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Defining clinical issues around tolerance, hyperalgesia, and addiction: A quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice

Jennifer P. Schneider, MD, PhD; Kenneth L. Kirsh, PhD

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ABSTRACT

Treatment with opioid medications has grown over the past decades, but has been surrounded by some ongoing controversy and debate to whether it is causing more harm than good for patients. To this end, the field of pain management has suffered from a lack of clarity about some basic definitions on concepts such as tolerance and hyperalgesia. Some characterize these issues as inevitable parts of opioid therapy while other schools of thought look at these issues as relatively rare occurrences. Unfortunately, most of the rhetoric around these topics has occurred with very little in the realm of real world data. To this end, the authors have reviewed the charts of 197 patients treated by a pain specialist for at least 1 year to better illustrate whether notions of tolerance and hyperalgesia are common occurrences and, more importantly, whether they occur within any type of specified timeframe. A total of 197 patient charts were reviewed. The sample had an average age of 49.39 years (range = 19-87 years; standard deviation [SD] = 12.48) and comprised 66 men (33.5 percent) and 131 women (66.5 percent). The patients were seen in the pain practice for an average of 56.52 months (range = 12-155 months; SD = 31.26). On average, the patients maintained an average daily dose of 180 mg morphine equivalents for a period of 35.1 months (range = 3-101 months; SD = 21.3). Looking at the pattern of medication usage change over time, 34.5 percent experienced dose stabilization after the initial titration, 13.2 percent had early dose stabilization within one dose change, and an additional 14.7 percent actually had dose decreases after surgeries or other interventional procedures. Only 6.6 percent of the sample had to be discharged or weaned from controlled substances over time in the clinic. Thus, it appears that tolerance and hyperalgesia are not foregone conclusions when considering placing a patient on long-term opioid therapy.

INTRODUCTION

Although opioids have been acknowledged to be the most effective painkillers for thousands of years and their overall prescribing is increasing, they are still widely debated for the treatment of chronic pain, in particular chronic noncancer pain.[1] A major reason for this is the widespread belief that beginning to treat a patient with an opioid is likely to lead to ongoing dose escalation, the need to endlessly increase the dose in order to maintain adequate pain relief. It is understandable that most practitioners are reluctant to even begin prescribing opioids for chronic pain if their vision of the future comprises unceasing requests by the patient for larger and larger doses.

Traditionally, the perceived need for dose escalation has been attributed to the presumed development of tolerance to the pain-relieving effect of opioids. More recently, however, another mechanism has been proposed to explain a need for dose escalation,

that is, the development of increased pain sensitivity (hyperalgesia) induced by opioid administration.[2] Further adding to many physicians' reluctance to prescribe opioids is a related belief that patients who are prescribed chronic opioids are inevitably going to become addicted to them. Addiction implies loss of control and is often confused with physical dependence, which is actually a different phenomenon. Unfortunately, confusion about these two phenomena is common and leads to misunderstanding by physicians about the motivations of many patients who request additional opioid prescriptions.[2]

These beliefs that patients will likely develop tolerance to the pain-relieving effects of opioids, that hyperalgesia is common and will result in increased pain, and that patients will become addicted to opioids are widespread among both patients and professionals.[3] They are frequently cited as reasons not to use opioids for chronic pain. The question is, are these explanations valid? What do we actually know about tolerance, hyperalgesia, and physical dependence? How do they impact a clinical practice? Published clinical studies that address these questions are sparse and of relatively short term, and the reality is that data have been lacking for both sides of this argument.[4] To remedy the deficiency, a chart review was conducted on 197 consecutive long-term patients from the office of a private practice pain management physician. The goal was to learn about their opioid use over a several years of period, with specific attention to their possible development of tolerance, hyperalgesia, and addiction.

