Opiophobia, Opiophilia, Opioagnosia

When you’re on a limb, how far out do you go?

The literature is replete with reviews, editorials, and opinion papers regarding the chronic use of opioids for non-malignant pain. Despite these, and despite a decade and a half of discussion, investigation, and clinical use, there continues to be polarization of opinion as well as practice. In a 1997 editorial, Dr. Peter Wilson noted, “There appears to be little hope for a rational outcome as the discussion is dominated by zealots at one extreme and nihilists at the other”[1]. Fortunately, this statement seems somewhat less true now than at the time he wrote it; however, there continue to be those who “just say no,” and those for whom opioids are the answer. Our situation seems to uphold the aphorism that the heat of argument is inversely proportional to the persuasiveness of the data, though some of the current divergence of opinion clearly results from incomplete dissemination of the available data.

The situation regarding opioid treatment of acute and cancer pain is much better than that regarding chronic pain treatment (at least in the United States). Occasionally one still hears of a physician who withholds opioids from terminal patients or from orthopedic surgery cases, but those who discuss it do so in the tones of incredulity generally reserved for those who harbor beliefs in phlogiston. The recent initiatives by JCAHO and the Veterans Administration should help to relegate such attitudes to the past.

There has been a severe failure to adequately treat acute and malignant pain. While this failure has been ascribed to “opiophobia,” philosophical opposition to use of adequate opioids in such situations was only part of the problem. Sadly, much suffering resulted from a simple failure of health professionals to notice. Adopting pain as a 5th vital sign ensures that we will know when our patients suffer unrelieved pain. Additionally, ethicists are reminding us to restore balance to our clinical work, which had embraced technology and its promises of cures to the exclusion of our other raison d’etre—to relieve suffering.

It is really only with chronic non-malignant pain (CNMP) that controversy continues. Our own organization has issued a position paper affirming the appropriateness of chronic opioids as a therapeutic tool in these conditions, and most states have adopted legislation or regulations that specifically endorse this form of treatment.

As an organization, we must support such policies and legislative liberalization; however, it is critical that what is permissible not be confused with what is obligatory, or even with what is helpful over long periods of time. I am stirred to write this message in part by 3 recent patients:

Case 1: This 50-year-old laborer had been disabled for 25 years with chronic low back and leg pain after lifting at work. For nearly 25 years he had been treated with opioids, recently in relatively high doses. Pain was worse with weight bearing, sitting, and stress, better with lying down, opioids and benzodiazepines. He spent approximately 22 hours a day reclining, was essentially housebound, virtually lived in pajamas, and at times required assistance with activities of daily living. His physician defended his opioid therapy as successful. Symptoms of depression were reported, along with panic attacks, though his affect seemed cheerful. Numerous orthopedic and neurosurgical evaluations revealed only narrowing of the L4 disc and congenital canal narrowing due to short pedicles. EMG/NCS were normal. Inconsistencies and non-physiological signs were evident on examination. Admission medications included morphine 720 mg/d, chlordiazepoxide 250 mg/d, and citalopram 20 mg qid. As medications were weaned he reported feeling as though he were “coming alive” after having “lost the last 25 years.” He reported improved cognition, alertness, and mood. At discharge on venlafaxine, doxepin, and gabapentin, he was animated and comfortable-appearing, though he reported only a slight reduction in pain.

Case 2: A 46-year-old executive was disabled 4 years with low back pain radiating down the right lower extremity. She also had neck and shoulder pain since college and had been diagnosed with degenerative disc disease. She had numbness in the fingertips of both hands for 6 months and had recently been dropping things. MRI showed central to right sided herniation at L4–5 and right lateral herniation at L1–2 with an extruded fragment projecting superiorly. Prior imaging had shown herniations at C5–6, 6–7, and T12-L1. Discogram was positive at L5-S1, negative at L4–5. Surgery was
not recommended, and she came to pain rehabilitation. Examination revealed spinal tenderness and reduced range of motion with no neurological deficits or signs of dural tension. Admission medications included sustained release oxycodone 1200 mg/d, transdermal fentanyl 225 μg/h, and sertraline 50 mg/d. Pain ranged from 5–9/10. She reported prior depression, considerably improved, and Beck Depression Inventory was normal at 7. After 3 weeks of pain rehabilitation and opioid elimination, pain was 4/10 and she showed improved function. Medications included Zanaflex 4 mg prn withdrawal symptoms, venlafaxine 75 mg/d, gabapentin 300 mg tid, and trazodone 50 mg hs.

