ORIGINAL ARTICLE

Breakthrough pain in opioid-treated patients with neuropathic pain

Steve Simon, MD, RPh
Daniel S. Bennett, MD
Richard Rauck, MD
Donald Taylor, MD
Steven Shoemaker, MD

ABSTRACT

Objective: *This report aims to describe the prevalence and characteristics of breakthrough pain in patients with neuropathic pain.*

Methods: *The study represents data from a subset of patients from a larger survey of 228 patients with chronic noncancer pain. Patients were identified from nine pain programs and were administered a telephone questionnaire. The study population comprised 45 chronic noncancer pain patients with primary neuropathic pain diagnoses who were being treated with opioids.*

Results: *Pain had been present for a median of six years. Medications used for pain in addition to opioids included nonsteroidal anti-inflammatory agents (29 percent), antidepressants (60 percent), and anticonvulsants (53 percent). Thirty-five of the patients (78 percent) described a total of 42 distinct types of breakthrough pain. The median number of episodes per day was two; the median time to maximum intensity was 10 minutes, and the median duration of pain was 60 minutes. Patients could identify a precipitant for 62 percent of the pains, and 88 percent of the precipitants were activity related. The onset of breakthrough pain could not be predicted for 48 percent of the pains and could only sometimes be predicted for 29 percent of the pains.*

Conclusion: *Breakthrough pain is common in opioid-treated patients with chronic neuropathic pain. Such pain often has a rapid onset and a relatively short duration, and it is frequently difficult to predict, similar to breakthrough pain in cancer patients.*

Key words: breakthrough pain, chronic pain, neuropathic pain, survey

INTRODUCTION

Neuropathic pain, defined as any pain initiated or caused by a primary lesion or dysfunction of the nervous system,[1] encompasses many heterogeneous conditions that can not be explained by a single etiology or a specific anatomical lesion.[2] Among the most common causes of neuropathic pain are painful diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, and degenerative spinal disease. Persistent neuropathic pain can impair a patient's quality of life by interfering with mood, sleep, mobility, work, social relations, leisure activities, emotional well-being, and enjoyment of life.[3,4]

Over the past 20 years there has been a greater effort on the part of the medical community to actively identify patients with painful conditions and provide them with adequate analgesia. Though considerable advances have been made in the field of pain management, neuropathic pain continues to present a clinical challenge because of the heterogeneity of diseases associated with neuropathic pain and the complexity of the nervous system. Indeed, pharmacotherapy for neuropathic pain has been reported to result in effective analgesia in less than half of patients.[2] Therefore, in order to identify specific therapies directed at neuropathic pain, there must be a clear understanding of the phenomena and clinical circumstances surrounding this type of chronic pain.

Chronic pain is typically characterized by persistent pain requiring around-the-clock analgesics. Chronic pain patients commonly experience transient exacerbations of pain, or breakthrough pain. The prevalence of breakthrough pain in patients with chronic pain (both cancer-related and noncancer pain) has been estimated at 50 to 90 percent, and it has been shown to be associated with functional impairment and psychological distress.[5-9] A survey of the prevalence and characteristics of breakthrough pain in 228 patients with chronic noncancer pain was recently completed.[7] The results of the survey indicated that the prevalence (74 percent) and characteristics of breakthrough pain in patients with chronic noncancer

Table 1. Patient demographics (N = 45 patients)			
	Patients with breakthrough pain (n = 35)	**Patients without breakthrough pain (n = 10)**	**Total (N = 45)**
Median (range) age, years	45 (21 to 74)	43.5 (34 to 59)	45 (21 to 74)
n (percent) female	21 (60 percent)	6 (60 percent)	27 (60 percent)
Median (range) years since diagnosis	7 (0.08 to 55)	4.25 (1 to 11)	6 (0.08 to 55)
Diagnosis, n (percent)			
Central pain	2 (6 percent)	0 (0 percent)	2 (4 percent)
Complex regional pain syndrome	14 (40 percent)	2 (20 percent)	16 (36 percent)
Postherpetic neuralgia	2 (6 percent)	0 (0 percent)	2 (4 percent)
Diabetic neuropathy	1 (3 percent)	0 (0 percent)	1 (2 percent)
Peripheral neuropathy	4 (11 percent)	0 (0 percent)	4 (9 percent)
Other neuropathy	12 (34 percent)	8 (80 percent)	20 (44 percent)
Severity of baseline pain, n (percent)			
Mild	6 (17 percent)	1 (10 percent)	7 (16 percent)
Moderate	29 (83 percent)	9 (90 percent)	38 (84 percent)

pain are similar to those in patients with cancer-related pain. To date, the prevalence and characteristics of breakthrough pain specifically in patients with neuropathic pain have not been described. This report is a subgroup analysis and describes breakthrough pain and its treatment in patients with neuropathic pain.

