REVIEW ARTICLE

Benefits of Extended-Release Opioid Analgesic Formulations in the Treatment of Chronic Pain

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■ **Abstract:** Chronic noncancer pain represents a major health problem that affects many patients, resulting in suffering, reduced productivity, and substantial health care costs. The patient with chronic noncancer pain is burdened by decreased quality of life, decreased sleep, interference with social relationships, diminished cognitive functions, interference with activities of daily living, decreased productivity, and increased anxiety and depression. A survey examining the burden of pain on health and productivity found decreases of 45% in physical health and 23% in mental health at a cost of $61.2 billion per year in productive work time. An American Pain Society survey of 800 patients with moderate to severe chronic pain reported that 47% felt their pain was not under control. The goal of pharmacological therapy for chronic noncancer pain is to provide sustained analgesia. Chronic pain management guidelines recommend the use of long-acting, extended-release (ER) analgesics because they provide prolonged, more consistent plasma concentrations of drug compared with short-acting agents, thus minimizing fluctuations that could contribute to end-of-dose breakthrough pain. ER analgesics offer more consistent and improved nighttime pain control, less need to awaken at night to take another dose of pain medication, and less clock-watching by patients in chronic noncancer pain. Among the available ER opioids, tramadol ER possesses a unique mechanism of action, making it a viable opioid of first choice for patients suffering from a variety of chronic noncancer pain conditions, such as osteoarthritis, low back pain, and neuropathic pain. ■

Key Words: analgesics, opioid, extended-release

INTRODUCTION

An estimated 20% to 30% of Americans suffer from chronic pain,[1] sometimes referred to as chronic noncancer pain, which is defined as pain that continues beyond the time normally associated with healing for a specific illness or initial injury.[1,2] Chronic noncancer pain represents a major health problem that affects a substantial number of patients, resulting in personal suffering, reduced productivity, and increased health care costs.[3–5] A survey examining the burden of pain on employee health and productivity reported that pain was associated with decreases of 45% and 23% in overall physical and mental health, respectively.[6]

Some of the most common chronic painful conditions include episodic migraine headaches, arthritis, back pain, and other musculoskeletal conditions. These conditions contributed to a 13% loss in U.S. workforce productivity and a $61.2 billion per year loss in productive work time.[7] The patient burden of chronic pain is characterized by overall decreased quality of life,[8] sleep disturbances including decreased time and quality of sleep,[9] interference with social

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relationships,[9] diminished cognitive function,[4] interference with activities of daily living,[4] decreased productivity,[3] and increased anxiety[10] and depression.[11] This review will highlight the impact of chronic pain on sleep disturbances, discuss the principles of managing chronic pain, and review the clinical efficacy and tolerability of long-acting formulations of opioid analgesics for treating moderate to moderately severe chronic noncancer pain.

SLEEP DISTURBANCES IN PATIENTS WITH CHRONIC PAIN

Chronic pain can disrupt sleep, and poor sleep can lower the pain threshold, which may contribute to increased pain.[12–14] Findings in healthy volunteers have shown that sleep deprivation produces hyperalgesia, but conversely that sleep recovery produces an analgesic effect.[12–14]

Effective management of chronic pain is complicated by the presence of additional conditions that arise in response to the pain, in particular pain-related sleep disturbances.[15] Approximately 65% of people with chronic pain report disrupted or nonrestorative sleep.[15] The most frequent sleep complaints include delayed onset of sleep, frequent awakenings, decreased sleep duration, daytime fatigue, and nonrestorative sleep.[16] Effective treatment of pain-related sleep disturbances should be considered a key component of the overall approach to managing chronic pain.[15] Because greater pain intensity has been associated with decreased sleep satisfaction, less total sleep time, delayed onset of sleep, and more awakenings due to pain,[17] effective pain control should improve sleep in patients with chronic pain. Thus, sleep disturbances may serve as a marker for the assessment of response to treatment for chronic noncancer pain.

TREATMENT FOR CHRONIC PAIN

Despite advances in understanding its etiology and pathophysiology, chronic noncancer pain remains inadequately treated. A survey conducted by the American Pain Society[18] of 800 patients with moderate to severe chronic, noncancer-related pain reported that 47% of patients felt that their pain was not adequately controlled. An important goal of analgesic therapy for chronic noncancer pain is to provide sustained analgesia; therefore, regular administration is required to ensure the next dose of an analgesic is given before the effects of the previous dose have dissipated.

Pharmacologic management of chronic pain includes the use of non-opioid analgesics (eg, nonsteroidal anti-inflammatory agents [NSAIDs], acetaminophen, and cyclooxygenase-2 [COX-2] inhibitors), antidepressants, anticonvulsants, scheduled opioid analgesics (eg, oxycodone), and nonscheduled opioid analgesics (eg, tramadol).[19–22] While opioids are widely used for the treatment of cancer pain, the use of opioid analgesics for treating chronic noncancer pain is more controversial.[23,24] Common concerns among both doctors and patients include the possibility of addiction, abuse, and side effects such as respiratory depression, gastrointestinal effects (particularly constipation), and urologic effects.[23,25] However, the use of opioids for treating chronic noncancer pain may be justified in patients who have not responded to other therapy.[23]

It is important to keep in mind that response to treatment may depend on the nature of the chronic pain (neuropathic or nociceptive). Neuropathic pain results from direct injury or dysfunction of sensory neurons in the peripheral or central nervous systems.[26] In neuropathic pain, the fundamental mechanism responsible for ongoing pain may not directly result from the original injury or damage.[26] Examples of neuropathic pain include diabetic neuropathy, post-herpetic neuralgia, phantom limb pain, and multiple sclerosis-related pain.[26] Nociceptive pain is a normal response to painful stimuli (ie, tissue injury).[26] Examples of nociceptive pain include mechanical low back pain, arthritis pain, and postoperative pain.[26] Neuropathic pain may be less likely to respond favorably to opioid therapy than nociceptive pain.[25]

