

# A Comparison of Long- and Short-Acting Opioids for the Treatment of Chronic Noncancer Pain: Tailoring Therapy to Meet Patient Needs

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Management of chronic noncancer pain (CNCP) requires a comprehensive assessment of the patient, the institution of a structured treatment regimen, an ongoing reassessment of the painful condition and its response to therapy, and a continual appraisal of the patient's adherence to treatment. For many patients with CNCP, the analgesic regimen will include opioids. Physicians should consider the available evidence of efficacy, the routes of administration, and the pharmacokinetics and pharmacodynamics of the various formulations as they relate to the temporal characteristics of the patient's pain. When making initial decisions, physicians should decide whether to prescribe a short-acting opioid (SAO) with a relatively quick onset of action and short duration of analgesic activity, a long-acting opioid (LAO) with a longer duration of analgesic action but a potentially longer onset of action, or both. Studies suggest that SAOs and LAOs are both effective for most types of CNCP. A review of published studies found no data to suggest that either SAOs or LAOs are generally more efficacious for treating any particular CNCP condition. The LAOs may provide more stable analgesia with less frequent dosing; however, opioid therapy should be tailored to the pain state and the individual patient, and SAOs may be appropriate for some patients with CNCP. MEDLINE and PubMed searches were conducted to locate relevant studies published from January 1975 to April 2008 using the following search terms: *opioids, short-acting opioids, long-acting opioids, chronic pain, chronic pain AND opioids, and narcotics*. English-only randomized controlled trials and nonrandomized studies were considered.

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ADL = activities of daily living; AE = adverse effect; ATC = around-the-clock; BPI = Brief Pain Inventory; CNCP = chronic noncancer pain; CR = controlled-release; DN = diabetic neuropathy; ER = extended-release; IR = immediate-release; LAO = long-acting opioid; LBP = low back pain; NSAID = nonsteroidal anti-inflammatory drug; PHN = postherpetic neuralgia; QOL = quality of life; SAO = short-acting opioid; SNRI = serotonin norepinephrine reuptake inhibitor; SR = sustained-release; TCA = tricyclic antidepressant

The International Association for the Study of Pain defines chronic pain as persistent pain lasting longer than the time required for normal tissue healing; for chronic noncancer pain (CNCP), this is generally defined as 3 months or longer.<sup>1,2</sup> Chronic pain affects an estimated 75 million people in the United States and is the nation's leading cause of disability.<sup>3</sup> Individuals with chronic pain may also experience depression, impaired sleep, and a diminished ability to perform normal activities of daily living (ADLs).<sup>4,5</sup> Chronic pain conditions have a substantial financial impact, accounting for an estimated annual total economic loss of \$100 billion (in 1998 dollars),<sup>6</sup> including \$61.2 billion attributed to lost workplace productivity.<sup>7</sup>

Management of chronic pain often requires a multimodal approach that integrates pharmacological and non-pharmacological treatments, such as rehabilitative measures and interventional techniques.<sup>8</sup> Many single-agent or combination pharmacological options for CNCP treatment are available, including nonselective and cyclooxygenase 2-specific nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, anticonvulsant agents, antidepressant agents, local anesthetics,  $\alpha_2$ -adrenergic agonists, and opioids.<sup>8</sup> Opioids often are used to manage moderate to severe CNCP<sup>9-11</sup> and are particularly advantageous because they are effective for many types of CNCP.<sup>9</sup> No evidence indicates that long-term use of single-agent opioid analgesic preparations results in end-organ failure, as may be seen with other analgesics (eg, NSAIDs), or with certain combination opioid analgesics.<sup>12</sup> In addition to their role in the management of cancer pain, opioids are recommended for the treatment of select patients with a variety of CNCP conditions, several of which are discussed in this review.<sup>13-17</sup> For example, opioids may be used in patients with chronic low back pain (LBP) who do not respond adequately to mild analgesic agents, such as acetaminophen or NSAIDs.<sup>15</sup> Opioids are recommended for various neuropathic pain states, particularly if trials of gabapentin, pregabalin, tricyclic antidepressants (TCAs), and/or serotonin norepinephrine reuptake inhibitors (SNRIs) fail to provide adequate analgesia.<sup>18-20</sup> A recent review of available data on the management of osteoarthritis led to a recommendation for weak opioids (eg, tramadol) when pain is refractory to treatment with nonopioid pharmacological approaches (eg, acetaminophen, NSAIDs, injected cortico-

**For editorial comment, see page 572**

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TABLE 1. Starting Doses of Selected Short- and Long-Acting Opioids<sup>a</sup>