METHODS

This paper presents a subgroup analysis based on a survey of breakthrough pain in opioid-treated patients with chronic noncancer pain.[7] The survey was conducted at nine pain treatment centers in the United States. Patients were recruited for participation in the study at the pain clinics and were subsequently interviewed via telephone regarding their pain experience. An Institutional Review Board approved the study protocol, and all subjects provided written informed consent. This report comprises data only from patients who had a pain diagnosis known to cause neuropathic pain.[10]

Patient selection and procedures

Investigators screened patients at the clinic for study eligibility. Eligible patients were between 18 and 75 years of age, had been experiencing pain for six months or longer, and had controlled baseline pain. Patients were considered to have controlled baseline pain if they provided an affirmative response to the following question: "Does your pain currently have a component you would describe as 'constant' or 'almost constant' or that would be constant or almost constant if not for the treatment you are receiving?" They also had to be following an opioid regimen that either 1) provided treatment for at least 12 hours per day and yielded a baseline pain that was, on average during the past week, absent, mild, or moderate, or 2) provided treatment for less than 12 hours per day

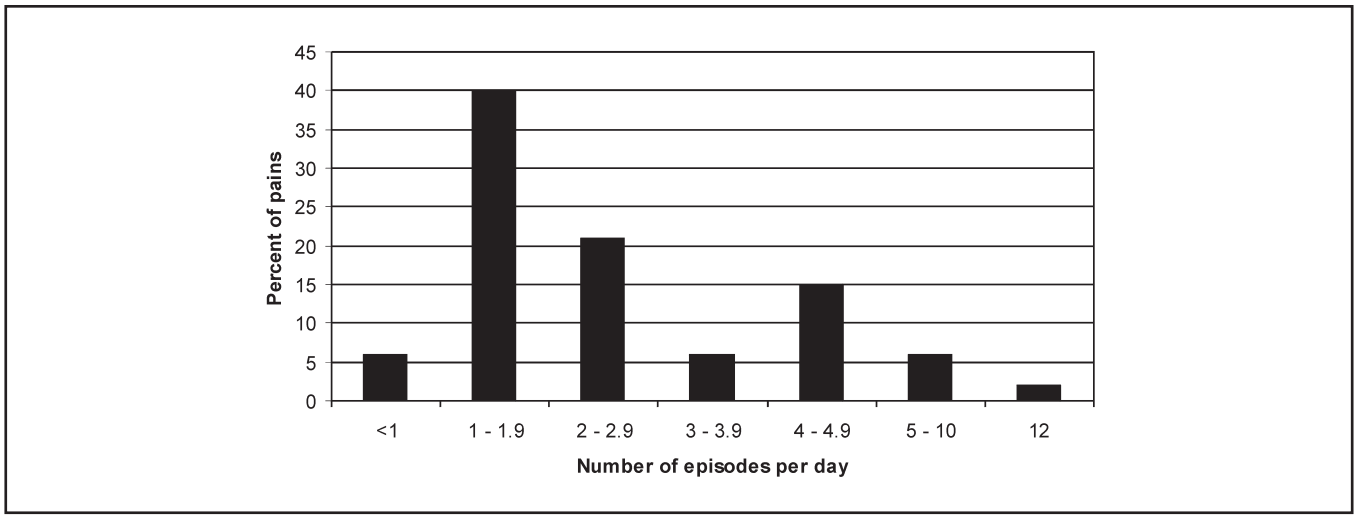

Figure 1. Breakthrough pain frequency (N = 42 pains).

