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The Use of a Responder Analysis to Identify Differences in Patient Outcomes Following a Self-Care Intervention to Improve Cancer Pain Management

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Abstract

Previously, we demonstrated, in a randomized clinical trial, the effectiveness of a psychoeducational intervention to decrease pain intensity scores and increase patients' knowledge of cancer pain management with a sample of oncology patients with pain from bone metastasis. In the present study, we evaluated for changes in mood states (measured using the Profile of Mood States), quality of life (QOL; measured using the Medical Outcomes Study Short Form-36 (SF-36)), and pain's level of interference with function (measured using the Brief Pain Inventory (BPI)) from baseline to the end of the intervention first between the intervention and the standard care groups and then within the intervention group based on the patients' level of response to the intervention (i.e., patients were classified as non-responders, partial responders, or responders). No differences were found in any of these outcome measures between patients in the standard care and intervention groups. However, when patients in the intervention group were categorized using a responder analysis approach, significant differences in the various outcome measures were found among the three respondent groups. Differences in the physical and mental component summary scores on the SF-36 and the interference items on the BPI, among the three respondent groups, were not only statistically significant but also clinically significant. The use of responder analysis in analgesic trials may help to identify unique subgroups of patients and lead to the development of more effective psychoeducational interventions.

Keywords

cancer pain; psychoeducational intervention; responder analysis; mood states; quality of life; pain interference with function; bone metastasis

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1. Introduction

Numerous studies have documented the undertreatment of cancer pain and its negative consequences on patient's mood, functional status, and quality of life (QOL; (Cleeland et al. 1994; Glover et al. 1995; Burrows et al. 1998; Cleeland 1998)). However, the number of randomized clinical trials (RCTs) that have tested the effectiveness of patient interventions to improve cancer pain management is extremely limited (for reviews see Allard et al. 2001; Miaskowski 2003; 2004) given the fact that 50% of oncology outpatients and 80% to 90% of patients in the terminal stages of cancer experience moderate to severe pain (Miaskowski et al. 2005).

In 2004, we published the results of a RCT that demonstrated the effectiveness of a psychoeducational intervention called the PRO-SELF© Pain Control Program compared with standard care to decrease pain intensity scores and improve analgesic prescriptions in oncology outpatients with pain from bone metastasis (Schumacher et al. 2002b; West et al. 2003; Kim et al. 2004; Miaskowski et al. 2004). To date, this is the only intervention study that has resulted in both statistically and clinically significant reductions in pain intensity scores, statistically significant improvements in the number of appropriate analgesic prescriptions (i.e., more prescriptions of around-the-clock with as needed opioids), and statistically significant increases in patients' knowledge regarding pain management.

Recent work under the auspices of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) identified important core outcomes for studies of chronic pain (Turk et al. 2003; Turk and Dworkin 2004). In addition to pain intensity scores, measures of pain's level of interference with function, mood, and QOL should be included in an evaluation of the effectiveness of an intervention for chronic pain. In the above mentioned RCT of a cancer pain management intervention (Miaskowski et al. 2004), these additional outcomes were evaluated at the beginning and at the end of the six week intervention. Initial comparisons of changes in mood states, QOL, and pain's level of interference with function between the standard care and the intervention groups failed to demonstrate significant treatment effects.

However, in a recent paper, Dionne and colleagues (Dionne et al. 2005) suggested that the use of "responder approaches in analgesic studies" might offer another valid, reliable, and clinically meaningful way to analyze data from RCTs. These approaches may address important differences at the level of the individual than are traditionally described using summaries of group means and standard deviations. Therefore, the purposes of this study, in a sample of oncology outpatients with pain from bone metastasis who received the psychoeducational intervention, were: to evaluate for changes in mood states, QOL, and pain's level of interference with function from baseline to the end of the intervention based on the patient's response to the intervention (i.e., patients were classified as non-responders, partial responders, or responders). Data on changes in these outcome measures, between the standard care and intervention groups, are presented for comparative purposes.

2. Methods

2.1. Sample and Settings

Two hundred and twelve oncology outpatients, who were experiencing pain from bone metastasis, were recruited from seven outpatient settings in Northern California (i.e., a university-based cancer center, two community-based oncology practices, one health maintenance organization, one outpatient radiation therapy center, one veteran's affairs facility, one military hospital). The participants were adult oncology outpatients (> 18 years old) who were able to read, write, and understand English. All participants had a Karnofsky Performance

Status (KPS) score of ≥ 50 ; an average pain intensity score of ≥ 2.5 ; and radiographic evidence of bone metastasis. The study was approved by the Human Subjects Committee at the University of California, San Francisco and at each of the study sites. All of the patients and family caregivers signed a written informed consent.