EXTENDED-RELEASE OPIOID ANALGESICS

For patients with continuous chronic noncancer pain, compliance with regular administration of short-acting analgesics is essential to help prevent gaps in pain relief, the result of which may be patients who are constantly "chasing their pain." Consequently, these patients may benefit from an extended-release (ER) analgesic that can be administered once or twice daily. Pain management guidelines recommend the use of long-acting agents in patients with chronic pain because they provide sustained analgesia for 12 to 24 hours.[19–22] ER analgesics can provide prolonged, more consistent plasma concentrations of drug compared with short-acting agents and minimize fluctuations that could contribute to end-of-dose breakthrough pain.[27]

A number of potential advantages exist for the use of ER analgesics for patients with moderate to moderately

Table 1. Extended-Release Oral Opioid Analgesic Products

Analgesic	Available dose strengths (mg)	Usual dosing interval (h)
Morphine ER	30, 60, 90, 12020, 30, 50, 60, 80, 100, 200	12–24
CR oxycodone	10, 20, 40, 80	12
Oxymorphone ER	5, 10, 20, 40	12
Tramadol ER	100, 200, 300	24

ER, extended release; CR, controlled release.

severe chronic pain.[28] ER formulations eliminate the need to wait until the pain returns before taking the next dose, thereby providing more consistent pain control. In addition, ER analgesics may provide better nighttime pain control with less need for nighttime dosing, which may improve pain-related sleep disturbances.[28] Patients also experience less clock-watching and improved convenience when taking these long-acting formulations. Several oral analgesics are available in ER formulations (Table 1). Oral analgesics such as oxymorphone ER, controlled release (CR) oxycodone, and morphine ER are used to treat moderate to severe chronic pain, while tramadol ER is indicated for moderate to moderately severe chronic pain. In addition, a transdermal ER formulation of fentanyl is available to treat patients with severe chronic pain.

OXYMORPHONE ER

An ER tablet formulation of oxymorphone (OPANA® ER; Endo Pharmaceuticals, Chadds Ford, PA)[29] has been evaluated in four randomized, double-blind, placebo-controlled studies of patients with moderate to severe osteoarthritis or chronic low back pain and has also been evaluated in one long-term, open-label study of patients with osteoarthritis.[30–34] Two studies of oxymorphone ER were conducted in patients with moderate to severe osteoarthritis.[30,31] The first was a 2 week study in 370 patients randomized to oxymorphone ER 10, 40, or 50 mg or placebo administered every 12 hours.[30] Least square means change from baseline to the final visit in pain intensity visual analog scale (VAS) scores were significantly greater with oxymorphone ER 40 and 50 mg compared with placebo ($P < 0.05$). The oxymorphone ER 40 and 50 mg doses also produced significant improvements in the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, which is a validated, multidimensional tool used to detect clinically important changes in disease status following employment of an intervention to treat osteoarthritis.[35] Specifically, improvements were seen in the subscale scores for pain, stiffness, and physical function ($P < 0.05$ for all parameters). The most common adverse events with oxymorphone ER included nausea (39%), vomiting (24%), dizziness (23%), constipation (22%), somnolence (18%), pruritus (17%), and headache (15%).

In the second study, 491 patients with osteoarthritis were randomized to oxymorphone ER 20 or 40 mg, oxycodone ER 20 mg, or placebo every 12 hours for 4 weeks.[31] At 3 weeks, the least square means change in pain intensity VAS was significantly improved with oxymorphone ER 20 and 40 mg compared with placebo ($P < 0.05$ for both doses). Adverse events included nausea, vomiting, constipation, dizziness, and somnolence.

Oxymorphone ER (10 to 110 mg) was compared with oxycodone CR (20 to 220 mg) and placebo every 12 hours in 213 patients with moderate to severe chronic low back pain during a 7- to 14-day dose titration phase.[33] Patients achieving effective analgesia at a stable opioid dose entered an 18 day double-blind treatment period and either continued opioid therapy or received placebo. Mean daily doses were 79.4 mg for oxymorphone ER and 155 mg for CR oxycodone. The least square means difference pain intensity (VAS) scores for the change from baseline were significantly different from placebo for both oxymorphone ER and CR oxycodone ($P < 0.001$). The most common adverse events with oxymorphone ER and CR oxycodone were constipation (35% and 29%) and sedation (17% and 20%), respectively.

Two long-term studies evaluated oxymorphone ER in the treatment of chronic low back pain in opioid-naive[34] and opioid-experienced[36] patients. In the first study, the efficacy and safety of oxymorphone ER was compared with that of placebo in 325 opioid-naïve patients with moderate to severe chronic low back pain, after titration to an effective dose.[34] The mean stabilized dose during the 12-week study was oxymorphone ER 40 mg daily. Pain intensity increased significantly more with placebo than with oxymorphone ER (least square means change 26.9 vs. 10.0, $P < 0.001$). During double-blind treatment, approximately 8.6% of patients in the oxymorphone ER group and 8.0% of patients in the placebo group discontinued due to an adverse event. The most commonly reported adverse events in the oxymorphone ER group included nausea (11.4%), vomiting (7.6%), constipation (6.7%), and diarrhea (5.7%). The second study evaluated the safety and efficacy of oxymorphone ER, compared with placebo, in opioid-experienced

patients.[36] The mean stabilized daily dose in this study was 87.2 mg. Similar to the results in opioid-naïve patients, pain intensity increased significantly more with placebo compared with oxymorphone ER (least squares mean change 31.1 vs. 8.7, $P < 0.001$). Discontinuations due to adverse events were similar among the groups (oxymorphone ER, 11%; placebo, 10%). The most common adverse events in the oxymorphone ER group included constipation (6%), somnolence (3%), and nausea (3%).

The safety, tolerability, and effectiveness of oxymorphone ER was evaluated in a 52-week open-label extension study of 153 patients with moderate to severe osteoarthritis pain.[32] The median daily dose was oxymorphone ER 40 mg. Sixty-one (40%) patients completed the study; however, half of the patients who discontinued from the study were opioid-naïve patients from the placebo group who participated in the previous controlled study. The most common adverse events cited by patients who withdrew were nausea (14%), vomiting (11%), constipation (5.9%), and dizziness (5.9%). At least 80% of patients rated the global satisfaction survey with oxymorphone ER as excellent, very good, or good at each assessment.

