Opioids for Chronic Nonterminal Pain

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Abstract: This article first reviews the evidence for and against chronic opioid therapy. Evidence supporting the opioid responsiveness of chronic pain, including neuropathic pain, includes multiple randomized trials conducted over months (up to 8 months). Observational studies are conducted for longer, and many also support opioid analgesic efficacy. Concerns have arisen about loss of efficacy with prolonged use, possibly related to tolerance or opioid-induced hyperalgesia. Mechanisms of tolerance and opioid-induced hyperalgesia are explored. Evidence on other important outcomes such as improvement in function and quality of life is mixed, and is less convincing than evidence supporting analgesic efficacy. It is clear from current evidence that many patients abandon chronic opioid therapy because of the unacceptability of side effects. There are also concerns about toxicity, especially when opioids are used in high doses for prolonged periods, related to hormonal and immune function.

The issue of addiction during opioid treatment of chronic pain is also explored. Addiction issues present many complex questions that have not been satisfactorily answered. Opioid treatment of pain has been, and remains, severely hampered because of actual and legal constraints related to addiction risk. Pain advocacy has focused on placing addiction risk into context so that addiction fears do not compromise effective treatment of pain. On the other hand, denying addiction risk during opioid treatment of chronic pain has not been helpful in terms of providing physicians with the tools needed for safe chronic opioid therapy. Here, a structured goal-directed approach to chronic opioid treatment is suggested; this aims to select and monitor patients carefully, and wean therapy if treatment goals are not reached.

Chronic opioid therapy for pain has not been a universal success since it was re-established during the last two decades of the twentieth century. It is now realized that the therapy is not as effective or as free from addiction risk as was once thought. Knowing this, many ethical dilemmas arise, especially in relation to patients’ right to treatment competing with physicians’ need to offer the treatment selectively. In the future, we must learn how to select patients for this therapy who are likely to achieve improvement in pain, function and quality of life without interference from addiction.

Efforts will also be made in the laboratory to identify opioids with lower abuse potential.

Key Words: pain, chronic disease, opioids, drug tolerance, addiction, neuroendocrine effects

Changes arising during the twentieth century profoundly altered the way opioids were used for the treatment of pain. These included the introduction in the first decade of drug regulations attempting to control the proliferation of addictive drugs; the subsequent difficulties of convincing patients and physicians that opioids could be used for the treatment of pain without fear of censure; the scientific breakthroughs of the early 1970s confirming the existence of endogenous opioid systems and their role in analgesia and addiction; the realization that pain is a destructive disease process that should be treated; the acceptance that opioids are indispensable for the treatment of acute and terminal cancer pain; and finally, during the last two decades of the century, the extension of opioid treatment to patients with

Key Points
• Opioid treatment was extended to patients with long-term (chronic) pain after it had been firmly established as safe and effective for acute and cancer pain.
• Two decades of experience with this therapy have taught that there are reasons for caution related to loss of efficacy over time, toxicity and higher than expected addiction risks.
• Most authorities agree that improved quality of life—regardless of whether this occurs in the presence of addiction—is a satisfactory outcome of chronic opioid therapy for pain.
• A cautious and selective treatment approach is recommended.
• Future efforts will be focused on developing screening tools to help identify patients at risk before and during treatment.
chronic, nonterminal pain.* Physicians must now accept that it is not considered legal, ethical or good medical practice to withhold opioids from patients whose lives could be improved with treatment. Yet chronic opioid management is not suitable for every patient; there are considerable risks involved, and the treatment is not universally effective. This article presents current evidence on the benefits and risks of long-term opioid therapy, suggests a structured approach to chronic opioid management for pain, and discusses some of the issues surrounding opioid treatment of chronic pain that make achieving a balance and satisfying the needs of patients a veritable challenge.