Drug	Oral administration			
	Dose (mg) <sup>b</sup>	Frequency (h)	Duration of effect (h)	Plasma half-life (h)
Codeine	15-60	3-6	4-6	3
Fentanyl	100-200 µg	6 <sup>c</sup>	0.5-1 (IV), 72 (TD), 2-4 (TM)	3.7
Hydrocodone	2.5-10.0	3-6	4-8	2.5-4.0
Hydromorphone	2-4	3-4	4-5	2-3
Levorphanol	2-4	6-8	6-8	12-16
Methadone	5-10	6-8	4-6	24
Morphine	15-30 (IR)	3-4 (IR)	3-6	2.0-3.5
Oxycodone	10 (CR), 5-10 (IR)	12 (CR), 3-6 (IR)	8-12 (CR), 3-4 (IR)	2.5-3.0
Oxymorphone	10 (IR), 5-10 (ER)	4-6 (IR), 12 (ER)	3-6	7.0-9.5
Propoxyphene	65-100	4	4-6	6-12
Tramadol	50-100 (IR), 100 (ER)	4-6 (IR), 24 (ER)	4-6 (IR), 24 (ER)	5-7

<sup>a</sup> CR = controlled-release; ER = extended-release; IR = immediate-release; IV = intravenous; TD = transdermal; TM = transmucosal.

<sup>b</sup> Doses are given in milligrams unless otherwise indicated.

<sup>c</sup> Not more than 4 doses per day.

Data from references 1, 32, and 34.

steroids) or when these agents are contraindicated; stronger opioids (eg, oxycodone, morphine) are recommended for the management of severe osteoarthritis-related pain that adversely affects patients' quality of life (QOL).<sup>21</sup>

To develop this comparison between short-acting opioids (SAOs) and long-acting opioids (LAOs), we searched the MEDLINE and PubMed databases for relevant studies published from January 1975 to April 2008 using the following search terms: *opioids*, *short-acting opioids*, *long-acting opioids*, *chronic pain*, *chronic pain AND opioids*, and *narcotics*. Only randomized controlled trials and nonrandomized studies published in English were considered.

Opioid formulations have been classified as short- or long-acting on the basis of their duration of action. The SAOs are distinguished from LAOs by a more rapid increase and decrease in serum levels; LAOs are formulated to release drug more gradually into the bloodstream or have a long half-life for prolonged activity.<sup>22</sup> Generally, SAOs are considered appropriate for transient pain types, such as acute, breakthrough, or chronic intermittent pain, which do not require long-lasting analgesia.<sup>22-24</sup> Commonly prescribed SAOs include immediate-release (IR) morphine, hydromorphone, oxymorphone, codeine, fentanyl, hydrocodone, and oxycodone<sup>22</sup>; codeine, hydrocodone, and oxycodone are also available in combination with acetaminophen or an NSAID,<sup>25-28</sup> which limits the maximum daily dose because of the risk of liver and gastrointestinal toxic effects. This ceiling effect, which is related only to the nonopioid component, may prevent titration to an adequate opioid analgesic dose.<sup>22</sup> However, these risks of toxic effects have not been shown to reduce misuse and abuse of these agents.

The LAO analgesic effect is generally more prolonged than that of SAOs.<sup>23,29-33</sup> Some LAOs (eg, methadone,

levorphanol) are inherently pharmacologically long acting (Table 1),<sup>32</sup> whereas others, such as extended-release (ER), sustained-release (SR), or controlled-release (CR) formulations of oxycodone,<sup>29</sup> oxymorphone,<sup>33</sup> fentanyl,<sup>35</sup> and morphine,<sup>30</sup> have been modified to temporally extend the release of drug into the bloodstream. The analgesic effects of LAOs generally last 8 to 72 hours,<sup>22</sup> making them appropriate for patients with persistent CNCP that requires stable, around-the-clock (ATC) dosing.<sup>22,36</sup> Table 1 outlines recommended starting doses of several LAOs and SAOs; tables such as this vary in their recommendations and generally are not based on empirical evidence. Data directly comparing the efficacy and safety of LAOs vs SAOs are scarce; this review discusses the available evidence for their respective roles in the management of CNCP.

## PHARMACOKINETICS AND PHARMACODYNAMICS OF LAOs AND SAOs

Few studies directly compare the pharmacokinetic and pharmacodynamic properties of SAOs and LAOs.<sup>37-41</sup> Compared with SAOs, LAOs are associated with fewer peak-trough fluctuations and thus provide more stable drug plasma concentrations, which may lead to fewer periods of inadequate pain control.<sup>42</sup> However, the analgesic effects of short- and long-acting formulations of the same opioid were similar when dosed consistently in several trials.<sup>37,43</sup>

Comparisons of similar opioid analgesics with distinct pharmacokinetic profiles have shown that the duration of stable blood plasma levels is significantly correlated with the overall duration of analgesia.<sup>38</sup> Moreover, evidence suggests that longer-acting agents provide more consistent blood plasma levels and may prevent end-of-dose failure.<sup>44</sup>