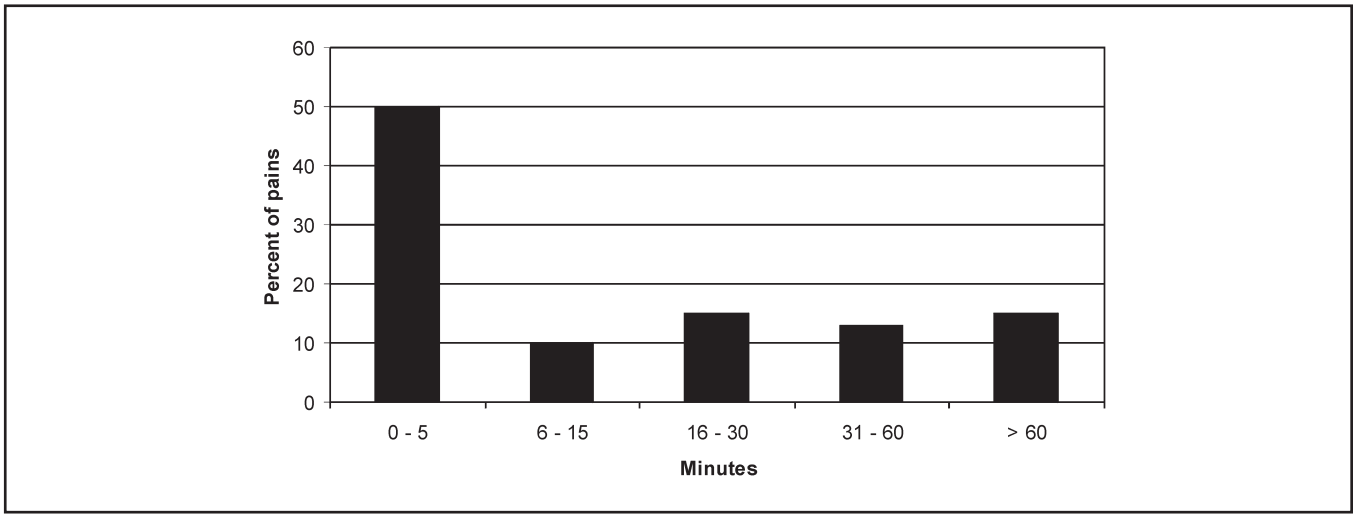

Figure 2. Time from first perception of pain to maximal intensity (N = 42 pains).

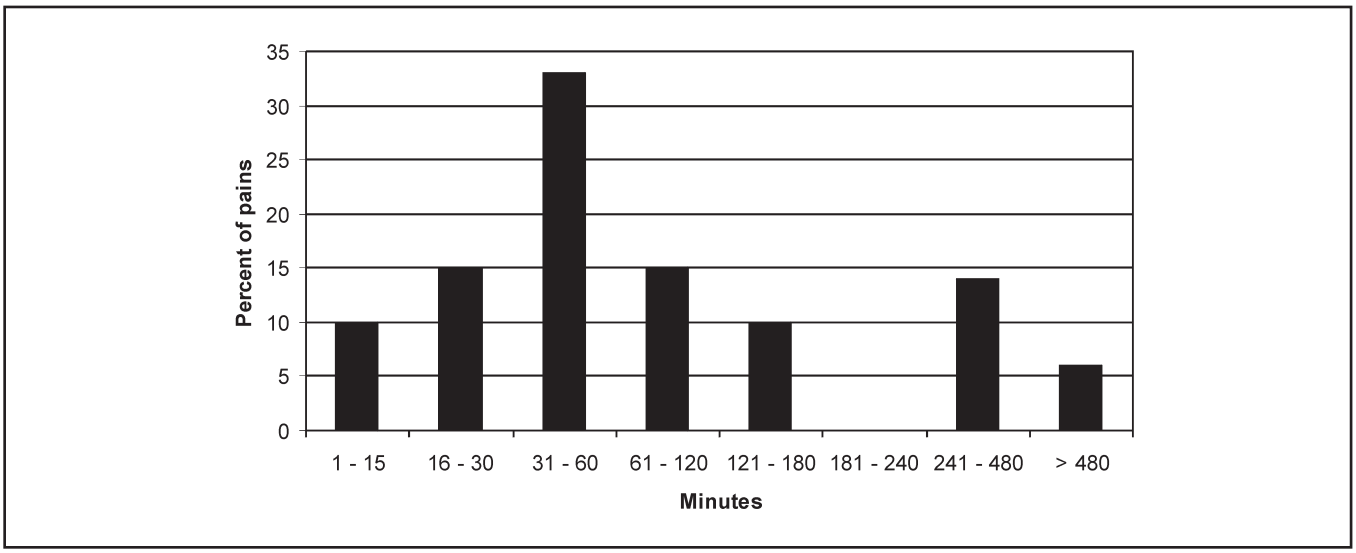

Figure 3. Duration of breakthrough pain (N = 41 pains; duration information was missing for one pain).