**Evaluating Chronic Opioid Therapy**

**Analgesic Efficacy**

Adding to concerns about addiction during opioid treatment of chronic pain, there has been a traditionally held view that chronic pain states such as neuropathic pain are not sensitive to opioids. Yet clinical observation suggests that chronic pain states are, in fact, relieved by opioid treatment. It was this uncertainty about the opioid sensitivity of chronic pain that prompted several investigators to conduct randomized controlled trials (RCTs) assessing the analgesic efficacy of opioids for chronic pain states such as the arthritides and neuropathic pain. In some trials, a single IV treatment was used, in others, oral treatment was used over longer periods of up to 32 weeks. Table 1 summarizes the controlled trials of oral treatment. In both types of trials, chronic pain conditions are seen to be sensitive to opioids. In fact, opioids provide superior analgesic efficacy when compared both to placebo and to established treatments (usually non-steroidal anti-inflammatory drugs) for a number of chronic pain conditions. In the case of neuropathic pain specifically, the dose-response curve is shifted to the right (a higher dose is needed), but the opioid sensitivity of neuropathic pain states is confirmed.

While the short-term efficacy of opioids for treating several chronic pain conditions now seems certain, the information from controlled trials is limited by their being conducted only for short periods. This limitation occurs largely because of the impracticability of conducting controlled trials over prolonged periods. The question of whether analgesic efficacy and other benefits of chronic opioid therapy can be maintained over years rather than months remains unanswered. Long-term analgesic efficacy is much more difficult to assess, not least because the factors that influence analgesic effect over time are complex. These factors include the development of tolerance, and the development of opioid-induced hyperalgesia and psychological factors such as changes in the placebo component. Reports in the literature comprise case and case series reports, surveys and open-label follow-up studies in association with some RCTs. These report treatment durations of up to 6 years. The general finding is that patients attain satisfactory analgesia using moderate nonescalating doses (up to 195 mg morphine equivalence per day), often accompanied by an improvement in function, and minimal risk of addiction. It must be remembered, though, that these studies are anecdotal, comprising reports written by experts who likely carried out the treatment with unusual care. This inherent bias is particularly relevant to chronic opioid therapy, which requires considerable dedication, patience and caution to be successful.

A slightly different picture emerges from recently published open-label follow-up studies, which suggests that the failure rate of chronic opioid therapy may be higher than was previously thought. The authors of a 2004 meta-analysis of chronic opioid therapy systematically assessed available follow-up studies and found a 56% drop-out rate. Although these reviewers were unable to distinguish drop out due to inadequate analgesia from drop out due to unacceptable side effects, the high drop-out rate does seem at odds with the high success rates reported in observational studies. Further study is needed to determine how many, and particularly which, patients respond well to long-term opioid therapy in terms of analgesic efficacy.

As more patients are treated with opioids, more patients present to physicians with severe pain despite opioid treatment – sometimes despite high-dose opioid treatment. Reports of difficulty controlling acute pain when it arises in opioid-treated or opioid-using patients, also suggest that something is interfering with analgesic efficacy. Several authors have reported that weaning some patients off opioids results in an improved sense of well being and no change in pain – sometimes pain may even improve. It seems that in these patients at least, there is virtually no analgesic effect, since treatment discontinuation results in no change in pain. Why should pain improve or remain the same upon discontinuing opioid treatment? Here, advances in basic science have helped us understand mechanisms that could account for analgesic failure. Opioid-induced hyperalgesia, for example, is now understood to coexist with opioid analgesia, with analgesia being predominant in most circumstances. N-methyl-D-aspartate (NMDA) receptor mechanisms are seen to be involved in the development of hyperalgesia, whether induced by opioid treatment or associated with neuropathic pain. The

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*The term nonterminal is used so that it includes cancer patients with long survival who suffer chronic pain.
Table 1. Controlled studies: Summary of results