DEFINITIONS AND REVIEW OF THE LITERATURE

Tolerance

There has been a longstanding basic definition of tolerance as a pharmacologic property highlighted by the need for increasing doses to maintain effects.[5,6] Although tolerance to opioids is often mistakenly defined, specifically as the need for increasing doses to maintain analgesia, the widely accepted 2001 definition by the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine makes it clear that such a definition is too narrow. Their consensus document states that tolerance "is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time."[7] Tolerance does not necessarily develop equally to all the effects of opioids.[8,9] We argue that it develops rapidly, within days, to the nauseating, sedating, and respiratory depressant effects and cognitive impairment; this is why opioids are begun at a low dose, but can be increased within days as tolerance to those effects sets in. Tolerance to constipation is uncommon, which is why a prophylactic bowel regimen is a key element of opioid prescribing. When tolerance to other effects of opioids occurs, it happens quickly, within days of initiating therapy or increasing the dose. Tolerance to the analgesic effect of opioids has been postulated to develop weeks to months after initiation of opioid therapy. However, there is no published evidence to support the view that tolerance to opioid analgesia is a late-developing phenomenon. Despite opinions to the contrary, analgesic tolerance seldom interferes with the clinical efficacy of opioid drugs.[10,11] Further, an extensive clinical experience with opioid drugs in the medical context has not confirmed that tolerance causes substantial problems.[12,13] Indeed, most patients attain stable doses associated with a favorable balance between analgesia and side effects for prolonged periods.

Opioids are usually begun at a low dose in order to minimize side effects and are increased as tolerance develops to the side effects. Early upward dosing is therefore expected. In addition, pain relief is often accompanied by an increase in physical activity (a desired outcome!), and the increased activity in itself often requires additional medication to provide adequate pain relief. This in itself can explain why early dose escalation is so frequently found. Later dose escalation, when it is required, usually heralds the appearance of a progressive painful lesion or other new pain concern.[14-16] Unlike tolerance to the side effects of opioids, we propose that clinically meaningful analgesic tolerance, which would yield the need for dose escalation to maintain analgesia in the absence of progressive disease, appears to be a rare phenomenon. Despite this clinical lore, however, we have so far suffered from a relative lack of actual patient outcome data to help substantiate this claim.

Only a few small clinical studies have followed opioid-treated patients for more than a few weeks. In one study, 106 patients with osteoarthritis were enrolled in an open-label 6-month trial of controlled-release oxycodone.[17] The dose of oxycodone became constant at approximately 40 mg/d by week 16, and the

pain intensity was stable. After week 8, when 35.2 percent required titration, the percentage requiring further titration declined. A clinical study of once-a-day sustained-release (SR) morphine included a 26-week open-label extension trial.[18] Following initial dose titration to optimal pain control, 49 percent remained on the same dose throughout the trial, "suggesting that tolerance was not experienced." Among 137 patients with rheumatic disease pain treated with opioids for more than 3 months, only 32 required dosage escalation, and in 28 of these patients, the increases were attributable to worsening of the underlying pain condition or a medical complication thereof rather than the development of tolerance.[19] In an open-label 3-year registry study of the long-term use of controlled-release oxycodone for noncancer pain, the percent of patients requiring dose escalation gradually decreased: 44 percent required an increase in total daily dose before the end of month 3, 23 percent during 4-6 month, and by 1 year stabilized at about 10 percent. The pain intensity ratings were subsequently stable or improved.[20] The authors conclude that the study provides evidence that the greatest need for opioid titration occurs during the first 3 months for most patients, after which further dose escalation may be gradual and minimal. Finally, a recent review of evidence relating to opioid prescribing asked the question, "How do dose-related responses for opioids change at different dose ranges or with long-term use?".[4] The authors reported that there have been no systematic reviews, randomized trials, case-control or cohort studies, or other cross-sectional studies relevant to this question.

Hyperalgesia

Hyperalgesia refers to an exaggerated pain response. This is a known feature of some neuropathic pain syndromes. Opioid-induced hyperalgesia (OIH) has been suggested as an explanation for the decreased analgesic efficacy of opioids in some patients requiring high doses. Several studies showed that patients who received acute intraoperative intravenous remifentanil, an opioid related to fentanyl, experienced increased postoperative pain, as determined by pain scores, morphine requirement, and/or sensory testing.[21] Such studies have been interpreted to show that acute opioid administration rapidly produces hyperalgesia. In a different study population, 355 patients who were on chronic pain medications were given a subcutaneous injection of lidocaine and their resulting pain was quantified. Both pain intensity and unpleasantness scores were significantly higher in subjects receiving opioid therapy than in those receiving nonopioid analgesics.[22] The authors concluded that opioid treatment enhances pain perception and that their study supports the possible presence of OIH in subjects using opioid therapy. Finally, an observational study compared the pain sensitivity in three groups of patients, those with noncancer chronic pain, nonpain patients maintained on methadone for addiction therapy, and a control group, and found that the first two groups had increased pain sensitivity to one stimulus (cold pressor test) but not another (electrical stimulation) and none of the groups exhibited allodynia.[23] The results suggest that chronic opioid use may increase sensitivity to specific pain stimuli but not others and does not produce allodynia. Despite these experimental studies, no published studies have either evaluated the relevance of hyperalgesia to clinical populations of chronic pain patients or provided evidence that OIH actually contributes to increased opioid need in chronic pain patients.