Table 2. Analgesics and co-analgesic medications of patients with and without breakthrough pain		
Medication	**Patients with breakthrough pain (n = 35)**	**Patients without breakthrough pain (n = 10)**
Opioid analgesics	35 (100 percent)	10 (100 percent)
Oral sustained-release	16 (46 percent)	2 (20 percent)
Transdermal	6 (17 percent)	0 (0 percent)
Methadone	5 (14 percent)	2 (20 percent)
Intrathecal	3 (9 percent)	0 (0 percent)
Short-acting opioids[a]	31 (89 percent)	7 (70 percent)
Others		
NSAIDs[b]	10 (29 percent)	3 (30 percent)
Antidepressants	21 (60 percent)	6 (60 percent)
Anticonvulsants	18 (51 percent)	6 (60 percent)

[a] Includes oral normal-release opioids (combined with acetaminophen or a nonsteroidal anti-inflammatory drug [NSAID] or not combined) and oral transmucosal fentanyl citrate. [b] Includes COX-2 selective and nonselective NSAIDs.

and yielded a baseline pain that was, on average during the past week, mild or moderate. Patients with cancer-related pain or who had recently (i.e., within the previous month) been hospitalized for uncontrolled pain were excluded. Patients were included in this analysis if they had a primary pain diagnosis indicative of the presence of neuropathic pain. At the clinic, demographic information was recorded and the telephone interview was scheduled. Within approximately one week of the clinic visit, a trained interviewer administered the survey to the patient. Data collection occurred from February through April of 2004.

Data collection

The survey instrument was adapted from a pain assessment algorithm used previously with cancer patients.[5,6] Information gathered regarding baseline pain included location, time since onset, and characteristics. To determine whether breakthrough pain was present, patients were asked if they experienced temporary flares (i.e., duration of ≤ 12 hours) of severe or excruciating pain in addition to their baseline pain. Only patients with breakthrough pain continued the interview. Information collected to characterize breakthrough pain included frequency, onset (time from first perception to maximal intensity), duration, severity (severe or excruciating), predictability, precipitants, and pain therapies and their success at alleviating the pain. If patients reported experiencing more than one type of breakthrough pain, they were asked to report first on the worst flare-up they had experienced within the previous 24-hour period and then on the remaining types separately.

RESULTS

Forty-five subjects with neuropathic pain were included in this subgroup analysis. The most common pain diagnoses were nondiabetic neuropathy (44 percent) and complex regional pain syndrome (36 percent). The median age of subjects was 45 years (range of 21 to 74 years). More than half (60 percent) of the subjects were female, and the median duration of pain was six years (Table 1). Of the 45 subjects, 35 (78 percent) reported flares of breakthrough pain. Several experienced more than one type of breakthrough pain, with a total of 42 distinct types of breakthrough pain identified by the 35 subjects.

The median frequency of breakthrough pain episodes was two per day and ranged from one per week to 12 per day (Figure 1). The median time to maximum intensity was 7.5 minutes and ranged from 0.2 to 180 minutes. Half of the pains reached maximum intensity within five minutes

(Figure 2). The median duration of pain was 60 minutes and ranged from five to 720 minutes (Figure 3). A precipitant could be identified for most of the pains (62 percent), with the most common precipitant being activity (88 percent). Forty-eight percent of the pains could never be predicted, and 29 percent could only sometimes be predicted. Most pains (93 percent) could be at least partially lessened by one or more of the following approaches: medication (81 percent); rest, lying down, or sitting (55 percent); heat (26 percent); cold (12 percent); movement, stretching, or physical therapy (5 percent); sleep (2 percent); massage (2 percent); spinal cord stimulation (2 percent); and distraction (2 percent). However, these interventions were reported to be consistently effective for only 28 percent of the pains.

All subjects were using opioids for their pain, as required for inclusion in the study (Table 2). Most subjects were using shorter-acting opioids for their pain (89 percent of subjects with breakthrough pain and 70 percent of subjects without breakthrough pain). Antidepressants and anticonvulsants were also used to manage pain in more than half of subjects.