In an open-label study of patients with moderate to severe noncancer pain treated with ER morphine once daily or CR morphine twice daily, the once-daily formulation showed fewer peak-trough fluctuations of serum morphine concentrations and, consequently, more stable plasma opioid levels.<sup>44</sup> In larger studies,<sup>30,43</sup> however, the mean values for the intensity of pain did not differ between the 2 groups, as was seen in a study comparing IR oxycodone with a longer-acting oxycodone formulation.<sup>37</sup> In that study, IR oxycodone was titrated to an effective analgesic dose before patients were randomized to an IR or a CR formulation. During the 4-hour period after dosing (IR oxycodone vs CR oxycodone or IR oxycodone vs placebo, depending on the time of day), plasma concentrations did not differ significantly between the 2 formulations, although the postdose plasma concentration of IR oxycodone tended to be higher before decreasing to the consistent concentration observed with CR oxycodone.<sup>37</sup>

Although extensive pharmacokinetic data comparing SAOs with LAOs are lacking, some conclusions can be drawn from the available evidence. When dosed according to a fixed schedule, SAOs and LAOs confer similar total systemic opioid concentrations and equivalent pain control.<sup>37,43</sup> Fluctuations in plasma concentrations are less common with LAOs than with ATC dosing of SAOs, and although the maximal concentrations may be lower, they are maintained for longer periods. To obtain stable opioid plasma levels and avoid end-of-dose failure, patients must be meticulous about their adherence to a frequent dosing schedule. The increased dosing interval associated with LAOs may improve treatment adherence, although few data specifically support nonadherence to treatment with SAOs in the general population when they are dosed appropriately.<sup>45-47</sup> The decision to use SAOs or LAOs to treat chronic pain needs to be individualized on the basis of the preceding considerations and of the patient's response to the chosen treatment regimen. Despite the benefits associated with LAOs, individual patients may prefer SAOs because they offer analgesic benefit, improve function, heighten QOL, and may be associated with fewer adverse effects (AEs).

### ANALGESIC EFFICACY OF LAOs AND SAOs IN COMMON CNCP CONDITIONS

The use of opioids for the treatment of CNCP is supported by a number of professional organizations, including the American Academy of Pain Medicine and the American Pain Society.<sup>16</sup> However, few studies have compared SAOs with LAOs head to head; most data concerning the efficacy of opioids are based on comparisons of the active study drug with a placebo control. Therefore, little evidence

shows that either SAOs or LAOs are superior for the treatment of CNCP.<sup>48-51</sup>

### OSTEOARTHRITIS

Osteoarthritis, the most common rheumatologic disorder and a primary cause of disability, is associated with structural malfunction of the synovial joints.<sup>52</sup> Osteoarthritis affects approximately half the population 65 years and older and currently affects 1 in 5 Americans overall.<sup>53</sup> The number of Americans 65 years and older is expected to double by 2030; therefore, the social burden of osteoarthritis will likely increase.<sup>53</sup> The American College of Rheumatology recommends opioid analgesics if other pharmacological therapies (eg, acetaminophen, NSAIDs) do not provide effective analgesia and pain interferes with QOL.<sup>54</sup> More recent guidelines for the treatment of osteoarthritis of the hip and knee continue to recommend opioids for treating refractory pain when other pharmacological treatment is inadequate or contraindicated.<sup>21</sup> These guidelines specify that opioid treatment should be considered in conjunction with the continued use of nonpharmacological modalities (eg, physical therapy, patient education).<sup>21</sup> Nonsteroidal anti-inflammatory drugs are commonly prescribed for patients with osteoarthritis; however, because osteoarthritis commonly affects older adults in whom the prolonged use of NSAIDs may be absolutely or relatively contraindicated as a result of the potential for serious renal, cardiac, and gastrointestinal complications, opioids may be a better analgesic choice for many of these patients.<sup>55</sup>

In studies lasting from 2 to 30 weeks, LAOs, including ER morphine,<sup>30</sup> ER oxymorphone,<sup>31,56</sup> CR oxycodone,<sup>31,57,58</sup> and transdermal fentanyl,<sup>59</sup> have consistently shown efficacy in treating moderate to severe chronic pain associated with osteoarthritis.<sup>30,31,57-59</sup> However, few studies have directly compared the analgesic efficacy of SAO regimens with that of LAO regimens in patients with osteoarthritis. The efficacy and safety of CR oxycodone twice daily or IR oxycodone-acetaminophen as needed were assessed in an open-label, randomized study of patients with osteoarthritis. A greater percentage of patients treated with CR oxycodone compared with IR oxycodone-acetaminophen reported improved pain relief after 4 months of treatment (63% vs 46%;  $P < .001$ ).<sup>60</sup> Total daily doses for each group in this study were not reported. Another study showed that IR oxycodone-acetaminophen 4 times daily or CR oxycodone twice daily significantly decreased pain compared with placebo in patients with osteoarthritis ( $P \leq .05$  for both regimens), and no significant difference was found between the levels of analgesia attained with the IR and CR formulations.<sup>48</sup> As-needed analgesic dosing may be suboptimal for patients with continuous pain because dosing will

not occur until pain onset; for these patients, ATC dosing is preferable. Limited data preclude drawing concrete conclusions regarding the relative efficacies of SAOs compared with LAOs for osteoarthritis-related pain; further research is needed on this topic.

