ORIGINAL ARTICLE

Establishing the safety and efficacy of an opioid titration protocol

Nancy Wells, DNSc, RN
Barbara Murphy, MD
Stacey Douglas, MSN, RN
Nancy Yelton, MSN, RN

ABSTRACT

The primary goal of this single-group study was to determine the safety of a standard opioid titration order sheet to manage pain in ambulatory cancer patients. Secondary goals were to examine opioid toxicity and efficacy of this pain protocol.

Twenty-seven patients who required fixed-dose opioids and who had uncontrolled pain were enrolled. All patients had their initial opioid dose titrated by the study physician using the opioid titration order sheet. Data were obtained by the study nurse during a weekly telephone interview and used to determine if pain was controlled. After initial titration, a trained study nurse titrated opioid doses based upon the standing order sheet. At each contact, patients were assessed for adverse effects, pain intensity, and analgesics used.

Patients who completed the four-week trial (n = 17) did not differ from patients who did not complete the trial. No adverse effects were observed in 39 opioid titrations completed by the study nurse. Opioid toxicities, worst pain, usual pain, and pain-related distress declined from baseline to week four. Patients who were adherent to their prescribed medications reported significantly lower pain intensity and distress (ps ≤ 0.06).

The opioid titration order sheet, used by a trained nurse, is safe to use in ambulatory cancer patients who have moderate to severe pain. Common opioid toxicities were reduced. The protocol also demonstrated initial efficacy in improving worst and usual pain and pain-related distress. Further research to establish efficacy of the protocol is recommended.

Key words: cancer pain, standing orders, opioid titration

INTRODUCTION

Cancer-related pain has been reported in 50 percent of all patients[1] and more than 85 percent of patients with terminal disease.[2] Given current pharmacological and intervention strategies, the majority of patients should be able to achieve controlled pain. Nonetheless, uncontrolled cancer pain remains a major symptom control issue. Extensive studies have been conducted to identify barriers to uncontrolled pain in order to develop and test interventions. Multiple factors have been identified that contribute to the undertreatment of cancer pain. One commonly cited cause is lack of knowledge by medical staff and patients about cancer pain and its treatment. Erroneous beliefs, particularly about the danger of opioid use, also prevent optimal pain control. One obvious solution to these barriers is pain education. Educational interventions aimed at both medical staff and patients have been tested. While education interventions can improve knowledge and beliefs, they have failed to result in consistent, clinically meaningful improvements in pain outcomes.[3] A more powerful and robust intervention strategy is necessary to effectively reduce cancer-related pain.

Achieving controlled pain is a complex process that requires interaction between healthcare providers (typically physicians and nurses) and the patient-family unit. We developed a conceptual model describing an ideal interaction between healthcare providers and patients that would result in optimal pain control. The ideal interaction involves five steps: 1) the patient effectively communicates pain issues to the provider; 2) the provider assesses current pain, the treatment plan, and reasons for poor pain control; 3) the provider modifies the treatment plan to provide more effective relief; 4) the provider reviews the revised plan with the patient and family; and 5) the patient follows the treatment plan. The first and the last steps in the process are patient driven, while the middle three steps are initiated by the provider (Figure 1). A great deal of work has been done to address the role of patient education to enhance patient adherence and communication with providers about pain control issues. As noted above, these interventions have failed to consistently improve pain control.[3] We chose to develop an intervention that addressed the provider role in pain control.

Based on our conceptual framework, the provider is

Step 1. Patient: Patient report of pain

Step 2. Provider: Assessment of pain

Step 3. Provider: Medication modifications

Step 4. Provider: Review of plan with patient

Step 5. Patient: Patient follows treatment plan

Figure 1. Critical steps for adequate pain outcome.

responsible for three specific tasks: 1) assessing pain control and related issues (such as side effects and adherence), 2) generating a treatment plan, and 3) communicating the plan to the patient. If the provider complies with these steps in the care process, we hypothesize that pain control will be enhanced (i.e., decreased pain intensity and side effects). Furthermore, we posit that the occurrence of a positive pain outcome, which is dependent upon the degree to which the patient follows the treatment plan, will increase the patient's willingness to report pain at the next healthcare encounter. Conversely, the process can break down if the provider does not follow the steps of the care process. In this instance, the feedback is negative, and patients may be less likely to communicate pain control problems to the provider during the next encounter.

