic pain, breakthrough pain, increased

pain due to tolerance to the drug's analgesic effects) [22, 23]. The NMDA antagonists may exert more influence on the altered central processing of pain signals than on the physiological transmission of painful impulses and may produce analgesia directly or reverse tolerance. Ketamine (a noncompetitive NMDA receptor antagonist) blocks the NMDA receptor-controlled ion channel on dorsal horn neurons when a nociceptive burst releases glutamate into the synaptic cleft. Consequently, ketamine may be more effective in modifying the central hyperexcitability and 'wind-up' processes related to neuropathic as opposed to acute pain [24]. Persson et al. [25] reported a synergism between ketamine and opioids. In this study, cancer patients who lost analgesia from high-dose morphine achieved substantial analgesia while halving their morphine doses after the addition of a low dose of ketamine (110 mg/day) to the treatment regimen. Moreover, in a double-blind, crossover study, Mercandante et al. [26] reported favorable results using ketamine (0.25–0.5 mg/kg) with morphine in cancer patients suffering from uncontrolled neuropathic pain. Undesirable psychotomimetic side effects (illusions, disturbing dreams, delirium) can occur with ketamine use, however, and should be monitored and preempted using benzodiazepines or haloperidol at doses of 2–4 mg/day [27].

Animal studies suggest a critical role of NMDA receptors in modulating chronic pain states; however, the clinical efficacy of NMDA receptors in human studies has yet to be established. Methadone produces analgesia by activating mu opioid receptors, but the drug also acts as an NMDA receptor antagonist. In fact, methadone is unique among opioids and may offer greater effectiveness than the other opioids in managing neuropathic or opioid-tolerant pain [28]. Likewise, dextromethorphan (DM) acts as an NMDA antagonist, and potentiates NSAID and morphine analgesia [29]. Because DM offers a convincing safety profile as an antitussive [30] and lacks psychomimetic side effects, it may be useful in treating chronic pain conditions. However, the evidence from randomized, controlled trials on the beneficial effects of clinically available NMDA antagonists is not convincing [31, 32].

It is well known that calcium channels play a critical role in presynaptic release of neurotransmitters; therefore, blocking these channels in the context of opioid use may facilitate antinociception. Santillan et al. [33] found that the calcium channel blocker nimodipine permitted a decrease in morphine use in 16 of 23 patients but failed in 2 patients and was discontinued in 5 patients. In 1996, Roca et al. [34] reported opposing results after administering nimodipine 30 mg p.o. q8 h to cancer patients who were concurrently taking sustained-release morphine. These investigators noted no enhanced analgesia in the treatment group. Incorporating calcium channel blockers into an analgesic regimen may be limited by their hemodynamic properties.

Clonidine shows promise in enhancing opioid responsiveness in chronic pain states. Clonidine is an α_2-adrenergic agonist and nonspecific analgesic that inhibits primary afferent transmission and substance P release from nociceptive neurons in the spinal cord [35]. The pain-relieving qualities of intraspinal clonidine have been demonstrated in patients with intractable, neuropathic cancer pain [36]. Clonidine's analgesic effect may be independent of opioid pathways [37] and may act synergistically with morphine to suppress dorsal horn neurons [38].

Growing evidence supports the role of low-dose opioid antagonists in enhancing the analgesic potency of morphine or other opioids. For instance, Levine et al. [39] demonstrated that low-dose naloxone given with pentazocine provides greater analgesia than high-dose morphine alone. These investigators studied more than 100 patients in a double-blind fashion following surgery for tooth extraction. In a double-blind study on 60 posthysterectomy patients, Gan et al. [40] infused low-dose naloxone during a 24-hour period and discovered that patient-controlled analgesia (PCA) usage of morphine decreased from 60 to 40 mg. Gan et al. concluded that naloxone increased morphine's potency, decreased tolerance, and reduced the nausea, vomiting, and pruritus associated with morphine treatment. Moreover, ultra-low-dose intravenous nalmefene (a pure mu receptor antagonist) enhanced postoperative analgesia with PCA morphine in 120 lower-abdominal surgery patients in a randomized, double-blind, placebo-controlled study [41]. The patients receiving nalmefene had a significantly decreased need for antiemetics and antipruritic medications while receiving PCA with morphine. These studies provide encouraging evidence that low-dose opioid antagonists given with opioids may enhance opioid responsiveness.