The effects of oxymorphone ER on sleep were also evaluated in three of the studies.[30,31,33] In the 2-week study of oxymorphone ER 10, 40, or 50 mg, osteoarthritis patients completed the Chronic Pain Sleep Inventory (CPSI) to assess sleep quality.[30] Overall improvements in sleep quality were 2-fold greater at Week 2 with oxymorphone ER 40 and 50 mg compared with placebo ($P \leq 0.05$). In addition, in the 4-week study comparing oxymorphone ER 20 or 40 mg, oxycodone ER 20 mg, or placebo every 12 hours, significant improvements in sleep quality were observed at Week 3 with oxymorphone ER 20 mg compared with placebo ($P < 0.05$). However, the oxymorphone ER 40 mg and the CR oxycodone 20-mg dose groups showed significant differences only from baseline to Week 4 ($P < 0.05$), compared with placebo.[31] In the third study, which compared oxymorphone ER with CR oxycodone and placebo in patients with chronic low back pain, interference with sleep was evaluated using the Brief Pain Inventory (BPI).[33] Interference with sleep was less in the oxymorphone ER group than in the placebo group (mean 4.8 vs. 5.8), although the difference was not significant.

THE CR OXYCODONE

A CR oral formulation of oxycodone hydrochloride (OxyContin®, Purdue Pharma L.P., Stamford, CT)[37] has been evaluated in three studies of patients with moderate to severe pain from osteoarthritis.[38–40] In a randomized, placebo-controlled study, 107 patients with moderate or severe osteoarthritis pain were randomized to CR oxycodone 10 mg or placebo every 12 hours for up to 90 days.[38] The dosage could be increased to a maximum dose of CR oxycodone 60 mg every 12 hours. The mean daily CR oxycodone dose after titration was 44 mg. Average pain intensity and pain-induced interference with general activity decreased significantly with CR oxycodone compared with placebo ($P < 0.05$ for both comparisons). Common adverse events were typical of opioid analgesics and included constipation (48%), nausea (41%), somnolence (32%), and dizziness (32%). In a second study, 167 patients with moderate to severe osteoarthritis pain were randomized after an open-label titration period to placebo, CR oxycodone or oxycodone immediate-release (IR) plus acetaminophen (APAP) for 30 days.[39] The mean daily dose of CR oxycodone after titration was approximately 40 mg. Pain intensity improved significantly in both oxycodone groups compared with placebo during double-blind treatment ($P \leq 0.05$). Nausea and dry mouth were less common with CR oxycodone than with oxycodone IR plus APAP. In another study, 133 patients with moderate or severe osteoarthritis pain were randomized to treatment with CR oxycodone 10 or 20 mg or placebo every 12 hours for 14 days.[40] Only the CR oxycodone 20-mg dose was significantly better than placebo for reducing pain intensity and interference with mood, sleep, and enjoyment of life ($P < 0.05$ for all parameters). During a 6-month open-label extension, pain intensity remained stable at a daily CR oxycodone dose of 40 mg. Nausea (41%), constipation (32%), and somnolence (27%) were the most common adverse events seen in the CR oxycodone 20-mg treatment group.

Each of these studies also evaluated the effects of CR oxycodone on pain-related sleep problems and showed significant improvements during short-term treatment.[38–40] The randomized, placebo-controlled study of 107 patients with moderate or severe osteoarthritis pain demonstrated a significant reduction in BPI scores indicating an improvement in sleep with CR oxycodone compared with placebo ($P < 0.001$).[38] In the second study, 167 patients with moderate to severe osteoarthritis pain were randomized after an open-label titration period to CR oxycodone, oxycodone IR plus APAP, or placebo for 30 days. The study evaluated global quality of sleep and showed that sleep quality was significantly reduced during treatment with placebo

but was maintained at baseline levels with CR oxycodone ($P \leq 0.05$ vs. placebo).[39] In the third study, 133 patients with moderate or severe osteoarthritis pain were randomized to treatment with CR oxycodone 10 or 20 mg or placebo every 12 hours for 14 days. The study also evaluated pain-related sleep problems with the BPI and demonstrated a significant improvement with CR oxycodone 20 mg compared with placebo after 2 weeks of treatment ($P < 0.05$).[40] During the long-term extension phase, the mean number of nighttime awakenings due to pain decreased from 1.6 at baseline to 0.7 at 6 months with CR oxycodone.

MORPHINE ER

Two ER formulations of morphine have been evaluated in four studies of patients with moderate or severe pain (AVINZA®, distributed by King Pharmaceuticals, Inc., Bristol, TN, and KADIAN®, manufactured by Alpharma Branded Products Division Inc., Elizabeth, NJ).[41,42] In a randomized, double-blind study, once-daily morphine ER (30 mg) compared with twice-daily morphine CR (15 mg) or placebo was evaluated in 295 patients with moderate to severe osteoarthritis pain who had failed to obtain adequate pain relief with NSAIDs and acetaminophen after 4 weeks of treatment.[43] Morphine ER significantly reduced pain and improved sleep measures compared with placebo ($P < 0.05$ for both parameters). The most common adverse events in the morphine ER treatment group were constipation (49%), nausea (21%), somnolence (16%), and dizziness (10%).

The ACTION study was a randomized, open-label, multicenter study comparing once-daily morphine ER to twice-daily CR oxycodone in 220 patients with moderate to severe chronic low back pain who were treated for 8 weeks.[44] The mean daily doses were 69.9 and 91.0 mg for morphine ER and CR oxycodone, respectively. Both drugs provided significant pain relief and improved sleep, according to the Pittsburgh Sleep Quality Index ($P < 0.05$). In patients who completed dose titration, morphine ER was significantly better than CR oxycodone in improving pain scores and pain-related sleep disturbances at a lower daily dose. An open-label study evaluated morphine ER in 491 patients with noncancer-related chronic pain.[45] The study showed improvement in pain ($P < 0.01$) and sleep quality ($P < 0.01$) over a 4-month treatment period with once-daily doses of morphine ER (60 mg). High rates of patient satisfaction were also reported in this study.