Within our conceptual framework, there are two critical components that determine the healthcare provider's ability to actualize their pain control tasks: 1) the knowledge base and expertise to allow for adequate assessment and treatment of pain, and 2) the time to obtain pertinent data (pain characteristics, barriers, and side effects) and communicate changes in the treatment plan to the patient. Unfortunately, it is evident that many physicians and nurses lack the skills needed to assess and treat pain.[4-6] Thus, providers enter practice lacking basic knowledge about how to assess and manage cancer pain. Providers, therefore, learn to manage pain through trial and error, consultation with more seasoned providers, or continuing education. This type of educational process is suboptimal and leads to large gaps in knowledge. One strategy used to reduce knowledge deficits is provider education. Many educational programs for physicians and nurses have demonstrated short-term improvements in knowledge and attitudes.[7-9] However, this increased knowledge has not resulted in long-term change in assessment and prescribing behaviors[10] or demonstrated a beneficial impact on pain outcomes.[11]

In addition to knowledge deficits, the medical delivery system used by most practicing oncologists prohibits timely and adequate response to cancer-related pain. A high volume of patient care problems and little time to address palliative issues burdens physicians. Lack of time has been identified as a critical barrier to good pain control.[12] In order to save time, most oncologists use nursing staff to assist in symptom control. The use of nurses with advanced training and skills may be an acceptable and appropriate way to ensure timely and adequate control of symptoms. Unfortunately, nurses are usually poorly trained in symptom management and learn these skills on the job. Furthermore, there are few tested guidelines to aid them in this task.

The literature suggests that specific, evidence-based recommendations in the form of pathways, protocols, and algorithms may result in improved clinical outcomes through reducing variation in clinical care. The more specific and accessible the recommendations are, the more likely that providers will adopt new clinical practices. In most instances, successful guideline implementation has incorporated a multifaceted approach with some mix of education, feedback, or monitoring, and patient-provider reminders.[13] We postulated that a well-developed protocol might enhance pain outcomes in the ambulatory cancer patient. We therefore undertook the development of a protocol specifically to address opioid titration. The protocol gives step-by-step instructions to providers, thus allowing providers with a limited knowledge base to use it effectively. In addition, it was designed to be nurse-managed, thus reducing the time required by physicians. The primary goal of this single-group design study was to test the safety of the opioid titration order sheet by examining the occurrence of severe adverse events. In addition, the study examined the efficacy of the protocol in reducing opioid toxicities and selected pain outcomes.

PATIENTS AND METHODS

Sample eligibility

Patients were recruited from a comprehensive cancer center located in a medical center in the southeastern United States. Eligible patients had: 1) histologically proven cancer, 2) uncontrolled cancer pain requiring opioids on a regular (fixed-dose) schedule, 3) the ability to read and understand English, 4) cognitive ability (Mini-Mental Status Examination [MMSE]) > 24, 5) a life expectancy of more than 12 weeks, and 6) an age of 18 years or older. Patients were excluded from the study if they: 1) had pure neuropathic pain; 2) presented in a pain crisis, which is defined as severe pain unresponsive to traditional opioid therapies; or 3) required immediate anesthesia or neurosurgical measures for pain control. Patients were removed from the study if they required hospitalization during the opioid titration trial, if they were transferred to hospice, or if they presented to the clinic or emergency department in a pain crisis. This study was approved by the Institutional Review Board, and all patients provided written informed consent prior to beginning the study.

Intervention

Patients who met eligibility criteria and expressed interest in study participation were screened using the MMSE[14] to ensure adequate mental capacity to complete self-report measures. Patients with adequate MMSE scores (> 24) were then enrolled in the study. Baseline evaluation included an assessment by a physician in order to adjust medications and to sign the titration order sheet. Patients then completed pain intensity and interference items of the Brief Pain Inventory (BPI),[15,16] a single-item distress scale,[17,18] and the Medication Side Effect Checklist (MSEC).[19] Patients and family (when available) underwent a baseline educational program that included a review of medication doses and schedule, written and oral explanation about toxicities, and an assessment of barriers. They were instructed in how to complete the daily diary, which included a daily measure of worst and usual pain and all medications taken to manage pain and side effects. Patients also were instructed to contact the study nurse for any pain related issues. Emergent problems that occurred at night or on weekends were referred to the on-call team.