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Type of pain</th>
<th>n/N</th>
<th>Drug</th>
<th>Daily dose (mg)</th>
<th>Follow up</th>
<th>Pain relief</th>
<th>Level of function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kjaersgaard-Andersen 90°</td>
<td>RCT</td>
<td>Osteoarthritis of the hip, in elderly patients</td>
<td>83/75</td>
<td>Codeine with acetaminophen vs. acetaminophen</td>
<td>180</td>
<td>4 weeks</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Moran 917</td>
<td>RCT, crossover</td>
<td>Rheumatoid arthritis</td>
<td>20</td>
<td>CR morphine vs. placebo</td>
<td>up to 120</td>
<td>10 weeks</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Arkinstall 95°</td>
<td>RCT</td>
<td>Musculoskeletal in most patients</td>
<td>46</td>
<td>CR codeine vs. placebo</td>
<td>200–400</td>
<td>1 week</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Moulin 96°</td>
<td>RCT, crossover</td>
<td>Musculoskeletal or soft tissue</td>
<td>46</td>
<td>CR morphine vs. active placebo (bentazopine)</td>
<td>up to 120</td>
<td>11 weeks</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Jamison 98°</td>
<td>RCT</td>
<td>Back pain</td>
<td>24/12</td>
<td>Oxycodone or CR morphine plus oxycodone vs. naproxen</td>
<td>up to 130 (morphine equivalent)</td>
<td>16–32 weeks</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sheather-Reid 98°11</td>
<td>RCT, crossover</td>
<td>Cervicobrachial syndrome, fibromyalgia</td>
<td>6</td>
<td>Codeine vs. ibuprofen or placebo</td>
<td>120</td>
<td>12 weeks</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Watson 98°12</td>
<td>RCT, crossover</td>
<td>Postsurgical neuralgia</td>
<td>38</td>
<td>CR oxycodone vs. placebo</td>
<td>28–62</td>
<td>8 weeks</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Caldwell 99°13</td>
<td>RCT</td>
<td>Osteoarthritis</td>
<td>71/36</td>
<td>CR oxycodone or oxycodone with acetaminophen vs. placebo</td>
<td>up to 60</td>
<td>8 weeks</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pelosi 00°14</td>
<td>RCT</td>
<td>Osteoarthritis, hip and knee</td>
<td>31/35</td>
<td>CR codeine vs. placebo</td>
<td>up to 400</td>
<td>4 weeks</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Roth 00°15</td>
<td>RCT</td>
<td>Osteoarthritis</td>
<td>44/44/45</td>
<td>CR oxycodone, high dose (or low dose) vs. placebo</td>
<td>up to 40</td>
<td>14 weeks</td>
<td>+ (0)</td>
<td>(0)</td>
</tr>
<tr>
<td>Huse 01°16</td>
<td>RCT, crossover</td>
<td>Phantom limb pain</td>
<td>12/12</td>
<td>CR morphine vs. placebo</td>
<td>70–160 (300 in one patient)</td>
<td>4 weeks</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Caldwell 02°17</td>
<td>RCT</td>
<td>Osteoarthritis</td>
<td>73/73/76/73</td>
<td>CR morphine (24 hr) or CR morphine (12 hr) vs. placebo</td>
<td>30</td>
<td>4 weeks</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Maier 02°18</td>
<td>RCT, crossover</td>
<td>Mixed</td>
<td>49</td>
<td>CR morphine vs. placebo</td>
<td>up to 180</td>
<td>2 weeks</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Raja 02°19</td>
<td>RCT, crossover</td>
<td>Postsurgical neuralgia</td>
<td>76/44</td>
<td>CR morphine or methadone vs. placebo (or tricyclic antidepressant)</td>
<td>15–225 morphine, 40–140 methadone</td>
<td>8–24 weeks</td>
<td>+ (0)</td>
<td>0</td>
</tr>
<tr>
<td>Gimbel 03°20</td>
<td>RCT</td>
<td>Diabetic neuropathy</td>
<td>63/52</td>
<td>CR oxycodone vs. placebo</td>
<td>20–120</td>
<td>6 weeks</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Morley 03°21</td>
<td>RCT, crossover</td>
<td>Mixed neuropathic</td>
<td>11/18</td>
<td>Methadone high dose (or low dose) vs. placebo</td>
<td>20 (10)</td>
<td>20 days</td>
<td>+ (0)</td>
<td></td>
</tr>
<tr>
<td>Rowbotham 03°22</td>
<td>RCT</td>
<td>Peripheral and central neuropathic pain</td>
<td>43/38</td>
<td>High-dose levorphanol vs. low-dose levorphanol</td>
<td>up to 11.8 (approximately 60 morphine equivalent)</td>
<td>8 weeks</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Watson 03°23</td>
<td>RCT, crossover</td>
<td>Diabetic neuropathy</td>
<td>35/36</td>
<td>CR oxycodone vs. active placebo (bentazopine)</td>
<td>10–40</td>
<td>4 weeks</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Where two numbers are given, the first is the number of patients in the experimental group and the second is the number in the control group.

Parentheses link treatment with outcome when more than two treatment groups are included in the study.

RCT, randomized controlled trials; CR, controlled release (study drugs not labeled CR were immediate-release preparations); +, statistically significant positive difference; 0, no statistically significant difference.