### LOW BACK PAIN

Chronic LBP occurs in 28.3% of adults 18 years or older<sup>61</sup> and is the fifth most common reason that Americans consult with a physician.<sup>62</sup> Opioid therapy, as part of a multimodal approach to pain management, may prove beneficial for some people with chronic LBP. The American College of Physicians and the American Pain Society consensus guidelines for the treatment of chronic LBP state that opioids are a treatment option for severe, disabling pain not controlled by acetaminophen or NSAIDs.<sup>15</sup>

The LAOs have been shown to lessen pain intensity in patients with chronic LBP for short periods, although evidence of their long-term efficacy remains sparse. In a randomized, double-blind study, chronic LBP was treated with either ER oxycodone or CR oxycodone; both treatments significantly reduced pain intensity compared with placebo control ( $P<.05$ ).<sup>63</sup> In a 6-month efficacy study, patients who attained stable analgesia (pain score  $\leq 4$  on a 0- to 10-point scale) for 8 weeks using either once-daily morphine or twice-daily CR oxycodone were followed up for 4 additional months.<sup>64,65</sup> In both groups, pain scores remained consistently lower through month 4 relative to baseline.

The SAO formulations are also an effective treatment option for some patients with moderate to severe chronic LBP. Treatment with IR oxycodone resulted in significantly improved pain scores in trials lasting up to 4 weeks.<sup>49,66</sup> In a study comparing CR oxycodone twice daily with IR oxycodone 4 times daily, both treatments, at equivalent daily doses, provided comparable reductions in pain intensity for patients with moderate to severe LBP.<sup>49</sup>

Given that certain SAOs and LAOs have been reported to provide substantial analgesia in patients with chronic LBP, it is important to analyze available data to determine whether one of these groups of medications is superior to the other. Neither group has been shown to have superior efficacy in studies comparing the effects of SAOs and LAOs with placebo or relative to baseline pain scores; evidence-based recommendations are limited<sup>22,67</sup> and sometimes influenced by confounding patient selection criteria.<sup>68</sup> A 16-week, randomized, open-label study compared pain relief in 36 patients using IR oxycodone (maximum dose, 5 mg 4 times daily) with that in patients administered a titrated dose of IR oxycodone plus SR morphine twice daily (combined maximum dose, 200 mg/d of morphine

equivalents).<sup>51</sup> After the initial 16-week experimental phase, all patients were eligible for the titration phase: titrated doses of IR oxycodone plus SR morphine twice daily. During the initial phase of the study, significantly lower average ( $P<.001$ ), current ( $P<.001$ ), highest ( $P<.001$ ), and lowest ( $P<.001$ ) pain scores were reported for the titrated group than for the group taking a set dose of IR oxycodone.<sup>51</sup> The titrated group also showed significantly improved mood ( $P<.001$ ). These data do not specifically support the addition of an LAO for the treatment of CNCP. The total daily dose of IR oxycodone during the initial study phase did not exceed 30 mg of morphine or morphine equivalents.<sup>69</sup> Patients in the group given a titrated dose of IR oxycodone plus the SR morphine, however, were treated with an average daily dose of 41 mg of morphine equivalents, with some patients receiving as much as 130 mg/d,<sup>51</sup> likely explaining the greater effect this regimen had on intensity of pain. The results suggest that patients receiving individualized care, with physicians closely monitoring therapeutic response and adjusting medication on the basis of current pain levels, may have better outcomes than patients not receiving individualized opioid therapy.

### NEUROPATHIC PAIN

Neuropathic pain, resulting from a lesion or dysfunction in the peripheral and/or central nervous system, is associated with such conditions as diabetic neuropathy (DN), post-herpetic neuralgia (PHN), and phantom limb pain.<sup>2</sup> The most recently published evidence-based guidelines call for the initial treatment of neuropathic pain with TCAs, the  $\alpha_2\delta$  ligands gabapentin and pregabalin, or selective SNRIs, alone or in combination.<sup>19,20</sup> These guidelines recommend that opioid analgesics be used when first-line treatments do not demonstrate a satisfactory response.<sup>20</sup> Opioids can also be used as first-line medications in combination with TCAs, SNRIs, or the  $\alpha_2\delta$  ligands in certain circumstances (eg, to obtain immediate pain relief during the titration of a nonopioid medication to an effective analgesic dose and/or to treat episodic exacerbations of severe pain).<sup>20</sup> Reasons for not including opioids as a first-line medication include the increased rates of both short- and long-term AEs relative to other treatments and the potential risk for misuse and abuse.<sup>20</sup> In addition, opioids and nonopioids may be combined in rationally developed multidrug regimens that seek additive or synergistic analgesia and/or a reduced AE load by targeting multiple targets along neural pain-transmitting pathways.<sup>70</sup> Guidelines specific for the treatment of diabetic peripheral neuropathic pain recommend the use of long-acting oxycodone as a first-tier agent, citing published demonstrations of efficacy.<sup>71</sup>