All follow up was conducted by one study nurse using telephone interviews. Patients were contacted a minimum of once each week for follow-up assessment. Follow-up assessments included an assessment of pain (results of the daily diary were reviewed and recorded), evaluation of adherence and barriers, and an evaluation of toxicity. The physician trained the study nurse in the use of the titration order sheet. The physician reviewed the study nurse dose calculations for the first month to ensure accuracy.

The opioid titration order sheet provides standing orders for opioid dose adjustment based on the level of pain and the use of breakthrough medications. The study nurse used the data obtained from the patient interview to calculate an appropriate dose modification. Once the dose modification was calculated, the patient was told how to take their medications. If adherence barriers were identified (e.g., fear of addiction), the study nurse addressed the barriers and encouraged the patient to take medications as prescribed. If opioid toxicities were identified, standing orders for side-effect management were implemented. Patients who had a dose modification for moderate pain or dose reductions were contacted within 48 to 72 hours after dose titration. Patients who had a dose modification for severe pain were contacted within 24 hours or the next working day. Patients experiencing a pain crisis or who developed new pain of unclear etiology were referred for evaluation by the primary oncologist.

The criteria for dose adjustment were based on pain level and the use of breakthrough medications. The pain level was categorized as mild (1 to 4), moderate (5 to 6), and severe (≥ 7).[20] For the purposes of this study, controlled pain was defined as a usual pain level of 4 or less, with four or fewer rescue doses per 24 hours. To eliminate dose titration based upon transient or isolated activity-dependent pain, the patient must meet the criteria for three consecutive days before titration would be initiated. Patients with severe escalating pain could be titrated more rapidly after consultation with the physician.

Patients who did not meet these criteria for controlled pain were instructed to modify their opioid dose. Patients with mild usual pain (1 to 4) taking more than four rescue doses per day were instructed to adjust their fixed dose by an amount equal to the daily rescue dose in an effort to decrease the frequency of need for breakthrough medications. Patients with moderate pain (5 to 6) were instructed to increase their 24-hour opioid total (fixed dose plus rescue doses taken) by 25 percent. Patients with severe pain (≥ 7) were instructed to increase the 24-hour opioid total by 50 percent. Rescue doses were then recalculated to equal 10 to 15 percent of the new daily fixed-dose opioid total. If a patient met the criteria for controlled pain (usual pain < 4 and use of more than four rescue doses in 24 hours) and desired a decrease in opioid dose, a 25 percent reduction in 24-hour opioid total was prescribed.

Outcome measures

The primary outcome measure for this study was adverse events due to opioid overdose. Adverse events were assessed at each follow-up telephone interview. Since toxicities secondary to opioids are common, we clearly defined the parameters that were considered adverse events. These included severe lethargy, obtund sensation, and respiratory depression with a rate less than 8 per minute.

Opioid toxicity was assessed at baseline and during each follow-up interview using the MSEC.[19] Side effects included on the six-item MSEC are those typically associated with opioid use, including constipation, drowsiness, nausea, vomiting, confusion, and dry mouth. The severity of each side effect that had been experienced in the past week was rated on an 11-point Numerical Rating Scale (NRS). Items were averaged to provide a mean weekly side effect score.

Adherence was assessed at each follow-up interview. Adherence to fixed-dose medications and the use of breakthrough dosing for moderate or severe pain was assessed. Patients were categorized as adherent if they: 1) took their fixed-dose opioids as prescribed, and 2) took rescue medications when usual pain was > 4.