Case 3: A 40-year-old disabled grocer was brought by ambulance for 18 months' of pain that had required 14 weeks of hospitalization during the previous 8 months. He'd developed head and right extremity pain following a whiplash injury. During the course of treatment, he developed a transient, drug-related pancreatitis. At admission he had spine pain from occiput to coccyx, plus pain in the right shoulder, arm, leg, and foot. Usual severity was 8/10. Brain, cervical and lumbar MRIs were normal. Epidural steroid injections and a L5 root block were not helpful, and his pain increased with trigger point injections. Cholecystectomy (“sludge”) led to improved appetite and weight gain. An intrathecal pump was implanted, infusing morphine and clonidine, with ~50% relief; however, he thought the pump caused constant pain in the left upper and lower quadrants, spreading to the right upper and lower quadrants. He was essentially housebound, required assistance bathing and dressing, and scored 52/70 on the Pain Disability Index. He had only occasionally sad mood, and Beck Depression Inventory of 15 suggested mild depression. Litigation was planned against the other driver.

Weakness was inconsistent and sensory loss non-dermatomal. Other non-physiologic signs were present.

Admission intrathecal medications were 7.15 mg/d of morphine (20 mg/ml) and clonidine (500 μg/ml), in addition to morphine 15 mg q4h prn (=75 mg/d).

He was admitted to pain rehabilitation, the pump was explanted (patient request), and morphine weaned to 60 mg/d, with clonidine prn withdrawal symptoms. Additionally he received gabapentin 1800 mg per day, and doxepin 125 mg hs. He increased his physical functioning, relinquished his cane, adopted a normal posture, became animated, comfortable appearing, and interactive with peers.

In each of these cases, it appears that aggressive opioid treatment had been continued and escalated in the face of clear failure and, in 2 of the cases, despite evidence the pain would not likely be opioid-responsive.

Evolution of Current Practice

Thirty years ago, when Pain Medicine was in its infancy, opioids were thought to be ill-advised in CNMP. Clinicians believed this, and regulators agreed [2]. The rationale for this position included beliefs that: (1) tolerance would lead to declining efficacy; (2) resulting dose escalation would produce dependence or addiction; (3) opioids would impede functional rehabilitation, and indeed were thought to promote regression in chronic use. Other concerns included reinforcement of pain behavior, diversion, organ toxicity in protracted use, and impaired cognition, alertness, and motor function. Perhaps there were even some Calvinists among us who believed that any drug able to induce pleasure must be morally wrong.

In truth, most pain specialists had a small number of patients for whom they provided maintenance opioids, but this was done as a last resort, often an act of desperation, and was not the standard of care. This standard began to change in response to articles and presentations by a few pain physicians who challenged this conventional wisdom.

In 1986, Portenoy and Foley described 38 patients with non-malignant pain who had seemingly done well with opioid maintenance [3]. In an article entitled “The Tragedy of Needless Pain” [4], Melzack opined that “...many people suffer not because their discomfort is untreatable but because physicians are often reluctant to prescribe morphine... many care givers, afraid of turning patients into addicts, deliver amounts that are too small or spaced too widely to control pain. Yet the fact is that when patients take morphine to combat pain, it is rare to see addiction... Addiction seems to arise only in... users who take the drug for its psychological effects, such as... euphoria and to relieve tension. Furthermore, patients who take morphine for pain do not develop the rapid physical tolerance to the drug that is often a sign of addiction.” While his position seemed to be supported primarily by data in acute and cancer pain, it prompted at new look at those with CNMP, and today there are few who would argue against his statements.