Physical dependence versus addiction

Physical dependence, a related construct, is defined solely by the occurrence of an abstinence syndrome (withdrawal) following abrupt dose reduction or administration of an antagonist.[5,6,24] Addiction, in contrast, is primarily a psychological disorder consisting of three elements: (1) loss of control or compulsive use, (2) continuation despite significant adverse consequences, and (3) preoccupation or obsession with obtaining, using, or recovering from the effects of a drug.[24] There is great confusion among clinicians about the differences between physical dependence and addiction. Physical dependence, like tolerance, has been suggested to be a component of addiction,[25,26] and the avoidance of withdrawal has been postulated to create behavioral contingencies that reinforce drug-seeking behavior.[27] These speculations, however, are not supported by our collective experience acquired during treating patients with opioid therapy for chronic pain. Physical dependence does not preclude the uncomplicated discontinuation of opioids during multidisciplinary pain management of nonmalignant pain,[28] and opioid therapy is routinely stopped without difficulty in the patients with

cancer whose pain disappears following effective antineoplastic therapy. Indirect evidence for a fundamental distinction between physical dependence and addiction is even provided by animal models of opioid self-administration, which have demonstrated that persistent drug-taking behavior can be maintained in the absence of physical dependence.[29] Clinical observation also fails to support the conclusion that analgesic tolerance is a substantial contributor to the development of addiction.

To address the current gap in the studies of long-term opioid use, a retrospective chart review was carried out on all patients who were followed for at least 1 year in a chronic pain practice. While clinical treatment of pain patients usually requires adjustments over time and medication regimens can change for a variety of reasons, it is time to begin exploring actual patient outcomes regarding stable dosing of opioids and whether the hypothesis of late-developing tolerance to analgesia has validity or whether tolerance to any opioid effect or side effect should be considered as a phenomenon developing rather rapidly after introduction of opioids as a treatment modality.

METHODS

The practice

The patients in this practice were seen by a single physician who was certified in internal medicine, addiction medicine, and pain management. No invasive procedures were used. The patients were frequently referred to physical therapy (for hands-on therapy, home exercises, transcutaneous electrical nerve stimulation units, etc), and also, as needed, to anesthesiologist pain specialists (for invasive procedures), orthopedic surgeons, neurologists, physiatrists, psychiatrists, psychologists, and other consultants. The physician saw exclusively pain management patients in a part-time practice in an urban setting. Several other noninvasive pain management physicians practiced in the community, but this physician was known to have experience in the appropriate use of opioids for chronic pain as well as in addiction medicine. As a result, the patients were frequently referred by other physicians after other modalities had been tried (including surgery and other invasive procedures, as well as nonopioid medications) with the expectation that this physician would initiate and/or take over opioid prescribing. The patients were prescribed a variety of medications, which could include anti-inflammatories, muscle relaxants, anticonvulsants (for neuropathic pain), antidepressants, stimulants (for opioid-induced sedation), testosterone (for opioid-induced hypogonadism), and sedative-hypnotics.

In this practice, on the first visit, the patients signed an opioid agreement describing their expected behavior (such as obtaining opioid prescriptions from only one doctor, no change in dosing without prior discussion with the physician, no early refills, permission for the physician to ask for a urine drug test [UDT] at any time, etc) and were asked to sign a release to obtain old records if these had not already arrived. Most commonly, a UDT was obtained on the first visit, as well as randomly every few months and also if the physician had any concerns. A urine screen (immunoassay) was followed in all cases by confirmatory testing if indicated (gas chromatography mass spectrometry [GCMS]). For patients on synthetic or semisynthetic opioids (which are often not picked up on screening), GCMS testing was automatically requested.