Table is also used in ASA Refresher Courses, Ballantyne JC "Opioid therapy: is it appropriate in patients with non-cancer pain? An evidence-based look at the issue" to be published in Anesthesiology Vol. 34, 2006.
NMDA receptor is also involved in the development of pharmacological opioid tolerance. Repeated administration of opioids results not only in the development of tolerance (a desensitization process), but also leads to a pro-nociceptive process (sensitization): thus pharmacological tolerance and induced hyperalgesia are seen to coexist, just as analgesia and hyperalgesia coexist. The clinical quandary is obvious – increasing doses could improve or worsen pain. A great deal of uncertainty remains about whether opioid dose, length of treatment or drug choice influences the development of hyperalgesia; and the exact clinical circumstances in which opioid-induced hyperalgesia interferes is also uncertain. Nevertheless, it has become clear that open-ended dose escalation often fails to sustain analgesic efficacy, and the premise that tolerance can always be overcome by dose escalation is now questioned. It is also clear that good analgesic efficacy is not always sustained over time, and that there are clinical situations in which pain and well being can be improved by weaning rather than continuing opioid treatment.

Function and Quality of Life

Many medical practitioners believe that improvements in function and quality of life are needed for long-term opioid treatment to be deemed a success, although a few believe that good pain relief, regardless of other markers of successful treatment, is enough to justify continued opioid treatment. Despite the importance of this debate, the literature provides surprisingly little evidence on nonanalgesia-related outcomes. Some randomized trials combine assessments of pain relief with assessment of function, but the focus of these assessments tends to vary with the primary interest of the investigators. While some investigators demonstrate improvements in limited measures of function, others find no difference (Table 1). Observational trials contribute little in the way of assessment of function. Although some report improvement in broad measures such as ability to perform activities of daily living and return to work, others do not comment. Few opioid trials measure quality of life, which is again surprising given the importance of this factor and the fact that there are several validated measurement instruments available.

Several studies have looked specifically at cognitive function, including the ability to drive and operate machinery while on opioids. This question is obviously critical in terms of whether opioid-treated patients should be encouraged to return to work, to normal daily activities and in particular, to driving. These studies find that cognitive function, manual dexterity and reaction times are maintained at normal levels provided a stable dose of opioid is used. This may not be true when dosing is irregular or escalates.

Side Effects and Complications

Opioid side effects are well known and include respiratory depression, nausea, sedation, euphoria or dysphoria, constipation and itching. With chronic use, most side effects subside since tolerance seems greater to side effects than to analgesic effects. Constipation is an exception, and there appears to be no tolerance to the direct slowing effects of opioids on the bowel, so that constipation remains a high risk and usually requires treatment. Although common side effects (except constipation), usually subside during chronic treatment, they can sometimes interfere to the extent that patients abandon the therapy. Respiratory depression is rarely seen during chronic opioid therapy, but since this is a potentially lethal side effect, one should remain vigilant. The situation in which it most likely arises during chronic opioid pain treatment is when the dose is rapidly escalated, dosing errors occur, or when drugs with unpredictable pharmacokinetics such as methadone are used. (Methadone's complexities are described under “Structured Opioid Therapy”). Other complications of opioid use are more insidious, tend to be associated with long-term rather than short-term use, and are complex and poorly understood. These include hormonal and immune effects, and addiction.

Hormonal and Immune Effects

Long-term opioid use results in clinically relevant suppression of both hypothalampituitary-adrenal and -gonadal axes, with suppression in luteinizing hormone, follicle-stimulating hormone, testosterone, estrogen and cortisol. These effects have been demonstrated in addicts, past addicts treated with methadone maintenance and more recently, in opioid-treated chronic pain patients. The effects are most prominent in patients treated with intrathecal opioids. The gonadal effects can result in male and female infertility and in decreased libido, drive and aggression. Clinically, testosterone deficiency is the most frequently manifest of the deficiencies, and male patients can benefit from testosterone replacement.

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Opioid drugs may affect immunity through their neuroendocrine effects, or through direct effects on the immune system. Preclinical research has shown that opioids alter the development, differentiation, and function of immune cells, and opioid receptors have been demonstrated on immune cells.57,58 Evidence of immune modulation in humans is limited, but opioids have been shown to exacerbate immunosuppression in HIV patients, which suggests that prolonged opioid use may affect the immune system, at least in immunocompromised persons.59 There are no studies of immune function in patients receiving long-term opioid therapy for chronic pain, but the direct evidence that opioids impair immune function in susceptible individuals is concerning. Pain itself can suppress immune function, so patients receiving prolonged opioid therapy without good pain relief are probably the most vulnerable.