A number of articles followed supporting opioid maintenance, and enthusiasm for this has grown rapidly. The condemnation of opioids in chronic pain has now been replaced in many places by unbridled enthusiasm. Headlines scream that there’s a
cure for pain but doctors are afraid to use it. Such articles in the popular press have at times produced unrealistic expectations.

**Current Understandings**

As with all health interventions, practice must be driven by the balance of benefit and risk and, of course, costs. It has been said, however, that all important decisions must be based on incomplete data, and this is no exception. We lack good data, but we cannot delay treatment until the answers are in. It thus behooves us to review what we do and do not know.

**Risks**

**Toxicity** One area of agreement is the lack of systemic toxicity in chronic opioid use. It is now known that decades of opioid use, as seen in former heroin addicts maintained with methadone, produce no organ toxicity or neurological damage. Respiratory depression occurs only when the dose is increased beyond the point of sedation, and tolerance to this effect develops quickly. The lack of toxicity to liver, kidneys, heart, brain, and GI tract contrasts dramatically with NSAIDs, acetaminophen, and such common drugs used in pain management as antidepressants, anticonvulsants, and sodium channel blockers. Agents that have toxic metabolites (meperidine, propoxyphene) are easily avoided. The drugs are, of course, lethal in overdose.

**Functional Impairment** This concern is of two forms, one being the question of sedation and confusion in treated patients, the other being a more subtle ‘failure to rehabilitate’. Studies in cancer patients demonstrate that following dose escalations there is a transient period of sedation and reduced cognitive efficiency; however, after a few days these effects wane [5,6]. Most residual impairment seems to be a slowing down rather than a loss of accuracy. While there may be mild increases in body sway and reaction time, the impairments are thought not to be sufficient to preclude safe driving and other activities [7,8]. Controlled studies as well as years of experience with methadone maintenance in heroin addicts indicate that chronic methadone use produces minimal functional impairment [9]. Such patients are safe to drive and work. Some studies actually found that healthy subjects and those with chronic pain had improved cognition when acutely given morphine [10, 11]. Those effects that do result from opioid administration must be compared not only with the effects of anticonvulsants, antidepressants, and tranquilizers, which can impair performance, but also with unrelieved pain, which substantially impairs performance on cognitive testing.

There is concern that in CNMP opioids can promote regression, dependence, the ‘sick role’, and perpetuate disability. While there are reports of patients who were able to return to work for the first time in years when provided opioid maintenance, patients are also seen who report being able to return to work only after they recovered from a “methadone haze.”

**Physical Dependence** This is another area in which controversy seems to be waning. As physical dependence has been conceptually distinguished from addictive disorder, the importance of this effect has been reassessed. Any animal placed on chronic opioids will develop physical dependence; i.e., it will exhibit an abstinence syndrome if antagonists are given or if the drug is withheld. Many common medications, such as \( \alpha_2 \) agonists and anticonvulsants among others, cannot be abruptly discontinued without an abstinence syndrome, yet this is not thought to impair their clinical utility. In the case of opioids, some regard physical dependence as only an inconvenience, a shifting of the dose/response curve to the right, or a factor that necessitates special arrangements to be sure patients are not left without medications when they or their physicians are out of town.

There has been concern, however, that with short acting agents, physical dependence could increase pain. This is because “micro-withdrawal” during trough levels could lead to muscle tension (increasing myogenic pain) and autonomic arousal (increasing neuropathic pain.) It has also been found that opioid withdrawal markedly activates the “on cells” in the rostral ventral medulla that facilitate pain transmission [12]. These phenomena can be eliminated by relying on longer acting agents.