The patients were seen initially once or twice a month. They were begun on low doses to minimize the side effects and were titrated up to obtain adequate pain relief. It was anticipated that early on, as the patient's activity level increased because of decreased pain, the dose might need to be increased. Once the patient was on the same dose for several months (ie, was "stable"), the medication dose was increased only if the patient reported an increased pain level. The physician had no arbitrary dose ceiling. Most patients received a combination of an SR opioid for round-the-clock dosing and a small quantity of immediate-release (IR) opioid for breakthrough pain. Stable patients were generally seen every 2 months.

A violation of the opioid agreement was evaluated on a case-by-case basis. For example, in response to a credible report that the pills were stolen from the patient's home, the patient was instructed to keep them locked up or even in a safe place away from the home. If a urine test showed the presence of an illicit substance, the patient was referred out to addiction treatment as a condition for continued opioid treatment by the physician. If agreement violations were egregious (eg, selling one's medication) or repeated, the patients were discharged. This was most likely during the first few months of treatment. Over a 13-year period, this comprised a total of 12 patients whom were

released for opioid misbehavior and an additional 10 patients were discharged for frequently missing appointments with no notice or simply lost to follow-up. Accordingly, patients who were seen for at least 1 year (the minimum for this chart review) were generally compliant.

Participants

A chart review was conducted on a consecutive series of 197 patients treated with opioids for at least 1 year, with an average of 4.7 years (range = 1-12.9 years) in the office of a private practice pain management physician. Each chart contained detailed medication lists listing the exact dose of every medication prescribed at each visit from the first to the final appointment so that reconstructing the patient's complete medication history was straightforward. The review was conducted by the treating physician, who was retiring. This study was determined to be exempt from Institutional Review Board review as it met criteria listed in 45 CFR 46.101(b)[4] as a review of existing data with no identifiers present or linked.

Instruments and procedure

A chart auditing tool was developed covering basic demographics such as age, gender, pain diagnosis, length of time in the pain practice, and type of opioid medication. In addition, attention was placed on recording the dosage of long- and short-acting opioid medications as well as the total number of months that a patient was deemed to be on a stable dose of opioids (as measured by 2 or more months on a fixed dosage of opioid therapy with notation that relief was meaningful to the patient). Finally, the results of UDTs were captured as well as an overall clinician rating of whether the individual patient displayed potential addiction-related behaviors and also a rating of why dose changes in medications occurred.

RESULTS

A total of 197 patient charts were reviewed for the study. The average age of the patients was 49.39 years (range = 19-87 years; SD = 12.48) and comprised 66 men (33.5 percent) and 131 women (66.5 percent). The patients were seen in the pain practice for an average of 56.52 months (range = 12-155 months; SD = 31.26). The primary pain diagnosis was most likely to be back pain (n = 99, 50.5 percent), followed by neck and shoulder pain (n = 19, 9.7 percent), and fibromyalgia (n = 18, 9.2 percent). In addition, 105 patients (53.3 percent) had a clearly defined secondary diagnosis and nearly 14 percent of the sample (n = 27) had three or more pain complaints (Table 1). Of the 197 patients, 77 (33.5 percent) were on Social Security Disability or Workers' Compensation at the time of the first visit;

Table 1. Listing of primary, secondary, and tertiary pain diagnoses*

Pain category	Primary diagnosis (n = 197)	Secondary diagnosis (n = 105)	Tertiary diagnosis (n = 27)
Back pain ± leg pain	99 (50.5)	23 (21.9)	5 (18.5)
Neck/shoulder pain	19 (9.7)	26 (24.8)	4 (14.8)
Fibromyalgia	18 (9.2)	11 (10.5)	2 (7.4)
Other myofascial pain	15 (7.7)	11 (10.5)	4 (14.8)
Pelvic pain	12 (6.1)	1 (1.0)	1 (3.7)
CRPS/RSD	9 (4.6)	3 (2.9)	
Neuropathy	7 (3.6)	4 (3.8)	
Hip and knee pain	6 (3.1)	15 (14.3)	3 (11.1)
Headache/migraine	6 (3.1)	6 (5.7)	4 (14.8)
Rheumatoid arthritis	3 (1.5)	1 (1/0)	
TMJ/other facial pain	2 (1.0)	4 (3.8)	4 (14.8)

Abbreviations: CRPS/RSD, complex regional pain syndrome/reflex sympathetic dystrophy; TMJ, temporomandibular joint disorder.
*Values in parenthesis are represented in percentage.

the remainder had private medical insurance, typically through an Health Maintenance Organization or Preferred Provider Organization, or were on the Arizona version of Medicaid. Sixty-one patients (31.0 percent) were employed outside or inside the home; 96.4 percent were ambulatory at the first visit; and 81.7 percent were driving. At the time of the final visit, 95.9 percent were ambulatory and 81.7 percent were driving.