Addiction

There is no doubt that the association of opioid use with addiction produces many conflicts with regard to opioid treatment of pain. When it became necessary to introduce drug regulations because the availability, use and abuse of opioids and other addictive drugs had reached unacceptable levels, this compounded the problem, adding a host of legal considerations to the existing moral and ethical dilemmas inherent in balancing humane care with protection from addiction. After the introduction of regulations, it took many years to reestablish opioid treatment as necessary and proper for the control of acute and terminal cancer pain. In fact, as opioid use was reestablished for these indications, it became clear that problematic addiction virtually never arose during the treatment of severe, acute and cancer pain.25,60 But long-term outpatient opioid treatment is likely to be associated with higher risk. Indeed, despite the somewhat optimistic picture painted by early reports such as the seminal report by Portenoy and Foley estimating addiction risk during chronic opioid treatment at approximately 5%,25 higher estimates of up to 19% (this being the upper limit of addiction rates found in a systematic review by Fishbain et al),61 are now accepted by the medical community. There is a problem, however, with all estimates of addiction risk, and that is that iatrogenic opioid addiction (addiction arising during opioid treatment of pain) is poorly defined and understood, despite years of effort to clarify its terminology and processes.62,63 It seems that iatrogenic opioid addiction is simply what the reporting person says it is, and that the vast range of published estimates of risk reflects the lack of an agreed definition. Portenoy and Foley understood at the outset that problematic addiction is unlikely to arise when treatment is provided in a controlled, careful and supportive setting. As they said: “It must be recognized . . . that the efficacy of this therapy and its successful management may relate as much to the quality of the personal relationship between physician and patient as to the characteristics of the patient, drug, or dosing regime.”25 As is the case with opioid maintenance for opioid addiction,54–66 a careful structured maintenance regimen is the best course for preventing the emergence of problematic opioid-seeking behaviors. It follows that observed addiction rates are likely to be higher when practice deviates from the careful controlled approach recommended in published guidelines.24,67,68

Summary of Evidence Supporting Long-term Opioid Use

Many years of clinical use of opioids for pain made it clear that opioids are strong and effective analgesics. Randomized trials confirm the sensitivity of several common chronic pain conditions to opioids, and demonstrate that a short course of treatment (up to 32 wk) using moderate doses (up to 180 mg morphine or equivalent) is effective.

With regard to sustained analgesic efficacy, many authors report (in case reports and case series) prolonged and satisfactory analgesia for up to 6 years using moderate doses of opioid (up to 195 mg morphine or equivalent). On the other hand, some investigators report that failed patients improve when taken off opioids. The suggestion that analgesic efficacy can always be maintained, and tolerance reliably overcome by continued dose escalation must therefore be questioned. With regard to broader outcomes such as function (ability to work and perform normal daily activity) and quality of life, which are considered the most important outcomes of chronic opioid therapy by many clinicians, evidence is limited.

Data on side effects suggest that common side effects such as sedation and nausea usually resolve during chronic treatment, but a significant minority of patients will abandon opioid therapy because of side effects. More insidious liabilities include hormonal and immune effects and addiction. With regard to the hormonal effects, which are known to arise in addicts and chronic pain patients, an important question is whether the effects, independent of other more direct opioid effects, contribute to the general poor psychological and physical health of opioid-treated patients. On the question of addiction and its prevalence during the treatment of pain with opioids, the literature is uncertain. While extremes of addiction and freedom from addiction may seem clear, it remains hard to determine whether the patients who fall between the extremes are addicted or not. There are no satisfactory definitions of iatrogenic opioid addiction, and the lack of an
accepted incidence stems from this lack of agreed definition. The published rate lies between 5% in some practice settings and 19% in others, but as stated earlier, these figures can only be interpreted as reflecting addiction as defined by the person reporting – not by a generally agreed definition.