Extended-release morphine was also evaluated in a prospective, randomized, open-label blinded endpoint study in 1,428 patients for the treatment of chronic, moderate to severe pain in a community based outpatient setting.[46] Patients were randomized to morphine ER daily in the morning or evening for a 4-week treatment period; dose increases were allowed, and switching to twice daily dosing was reserved until Week 2. The median starting dose for morphine ER was 40 mg/day. Improvements were seen in pain and sleep scores and patients and clinician global assessment scores ($P < 0.001$ for all comparisons). The most common adverse events reported were constipation (11.6%) and nausea (9.2%).

TRANSDERMAL ER FENTANYL

An ER transdermal formulation of fentanyl (Duragesic®; manufactured by Alza Corporation, Mountain View, CA; distributed by Janssen Pharmaceutica Products, L.P., Titusville, NJ) has been evaluated in four studies of patients with moderate or severe pain due to osteoarthritis or rheumatoid arthritis not adequately controlled with non-opioid or weak opioid analgesics.[47–50] In a randomized, placebo-controlled study, 399 patients with moderate to severe osteoarthritis pain (defined as a mean daily VAS pain score ≥50 at the start and end of a 7-day pretreatment run-in phase during which patients received their usual medication) were randomized to receive treatment with transdermal fentanyl beginning at a dosage of 25 mcg/hour ($n = 202$) or transdermal placebo ($n = 197$) for 6 weeks.[48] Transdermal patches were replaced every 72 hours with the option to increase the dosage to achieve adequate pain control. At the end of the 6-week treatment phase, patients were tapered off the drug by removing one transdermal patch every 3 days. Transdermal fentanyl provided significantly greater pain relief and significantly improved WOMAC Osteoarthritis Index subscale scores for pain and overall from baseline to Week 6, compared with placebo (all $P < 0.01$),[48] and WOMAC scores for stiffness and physical functioning showed a statistically nonsignificant trend in favor of transdermal fentanyl. In addition, transdermal fentanyl was significantly better than placebo for improving quality of life based on Short Form-36 (SF-36) scores for pain index and mental component from baseline to study end (both $P < 0.05$). The most commonly reported adverse events during the treatment phase in the transdermal fentanyl group were nausea (44%), vomiting (28%), and somnolence (22%; all $P < 0.001$). During the tapering-off phase, insomnia (9%), muscle

contractions (7%), and nausea (6%) were the most commonly reported adverse events in the transdermal fentanyl treatment group.[48]

In an open-label study, patients with moderate or severe pain due to rheumatoid arthritis ($n = 104$) or osteoarthritis of the knee or hip ($n = 159$) received transdermal fentanyl beginning at 25 mcg/hour for 28 days followed by a 1-week tapering-off period.[50] Transdermal patches were replaced every 72 hours with the option to increase dosage (maximum dosage was 125 mcg/hour) to achieve adequate pain control. The most frequently used maximum dosage was 25 mcg/hour; 75% of patients at Week 1 and 88% at Day 28 had good, moderate, or excellent pain control. The results of this study revealed that transdermal fentanyl significantly reduced pain, as measured using the Wisconsin BPI ($P < 0.001$); based on the SF-36 Survey, patients reported significant improvements in quality of life (both physical and mental components; $P < 0.001$ and $P < 0.05$, respectively). The most commonly reported adverse events were nausea (32% vs. 9%) and vomiting (23% vs. 6%) during the treatment and tapering-off phases, respectively.[50]

A prospective, open-label study evaluated transdermal fentanyl in patients with moderate or severe pain due to osteoarthritis of the knee ($n = 102$) or hip ($n = 57$).[49] Patients received transdermal fentanyl beginning at 25 mcg/hour for 28 days followed by a 1-week tapering-off period. Transdermal patches were replaced every 72 hours with the option to increase dosage to achieve adequate pain control. The daily doses ranged from 25 to 125 mcg/hour; the mean daily dosage increased from 26 mcg/hour at Week 1 to 37 mcg/hour at Week 4. Seventy-four percent and 88% of patients reported moderate, good, or excellent pain control at Week 1 and Day 28, respectively. The results of the study showed that transdermal fentanyl significantly reduced pain from baseline to endpoint, as measured using the Wisconsin BPI ($P < 0.001$).[49] In addition, the WOMAC Osteoarthritis Index subscale scores for pain, stiffness, and physical functioning improved significantly from baseline to endpoint following treatment with transdermal fentanyl (all $P < 0.001$). Patients also reported significant improvements in quality of life, as demonstrated by significant improvements in all SF-36 domains (all $P < 0.05$). The most commonly reported adverse events during the treatment and tapering-off phases, respectively, were nausea (32% vs. 10%) and vomiting (26% vs. 6%).[49]

Transdermal fentanyl was also evaluated in a prospective, open-label study, in which 104 patients with moderate or severe pain due to rheumatoid arthritis received transdermal fentanyl beginning at 25 mcg/hour for 28 days followed by a 1-week tapering-off period.[47] Transdermal patches were replaced every 72 hours with the option to increase dosage to a maximum of 125 mcg/hour to achieve adequate pain control. The mean daily dose was 32.8 ± 1.51 mcg/hour; at Week 1, 43%, 33%, and 1% of patients reported moderate, good, and excellent pain control, respectively, with transdermal fentanyl. At Days 14 and 28, respectively, 79% and 88% of patients reported adequate pain control. The results of this study demonstrated that transdermal fentanyl significantly reduced pain, as measured using the Wisconsin BPI ($P < 0.001$).[47] Transdermal fentanyl significantly reduced "pain right now" in the first 24 hours of treatment and the degree of pain from baseline to study endpoint (both $P < 0.001$). In addition, patients reported significant improvements in the majority of items on the Health Assessment Questionnaire and all domains on the SF-36 questionnaire, except role-emotional (all $P < 0.05$). The most commonly reported adverse events during the treatment and tapering-off phases of the study, respectively, were nausea (32% vs. 7%) and vomiting (18% vs. 5%).[47]