**Addiction** Historically, the most feared consequence of opioid maintenance is iatrogenic addictive disorder. The risks of this have been disputed, largely due to contradictory evidence from different fields. While clinical experience and controlled studies indicate that it is rare to create addictive disorder by prescription of opioids for pain, in surveys of recreational addicts many report having been introduced to drugs medically. Experience suggests that those who demonstrate an addictive disorder to prescribed opioids have usually had a prior chemical
dependence, often to alcohol or cannabis. Supporting this is a recent investigation by Jamison, in which many patients in methadone maintenance clinics reported having become addicted medically, yet had histories suggesting prior addiction [13]. Fears of iatrogenic addiction have been fueled by misunderstanding of pseudoaddiction [14]. While several studies have demonstrated the rarity of addictive disorder in those who did not have a preexisting addiction, unfortunately, the preponderance of them were short term (<6 months), and there are no studies of very long term (>2 years) use of opioids for analgesia. It is expensive and difficult to investigate the effects of years of any treatment; however, until this is done, the risk of producing addiction in chronic treatment will remain unknown. It is reassuring to learn that the increased medical use of opioids has not led to an increase in evidence of abuse [15].

Benefits

The primary remaining question regarding chronic opioid therapy seems to be that of efficacy—in what conditions are these agents effective and for how long? There is now a large body of literature confirming that many pains thought to be opioid resistant actually can be relieved by acceptable doses of opioids. That such a seemingly simple question continues to provoke dispute after decades of experience may be explained by 2 phenomena.

One is the dispute as to whether the appropriate goal in CNMP is rehabilitation or palliation. It would seem that if a person with chronic backache is non-functional because of pain, then palliation would mitigate obstacles to function, and both goals would be achieved. This occurs in some patients and some studies, but not in all.

Pseudoanalgesia could be used to describe the illusion of benefit that some patients receive from opioids, and indeed from a number of substances. Alcohol provides a useful analogy. A person may use alcohol to feel cheerful, to relax, to be sociable, or to get a good night’s sleep. The alcohol abuser, however, is depressed, anxious, isolated, and unable to sleep. With elimination of the substance, mood, sleep, and anxiety often normalize. Smokers find that nicotine provides tranquilization, improved concentration, modulation of such affects as anger and sadness. Yet, after a year without nicotine, smokers are not apparently worse off, with the exception of weight gain.

These situations demonstrate that acute pharmaceutical effects can be dissociated from long-term effects, in which case the consumer may be more aware of the acute effects than the chronic ones. For 25 years, many chronic pain rehabilitation programs have weaned most patients off opioids, and the recurring scenario is of a patient who is certain that opioids “take the edge off” and who is shocked to find a significantly reduced pain level following their elimination. The fact that a patient reports benefit following drug ingestion may indicate only that peak levels are more comfortable than trough. Actual demonstration of benefit would require assessment prior to administration, and at some time following chronic use.

Early Opioid Effects in CNMP

Numerous case reports and studies of chronic opioid treatment confirm that a large number of patients have benefited; however, the literature is weak, and in fact is silent on the question of long-term analgesia. In a 1996 review of opioids for back pain, Brown found no controlled studies. Case series reports on a total of 566 patients suggested that opioid maintenance was safe and effective for many [16].

Zenz et al. provided morphine (20–2000 mg/d, mean = 255) to 100 patients, most with chronic neuropathic or back pain, for a mean of 7 months [17]. Doses stabilized after 14–21 days titration. There was good relief (≥50%) in 51 and partial relief (25–50%) in 28. Pain relief correlated with performance improvement. There were no cases of addiction. Six of eight patients with face and head pain had poor relief.

Haythornthwaite et al. studied 19 patients prior to and following opioid maintenance and compared them with 10 similar patients receiving ‘usual care’ [18]. Opioid maintenance not only reduced pain, it also improved anxiety and hostility. There were no noted cognitive decrements; in fact, psychomotor speed and sustained attention improved. Interpretation is impeded by the fact that 80% of both groups were taking short acting opioids at baseline, and the “usual treatment” group continued to do so. Mean follow up was <6 months.