Patients completed a daily diary from baseline through week four of the trial.[21,22] Usual and worst pain, fixed-dose opioid use, rescue medications taken, and other coanalgesics used were recorded in the daily diary. At baseline, week one, and week four, patients completed the interference items from the BPI[15,16,20] and the pain-related distress item.[17,18] Worst and usual pain intensity

Table 1. Sample description				
Variable	**Did not complete study**		**Completed study**	
	Number of Ss	**Percent in group**	**Number of Ss**	**Percent in group**
Gender				
Male	8	80	8	47
Female	2	20	9	53
Ethnic background				
White	10	100	13	76.5
African-American	0		4	23.5
Marital status				
Married	3	60	12	75
Single/divorced	2	40	4	25
	Mean	**SD**	**Mean**	**SD**
Age in years	57.1	11.38	54.59	9.67
Cancer dx in months	11.3	12.35	32.0	52.45
Pain duration months	8.96	13.49	16.6	17.15
Mental status	29	1.63	28.2	2.41
Worst pain (0-10)	7.3	1.64	6.24	2.95
Usual pain (0-10)	5.8	1.03	4.47	2.92
Side effects (0-10)	1.96	1.63	2.45	1.50
Distress (0-10)	5.9	2.85	5.0	2.88
Interference (0-10)	4.38	2.70	3.78	2.57

and pain-related distress were obtained using 0 to 10 NRSs. Interference because of pain is a seven-item scale, which includes interference with ability to walk, general activity, usual work, mood, sleep, relations with others, and enjoyment in life. Each item was rated on an 11-point NRS, and responses were averaged for a total interference score. All instruments have established reliability and validity.

Data analysis

The sample size was based upon the ability to detect a 10 percent rate of adverse events. Demographic and clinical variables were examined using descriptive statistics. A weekly average of worst and usual pain was computed from the daily diary. The average number of rescue doses per day was computed. Average scores were computed for the interference and side effects scales. Differences in demographic, clinical, and baseline variables between patients who completed and did not complete the study were examined using χ-square for categorical and independent t-test for continuous variables. Toxicities were examined in two ways: 1) the proportion of patients with no toxicities was compared to patients with toxicities using χ-square, and 2) the change in mean severity of toxicities was tested using repeated measures analysis of variance (ANOVA). Efficacy of the intervention was examined using a two-factor repeated measure ANOVA. In each analysis, time was the factor within subjects and adherence was the factor between subjects. Dependent variables included worst pain, usual pain (5 data points), pain-related distress, and interference because of pain (3 data points). This type of analysis allowed us to examine main effects for time and adherence and to determine if there were interactions between time and adherence for the selected pain outcomes. Level of significance was $p \leq .10$ for this pilot study. This level of significance was selected to increase our ability to detect differences over time, which may be clinically significant.

RESULTS

Patient characteristics

Out of a total of 27 patients who enrolled in the study, 17 completed the four-week trial (63 percent retention).

Table 2. Use of rescue medications over time						
	Rescue doses per day			Rescue doses per week		
	Mean	Median	Range	Mean	Median	Range
Week 1	1.79	1.20	0 – 6	12.25	7.0	0 – 42
Week 2	1.82	1.79	0 – 5.29	11.86	11.0	0 – 37
Week 3	2.08	2.07	0 – 5.29	13.0	12.5	0 – 37
Week 4	1.84	1.85	0 – 4.14	12.29	8.0	0 – 29

Reasons for discontinuing the study were hospitalization (n = 3), referral to hospice (n = 1), death unrelated to disease progression (n = 1), and loss to follow up (n = 5). There were no significant differences between patients who did and did not complete the study on any baseline variable (Table 1). The final sample (n = 17) was predominantly white and married, with a mean age of 57 years. They had been diagnosed with cancer for 11 months and had experienced pain related to the cancer for nine months. Fifty-nine percent were undergoing active treatment at the time of enrollment.

Adverse events associated with opioid titration

Patients were prescribed a long-acting opioid on a fixed schedule and a rescue medication when entered into the study. The dose range of long-acting opioids was as follows: Duragesic (25 to 400 mcg q 72 h), sustained release morphine (30 to 450 mg qd), and sustained release oxycontin (40 to 271 mg qd). Morphine sulfate immediate release tablets or liquid was the most frequently prescribed opioid for rescue dosing. Over the four-week trial, patients averaged approximately two rescue doses per day, however, there was a high degree of variation across patients in use of rescue medications (Table 2).

All patients had a dose adjustment upon entry into the study. Over the four-week study period, 15 patients (88 percent) had dose escalations: eight patients had one additional dose escalation, and seven patients had between two and five dose escalations. One patient tolerated two dose decreases. One patient required no additional dose modification. Each patient had initial opioids titrated by the physician (27 titrations). The study nurse successfully managed an additional 39 titrations. No patient experienced any adverse effect (severe lethargy, obtund sensation, or respiratory depression) over the course of the trial.