THE ER TRAMADOL

An ER formulation of tramadol (ULTRAM® ER; manufactured by Biovail Corporation, Mississauga, Canada; distributed by PriCara™, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., Raritan, NJ) was developed to provide pain relief with once-daily dosing.[51] This is the first ER formulation of tramadol approved by the U.S. Food and Drug Administration and is indicated for the treatment of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.[51] Tramadol is a centrally acting synthetic opioid analgesic that exerts its analgesic effects through the binding of both the parent compound and its O-demethylated (M1) metabolite to μ-opioid receptors.[52–54] In addition, tramadol weakly inhibits norepinephrine and serotonin reuptake in the central nervous system to increase neurotransmitter concentrations and modulate analgesic activity.[52–54]

Two randomized, double-blind, placebo-controlled studies evaluated tramadol ER in osteoarthritis patients with chronic pain.[55,56] In a 12-week, randomized, double-blind, placebo-controlled, parallel-group study,

246 patients with moderate to severe chronic pain from osteoarthritis received either tramadol ER ($n = 124$) at doses of 200 to 400 mg daily (mean daily dose, 276 mg) or placebo ($n = 122$).[55] In this study, the mean change from baseline in arthritis pain intensity VAS score (averaged over the 12-week study period) was significantly greater for patients who received tramadol ER compared with those who received placebo: the least squares mean change from baseline was 30.4 mm vs. 17.7 mm, respectively; $P < 0.001$). Using the WOMAC Osteoarthritis Index subscales to evaluate pain, stiffness, and physical functioning, patients receiving tramadol ER achieved significantly greater mean changes from baseline averaged over 12 weeks than those receiving placebo. The change from baseline in pain subscale score was 120.1 mm for tramadol ER vs. 69.0 mm for placebo; physical function subscale scores were 407.0 mm vs. 208.5 mm; and stiffness subscale scores were 48.9 mm vs. 27.3 mm, respectively ($P < 0.001$ for all comparisons). In addition, the tramadol ER group had a significantly lower rate of study discontinuations because of lack of analgesic efficacy than the placebo group (15.3% vs. 36.9%, respectively; $P < 0.001$). The most commonly reported adverse events included dizziness (33%), constipation (26%), nausea (24%), headache (15%), diarrhea (10%), somnolence (8%), vomiting (7%), and pruritus (7%) for patients treated with tramadol ER and headache (16%), dizziness (12%), nausea (8%), and constipation (6%) for patients treated with placebo.

In addition, tramadol ER has been evaluated in a multicenter, randomized, double-blind, placebo-controlled study of 1,020 patients with osteoarthritis pain of the knee or hip.[56] Patients either received placebo or were titrated to tramadol ER doses of 100, 200, 300, or 400 mg once daily for 12 weeks. All doses of tramadol ER were more effective than placebo, producing significantly greater improvements from baseline to Week 12 in WOMAC Osteoarthritis Index pain, physical function and joint stiffness subscale and composite scores, and arthritis pain intensity VAS scores for the index joint ($P \leq 0.05$ for all comparisons). Each patient maintained a daily diary to rate their daily pain intensity, and mean improvement in daily pain scores was significantly greater for the pooled tramadol ER groups compared with placebo on each day of the study, beginning on Day 1 ($P \leq 0.05$). The most commonly reported adverse events in the tramadol ER groups were constipation (range, 12.9% to 29.7%), dizziness (16.8% to 28.2%), nausea (14.9% to 25.7%), somnolence (8.4% to 20.3%), headache (10.4% to 15.8%), flushing (8.9% to 15.8%), pruritus (5.9% to 11.9%), and insomnia (6.5% to 11.4%). The adverse events occurred most frequently in the tramadol ER 400-mg dose group.[56] The maximum recommended dose for tramadol ER is 300 mg per day.[51]

Tramadol ER treatment was also associated with significant improvements in pain-related sleep disturbances in both studies. In the study involving the 246 patients, tramadol ER treatment was associated with statistically significant mean improvements from baseline averaged over 12 weeks of the study in pain-related sleep disturbances when compared with placebo treatment using the CPSI.[55] Specifically, improvements were seen in trouble falling asleep due to pain ($P = 0.016$), being awakened by pain during the night ($P = 0.005$), being awakened by pain in the morning ($P = 0.004$), and overall sleep quality ($P = 0.013$). In addition, the study involving 1,020 patients showed significant improvements in trouble falling asleep due to pain, being awakened by pain during the night and in the morning, and in overall sleep quality in patients receiving tramadol ER compared with placebo at the final visit ($P \leq 0.05$ for all parameters).[56]

The efficacy of tramadol ER in reducing pain-related sleep disturbances associated with chronic osteoarthritis pain of the knee or hip was evaluated in a post hoc analysis from patients who were enrolled in both clinical studies.[57] A sleep problems index composed of three items from the CPSI (having trouble falling asleep due to pain, being awakened by pain during the night and in the morning) was used as a valid and reliable measure of sleep problems. A significant improvement in the sleep problems index from baseline to Week 12 ($P < 0.05$) was demonstrated in both studies. A significant improvement, as early as Week 1, was demonstrated in the study involving 1,020 patients ($P < 0.05$). Furthermore, once pain-related sleep improvements were seen, they continued throughout the duration of both studies. The findings from this post hoc analysis demonstrated a benefit from treating pain with tramadol ER because there was a significant reduction in pain-related sleep disturbances in patients with chronic osteoarthritis pain.