It was of interest to note whether patients had received interventional procedures before coming to the pain practice as well as during their time in the clinic. A total of 81 patients (41.1 percent) had received some form of interventional procedure before coming to the pain practice. This was most likely to be lumbar laminectomies (n = 33, 40.7 percent) or cervical laminectomies (n = 10, 12.3 percent). During their time in the private practice, only 34 patients (17.3 percent) had interventional procedures, with 16 (47.1 percent of the 34) having lumbar laminectomies, 5 (14.7 percent) having joint replacements, and 4 (11.8 percent) undergoing cervical laminectomies.

A total of 184 patients (94.8 percent) were prescribed a long-acting opioid at some point during their time in the clinic. The opioid chosen was most likely oxycodone (n = 66, 35.5 percent), morphine (n = 54, 29.0 percent), methadone (n = 39, 21.0 percent), or fentanyl (n = 27, 14.5 percent). On average, these patients maintained an average daily dose of 180 mg morphine equivalents for a period of 35.1 months (range = 3-101 months; SD = 21.3). A subset of 31 patients (16.8 percent) receiving a long-acting opioid had to transfer to a second long-acting agent at some point in their treatment. This switch to the second long-acting agent was most likely to be to methadone (n = 14, 45.2 percent), oxycodone (n = 6, 19.4 percent), morphine (n = 6, 19.4 percent), or fentanyl (n = 5, 16.1 percent). This subgroup required an average daily dose of 221.3 mg morphine equivalents and maintained this dose for an average of 30.5 months (range = 4-67 months; SD = 17.4).

Short-acting or IR opioid formulation use was also tracked. A total of 165 patients (86.4 percent) were prescribed a short-acting opioid medication during their time in the clinic. Agents selected for IR use were most often oxycodone (n = 104, 63.8 percent), hydrocodone (n = 34, 20.9 percent), morphine (n = 17, 10.4 percent), or hydromorphone (n = 8, 4.9 percent). Patients requiring a short-acting opioid took an average of 48.8 mg morphine equivalents per day and maintained stable use for an average of 33.9 months (range = 1-99 months; SD = 20.0).

The main focus of exploring whether tolerance developed to opioids over time was to determine how long patients were able to be maintained on a stable dose of opioids. To determine this, the total number of months on a consistent dose of the combination of long-acting and short-acting opioids was calculated. The patients had an average total stable dose of opioids lasting 29.9 months (range = 3-84 months; SD = 17.7). Once a stable dose was achieved, a total of 76 patients (38.6 percent) ended up requiring an increase in their opioid dose at some point. This was rated by the pain physician as being related to disease progression in 50 cases (65.8 percent), increased activity in five cases (6.5 percent), and due to unknown causes in 21 patients (27.6 percent).

Several other domains were of interest in relation to the pain practice and outcomes of the patients. The majority of patients (n = 161, 82.1 percent) had one or more UDTs ordered as part of their clinic care at some point during their tenure in the clinic. Of these, only 14 patients (8.7 percent) had inconsistent urine findings (ie, the presence of illicit substances or nonprescribed controlled substances in the urine or the absence of a prescribed drug). A total of 31 patients (15.7 percent) had aberrant drug-related behaviors suggestive of abuse or addiction noted in their charts (ie, obtaining opioid prescriptions from more than one prescriber without a credible explanation, increasing medication dose without authorization, repeatedly running out early, inconsistent UDT results, and frequent medication "loss"). An independent samples t-test utilizing the presence or absence of aberrant/addiction behaviors indicated that the patients exhibiting these problematic behaviors were less likely to have total stable opioid doses for long periods ($t_{1,189} = -2.66$, $p < 0.008$). In addition, this subgroup was highly related to patients showing problematic urine findings ($r = 0.50$, $p < 0.001$).