Use of LAOs may be appropriate for the relief of different types of neuropathic pain. In patients with PHN, the analgesic effect of CR oxycodone twice daily was evaluated in comparison with placebo.<sup>72</sup> Patients reported significantly greater relief of daily pain ( $P=.0001$ ) and a significantly lower mean intensity of daily pain ( $P=.0001$ ).<sup>72</sup> Similar results were observed for CR oxycodone in patients with painful DN, which provided significantly lower mean levels of daily, steady, brief, skin, and total pain compared with placebo ( $P=.0001$ ).<sup>73</sup> Another study looked at patients with PHN or DN pain receiving SR morphine for a 5-week period and compared them with patients receiving placebo; the patients receiving SR morphine reported a significantly decreased mean level of daily pain ( $P=.01$ ).<sup>70</sup>

Few studies have examined the efficacy of SAO formulations for neuropathic pain. In a randomized, placebo-controlled study of tramadol in patients with DN, tramadol provided significant reductions in pain intensity ( $P<.001$ ) and increases in pain relief ( $P<.001$ ) compared with placebo during the 6-week treatment period.<sup>74</sup> Maintenance of pain relief was continued through a 6-month open-label extension<sup>75</sup>; patients who were randomized to placebo in the original trial and subsequently given tramadol titrated to a maximum of 400 mg in the extension had improved pain scores relative to baseline; they reported scores of pain intensity and relief matching those of patients initially randomized to tramadol in the double-blind portion of the study.<sup>75</sup>

No studies have compared directly the effectiveness of LAOs and SAOs in patients with neuropathic pain. Thus, the decision to initiate opioid therapy and the selection of an appropriate agent for neuropathic pain must be based on a comprehensive assessment of each patient's medical and social circumstances, an individual characterization of the pain profile, the agreed-on functional goals of treatment, and the observed response of the patient to the treatment regimen.

## QUALITY OF LIFE

Pain is a complex experience for patients, encompassing psychological and emotional aspects that can be difficult to fully articulate. Pain affects the physical, mental, and social functions that allow patients to take part in ADLs. Conventional numeric pain scales ranging from 0 to 10 do not distinguish between the physical and emotional pain components. Learning how pain affects QOL may help to improve function, a critical goal of pain therapy. To aid the physician in identifying baseline and ongoing changes in function, several questionnaires have been developed, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the 36-Item Short-Form

Health Survey, and the Brief Pain Inventory (BPI). These tools allow multiple outcomes to be measured (eg, stiffness, mental health, relationships with others), providing a better understanding of how pain interferes with daily function.

The LAOs have been shown to improve QOL measures in patients with CNCP. In 2 independent studies of patients using CR oxycodone twice daily for the treatment of osteoarthritis-related pain, patients reported significant improvements in overall mood, as measured by the BPI pain interference scales (BPI,  $P<.05$  and  $P=.018$ ) and enjoyment of life (BPI,  $P<.05$  and  $P=.012$ ).<sup>57,58</sup> Although the BPI has been validated as a reliable measure of pain severity and interference in patients with CNCP,<sup>76</sup> the individual items of the BPI pain interference scale have not been validated and therefore results are subject to interpretation.<sup>77</sup> These improvements in QOL extended to social and overall physical function (WOMAC,  $P<.001$ )<sup>58</sup> and to activities associated with work outside the home and household chores (BPI,  $P=.006$ ).<sup>58</sup> Similar results were attained in a study of patients with DN or PHN treated with SR morphine twice daily.<sup>70</sup> In that study, patients reported significantly improved enjoyment of life and ability to perform general ADLs and normal work activities (BPI,  $P<.05$ ).<sup>70</sup> In another study, patients with LBP using either morphine once daily or CR oxycodone twice daily reported significant improvement in overall function using the 12-Item Short-Form Health Survey ( $P<.0005$  for both agents).<sup>64,65</sup> Improvements in general mental health also have been observed when chronic pain was treated with LAOs.

The SAOs can also improve measured variables associated with QOL in patients with CNCP. In a 4-week study comparing various doses of oxycodone-acetaminophen 3 times daily (mean daily dose, 24.6 mg) with placebo for LBP, the patients given active treatment reported significant improvement in relationships, mood, sleep, general activities, walking, normal work, and enjoyment of life vs the patients given placebo (BPI,  $P<.0004$  for each).<sup>66</sup> In a 3-month study examining the efficacy of tramadol-acetaminophen in patients with chronic LBP, significant improvements were seen in the physical role ( $P=.005$ ), emotional role ( $P=.001$ ), mental health ( $P=.026$ ), and mental health summary ( $P=.008$ ) domains of the 36-Item Short-Form Health Survey.<sup>78</sup>