Structured Opioid Therapy

Given the uncertainty that exists about the extent to which iatrogenic opioid addiction arises, and which patients will be affected, the concept of “universal precautions” applied to chronic opioid therapy has recently arisen. This approach suggests that since current understanding precludes making reliable assessments of which patients are at risk of developing problematic addiction, or indeed, which patients have already developed precursor tendencies toward addiction, the treatment should be applied in a uniformly careful and structured manner. The following describes one such approach.

When a patient first presents with debilitating pain, early aggressive treatment using a rehabilitative approach that aims to restore function and reduce reliance on medications is often the best approach. Opioids can and should be used as needed to facilitate this approach, preferably for a short time only. If this fails, and the physician and patient decide on a long-term commitment to opioid treatment, then the treatment should be goal-directed, and carefully controlled. This means selecting patients with the best chance of benefiting, continuously monitoring for the achievement of preset goals and onset of problematic behavior, and maintaining the lowest effective dose to maintain analgesia and minimize complications. The principles of structured long-term opioid therapy are set out in Table 2.

Selecting patients who are suitable for chronic opioid therapy remains one of the greatest challenges surrounding the therapy, and there is little hard information to guide this selection. Although there are well-established addiction comorbidities including depression, anxiety disorder, personality disorder, history of physical or psychological trauma and history of substance abuse, it is unclear whether patients in controlled and consistent treatment programs are at risk of developing problematic addiction. Present evidence suggests that “at risk” patients do well in controlled programs, and should not be denied opioid treatment of pain solely on the basis of existing addiction comorbidities.

The commitment to long-term opioid therapy is a serious one, and should be considered such by both patients and physicians. Often, opioid therapy has already been started, but this does not obviate the need for careful review of the implications of long-term treatment once the long-term treatment phase is entered. The pain diagnosis should be clearly established and documented. Both parties should be satisfied that all other treatment options have been explored and do not provide adequate relief. Physicians should carefully describe the complications and risks of long-term opioid therapy, explain the monitoring policies of the clinic or practice, and allow patients to express their anxieties. It may be helpful to have an explicit record of the patient’s understanding of the liabilities of long-term treatment and the clinic’s policies for monitoring, and this could be in the form of a signed written agreement or consent. It is also helpful, at this stage, to establish and document the goals of treatment.

After an initial titration to an effective dose, patients should ideally be maintained on a stable dose. In fact, the ability to maintain a stable dose is often an indication of successful treatment. For several reasons, including less likelihood of developing euphoria and therefore addiction, less disruption of normal activity, and less likelihood of focusing on medication throughout the day, long-acting opioid preparations administered round the clock are usually chosen when treating long-term pain. The exact choice of opioid is less important, and for a detailed description of opioid drugs, the reader is referred to the standard texts. It is worth describing some of the problems that arise during treatment with methadone. Since methadone has an intrinsically long half-life, it can be used as a long-acting preparation. It does not need pharmacological manipulation to extend its activity, therefore it is cheap. It has often been recommended as a substitute for long-acting morphine and oxycodone preparations, partly on

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**Table 2. Principles of chronic opioid therapy**

- First try aggressive rehabilitative approach that may utilize opioids, but aims to restore function and reduce reliance on medications
- Consider longer term treatment a serious undertaking that will require the commitment of both physician and patient
- Ensure that other treatment options have been maximized
- Consider opioid therapy as an adjunct; sole opioid therapy is rarely successful
- Use goal-directed therapy; set limits and goals and agree to these
- Use of a written agreement, contract or consent is helpful for setting out terms of treatment, terms for discontinuing treatment, and a clear statement of likely benefits and risks
- Unless pain is occasional, base regimen on long-acting opioids, and avoid breakthrough medication
- Ensure careful and regular follow up
- Monitoring of opioid use is helpful using pharmacy databases, pill-counting or urine toxicology
- Be prepared to wean and discontinue if treatment goals are not met
- Maintain good documentation

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If the physician and patient decide on a long-term commitment to opioid treatment, then the treatment should be goal-directed and carefully controlled.
the basis of price, and partly because of the problems that occurred when OxyContin became a popular drug of abuse. However, methadone’s metabolism, though prolonged, is variable and idiosyncratic. This means that the degree to which the drug accumulates varies from patient to patient. Deaths due to respiratory depression have occurred because of this unpredictability. Moreover, there can be serious interactions, notably with antibiotics and antifungals, as well as rare but dangerous prolongation of the QTc interval on the electrocardiogram.