In addition to its unique mechanism of action, tramadol has been used in combination with NSAIDs and acetaminophen.[58,59] Moreover, the tramadol molecule results in fewer adverse events than morphine for the level of analgesia achieved.[60] Therefore, for patients who have progressed from mild pain (first step on the analgesic pain management ladder; Figure 1) to moder-

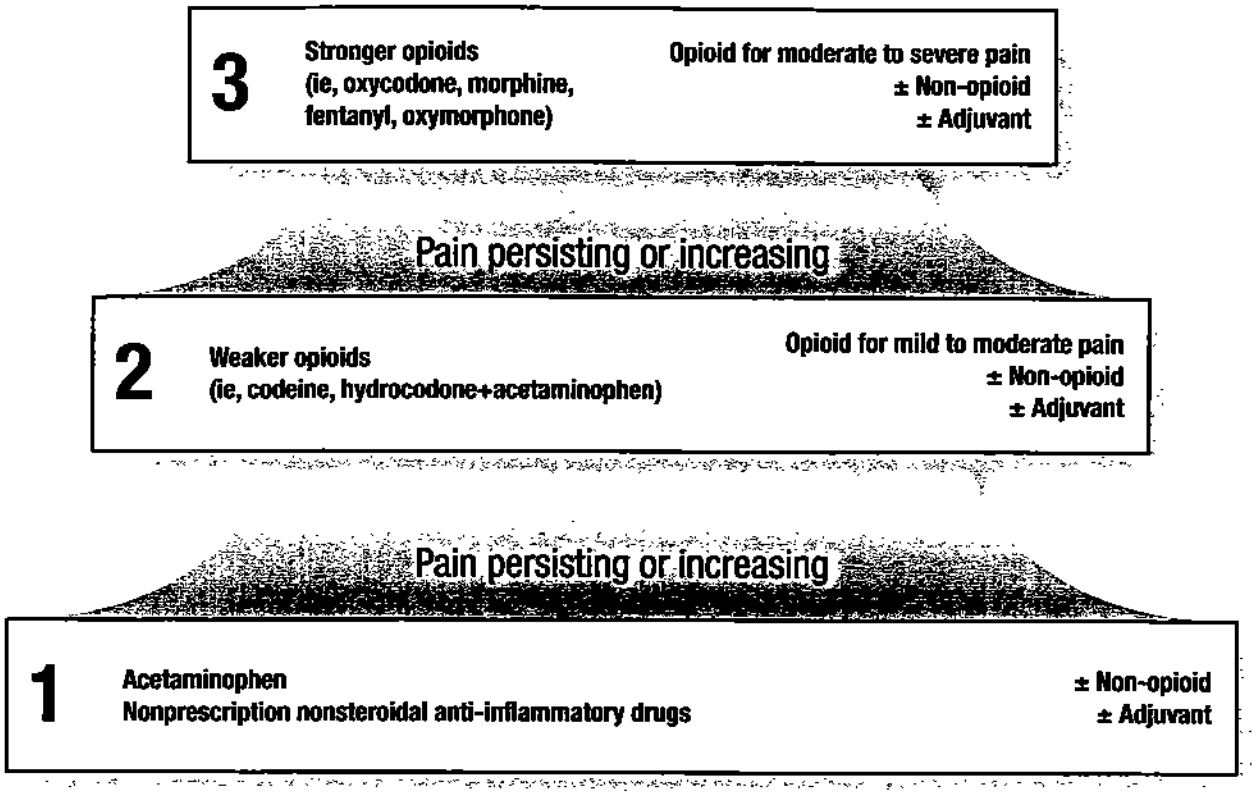

Figure 1. Analgesic Pain Management Ladder.

ate chronic noncancer pain (second step on pain ladder) who require around-the-clock treatment for their pain, it is reasonable to consider treatment with once-daily tramadol ER for pain management.

Although studies with tramadol ER have not been conducted in patients with neuropathic pain, the short-acting formulation of tramadol has demonstrated efficacy in the treatment of neuropathic pain.[61,62] In addition, tramadol in combination with tricyclic antidepressants may be effective in treating patients with neuropathic pain.[63] However, the prescribing information indicates that concomitant use of tramadol and tricyclic antidepressants increases seizure risk.[51,64] Because tramadol in combination with antidepressants may provide increased analgesia, it is hypothesized that a once-daily formulation of tramadol such as tramadol ER may be advantageous in reducing the pill burden in patients being treated with concomitant antidepressants;[65] however, further study is warranted. Tramadol also may be effective in combination with pregabalin or gabapentin for treating painful diabetic neuropathy,[66] although no controlled studies have been reported with these combinations. Because the formation of the M1 metabolite of tramadol is mediated by CYP2D6, other drugs that affect CYP2D6 activity may alter the effects of tramadol. For example, it has been shown that quinidine, a selective inhibitor of CYP2D6, results in a 50% to 60% increased exposure to tramadol, and a similar reduction in M1 exposure, although the clinical implications of these findings are unknown. Similarly, coadministration of other CYP2D6 inhibitors such as fluoxetine, paroxetine, and amitriptyline may also reduce the metabolism of and therapeutic response to tramadol.[51] Haloperidol and carbamazepine in combination with short-acting tramadol may attenuate analgesia.[67] Concomitant administration of tramadol and carbamazepine can increase the metabolism of tramadol; the dosage of tramadol may need to be adjusted in these patients.[53]

CONSIDERATIONS FOR CHOOSING AN ER OPIOID ANALGESIC

An ER analgesic should provide around-the-clock efficacy, result in fewer changes in drug plasma concentra-

tions when compared with short-acting analgesics, provide maximal tolerability, and have minimal long-term adverse events with prolonged use. As with any medication, when choosing an ER analgesic, physicians must consider possible interactions between the analgesic and concomitant medications. Tramadol ER is an alternative to scheduled stronger opioid analgesics that may provide a foundation for overall analgesic management, which could diminish the intensity and frequency of end-of-dose breakthrough pain.

CONCLUSIONS

Extended-release opioid analgesics offer a number of advantages over IR formulations. Advantages include more consistent pain control, improved nighttime pain control, less need to awaken at night to take another dose of pain medication, and less clock-watching by patients with chronic noncancer pain. Patients with chronic noncancer pain frequently experience sleep disturbances, which interfere with many aspects of daily life. Therefore, once-daily administration of ER opioid analgesics should provide pain relief and subsequently improve pain-related sleep disturbances, thereby improving health-related quality of life.