Ytterberg et al. retrospectively reviewed opioid treatment in 266 rheumatology patients, half of whom had been treated ≥3 months and half <3 months. They reported substantial pain reduction and few complications. Mean treatment dose was less than the equivalent of 3.5–50 mg codeine tablets/d [19]. On the other hand, in a prospective study of 60 patients given morphine for neuropathic and musculoskeletal pain, Schulzeck et al found that only 10 patients had acceptable analgesia and side effects during the observation time of 241 (36–1486) days [20].
Even in the case of those with pre-existing substance abuse or addictive disorder, a small literature shows that opioid treatment can be successful [21,22].

**Long Term Opioid Effects**

The remarkable efficacy of opioids in acute and cancer pain and the tragedy of their underutilization in these conditions have stimulated recommendations for their expanded use in CNMP. Specialists in pain medicine are seeing patients whose lives are essentially restored by this therapy, leading to great enthusiasm for their use. However, this use is a journey in uncharted waters. Studies are short term, and indeed it will be difficult to fund studies whose duration approaches that of the treatment planned. A relatively recent concern is the possibility that chronic opioids could actually increase sensitivity to pain, thus worsening the symptom we are attempting to relieve.

Several investigators have compared matched groups of patients with CNMP to determine how those receiving opioids differ from those not receiving them. In a tertiary care multidisciplinary pain program, Harden et al. compared a random sample of 100 patients taking daily opioids with an equal number taking no opioids [23]. The groups did not differ regarding pain type, duration, location, or surgical history. Opioid patients were more often taking anxiolytics ($P < .05$) and muscle relaxants ($P < .01$), reported higher ($P < .05$) current pain and more frequently ($P < .05$) reported current or past clinical depression or anxiety. No significant differences were noted in pain, psychological status, or functioning. Statistical removal of the effects of differences in pain did not alter the pattern of results for psychological and functional measures.

Jamison et al. surveyed 112 patients, most of whom had chronic back pain, who were maintained on opioids [24]. Of these, 83% reported ≥ moderate relief, 82% reported minimal to no side effects, and 60% reported minimal to no need to increase medication over time. Although the retrospective nature of the study prevented conclusions, it was noted that the patients using opioids, in comparison with those not using them, were less educated, more likely to be unemployed, and had more severe pain pre and post treatment. Surveys such as those of Harden and Jamison provide limited information, given that there is no information as to how treatment decisions were made. They do demonstrate rather convincingly that opioid administration is not the end of pain.

One measure of the efficacy of a maintenance treatment is to remove it. Again the literature is weak, but it is apparent that some patients with CNMP have improved function and reduced pain when opioids are discontinued. Finlayson et al. found that treatment of chronic pain on an addictive disorders unit [25] led to reduced pain, improved relationships and sexual activity, and vocational recovery at 3 year follow up. The fact that these patients were diagnosed with addictive disorders prevents generalizing to those who are free of this condition.

In 124 outpatients with 11 years mean pain, Kell reported that methadone 70–100 mg/d produced a good response in 90%, with 20 month mean follow-up. He noted no significant tolerance and no change in such acute pains as menses and injury [26]. It is perplexing to consider how an analgesic can retain the ability to ameliorate severe chronic pain, yet have no effect on dysmenorrhea. It is congruent with clinical experience that formerly heroin dependent patients on methadone maintenance who undergo injury or surgery require both maintenance methadone and additional opioids for analgesia [27, 28]. We must address the disparity between reports of long term analgesia from opioids and reports that methadone maintenance produces no analgesia for acute pains.

Taylor et al. found, in a small number of patients, that “detoxification” plus brief relaxation training led to improvements in pain, mood, and activity level [29]. Brodner and Taub in another small group found improved pain and return to work following opioid elimination [30].