During the stable phase of treatment, it is mandatory (by law in most states) to provide prescriptions on a monthly basis, and advisable to conduct comprehensive follow-up on a regular basis, assessing pain, the effect of pain on well-being, the achievement of treatment goals, level of function, and quality of life. The patients’ appearance in the clinic on a monthly basis provides an opportunity to observe aberrant behaviors. Extra visits, requests for interim prescriptions and frequent telephone calls to the clinic are considered warning signs for addiction, although it is often impossible to determine whether these type of “nuisance” behaviors reflect desperation with uncontrolled pain, fear of withdrawal associated with physical dependence, or a chaotic lifestyle, rather than addiction. Toxicology screening can be a helpful adjunct to monitoring for problematic opioid use, including for addiction and diversion. Some practitioners believe that all opioid-treated patients should be subjected to random urine screening. In support of this view, in one pain clinic, 43% of opioid-treated chronic nonterminal pain (CNTP) patients were judged “problematic,” and of these, 49% were identified using toxicology screening, not behavioral parameters. In some practice settings, however, routine or random testing would seem unnecessary.

Sometimes an increase in dose will be needed, but careful consideration should be given before each dose escalation. Tolerance to the analgesic effects of opioids can develop over time, but the more common experience is that tolerance levels out, and most patients can be maintained at a stable dose. Thus, if an increase in dose is needed, it should always alert the physician to the possibility that there are other reasons for the need for an increased dose. There may be a change in the patient’s pain or underlying disease, which should be sought and treated if necessary. The need for a higher dose may also be a manifestation of psychological need or addiction, which should also be identified and treated if necessary. At high doses, apparent tolerance may be a sign of opioid-induced hyperalgesia, which will be made worse by dose escalation.

Nevertheless, it is always reasonable to try a controlled dose escalation and see if this improves the pain and overall status of the patient. The aim of each dose escalation is to reach a new, stable dose. For severe pain, it may be helpful to admit the patient to the hospital to help with diagnosis and rapid titration.

The use of very high doses of opioids is rarely helpful. It is hard to say exactly what dose should be considered a high dose, and the issue of whether there is a clinical dose ceiling is much debated. The traditional teaching is that an opioid dose can be increased in a limitless fashion, and that dose increases are capable of overcoming pain. However, there are several clinical situations in which continued dose escalation does not seem to help, and patients complain of severe pain despite high-dose opioid therapy. For example, now that we see very long survival in cancer patients, we also see cancer pain that gets out of control, and dose increases that do not seem to help. This observation, together with the basic science observation that there are multiple splice variants of endogenous opioid receptors resulting in much cross-sensitivity between various opioids, was the genesis of the clinical practice of opioid rotation. A switch to a different opioid can provide equal or better analgesia at half or less of the equivalent dose of the first opioid, and opioid rotation is a reasonable way to control dose escalation. Purely on the basis that the highest daily dose of opioid used in existing trials is 180 mg morphine or morphine equivalent, this dose is suggested as the point one should begin to consider dose reduction or opioid rotation. That is not to say that some patients do not do well on higher daily doses, but rather, that clinical experience suggests that the majority of patients do better if the daily dose is maintained below this level. One should also consider that some liabilities, including neurotoxicity, hyperalgesia, hormonal and immune effects and problematic behavior predominate when high doses are used.

To decide whether to maintain or terminate opioid treatment, one must establish criteria for success and failure. These criteria tend to be subjective, and highly dependent on the treating physician’s viewpoint. Pain relief that improves well being, progress toward achieving treatment goals, improved function, and improved quality of life, are all reasonable criteria for success and continuing therapy. Criteria for failure might include failure to reach any of the criteria for success, or deterioration in the cooperative relationship between physician and patient.

If the treatment fails, as determined by agreed criteria, it should be weaned and discontinued. It is important to wean cautiously to avoid unpleasant withdrawal, the experience of which can make it hard for the patient to give up the medication a second time. Weaning can usually be accomplished over 10 days, but the exact weaning schedule will depend on dose, drug and duration of treatment. If there is addiction,
discontinuation may not be the appropriate course of action, but specialized treatment by a psychiatric or addictionist may be needed. Many patients, especially those who are not doing well on opioids, report an improvement in well being, and possibly also in pain, after an opioid wean. If necessary, opioid treatment can be restarted after a period of abstinence. Opioid weaning is not always straightforward, and it is often helpful to undergo the wean in a rehabilitation setting.