Comparisons were also made regarding patient functionality as they entered the practice as well as on exit from the clinic. On entrance to the clinic, 189 patients (96.4 percent) were classified as ambulatory, which remained consistent at the last clinic visit (n = 188, 95.9 percent). Similarly, 158 patients (80.6 percent) were able to drive when initially coming to the clinic, and this rate remained the same at the last clinic visit (n = 158, 80.6 percent). Finally, employment status was examined at the last

visit, with only 37 patients (19.6 percent) being employed. Data on employment status at clinic entrance were not available.

As a final note, 124 patients (63.6 percent) from the selected sample had completed an exit survey from the pain clinic. One of the main questions posed to the patients was whether they felt they were addicted to their opioid pain medications. Of the responders, 48 patients (38.7 percent) felt that they were addicted to their pain medications, 72 (58.1 percent) stated they were not addicted, and the remaining 4 (3.2 percent) were unsure. We also examined the time course of each patient's opioid dosing during the years that he or she was seen at this practice. The results are summarized in Table 2.

In a few cases, there was some overlap of categories. Of the 197 patients studied, 68 (34.5 percent) maintained a stable dose after the initial titration, or

Table 2. Time course of opioid treatment (N = 197)*

	Number	**Subtotals, percent**
Categorization of patient outcome		
Dose stable after initial titration	56	
Patients with long-term stability on low-dose immediate-release medications	4	
Referred from local methadone clinic	8	
Stable		68/197 = 34.5
Initial stability, then stable after one increase	26	
Early stabilization		26/197 = 13.2
After initial titration and stability, dose decreased	19	
Dose decreased after surgery	10	
Dose decreased		29/197 = 14.7
Multiple increases each with period of stability	26	
Increases for patients who worked full-time	5	
Late stabilization		31/197 = 15.7
Multiple increases and never stabilized	10	
Never stabilized		10/197 = 5.1
Complex patients with several increases/decreases of medications, operations, and procedures	30	
Complex management		30/197 = 15.2
Patients discharged for aberrant drug-related behaviors	10	
Discharged		10/197 = 5.1
Patients weaned off opioids because of aberrant drug-related behaviors	3	
Weaned from opioids		3/197 = 1.52
Alternate categorization of sample	Number	Percent
Patients with addiction history, but had good outcomes	19	9.6
Patients with compliance issues (not discharged)	5	2.5
Patients on 400-1000 morphine equivalents per day	14	7.1
Patients on at least 1000 morphine equivalents per day	3	1.52
*Note: N = 207 as 10 patients were in more than one category.		

from their first visit if they had transferred from another physician, for the entire duration of their treatment at the clinic.

Case 1: Early titration and then long-term stability

"N" was a woman in her 30s seen for chronic pelvic pain of long duration. Extensive workup had not revealed a specific diagnosis. She was also seeing an anesthesiologist pain specialist who regularly gave her local injections which provided some relief. Her initial opioid dose was 80 mg of methadone. After 11 months, the dose was increased to 85 mg, and 20 months later, it was increased to 100 mg/d. The patient remained on this dose for the remaining 97 months (8.1 years), until her physician retired. The only pain medication change during that time was the addition of 5 mg hydrocodone per day as needed for the final 84 months of that time. Her pain level remained at 4-6/10. During these years, the patient underwent several abdominal procedures, including a hysterectomy, lysis of abdominal adhesions, right ovariectomy, left ovariectomy (both for ovarian cysts), and a cholecystectomy. While she was a patient at this clinic for more than 11 years, she was fully ambulatory, drove, and was a full-time caregiver for her two ill parents.

Of the 197 patients, 29 (14.7 percent) were able to decrease their opioid dose after a lengthy period of stability. The reasons included surgery (10 patients), initiation of a new effective nonopioid medication such as pregabalin, or for reasons that were less clear but could have reflected increased muscle strength related to improved functioning resulting from decreased pain. Other patients were able to decrease their opioid dose following surgery, whereas others experienced improvement in their pain over time, perhaps because of improvement in their disease or because of increased activity and muscle strength.

Case 2

"B" was a woman in her 40s referred by her primary care physician for medication management of her chronic shoulder and back pain that began 10 years earlier in the aftermath of a motor vehicle accident. Computed tomography, magnetic resonance imaging, and X-rays had shown "nothing surgical," and she underwent local injections, physical therapy, and other modalities. Five years earlier, a physiatrist initiated opioid therapy which she had been on until the current visit. She was on 160 mg/d SR oxycodone plus up to 20 mg/d IR oxycodone. Her pain level was 4-5/10. She was ambulatory, drove, and was a self-employed artist.