However, in choosing an ER opioid analgesic, physicians must consider efficacy, adverse event profiles, concomitant medical conditions and the medication(s) used to treat them, and abuse potential. Patients initially presenting with mild pain may be treated with IR analgesics, such as acetaminophen and over-the-counter NSAIDs (first step on the analgesic pain management ladder; Figure 1). Over time, however, a patient's chronic pain condition may progress such that painful episodes become more intense and frequent, and patients fail to obtain adequate pain relief with these agents. At this stage, individuals with chronic noncancer moderate pain may not only require a stronger medication of the opioid type but also require around-the-clock treatment of their chronic pain for an extended period of time. Early use of an ER analgesic, when pain is moderate rather than severe, may also reduce the need for prescription NSAIDs or COX-2 inhibitors (a so-called NSAID-sparing effect).

REFERENCES

1. Glickman-simon R. Persistent pain and palliative care. Medscape coverage of the American College of Physicians 2006 Annual Session. Available at: http://www.medscape.com/viewarticle/535720(accessed January 24, 2007).

2. Siddall PJ, Cousins MJ. Persistent pain as a disease entity: implications for clinical management. *Anesth Analg.* 2004;99:510–520, table.

3. Department of Health and Human Services, National Institutes of Health. New Directions in Pain Research: I. Available at: http://grants.nih.gov/grants/guide/pa-files/PA-98-102.html (accessed February 21, 2007).

4. Ortho-McNeil Pharmaceutical. 1999 National Pain Survey. Available at: http://www.chiro.org/LINKS/FULL/1999_National_Pain_Survey.html (accessed February 21, 2007).

5. Katz WA. Musculoskeletal pain and its socioeconomic implications. *Clin Rheumatol.* 2002;21(suppl 1):S2–S4.

6. Allen H, Hubbard D, Sullivan S. The burden of pain on employee health and productivity at a major provider of business services. *J Occup Environ Med.* 2005;47:658–670.

7. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA.* 2003;290:2443–2454.

8. Elliott TE, Renier CM, Palcher JA. Chronic pain depression, and quality of life: correlations and predictive value of the SF-36. *Pain Med.* 2003;4:331–339.

9. Power JD, Perruccio AV, Badley EM. Pain as a mediator of sleep problems in arthritis and other chronic conditions. *Arthritis Rheum.* 2005;53:911–919.

10. Otis JD, Keane TM, Kerns RD. An examination of the relationship between chronic pain and post-traumatic stress disorder. *J Rehabil Res Dev.* 2003;40:397–405.

11. Romano JM, Turner JA. Chronic pain and depression: does the evidence support a relationship? *Psychol Bull.* 1985;97:18–34.

12. Drewes AM. Pain and sleep disturbances with special reference to fibromyalgia and rheumatoid arthritis. *Rheumatology (Oxford).* 1999;38:1035–1038.

13. Kundermann B, Spernal J, Huber MT, Krieg JC, Lautenbacher S. Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers. *Psychosom Med.* 2004;66:932–937.

14. Onen SH, Alloui A, Gross A, Eschallier A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res.* 2001;10:35–42.

15. Deardorff W. Breaking the cycle of chronic pain and insomnia. Available at: http://www.spine-health.com/topics/conserv/insomnia/insomnia1.html (accessed February 21, 2007).

16. Cohen MJM, Menefee LA, Doghramji K, Anderson WR, Frank ED. Sleep in chronic pain: problems and treatments. *Int Rev Psychiatry.* 2000;12:115–126.

17. Atkinson JH, Slater MA, Patterson TL, Grant I, Garfin SR. Prevalence, onset, and risk of psychiatric disorders in men with chronic low back pain: a controlled study. *Pain.* 1991;45:111–121.

18. Americans Living With Pain Survey. Executive Summary of Results. Survey conducted on behalf of the American Chronic Pain Association. Sponsored by Endo Pharmaceuticals. April 2004. Available at: http://theacpa.org/documents/FINAL%20PAIN%20SURVEY%20RESULTS%20REPORT.pdf (accessed February 21, 2007).

19. Collett BJ. Chronic opioid therapy for non-cancer pain. *Br J Anaesth*. 2001;87: 133–143.

20. Nicholson B. Responsible prescribing of opioids for the management of chronic pain. *Drugs*. 2003;63:17–32.

21. Vallerand AH. The use of long-acting opioids in chronic pain management. *Nurs Clin North Am*. 2003; 38:435–445.

22. Wisconsin Medical Society Task Force on Pain Management. Guidelines for the assessment and management of chronic pain. *WMJ*. 2004;103:13–42.

23. Dews TE, Mekhail N. Safe use of opioids in chronic noncancer pain. *Cleve Clin J Med*. 2004;71:897–904.

24. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ*. 2006;174:1589–1594.

25. Bannwarth B. Risk-benefit assessment of opioids in chronic noncancer pain. *Drug Saf*. 1999;21:283–296.

26. Nicholson B. Differential diagnosis: nociceptive and neuropathic pain. *Am J Manag Care*. 2006;9(suppl 12):S256–S262.

27. McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther*. 2001;8:181–186.

28. Sloan P, Babul N. Extended-release opioids for the management of chronic non-malignant pain. *Expert Opin Drug Deliv*. 2006;3:489–497.

29. OPANA® ER (Oxymorphone Hydrochloride) Extended-release Tablets [Package Insert]. Chadds Ford, PA: Endo Pharmaceuticals Inc.; 2007.

30. Kivitz A, Ma C, Ahdieh H, Galer BS. A 2 week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. *Clin Ther*. 2006;28:352–364.

31. Matsumoto AK, Babul N, Ahdieh H. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase III trial. *Pain Med*. 2005;6:357–366.