Opioid toxicities

At baseline, less than 20 percent of patients reported no toxicities associated with opioid use (Table 3). Drowsiness and dry mouth were most frequently reported and remained the most frequent toxicities experienced after opioid titration. The proportion of patients with no toxicities gradually rose from week one to week four. Chi-square analyses indicated the proportion with toxicities differed significantly from expected at baseline ($p = 0.008$), but no significant differences were found after opioid titration ($ps > 0.10$). The mean score on the MSEC was 1.96 at baseline, with a significant reduction in mean toxicity over time ($p = 0.07$).

Adherence

Nine patients (53 percent) were adherent to both fixed- and rescue-dose analgesic regimens. The majority of patients took their fixed-dose opioids as prescribed. Nonadherence was primarily related to failure to take rescue doses when usual pain rose above four-tenths on the NRS. When queried about failure to adhere to the breakthrough regimen, most patients replied "the pain wasn't that bad," and "they did not need the medication."

Effect of titration on pain outcomes

The opioid titration order sheet had a beneficial effect on pain outcomes. Repeated measures ANOVA indicated a significant main effect for time on worst pain ($p = 0.10$), usual pain ($p = 0.02$), and pain-related distress ($p = 0.03$). All outcomes showed a decline over time. Interference because of pain did show a slight decline over time, but the change was not statistically significant. A main effect for adherence also was significant for worst pain ($p = 0.05$), usual pain ($p = 0.006$), and distress ($p = 0.05$). As expected, patients who took their medications as prescribed reported lower pain and distress than those who did not. No significant differences were found between patients who were and were not adherent for interference because of pain. No significant interaction between time and adherence was found for any pain outcome.

Table 3. Toxicities during trial					
Toxicity	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**
Constipation*	46.7	21.1	16.7	18.2	7.7
Drowsiness*	66.6	38.5	59.3	60.0	30.8
Nausea*	46.7	21.1	33.3	27.3	23.1
Vomiting*	20.0	21.1	8.3	18.2	15.4
Confusion*	33.3	21.1	16.7	36.4	23.1
Dry mouth*	80.0	53.8	75.0	81.8	43.8
Number of toxicities					
0	17.6	52.9	41.2	40.0	58.8
1	11.8	0	17.6	6.4	17.6
2 – 6	70.6	47.1	42.1	53.3	23.5
Severity**					
Mean	1.96	0.83	0.94	0.99	0.64
SD	1.63	1.23	1.15	1.10	0.98
Range	0 – 5.67	0 – 3.33	0 – 3.67	0 – 3.0	0 – 3.17
* Percent with toxicity; ** Possible range 0 – 10.					

DISCUSSION

The results of this study confirm the safety of an opioid titration order sheet that is managed by a trained nurse with appropriate physician oversight. The primary outcome measure for this study was adverse events. No adverse events were observed in the 66 titrations completed in this trial. Interestingly, despite the large number of dose titrations during the study period, opioid toxicity decreased over time. This may be related to the aggressive assessment of toxicity coupled with the timely institution of standard therapy to manage opioid side effects.

To capture the effect of the intervention on pain control, it is critical to select appropriate outcome measures. The most commonly used outcome measure for cancer pain is pain intensity. A standard measure of pain intensity in the cancer population is the BPI.[15,16,20] Usual pain is considered a measure of basal pain, while worst pain reflects breakthrough pain. Results from this pilot trial indicate that opioid titration using the opioid titration order sheet resulted in improvement in usual and worst pain.

Pain, like other symptoms, is characterized by multiple dimensions.[23] Distress, which is defined as the amount of anguish or bother caused by the symptom,[23,24] also may have a significant impact on intensity, duration, and secondary outcomes.[23-25] In previous work, pain-related distress explained a greater proportion of unique variance in interference than pain intensity (worst or usual), mood disturbance, or analgesics used.[26] Use of the opioid titration order sheet resulted in a significant reduction in distress once the patient had been placed on the protocol and had medications titrated. These findings suggest that distress may be a particularly salient outcome in analgesic trials and merits further study. The lack of effect of the opioid titration protocol on interference because of pain is consistent with previous work,[27] which is an outcome that may be influenced by a number of factors in addition to adequate pain control. Another explanation is that this scale may not be as sensitive to change as the single item pain intensity and distress items.