The patient was continued on the same medication doses for the next 24 months. At that time, because her pain level had decreased to 3/10, the dose of OxyContin was reduced to 120 mg/d for 10 months, and then again to 80 mg/d for the remaining 27 months through her final visit. She continued taking up to 20 mg/d IR oxycodone as needed. She also continued walking, swimming, and doing regular stretches.

Eight patients had been referred from a local methadone clinic. These were chronic pain patients who had a history of intravenous drug abuse, doctor shopping, or use of nonprescribed opioids, but had demonstrated good compliance with the methadone program. Recognizing that methadone is not a long-acting pain medication despite its protracted serum half-life, the methadone clinic chose to refer them to a pain practice. All the patients proved to be compliant and benefited from the change.

Of the 197 patients, 30 (15.2 percent) were characterized as complex because they required several increases and decreases of dose related to operations and procedures or changes in ongoing pain intensity, changes in medication related to insurance issues or side effects, and with intermittent periods of stability.

DISCUSSION

This chart review study presents an attempt to address the complex issue of whether the development of tolerance to opioid analgesics or OIH is an inevitable part of opioid therapy or if we need to clarify the terminology commonly used by both professionals and the lay public alike. Regarding the role of tolerance in opioid treatment of chronic pain, Portenoy has written

> "A large body of clinical experience indicates that tolerance to analgesic effects is rarely the driving force for declining analgesic effect. Opioid doses typically stabilize during long-term administration, and when analgesic effects decline, a worsening physical lesion or changing psychological status is usually apparent. Contrary to conventional thinking, the development of analgesic tolerance appears to be a rare cause of failure of long-term opioid therapy."[30]

The 197 patients were seen in the pain clinic and treated with opioids for a mean of 4.7 years (56 months), with a range spanning 1 to 12.9 years. After an initial period of adjustment of several months, they remained on a stable total opioid dose for a mean of 2.5 years (30 months), ranging from 3 months to 7 years. More than 61 percent of patients who were stabilized on a particular opioid regimen required no further dose adjustment and were still on the same dose at the end of the study period. These patients can be expected to continue to receive the same dose following the end of the study period.

It is evident from this retrospective study that when initiating opioid treatment, it does take a while to find the correct dose for each individual patient. There are two obvious reasons for this. The first is that no matter how high are the pain levels, opioids must generally be initiated at low doses to minimize the anticipated side effects of nausea, sedation, and respiratory depression. Fortunately, tolerance to these side effects develops very quickly, within days, so that the opioid dose can be titrated upward until adequate pain relief is obtained. The second reason is that increased physical activity is likely to initially generate increased pain. As the patient begins to obtain significant pain relief, his or her activity level will (hopefully) increase, resulting in increased pain and thus a need for increased opioid dosing. This is the most common explanation for an early need for dose escalation, and then the finding that in a majority of cases the opioid dose stabilizes suggests that OIH and tolerance to analgesia are not significant factors.

These results demonstrate that a significant proportion of opioid-treated chronic pain patients can remain on the same dose of opioid for years. The mean stable daily dose of long-acting opioids in this study was 180 mg morphine equivalents. Additionally, most of the patients were on an IR opioid for breakthrough pain, at mean stable dose of 49 mg/d. Thus, the patients in this practice were on opioid doses that some researchers have arbitrarily concluded to exceed the maximal effective opioid dose (200 mg/d).[31] Yet, these stable patients continued to have adequate pain relief, were ambulatory, most were driving, and they believed that they were benefiting from their treatment. They showed no apparent evidence of tolerance or hyperalgesia, despite being on what are considered moderate to high opioid doses.

Among the study patients, 123 (62.4 percent) were on stable or reduced doses for a long period of time. Of the remaining patients, 61 (30.9 percent) had periods of stability interspersed with increased pain, changes of medication, operations, and procedures, etc, and an additional 10 (5.1 percent) never stabilized. In some cases, it was apparent that disease progression was a major contributor, whereas in other cases, the causes of the increased opioid requirement could not be determined with certainty.