32. McIlwain H, Ahdieh H. Safety, tolerability, and effectiveness of oxymorphone extended release for moderate to severe osteoarthritis pain: a one-year study. *Am J Ther*. 2005;12:106–112.

33. Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain*. 2005;6:21–28.

34. Katz N, Rauck R, Ahdieh H, et al. A 12 week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. *Curr Med Res Opin*. 2007;23:117–128.

35. Orthoteers Orthopaedic Educational Resource. WOMAC. Available at: http://www.orthoteers.org/(S(1yekeg55ee0ong55lf3shj45))/content/contentnoframeset.aspx?article=367&c=1 (accessed November 28, 2007).

36. Hale ME, Ahdieh H, Ma T, Rauck R. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12 week, randomized, double-blind, placebo-controlled study. *J Pain*. 2007;8:175–184.

37. OXYCONTIN® (Oxycodone HCl Controlled-release) Tablets [Package Insert]. Stamford, CT: Purdue Pharma L.P.; 2007.

38. Markenson JA, Croft J, Zhang PG, Richards P. Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *Clin J Pain*. 2005;21:524–535.

39. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol*. 1999;26:862–869.

40. Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. *Arch Intern Med*. 2000;160:853–860.

41. AVINZA® (Morphine Sulfate Extended-Release Capsules) [Package Insert]. Bristol, TN: King Pharmaceuticals, Inc.; 2006.

42. KADIAN® (Morphine Sulfate Extended-Release) Capsules [Package Insert]. Piscataway, NJ: Alpharma Pharmaceuticals LLC; 2007.

43. Caldwell JR, Rapoport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage*. 2002;23:278–291.

44. Rauck RL, Bookbinder SA, Bunker TR, et al. The ACTION study: a randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin) for the treatment of chronic, moderate to severe low back pain. *J Opioid Manag*. 2006;2:155–166.

45. Adams EH, Chwiecko P, Ace-Wagoner Y, et al. A study of AVINZA (morphine sulfate extended-release capsules) for chronic moderate-to-severe noncancer pain con-

ducted under real-world treatment conditions—the ACCPT Study. *Pain Pract.* 2006;6:254–264.

46. Nicholson B, Ross E, Weil A, Sasaki J, Sacks G. Treatment of chronic moderate-to-severe non-malignant pain with polymer-coated extended-release morphine sulfate capsules. *Curr Med Res Opin.* 2006;22:539–550.

47. Herrero-Beaumont G, Bjorneboe O, Richarz U. Transdermal fentanyl for the treatment of pain caused by rheumatoid arthritis. *Rheumatol Int.* 2004;24:325–332.

48. Langford R, McKenna F, Ratcliffe S, Vojtassak J, Richarz U. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis: a randomized, placebo-controlled trial. *Arthritis Rheum.* 2006;54:1829–1837.

49. Le Loet X, Pavelka K, Richarz U. Transdermal fentanyl for the treatment of pain caused by osteoarthritis of the knee or hip: an open, multicentre study. *BMC Musculoskelet Disord.* 2005;6:31.

50. Pavelka K, Le Loet X, Bjorneboe O, Herrero-Beaumont G, Richarz U. Benefits of transdermal fentanyl in patients with rheumatoid arthritis or with osteoarthritis of the knee or hip: an open-label study to assess pain control. *Curr Med Res Opin.* 2004;20:1967–1977.

51. ULTRAM® ER (Tramadol HCl) Extended-Release Tablets [Package Insert]. Raritan, NJ: PriCara™, a unit of Ortho-McNeil, Inc.; 2006.

52. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet.* 2004;43:879–923.

53. Lewis KS, Han NH. Tramadol: a new centrally acting analgesic. *Am J Health Syst Pharm.* 1997;54:643–652.

54. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of Tramadol, an "atypical" opioid analgesic. *J Pharmacol Exp Ther.* 1992;260:275–285.

55. Babul N, Noveck R, Chipman H, Roth SH, Gana T, Albert K. Efficacy and safety of extended-release, once-daily Tramadol in chronic pain: a randomized 12 week clinical trial in osteoarthritis of the knee. *J Pain Symptom Manage.* 2004;28:59–71.

56. Gana TJ, Pascual MLG, Fleming RRB, et al. Extended-release Tramadol in the treatment of osteoarthritis: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Curr Med Res Opin.* 2006;22: 1391–1401.

57. Janagap C, Schein J, Kosinski M, Vorsanger G. *Extended-Release Tramadol Improves Sleep in Osteoarthritis.* Poster presented at the 17th Annual Clinical Meeting of the American Academy of Pain Management, September 7–10, 2006, Orlando, Florida. 2006.

58. Emkey R, Rosenthal N, Wu SC, Jordan D, Kamin M. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. *J Rheumatol.* 2004;31:150–156.

59. Schug SA. Combination analgesia in 2005—a rational approach: focus on paracetamol-tramadol. *Clin Rheumatol.* 2006;25(suppl 1):S16–S21.

60. Klotz U. Tramadol—the impact of its pharmacokinetic and pharmacodynamic properties on the clinical management of pain. *Arzneimittelforschung.* 2003;53:681–687.

61. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology.* 1998;50:1842–1846.

62. Hollingshead J, Duhmke RM, Cornblath DR. Tramadol for neuropathic pain. *Cochrane Database Syst Rev.* 2006;3:CD003726.

63. Reig E. Tramadol in musculoskeletal pain—a survey. *Clin Rheumatol.* 2002;21(suppl 1):S9–11.

64. ULTRAM® (Tramadol Hydrochloride Tablets) [Package Insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc.; 2004.

65. Mattia C, Coluzzi F. Once-daily tramadol in rheumatological pain. *Expert Opin Pharmacother.* 2006;7:1811–1823.

66. American Society of Pain Educators. Diabetic peripheral neuropathic pain. Consensus guidelines for treatment. *J Fam Pract.* 2006;June(Suppl.):1–19.

67. Leppert W, Luczak J. The role of tramadol in cancer pain treatment–a review. *Support Care Cancer.* 2005;13:5–17.