In our study, only half of the patients adhered to the prescribed regimen. While most patients took their fixed-dose regimen, adherence to the breakthrough regimen was poor. These results confirm the findings of other investigators. In a study by Miaskowski et al.,[28] the lack of adherence to medications prescribed to control metastatic cancer pain was substantial. Adherence rates, over a five-week period, were high (90.0 percent) for medications prescribed on a fixed schedule and notably lower for rescue-dose analgesics (24.7 percent). This study

highlights the problem of medication adherence in patients with cancer pain and provides a reasonable explanation for undertreatment.

Furthermore, we demonstrated that patients who adhere to their regimen are more likely to have improved pain outcomes. Our findings also support the work of Du Pen and colleagues,[27] who tested a pain algorithm in a randomized clinical trial. Use of the pain algorithm resulted in a significant reduction in usual pain for all patients in treatment and a significant reduction in usual and worst pain for patients who adhered to the prescribed regimen. In their sample, the pain algorithm did not affect symptoms experienced, interference because of pain, or quality of life. Thus, Du Pen and colleagues demonstrated the importance of adherence in achieving improvement in pain intensity when patients are managed with a pain algorithm. Both the pain algorithm and the opioid titration order sheet represent strategies that may produce successful implementation of existing pain guidelines.[29,30]

Limitations

Several limitations of this study must be noted. Because of the single-group design, we cannot compare the impact of this protocol with standing titration orders to usual care. The ability to generalize the results of this study are limited by the small sample size and attrition of patients from the study. Thus, future research using a randomized design with a usual care comparison group is recommended.

CONCLUSION

The opioid titration order sheet is a clinical tool that addresses the provider-driven steps of our conceptual model. The order sheet specifies the timing and content of pain assessment, the criteria indicating need for opioid dose adjustment, a standing order for dose titration, and an outline for provider communication of the treatment plan to the patient. After initial assessment by the physician, the standing orders can be used by trained nurses, thus reducing the barriers to effective pain management, knowledge deficits, and time constraints. Our pilot study suggests that this type of clinical tool is safe and effective in improving several critical pain outcomes for ambulatory patients with cancer. The protocol with standing orders also addresses barriers to clinical guideline implementation. Because of their level of specificity, algorithms and protocols may be more easily adopted in clinical settings, thus reducing one of the implementation problems inherent in guidelines. To extend this line of research, we need to determine the applicability of a pain protocol with standing orders for dose titration for community-based providers.

ACKNOWLEDGMENTS

This study was supported by funds from the Vanderbilt-Ingram Cancer Center Pilot Study award.

Preliminary findings from the first 17 subjects were presented at the 2001 ASCO scientific meeting. Wells N, Murphy B, Siet D: Standardized opioid titration order Sheet (SOTOS) for cancer pain. Proc Amer Soc Clin Oncol. 2001; 20: 2983, abstract #2943. The complete study was presented in poster form at the Pain in Europe conference, September 2003.

Nancy Wells, DNSc, RN, Vanderbilt University Medical Center, Vanderbilt University School of Nursing, Nashville, Tennessee.
Barbara Murphy, MD, Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, Tennessee.
Stacey Douglas, MSN, RN, Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, Tennessee.
Nancy Yelton, MSN, RN, Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, Tennessee.