In a study comparing IR oxycodone at a maximum dose of 5 mg 4 times daily (approximately 30 mg/d of morphine equivalents) with IR oxycodone plus SR morphine twice daily titrated to a combined maximum dose of 200 mg/d of morphine equivalents, significantly lower levels of anxiety, depression, and irritability were observed in the combination group ( $P<.001$  for all comparisons).<sup>51</sup> As previously discussed, the combination arm in this group was receiving

a greater total daily dose of opioids, and their dosage was adjusted weekly on the basis of current levels of pain. The data show that individualized care and appropriate patient selection and management can result in QOL improvement. At the end of the year-long study, more patients reported a preference for the SAO. This preference was seen after the titration phase, during which all patients were taking an SAO and an LAO and were allowed, under supervision, to modify their total daily dose on the basis of pain intensity.<sup>51</sup>

The goals of pain management therapy include not only reductions in pain but also improvements in psychosocial functioning relative to baseline, including emotional well-being and the ability to perform ADLs. The experience of pain is unique for every patient; therefore, treatment goals are tailored to the needs of each patient. For some patients, controlling constant pain with LAOs may be best, if less frequent dosing and sufficient pain relief allow them to resume at least some, if not all, normal activities; other patients may find that an SAO provides them with the same outcome and is more effective than an LAO.

### SLEEP

Comorbid pain-related sleep disturbances are reported by 88.9% of patients with chronic pain.<sup>79</sup> The pain-sleep relationship is such that pain may exacerbate sleep disturbances, which, in turn, may further intensify physical and mental symptoms, such as pain, disability, impaired daily functioning, and depression.<sup>4,79</sup> Therefore, providing effective analgesia may relieve pain-related sleep disorders (Figure).<sup>80</sup>

The LAO formulations may effectively improve sleep in some patients with chronic pain. In a randomized, double-blind, placebo-controlled trial, patients with painful DN who took CR oxycodone twice daily showed significant improvements in sleep quality compared with patients using placebo ( $P=.024$ ).<sup>81</sup> A second randomized, 4-week, double-blind trial, followed by an open-label, 26-week extension study, compared the efficacy of once-daily morphine with that of placebo among patients with osteoarthritis.<sup>30</sup> During the initial 4-week study, patients using once-daily morphine reported significantly improved overall quality of sleep, less need for sleep medication, increased hours of sleep, and less trouble falling asleep because of pain ( $P\leq .05$ ).<sup>30</sup> During the 26-week extension trial, statistically significant improvements continued in these areas ( $P\leq .05$ ).<sup>30</sup> In a similar study of patients with chronic LBP, once-daily morphine provided significant improvement in sleep scores after 12 weeks of treatment ( $P=.004$ ).<sup>65</sup> An open-label, randomized, large-sample ( $N=266$ ) study of once-daily morphine and twice-daily oxycodone used

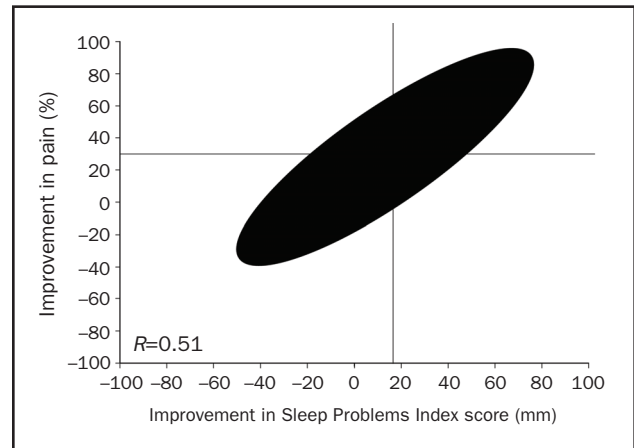


FIGURE. The relationship between intensity of pain and quality of sleep. From *Curr Med Res Opin*,<sup>80</sup> with permission.

the Pittsburgh Sleep Quality Index to measure subjective sleep quality during an 8-week evaluation period. Pittsburgh Sleep Quality Index scores improved significantly with both ER morphine and CR oxycodone.<sup>64</sup>

Objective evidence obtained in a pilot study supports subjective reports that pain control with LAOs can improve sleep quality.<sup>82</sup> Patients with difficulty sleeping because of chronic knee or hip osteoarthritis were treated with once-daily ER morphine, and polysomnography was used to assess sleep quality. Polysomnography confirmed reports of better sleep by patients, whose total sleep time ( $P<.05$ ) and sleep efficiency ( $P<.05$ ) were significantly increased compared with polysomnography scores obtained before the study.<sup>82</sup> Furthermore, the amount of time it took to fall asleep (sleep latency), wake time after sleep, and the time it took to reach a deep sleep were all reduced compared with placebo baseline polysomnography scores.<sup>82</sup> Rapid eye movement sleep latency numbers reached statistical significance ( $P<.05$ ). This study provides objective data of improved sleep in these patients, supporting the subjective self-reported improvements in sleep of patients with chronic pain undergoing LAO therapy.