DISCUSSION

Chronic neuropathic pain is a serious medical condition that affects more than 2 million Americans.[11] Neuropathic pain often proves difficult to relieve, and unfortunately it is not yet treated effectively in most patients.[2] Undertreated neuropathic pain can result in severe limitations for patients and can have profound negative effects on their quality of life.[12] To improve the likelihood of an effective treatment outcome for patients, a clear understanding of the nature of the pain must be achieved. The results of this study indicate that patients with neuropathic pain experience breakthrough pain in a similar proportion and with similar characteristics as patients with chronic pain of a non-neuropathic origin.[5,7,9] Such pain often has a rapid onset and a relatively short duration, and it is frequently difficult to predict. Although the phenomenon of breakthrough pain has been demonstrated to be a pervasive and debilitating condition, studies to evaluate the treatment options in this population are limited.

Current treatment options for relieving chronic neuropathic pain include tricyclics, selective serotonin reuptake inhibitors, anticonvulsants, capsaicin, levodopa, ion channel blockers, and opioids.[2,13-16] In patients for whom treatment with nonsteroidal anti-inflammatory drugs and acetaminophen no longer provides adequate pain control, opioids are the therapy of choice.[14,17] The use of opioids for chronic neuropathic pain, however, remains controversial due to experimental studies and some studies in humans that suggest that this type of pain is less responsive to opioid therapy.[18-20] Clinicians who are already reluctant to prescribe opioids to patients with noncancer pain because of concerns about opioid abuse may be even more reluctant to prescribe opioids to patients with neuropathic pain due to added concerns about the responsiveness of such pain to opioid treatment.[21] However, over the past few years several controlled studies have demonstrated the efficacy of opioids in relieving pain associated with diabetic neuropathy[22,23] and postherpetic neuralgia.[24] A recent review of randomized, controlled studies on the safety and efficacy of opioid agonists in combating neuropathic pain of noncancer origin concluded that short-term studies yielded mixed results with respect to the analgesic efficacy of opioids, while intermediate-term trials showed consistent opioid analgesic efficacy.[25] To date, the body of support for the use of opioids for neuropathic pain is continuing to grow.[11]

Our study suffers from some important limitations. First, we are reporting on a small sample of patients who were being treated at pain clinics and receiving opioids for their pain. Patients whose neuropathic pain is being managed outside of a pain clinic may have a different experience with their pain. Second, this survey depended on self-report of patients, and although the questionnaire has been used in previous studies,[5,6] it has not yet been validated. Despite these limitations, this study adds to the expanding literature of the characteristics and management of neuropathic pain, a prerequisite for finding effective treatments for this difficult pain condition.

The results show that breakthrough pain is highly prevalent in patients with chronic neuropathic pain, and the characteristics suggest the need for therapies that provide effective pain relief involving analgesics with rapid onset and a relatively short duration.

DISCLOSURE STATEMENT

This study was supported by a grant from Cephalon, Inc. (Frazer, Pennsylvania). Dr. Simon, Dr. Bennett, Dr. Taylor, and Dr. Shoemaker are consultants to and are on the Speaker's Bureau for Cephalon.

ACKNOWLEDGMENTS

Participating investigators included: Daniel Bennett, MD, Integrative Treatment Centers, Denver, CO; Michael J. Brennan, MD, The Pain Center of Fairfield, Fairfield, CT; Samyadev Datta, MD, Teaneck, NJ; Daniel M. Gruener, MD, Abington, PA; Cynthia King, PhD, NP, RN, Wake Forest University Baptist Medical Center, Winston-Salem, NC; Richard Rauck, MD, Center for Clinical Research, Winston-Salem, NC; Scott D. Segal, MD, Segal Institute for Clinical Research, North Miami, FL; Steven Simon, MD, The Pain Management Institute, Overland Park, KS; and Donald Taylor, MD, Comprehensive Pain Care, P.C., Marietta, GA.

Steve Simon, MD, RPh, The Pain Management Institute, Overland Park, Kansas.
Daniel S. Bennett, MD, Integrative Treatment Centers, Denver, Colorado.
Richard Rauck, MD, Center for Clinical Research, Winston-Salem, North Carolina.
Donald Taylor, MD, Comprehensive Pain Care, P.C., Marietta, Georgia.
Steven Shoemaker, MD, Sagemed, Inc., Boulder, Colorado.