Addiction

The role of opioids for the treatment of chronic, nonmalignant pain remains controversial, despite growing acceptance of this practice. The literature confirms the beneficial use of opioids for noncancer pain [42] but more long-term studies are needed to support the use of opioids in non-cancer pain patients.

When using opioids to manage chronic nonmalignant pain, clinicians must consider (1) whether opioids improve the patient's physical and psychological functioning and (2) the patient's potential for addiction. Pain specialists struggle to achieve a balance between improving a patient's pain through opioid use and interfering with a patient's functioning in a manner that could worsen disability or even obviate the gain in pain control. The data demonstrate that

addiction is unlikely to occur due to opioid exposure in the presence of chronic pain [43], and it is not clear that the prevalence of addiction is greater in the chronic pain population than in the general population. Clinical experience in using opioids to treat cancer pain demonstrates low abuse potential in this group, unless there is a history of substance abuse; therefore, assessment for aberrant drug-related behavior among chronic pain patients is important to manage these patients with opioid therapy properly.

The prevalence of drug abuse, dependence, or addiction in chronic pain patients ranges from approximately 3 to 19% [44]. Yet, addictive disorders occur in approximately 3–26% of the general population [45, 46] and in 40–60% of patients who suffered major trauma [47–49]. Therefore, pain physicians are likely to encounter patients with a concurrent addictive disorder. Recognizing aberrant drug-related behavior can assist in effectively screening patients for addiction in pain treatment settings.

To refine the concept of addiction in the context of chronic pain, the American Society of Addiction Medicine, the American Pain Society, and the American Academy of Pain Medicine agreed on the following definition that supports our neurobiologic and psychologic understanding of addiction [50]: '[Addiction is] a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, continued use despite harm, compulsive use, and craving'. In order to treat pain effectively, aberrant drug-related behavior should be noted, and addiction should be addressed concurrently.

In assessing for addiction during opioid use, the clinician should collect the patient's personal and family history of substance abuse as well as relevant objective information from the physical examination, observation, and laboratory tests. The clinician should also use appropriate screening instruments, such as the CAGE-AID [51].

When treating patients with opioids for long periods of time, it is important to follow them regularly and identify behavior suggestive of addiction. Behavior that should prompt investigation includes: continued use of drugs despite adverse consequences or harm secondary to use, loss of control over drug use, and preoccupation with use due to craving. A pattern of such behavior, rather than intermittent manifestation of one or two of these actions, warrants further assessment. Further examination into each behavior will assist in identifying key features of aberrant behavior.

The beneficial effects of opioids may be hindered by the phenomenon of tolerance. Patients deriving benefit from opioids should experience a reduction in pain and maintenance or improvement of function in areas such as relationships, work, sleep, and mood. When using opioids improperly, however,

patients tend to develop impaired psychosocial functioning. For instance, addicted patients tend to lose function in critical aspects of life relating to their jobs, friendships, mood, and familial relationships. Consequently, patients being treated with opioids who persist in their disability or experience deterioration in the functional activities of living despite rehabilitative support may suffer from addiction or substance abuse. Likewise, changes in mental status or intoxication from opioids may reflect a desire for the euphoric reward of the medication rather than a need for its analgesic benefit. Tolerance to the analgesic effects of opioids does not develop quickly in patients receiving the medication properly for pain [52]. Tolerance to opioid-induced euphoria, however, does develop rapidly, necessitating higher doses to achieve the same effect. Patients with active addiction thus tend to escalate the dose of opioid to attain this euphoric state [53]. This pattern of behavior probably highlights an addictive response to the opioid in a way that promotes continued use of the drug despite adverse consequences.