The SAOs also improve the sleep characteristics associated with CNCP. In a study in which BPI was used to measure sleep, patients taking IR oxycodone-acetaminophen 3 times daily for chronic LBP reported significant sleep improvement after 4 weeks ( $P<.0001$ ).<sup>66</sup>

Comparative studies assessing whether SAOs or LAOs are more effective for improving sleep are limited. In one study, patients with osteoarthritis-associated pain were treated with CR oxycodone twice daily or IR oxycodone-acetaminophen 4 times daily for 4 weeks after a 4-week titration period.<sup>48</sup> Although both treatments improved quality of sleep significantly more than did placebo ( $P\leq .05$ ), the

CR group reported significantly better quality of sleep compared with the IR group ( $P=.0382$ ); however, the latter group had reported significantly better quality of sleep before randomization ( $P=.0068$ ).<sup>48</sup> These data demonstrate that effective pain control with SAOs or LAOs improves sleep in patients with CNCP, although SAOs, because of their pharmacokinetic characteristics, may not provide the same benefits in patients who experience waking in the middle of the night and early morning pain. The critical determinant in improving sleep in patients with CNCP is effective pain relief, which can be obtained with either SAOs or LAOs in patients selected because of their specific needs and the nature of their pain.

As with all therapies, a careful risk-benefit analysis must be performed to determine the relative merits of opioid therapy. Although numerous studies have shown opioid therapy to positively affect sleep in patients with CNCP, some patients undergoing long-term opioid therapy may exhibit an increase in sleep disturbances, particularly central sleep apnea.<sup>83,84</sup> Further research into this phenomenon is needed because a significant, negative relationship between opioid therapy and sleep apnea was shown only for methadone, but not other opioids, in a single large-scale study.<sup>84</sup> Other studies, however, have shown a dose-dependent relationship between the long-term (>6 months) use of both methadone and nonmethadone opioids (eg, hydrocodone, oxycodone, and morphine) and sleep apnea.<sup>83</sup>

### ADVERSE EFFECTS

Patients being treated for CNCP should be monitored for AEs, which may influence the decision to continue, adjust, or discontinue a pharmacological regimen. Moreover, because of response variability to treatment, AE profiles for medications or classes of agents may differ.<sup>85</sup> With opioid therapy, common AEs include constipation, nausea, vomiting, dry mouth, and sedation.<sup>86</sup> In several studies comparing SAOs and LAOs, no definitive evidence linked the pharmacokinetic profile of the formulation and the number of peak-trough fluctuations to the overall incidence of AEs.<sup>37,43,44,48,87,88</sup> For example, some evidence suggests that longer-acting formulations somewhat reduce the incidence of certain AEs (eg, nausea,<sup>85,87</sup> pruritus,<sup>43</sup> constipation<sup>44</sup>), whereas other LAO studies show slightly increased incidence rates of these AEs.<sup>37,47,48</sup> Several reports have posited a correlation between prolonged use of opioid analgesics and hypogonadism.<sup>88,89</sup> Opioid-induced changes in immune function have been discussed in the literature,<sup>11</sup> although the effect of long-term opioid analgesia is not well understood. Hyperalgesia has also been reported to be associated with long-term opioid administration, a possible contributing factor to the development of apparent analgesic tolerance.<sup>90,91</sup>

Recently published clinical guidelines developed after a systematic review of the available literature regarding the use of long-term opioid therapy in CNCP make the following recommendations regarding opioid-related AEs: "Clinicians should anticipate, identify, and treat common opioid-associated side effects."<sup>92</sup> The authors of these guidelines note that most patients undergoing long-term opioid therapy will develop some degree of constipation. They also note that sedation tends to wane over time and conclude that evidence is insufficient to recommend specific medical therapies for ongoing opioid-related sedation. With respect to the long-term use of opioids while driving or working, these same guidelines specifically recommend the following: "Clinicians should counsel patients on chronic opioid therapy about transient or lasting cognitive impairment that may affect driving and work safety. Patients should be counseled not to drive or engage in potentially dangerous activities when impaired or if they describe or demonstrate signs of impairment." The authors noted, however, that epidemiologic studies did not suggest that motor vehicle accidents, fatalities, or citations for impaired driving were more likely to occur because of long-term opioid use.<sup>92</sup> Historically, SAOs have been used during the initial stages of opioid treatment for chronic pain to titrate an effective analgesic dose. This approach allows the physician to obtain information about the pharmacological effects of the drug without causing long periods of discomfort if the drug produces intolerable AEs. Patients with persistent pain are then transitioned to an LAO and are often treated with an equianalgesic daily dose.<sup>22</sup> However, support currently is increasing for using LAOs earlier in treatment, particularly for patients who are opioid experienced.<sup>49,50</sup> These patients may have a decreased risk of certain AEs (eg, respiratory depression, nausea), which may otherwise arise during titration with LAOs.