REFERENCES

1. International Association for the Study of Pain: *IASP Pain Terminology*. IASP Web site. Available at *www.iasp-pain.org/terms-p.html*. Accessed August 21, 2006.
2. Sindrup HJ, Jensen TS: Efficacy of pharmacological treatments of neuropathic pain: An update and effect related to mechanism of drug action. *Pain*. 1999; 83(3): 389-400.
3. Raja SN, Haythornthwaite JA: Combination therapy for neuropathic pain—which drugs, which combination, which patients? *N Engl J Med*. 2005; 352(13): 1373-1375.
4. Schmader KE: Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain*. 2002; 18(6): 350-354.
5. Portenoy RK, Hagen NA: Breakthrough pain: Definition, prevalence and characteristics. *Pain*. 1990; 41(3): 273-281.
6. Portenoy RK, Payne D, Jacobsen P: Breakthrough pain: Characteristics and impact in patients with cancer pain. *Pain*. 1999; 81(1-2): 129-134.
7. Portenoy RK, Bennett DS, Rauck R, et al.: The prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. *Clin J Pain*. 2005 (in press).
8. Svendsen KB, Andersen S, Arnason S, et al.: Breakthrough pain in malignant and non-malignant diseases: A review of prevalence, characteristics and mechanisms. *Eur J Pain*. 2005; 9(2): 195-206.
9. Zeppetella G, O'Doherty CA, Collins S: Prevalence and characteristics of breakthrough pain in patients with non-malignant terminal disease admitted to a hospice. *Palliat Med*. 2001; 15(3): 243-246.
10. Bouhassira D, Attal N, Alchaar H, et al.: Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*. 2005; 114(1-2): 29-36.
11. Foley KM: Opioids and chronic neuropathic pain. *N Engl J Med*. 2003; 348(13): 1279-1281.
12. Haythornthwaite JA, Benrud-Larson LM: Psychological aspects of neuropathic pain. *Clin J Pain*. 2000; 16(2 Suppl): S101-S105.
13. Beniczky S, Tajti J, Timea Varga E, et al.: Evidence-based pharmacological treatment of neuropathic pain syndromes. *J Neural Transm*. 2005; 112(6): 735-749.
14. Dworkin RH, Backonja M, Rowbotham MC, et al.: Advances in neuropathic pain: Diagnosis, mechanisms, and treatment recommendations. *Arch Neurol*. 2003; 60(11): 1524-1534.
15. Hansson PT, Dickenson AH: Pharmacological treatment of peripheral neuropathic pain conditions based on shared commonalities despite multiple etiologies. *Pain*. 2005; 113(3): 251-254.
16. Rowbotham MC, Twilling L, Davies PS, et al.: Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med*. 2003; 348(13): 1223-1232.
17. World Health Organization: *Cancer Pain Relief and Palliative Care*. Geneva: World Health Organization, 1990.
18. Mao J, Price DD, Mayer DJ: Experimental mononeuropathy reduces the antinociceptive effects of morphine: Implications for common intracellular mechanisms involved in morphine tolerance and neuropathic pain. *Pain*. 1995; 61(3): 353-364.
19. Mercadante S, Maddaloni S, Roccella S, et al.: Predictive factors in advanced cancer pain treated only by analgesics. *Pain*. 1992; 50(2): 151-155.
20. Cherny NI, Thaler HT, Friedlander-Klar H, et al.: Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: A combined analysis of controlled, single-dose studies. *Neurology*. 1994; 44(5): 857-861.
21. Scanlon MN, Chugh U: Exploring physicians' comfort level with opioids for chronic noncancer pain. *Pain Res Manag*. 2004; 9(4): 195-201.
22. Watson CP, Moulin D, Watt-Watson J, et al.: Controlled-release oxycodone relieves neuropathic pain: A randomized controlled trial in painful diabetic neuropathy. *Pain*. 2003; 105(1-2): 71-78.
23. Gimbel JS, Richards P, Portenoy RK: Controlled-release oxycodone for pain in diabetic neuropathy: A randomized controlled trial. *Neurology*. 2003; 60(6): 927-934.
24. Watson CP, Babul N: Efficacy of oxycodone in neuropathic pain: A randomized trial in postherpetic neuralgia. *Neurology*. 1998; 50(6): 1837-1841.
25. Eisenberg E, McNicol ED, Carr DB: Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: Systematic review and metaanalysis of randomized controlled trials. *JAMA*. 2005; 293(24): 3043-3052.