Of course, pain specialists should consider other possible causes of aberrant behavior such as pseudoaddiction, i.e., drug-seeking behavior due to inadequate dosage of opioid [54], opioid-resistant pain, continual sedation at analgesic doses, and opioid-induced hyperalgesia. Recognizing patterns of aberrant behaviors, rather than isolated behaviors, will aid in assessing for addiction.

Compulsive use of opioids leads to a loss of control over drug use and represents addictive behavior. In this circumstance, patients lose control over medication use due to an intense craving for the substance. In the context of treating chronic pain, patients may overuse opioids and request early prescription refills. Such patients may report theft or loss of medications, pills falling into the toilet or down the drain, or pets consuming opioid prescriptions. Indeed, these excuses may indicate impaired control over opioid medications. Patients may also impute overuse of opioids to inadequate treatment of pain and display withdrawal symptoms at the appointment because they have depleted the opioid supply in advance. While these circumstances may occasionally occur in patients using opioids properly, a pattern of such aberrant behavior should raise concern about addiction.

When assessing for possible addiction in chronic pain patients receiving opioids, it is important to examine a preoccupation with drug use due to craving. Many patients who receive opioids for chronic pain understandably desire continual relief of pain through an uninterrupted supply of opioids. Such patients may show intense interest in maintaining regular availability of opioids to ensure analgesia and forestall withdrawal. Further, they may inquire about the physician's vacation plans or demand reminders about clinic hours. Though this behavior does not indicate addiction, it may suggest an addictive response

to opioids if the patient fails to comply with other treatment modalities. For instance, the pain specialist should confirm whether the patient actively participates in physical therapy, occupational therapy, and cognitive behavioral interventions, takes adjuvant medications, and appears amenable to considering other strategies for managing pain. If patients display no interest in applying nonopioid approaches to their analgesic regimen, then their preoccupation with opioid use suggests addiction.

If the pain specialist does not detect a pattern of aberrant behavior, he or she can be fairly confident that the patient does not suffer from an active addictive disorder. In general, patients in the pain treatment setting who comply with recommended interventions, report meaningful pain relief from opioid therapy, use opioids as prescribed, and improve their functional capacity are likely responding to the medications appropriately and not engaging in addictive behavior. Although patterns of positive behavior support the proper use of opioids, growing evidence reveals that monitoring behavior without confirmatory urine toxicology screening may fail to detect opioid misuse. For instance, both Katz and Fanicullo [55] and Belgrade [56] found that self-reports of inappropriate drug use among chronic pain patients correlated poorly with urine toxicology findings. In short, incorporating observed patterns of behavior, interviews with significant others, review of medical records, and urine toxicology monitoring can improve patient management with chronic opioid therapy.

Depression

Many physicians have argued that chronic opioid therapy increases depressed mood and disability. Yet few studies demonstrate such a correlation. An examination of the relationship between chronic pain and depression may permit a more thorough understanding of the influence of depression on patients suffering from chronic pain.

Depression seems to be a pervasive component of chronic pain [57]. In fact, patients with chronic pain and depression tend to report greater pain intensity, greater disability, decreased activity levels, poor adjustment, and poor treatment outcome compared with chronic pain patients who are not depressed [58]. Yet, the literature fails to describe the extent to which chronic pain and depression coexist, whether a causal relationship exists, or the mechanism through which depression and pain intermingle.

The reported prevalence of depression among chronic pain patients ranges from 10 to 100% [59, 60]. Such variability probably stems from inconsistencies in defining a case as well as from variability in assessment methods for

depression. Depression rates may include patients with major depressive disorder (MDD), depressive symptoms, or affective disorders like dysthymia or adjustment disorder. Hence, only some of the studies report accurate rates of depression based on standardized diagnostic criteria. Overlapping symptomatology between depression and chronic pain further complicates the accurate assessment of depression in this population. For instance, chronic pain symptoms, such as loss of energy, sleep disturbance, and appetite and weight changes, are also diagnostic features of MDD.