Success

Pain relief that improves well being, progress toward achieving treatment goals, improved function, and improved quality of life.

Failure

Failure to reach any of the criteria for success, or deterioration in the cooperative relationship between physician and patient.

Ethical Dilemmas

Rapid changes in medical science, technology and funding during the past century have had a profound effect on the role of physicians in society and their relationship with patients. Physicians are provided with tools that can alter life itself, so patients are no longer content to put medical decisions solely in the hands of physicians. The Hippocratic tradition of benevolent paternalism, protecting patients through an ethical code "producing good for the patient and protecting that patient from harm," has been replaced by a guidance-cooperation model where the physician steers the patient, but the patient is the primary decision maker. Increasingly, moral and ethical decisions are removed from the confines of individual physician-patient relationships, and move into the realm of public morality. As part of this trend, medical practice is directed more by guidelines, laws and mandates, and less by the dictates of individual physicians. Patients' right to direct their own treatment is expressed in the Patients Bill of Rights, and their right to pain and opioid treatment expressed in "intractable pain" statutes. Physicians are encouraged to provide pain and opioid treatment by Federal Agencies, State Medical Boards, and credentialing bodies. But they are also constrained by legal barriers that tend to inhibit prescribing, and that compound the moral and ethical dilemmas that are inherent in the provision of opioids because of their indispensable role in pain management pitched against their tendency to produce addiction. Against a background of conflicting directives, physicians face real patients, all presenting with a cry for relief, all complex, and many whose decision-making capacity is compromised by the pervasive effect of pain or the drugs used to treat pain. The challenge of balancing the needs and rights of patients, and the safety of patients and community is enormous.

Future Directions

Early, when opioid treatment was extended to patients with chronic pain, and the medical community was buoyed by the success of opioid therapy for acute and cancer pain and the negligible addiction rates associated with these, there was a great deal of confidence that the tenets of opioid treatment for acute and cancer pain would apply equally to chronic pain. Moreover, it was no longer acceptable to deny this treatment to those in need, who now had an indisputable right to be treated. Opioid prescribing for chronic pain increased exponentially during the last two decades of the twentieth century, but so also did prescription drug abuse and the medical community's concern over addiction during opioid treatment of chronic pain. It was realized that the pendulum had swung too far and indeed, opioid prescribing and prescription drug abuse have leveled off since the year 2000. Despite the cost, the lessons learned from this experience have been invaluable. It is now understood that opioid efficacy can diminish over time, and that open-ended dose escalation does not always overcome apparent tolerance. It has become clear how little is understood about the complex relationship between pain, analgesia and addiction, and this has prompted the adoption of structured management protocols that aim to minimize addiction. Concerns about efficacy and addiction have prompted an urgent search to discover more about the basic mechanisms of opioid analgesia, tolerance, dependence and addiction. Insidious opioid complications, such as hormonal suppression, that potentially worsen pain's disability, have emerged as a valid additional reason for keeping doses within a moderate range. But perhaps the greatest lesson is that it does not help to deny the addiction risk, or to fragment pain and addiction care. Remembering that opioid maintenance treatment for opioid addiction has shown remarkable success in keeping addiction under control and allowing afflicted individuals to lead near normal lives, careful structured opioid treatment of pain is the best way known to protect opioid-treated pain patients from becoming addicted. The surest way to hurt them (and society) is to abandon them when they deviate from the constructive relationship envisaged by the treating practitioner, only to trail from physician to physician to obtain the drug they need, or worse still, seek illicit supplies.

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to obtain the drug they need, or worse still, seek illicit supplies. There is still a lot to be learned about basic opioid mechanisms, and about how to predict success and avoid disaster. Several groups are in the process of developing tools to help identify and predict risk, and these efforts are likely to help physicians who are currently torn between their duty to help them. In the meantime, existing evidence strongly suggests that the best way to help patients needing opioid treatment for chronic pain is to provide the treatment in a cautious, selective and supportive manner.

References

Ballantyne • Opioids for Chronic Nonterminal Pain


Begin challenging your own assumptions. Your assumptions are your windows on the world. Scrub them off every once in awhile, or the light won’t come in.

—Alan Alda