Among this population were patients whose medication needs increased with time, and there were others who required progressively less opioid medication. In some cases, the reason for the change in pain level was apparent—increased pain because of disease progression, decreased pain following surgery or other invasive procedures, or because new nonopioid medications helped alleviate their pain. However, there were other cases in which the pain increased or decreased for no obvious reason. Studies have shown that in some 80 percent of patients with chronic low back pain, the specific pain generator is unclear despite a thorough evaluation[2,32]; no wonder that assessment of change in pain status in such patients is difficult. It is tempting to explain the increases in pain on the basis of OIH or tolerance to the analgesic effect of opioids despite the absence of published clinical evidence in chronic pain patients treated with oral or transdermal opioids. This study of long-term opioid-treated patients offers indication that the majority did not require multiple dose increases and are unlikely to experience hyperalgesia or tolerance. Therefore, it appears that the assertion of OIH may have found its greatest usefulness by physicians and regulators seeking justification to limit opioid prescribing and by some cost-conscious insurance companies seeking a medical reason to deny payment for high doses of opioids.

Treating chronic pain with opioids inevitably involves the clinician with addiction issues. The patients must be monitored on an ongoing basis, with careful attention paid to assessing adherence by means of UDTs, careful record keeping of prescriptions provided, and thorough evaluation of aberrant drug-related behaviors.[31,33] Of this patient population, only 10 (5.1 percent) were discharged because of such behaviors, three were weaned off opioids, and an additional five had compliance issues that were able to be resolved. These are actually very low figures. The most likely explanation is

that to qualify for this study, patients had to have been prescribed opioids for at least 1 year. Most of the patients in this practice who were found to have problems with addiction, abuse, or noncompliance for various reasons were identified within the first year and were discharged so that they were not a part of the study.

Although addiction is not the focus of this study, it is instructive to note that 19 patients (9.6 percent) who exhibited good compliance had a history of drug addiction or abuse, including four patients with a history of intravenous heroin use who were referred by a local methadone clinic. An additional four patients referred by the methadone clinic had been seen there only for pain relief after being unable to find a physician willing to treat their pain. A history of addiction or abuse is not an absolute contraindication to the use of opioids for chronic pain, but it does require diligence in monitoring the patients.

It is also interesting that nearly 40 percent of those surveyed felt they were "addicted" to their pain medications. Some explanations were as follows: "If I were to stop I would go into withdrawal"; "I think I'm dependent on meds and would be in bed many more hours if I didn't have pain meds"; "Because everyone says you can get addicted"; "I was advised by another physician I was addicted and I get shivers and yawn constantly at about 7 hours after the last dose"; and "I have tried to stop, but the pain becomes severe." In this clinic, all patients received an explanation about the difference between physical dependence and addiction, about withdrawal symptoms, and about tolerance, and it was somewhat discouraging to learn that many of the patients still misunderstood these concepts. Many clinicians too often confuse addiction and physical dependence and provide erroneous information to their patients. It is evident that we still have a long way to go with educating patients and ourselves on tolerance and dependence.

An obvious limitation of this study is that its results may differ from those of an academic medical center. In a previous publication,[34] it was noted that only 15.4 percent of patients in the pain practice described herein had "inconsistent" urine drug screens when compared with 45 percent of chronic pain patients on opioids in an urban teaching hospital,[35] and it was opined that the long-term relationship with a single doctor who got to know the patients well might have led to a better outcome than an academic center where there is constant turnover of medical providers. It is possible that patients do better in the long term in a small private practice and are better able to stabilize. This does not, however, change the main conclusion of this review, which shows that tolerance to the pain-relieving effects of opioids is not necessarily a normal or expected outcome.

In summary, we attempted to shed some light on the issues of tolerance and hyperalgesia, especially in relation to redefining when these terms become applicable in real world cases. This chart review of 197 patients does offer initial evidence that pain patients are very complex and that using reductionistic ideas about what drives dose increases and changes is flawed. Indeed, many patients were able to maintain stable doses on an opioid regimen for a protracted amount of time along with corresponding increases in functioning. To be sure, there are limitations to the current study, including the very nature of chart review studies, which always yield limited data for predictive purposes. Also, this is a review of only one pain physician's practice and there will surely be differences when comparing practice styles, philosophical approaches, and regional impact. Future work will explore these trends in dose changing in a prospective fashion among multiple prescribers and different geographic regions.

Jennifer P. Schneider, MD, PhD, Retired, Tucson, Arizona. www.jenniferschneider.com

Kenneth L. Kirsh, PhD, Director, Behavioral Medicine, The Pain Treatment Center of the Bluegrass, Lexington, Kentucky.

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