REFERENCES

1. Portenoy RK: Cancer pain: Epidemiology and syndromes. *Cancer.* 1989; 63(11 Suppl): 2298-2307.
2. Zeppetella G, O'Dorhery CA, Collins S: Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. *J Pain Symptom Manage.* 2000; 20(2): 87-92.
3. Wells N, Hepworth J, Murphy BA, et al.: Improving cancer pain management through patient and family education. *J Pain Symptom Manage.* 2003; 25(4): 344-356.
4. Marks RM, Sachar EJ: Undertreatment of medical inpatients with narcotic analgesics. *Ann Intern Med.* 1973; 78(2): 173-181.
5. McCaffery M, Ferrell B: Nurses' knowledge of pain assessment and management: How much progress have we made? *J Pain Symptom Manage.* 1997; 14(3): 175-188.
6. Field MJ, Cassel CK (eds.): *Approaching Death: Improving Care at the End of Life.* Washington DC: National Academy Press, 1997.
7. Weissman DE, Dahl JL: Update on the cancer pain role model education program. *J Pain Symptom Manage.* 1995; 10(4): 292-297.
8. Janjan NA, Martin CG, Payne R, et al.: Teaching cancer pain management: Durability of educational effects of a role model program. *Cancer.* 1996; 77(5): 996-1001.
9. Oneschuk DFR, Hanson J, Bruera E: Assessment and knowledge in palliative care in second year family medicine residents. *J Pain Symptom Manage.* 1997; 14(5): 265-273.
10. Smith WR: Evidence for the effectiveness of techniques to change physician behavior. *Chest.* 2000; 118 (2 Suppl): 8S-17S.
11. Smith JL (unpublished data), 1997.
12. Anderson KO, Mendoza TR, Valeroo N, et al.: Minority cancer patients and their providers: Pain management attitudes and practice. *Cancer.* 2000; 88(8): 1929-1938.
13. Grimshaw JM, Sheran L, Thomas R, et al: Changing provider behavior: An overview systematic reviews of interventions. *Med Care.* 2001; 39(8 Suppl 2): II-2-II-45.
14. Folstein MF, Folstein S, McHugh PR: "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12(3): 189-198.
15. Daut RL, Cleeland CS, Flanery RC: Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain.* 1983; 17(2): 197-210.
16. Cleeland CS. Assessment of pain in cancer: measurement

issues. In: Foley KM, Bonica JJ, Ventafridda V (eds.): *Advances in Pain Research and Therapy, Vol. 16*. New York: Raven Press, 1990: 47-55.
17. Price D, McGrath PA, Rafii A, et al.: The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*. 1983; 17(1): 45-56.
18. Price DD, Harkins SW, Baker C: Sensory-affective relationships among different types of clinical and experimental pain. *Pain*. 1987; 28(3): 297-307.
19. Ward SE, Carlson-Dakes K, Hughes SH, et al.: The impact on quality of life of patient-related barriers to pain management. *Res Nurs Health*. 1998; 21(5): 405-413.
20. Serlin RC, Mendoza TR, Nakamura Y, et al.: When is cancer pain mild, moderate, or severe? Grading pain severity by its interference with function. *Pain*. 1995; 61(2): 277-284.
21. de Wit R, van Dam F, Hanneman M, et al.: Evaluation of the use of a pain diary in chronic cancer pain patients at home. *Pain*. 1999; 79(1): 89-99.
22. Maunsell E, Allard P, Dorval M, et al.: A brief pain diary for ambulatory patients with cancer: Acceptability and validity. *Cancer*. 2000; 88(10): 2387-2397.
23. Portenoy RK, Thaler HT, Kornblith AB, et al.: The Memorial Symptom Assessment Scale: An instrument for the evaluation of symptom prevalence, characteristics, and distress. *Eur J Cancer*. 1994; 30A(9): 1326-1336.
24. Rhodes VA, Watson PM: Symptom distress—The concept: Past and present. *Semin Oncol Nurs*. 1987; 3(4): 242-247.
25. Cleeland CS, Mendoza TR, Wang XS, et al.: Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer*. 2000; 89(7): 1634-1646.
26. Wells N, Murphy B, Wujcik D, et al.: Pain-related distress and pain interference in ambulatory patients with cancer pain. *Oncol Nurs Forum*. 2003; 30(6): 977-986.
27. Du Pen SL, Du Pen AR, Palissar N, et al.: Implementing guidelines for cancer pain management: Results of a randomized controlled clinical trial. *J Clin Oncol*. 1999; 17(1): 361-370.
28. Miaskowski C, Dodd MJ, West C, et al.: Lack of adherence with the analgesic regimen: A significant barrier to effective cancer pain management. *J Clin Oncol*. 2001; 19(23): 4275-4279.
29. Agency for Health Care Policy Research: *Cancer Guidelines. Clinical Practice Guidelines*. Publication No. 94-0592. Vol. 9, 1994.
30. World Health Organization: *Cancer Pain Relief*. Geneva, Switzerland, 1986.