**Opiogenic Pain?**

Several clinical and laboratory findings cause concern regarding the efficacy of long-term opioid therapy. Animal models clearly demonstrate that opioid tolerance is associated with hyperalgesia [31]. Fentanyl, given subcutaneously to rats, produced analgesia for 2 to 5 hours, followed by hyperalgesia that lasted up to 5 days [32]. Ketamine had no effect on initial analgesia, but prevented development of hyperalgesia. A similar phenomenon occurs in humans following heroin [33]. Indeed, former addicts on methadone have lower pain thresholds in the cold pressor test than drug free opioid abusers [34]. Mean methadone dose in users was 66 mg/d, and, surprisingly, pain tolerance decreased as methadone dose increased. Conversely, in patients with opioid addiction, pain tolerance was higher when they were treated with naltrexone, a µ-blocking agent, than 6 weeks following its discontinuation [35]. In 200 mixed headache patients, prophylactic agents were most effective in those who were weaned from opioids [36].
Extensive animal literature over the last decade has demonstrated that the neurophysiologic changes in the dorsal horn that are associated with tolerance to opioids are very similar to the changes associated with the central sensitization thought to explain hyperalgesia and allodynia. These changes include activation of the second and third messenger intracellular cascades in dorsal horn cells that progress through protein kinase C translocation, removal of the Mg$^{+1}$ block of the NMDA receptor, calcium release/entry, and ultimately nitric oxide formation and release with production of transsynaptic degeneration of inhibitory (?) interneurons [37,38].

Conclusions

We have learned that our approach to the use of opioids for acute and malignant pain was misguided. The same is probably true for those with other tissue threatening but chronic or intermittent conditions, such as HIV-AIDs, sickle cell disease, scleroderma, and peripheral vascular insufficiency.

We have learned that opioids are safe and effective when used in short-term treatment of those with long-term pain.

What we do not yet know is what the effects will be of years, in fact decades, of opioid treatment of intractable pain. From those with addictive disorder maintained on methadone we make the well-supported assumption that we will not be causing organ toxicity, dementia, psychiatric disorder, or motor vehicle accidents.

When we place patients on long term opioids, we do not know whether 5 years hence they will be better off, or whether they will be hyperalgesic. Experience with methadone maintenance and animal models suggests the latter, unless a clinically acceptable way is found to mitigate opioid tolerance or hyperalgesia.

If, as a specialty, we extol the virtues of opioid therapy as the solution to intractable pain—the clear implication of articles that start with, “People no longer have to live with chronic pain, it can be treated,”—we are selling the public more than we can deliver. And we may be placing our specialty far out on a limb that could be cut off should prolonged opioid treatment actually produce more hyperalgesia than analgesia.

What is a reasonable clinical strategy, given the uncertainties we face? I suggest several principles:

1. One should not embark on a plan of protracted opioid therapy in a cavalier fashion. It has serious implications.

2. Those in chronic pain should have analgesia optimized using non-opioids when practicable.

3. Patients should be advised that opioid therapy may be the best option available now, but that we do not know what effect it will have on their pain a decade hence.

4. Patients should be informed that evidence suggests the risk of addictive disorder in short term (<2 years) treatment appears to be low.

5. There must be clear documentation of baseline levels of pain and functional impairment, so that there is no ambiguity as to whether these have improved or deteriorated over time.

6. While a brief (6-month) trial of opioids appears very low risk, it is essential to avoid the indefensible error of continuing a treatment that has demonstrably failed. This seems to be the primary cause of patients and physicians getting into trouble with opioids, and is easily avoidable.

The 3 cases presented here are not so much demonstrations of opioid hyperalgesia as of dogged persistence in a demonstrably failed therapeutic strategy.

Our new specialty is trivialized by the occasional misconception that we treat one disease (intractable pain) with one class of drugs (opioids). The rich diversity of conditions we see, patients who have them, effective therapies, and their varying effects over time are the basis of the scientific and clinical complexity that makes pain medicine a specialty.

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References


President’s Message