### APPROACHES TO RISK ASSESSMENT AND MANAGEMENT WITH SAOs AND LAOs

Opioid therapy is associated with risks for misuse and abuse. In recent years, an increasing number of Americans have been using prescription pain relievers for nonmedical purposes; 5.2 million people abused pain relievers in 2006, an increase from 4.7 million in 2005.<sup>93</sup> Historically, conventional wisdom suggested that SAOs are more likely to lead to abuse and that aberrant behavior is less likely with LAOs because of their pharmacokinetic and pharmacodynamic features.<sup>94,95</sup> Several studies, however, have shown that abuse of both SAOs and LAOs is a serious problem. Hydrocodone preparations are the most frequently prescribed SAOs for the management of chronic pain<sup>94</sup> and are the most frequently prescribed opioid analgesics in emer-

**TABLE 2. Universal Precautions for the Opioid Treatment of Patients With Chronic Noncancer Pain**

Careful diagnosis with an appropriate differential
Psychological assessment, including risk of addictive disorders
Informed consent
Treatment agreement
Preintervention and postintervention assessment of pain level and function
Appropriate trial of opioid therapy with or without adjunctive medications
Reassessment of pain level and function
Regular assessment of the 4 As:
<b>Analgesia:</b> Is the patient's pain being controlled?
<b>Activities of daily living:</b> Have the patient's functional abilities increased?
<b>Adverse effects:</b> What adverse effects are present and are the consequences outweighing the beneficial effects of therapy?
<b>Aberrant behavior:</b> Is the patient exhibiting any behaviors indicative of possible misuse or abuse?
Periodic review of pain diagnosis and comorbid disorders, including addictive disorders
Documentation

Data from reference 100.

gency departments.<sup>96</sup> Thus, it is not surprising that hydrocodone was the most commonly cited opioid responsible for nonmedical emergency department visits in the 2005 Drug Abuse Warning Network<sup>97</sup> and, along with ER oxycodone, is the most commonly abused opioid when the rate is based on the total population (1.66 cases of abuse per 100,000 people).<sup>98</sup> However, if the rate of abuse is calculated based on the number of prescriptions, then LAOs (eg, ER oxycodone) are most often abused (6.45 cases of abuse per 1000 persons filling a prescription).<sup>98</sup> Through physical tampering, some LAOs can be converted to SAOs, making them more attractive to some abusers. It is clear that addressing the problem of opioid misuse and abuse is not a simple issue of long- vs short-acting formulations but one of identifying patients at risk for abuse and continually monitoring them for problematic behaviors.

A comprehensive risk assessment to stratify patients according to possible risk for opioid misuse considers their medical, psychiatric, social, and family histories, in addition to findings on physical examination.<sup>99</sup> Many physicians have adopted a universal precautions approach to pain management.<sup>100</sup> This approach posits that optimal care not only relieves pain but also reduces the opioid-associated stigma and protects against misuse and abuse risks (Table 2). Such an approach codifies many physician practices already in use and applies them specifically to cases that may present a risk of abuse. It also encourages the evaluation of biological, psychological, and social characteristics that correlate with misuse or abuse potential.<sup>100-102</sup> For example, depression, prior legal problems, and a family history of drug abuse are all factors that may help a physician identify risk of opioid abuse. In addition, several

validated screening questionnaires (eg, Opioid Risk Tool,<sup>102</sup> Revised Screener and Opioid Assessment for Patients with Pain<sup>103</sup>) are available to help stratify patients into low-, moderate-, and high-risk categories.<sup>102-104</sup> Risk stratification allows physicians to appropriately structure therapy and monitoring and to identify those patients who may require consultation with a pain specialist or, in some instances, an addiction specialist. When appropriately used, urine drug tests and opioid treatment agreements can be useful tools for physicians. Opioid treatment agreements codify the responsibilities of both the patient and physician. Urine drug testing allows the physician to monitor patient adherence and identify the use of illicit drugs. Standardizing risk assessment procedures and individualizing the level of monitoring can help improve patient outcomes and protect the health care professional from legal risk.

### IMPLICATIONS FOR MANAGEMENT OF CHRONIC PAIN

Although SAOs and LAOs are efficacious in a variety of chronic pain conditions, their appropriate roles in the management of chronic pain are specific to the individual patient. Chronic noncancer pain should be managed like other chronic conditions. For example, in the treatment of hypertension, the goal is to maintain consistent control over the condition as soon as possible, using medications that provide consistent blood pressure control. In appropriately selected patients with chronic pain who are prescribed SAOs, a change to LAOs shortly after titration to effective analgesia may be appropriate to provide consistent pain reduction. The pharmacokinetic profiles of LAOs, which result in more sustained and stable plasma opioid concentrations compared with SAOs, may allow more consistent and prolonged analgesia. Such analgesia could be vitally important for patients with CNCP and unremitting levels of daytime pain or those seeking improved nighttime sleep. By definition, LAOs are associated with less frequent dosing than SAOs, which may improve adherence to the therapeutic schedule in older adults and any patient dealing with polypharmacy. However, some patients with CNCP are comforted by the rapid onset of analgesia associated with SAOs, particularly to address intermittent or breakthrough pain.

### CONCLUSION

Management of CNCP should be tailored to the individual patient. Because patients will have different pain profiles and therapeutic goals, optimal treatment must be individualized, accounting for not only the characteristics of the pain state but also its effects on QOL and the therapeutic goals.

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