Several authors estimate that 30–54% of outpatient chronic pain patients suffer from MDD [61, 62]. This exceeds the current (5%) and lifetime (17%) prevalence estimates for MDD in the general population [63]. In comparing depression rates in chronic pain with other chronic medical conditions, Banks and Kerns [64] were unable to make a definitive conclusion that MDD is more common in patients suffering with chronic pain than in other chronic medical populations. They did conclude, however, that empirical data supported the notion that higher depression rates exist among patients with chronic pain. A growing body of empirical evidence from retrospective studies suggests that chronic pain leads to depression [65, 66].

Magni et al. [67] conducted a longitudinal study of 2,324 patients with musculoskeletal pain to determine whether pain predicts depressive symptoms or vice versa. They found that pain is the strongest predictor of depression in comparison with other demographic variables. The researchers hypothesized that certain pain states may be more likely to elicit depression, though depression may also be associated with the onset of specific types of pain.

The observation that a greater proportion of patients with chronic pain may develop MDD than of those with other chronic medical conditions suggests that a component of the pain syndrome accounts for the higher comorbidity. Banks and Kerns [64] proposed that chronic pain patients may think and behave differently in response to pain and that this modulation of thought may elicit depression. Specifically, the way in which a patient in chronic pain processes the pain experience (changes in life activities, duration, controllability, severity, or suffering) may predispose him/her to depression. Other factors that may contribute to depression in chronic pain patients include the type of behavior exhibited by the patient in pain as well as the response given by others to the patient's pain behavior.

Cognitive Dysfunction

Concern about potential cognitive impairment is one of the main reasons for limiting the use of opioids in the elderly. The available research has not

demonstrated deleterious effects on neuropsychological testing or EEG except in patients who were prescribed multiple types of medications, especially sedatives and hypnotics [68, 69]. Data on the cognitive side effects of opioid therapy indicate short-term effects on some aspects of cognitive functioning, but few long-term effects once stable dosing is achieved. However, a number of methodological issues weaken the strength of these conclusions and further study is warranted, particularly in specific populations, such as the elderly [70]. Studies examining cognitive side effects of opioids generally fall into two classes: short-term exposure under laboratory or clinical conditions and long-term, stable dosing under clinical conditions. Studies of short-term exposure indicate few deleterious effects of morphine [71–73] but suggest cognitive declines may occur following short-term exposure to hydromorphone [72]. Clinical trial data indicate slight reductions in memory, but no change in attention or concentration, following 6 weeks of treatment with sustained-release morphine in patients with chronic pain [74]. Other studies suggest that improvements in cognitive function may occur when pain is reduced with opioids, [75, 76] even low-dose opioids [14]. However, patients in these studies were generally young (mean age 40 years) and benefits were not observed in a very small group of patients greater than 60 years [76]. A recent report from our group indicates that controlled-release morphine is not associated with significant cognitive deficits in an elderly population with postherpetic neuralgia [15].

Conclusion

Recent controlled clinical trials provide evidence that opioids are effective in treating most chronic pain states, malignant and nonmalignant, over a period of several weeks. Additional studies, however, are needed to determine if these opioid analgesic effects persist over longer periods of drug therapy. Three factors influence opioid responsiveness in the chronic pain population: patient-centered characteristics, pain-centered characteristics, and drug-centered characteristics. Applying these concepts to the use of opioids in treating chronic pain can help achieve maximum pain relief with limited side effects. Studies on the analgesic efficacy of NMDA antagonists in human pain states reveal both a reduction in pain (ketamine) and no difference in pain (DM). Animal studies, however, suggest a more convincing role for the use of NMDA antagonists in treating chronic pain. The abuse potential and concerns about addiction in the chronic pain population may be reduced by frequent and comprehensive assessments of aberrant behavior. The prevalence of illicit drug use in the chronic pain population may be higher than in the general population; therefore, clinicians should monitor patterns of aberrant drug behavior as well as urine toxicology

results to ensure compliance with opioid treatment. Patients in chronic pain exhibit a high prevalence of MDD that demands concurrent treatment to avoid functional disability. Controversy continues over a causal relationship between chronic pain and depression; yet, clinical evidence suggests that chronic pain exacerbates depressive symptomatology.

Acknowledgment

This study was supported in part by NIH Gant NS-26363 (SNR).

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