2.2. Intervention

Specific details of the study procedures are described elsewhere (Schumacher et al. 2002a; West et al. 2003; Miaskowski et al. 2004). In brief, patients were approached in the outpatient setting by a recruitment nurse who explained the study and obtained written informed consent. Patients were stratified by site and on the basis of whether they participated by themselves or with a family caregiver. Both patients and clinicians at the study sites were blinded to the patient's group assignment. Patients were randomly assigned to either the PRO-SELF© or the standard care group. At the time of enrollment, patients completed a demographic questionnaire, the KPS score (Karnofsky 1977), and for one week before the first study visit, patients rated their level of pain intensity on a daily basis.

Patients in the standard care group received the patient version of the Cancer Pain Guideline published by the Agency for Health Care Policy and Research (AHCPR) (Jacox et al. 1994) and were seen by a research nurse in their homes at weeks 1, 3, and 6. Telephone interviews were conducted at weeks 2, 4, and 5. The focus of the visits and phone calls was on monitoring the patients' level of adherence with completing the Pain Management Diary.

Patients in the PRO-SELF© group received the psychoeducational intervention by a different group of specially trained oncology nurses. At week 1, the PRO-SELF© nurse conducted the academic detailing session with the patient and the family caregiver (Avorn and Soumerai 1983; Soumerai and Avorn 1990). This academic detailing session was tailored to meet the individual learning needs of the patient and family caregiver based on their responses to a knowledge and attitude survey about cancer pain management (Ferrell et al. 1993). The nurse identified the specific areas of knowledge deficit and focused the education in these areas. In addition, patients were given written instructions regarding pain and side effect management; were taught how to use a weekly pillbox; and were taught how to use a script to assist them in communicating with their physician or nurse about unrelieved pain and the need for a change in their analgesic prescription (West et al. 2003).

During weeks 2, 4, and 5, the PRO-SELF© nurse contacted patients in the intervention group by phone and reviewed their pain intensity scores and medication intake. The educational content of the PRO-SELF© Program was reinforced and patients were coached about how to modify their pain management plan or how to contact their physicians or nurses to improve pain outcomes. Most of the coaching took place during the phone calls and follow-up visits. The PRO-SELF© nurse made home visits during weeks 3 and 6. Again, previous teaching was reinforced and patients were coached about how to make changes in their pain management plan.

2.3. Outcome Measures

At the beginning of the study, patients completed a demographic questionnaire that obtained information on age, gender, education, living arrangements, marital status, and ethnicity. The patient's medical record was reviewed for disease and treatment information.

At the beginning and end of the study, patients completed the Profile of Mood States (POMS; (McNair et al. 1971; Baker et al. 2002)), the Medical Outcomes Study-Short Form (SF-36, (Ware 2000; 2003), and the interference items from the Brief Pain Inventory (BPI; (Daut et al. 1983)). In addition, on a daily basis, they completed a Pain Management Diary (Schumacher

et al. 2002a) that consisted of descriptive numeric rating scales (NRSs) for average and worst pain intensity and space for recording analgesic intake. Patients were asked to rate their average and worst pain using a 0 to 10 NRS prior to going to bed.

Mood states were evaluated using the short form of the POMS (Shacham 1983). The short form consists of 37 items from the original 65-item questionnaire developed by McNair et al. (McNair et al. 1971) and has six subscales that measure tension, depression, anger, fatigue, confusion, and vigor. A composite score, the total mood disturbance (TMD) score is calculated by summing each of the individual scores with the vigor items weighted negatively. In a previous study of oncology outpatients and their family caregivers (Miaskowski et al. 1997), the Cronbach's α for the POMS subscales ranged from 0.83 to 0.95.

QOL was evaluated using the SF-36 that consists of 36 items that evaluate eight conceptual domains: physical functioning (PF), role limitations due to physical health (RP), bodily pain (BP), general health (GH), vitality (VT); social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). In addition, two standardized composite scores were calculated (i.e., physical component summary (PCS), mental component summary (MCS)). The SF-36 is scored so that each domain's score ranges from 0 to 100 with higher scores indicating a better QOL. The SF-36 is an internationally accepted measure of QOL with excellent validity and reliability (Ware et al. 1995; Ware et al. 1998a; Ware et al. 1998b; Ware 2000; Ware and Kosinski 2001; Ware 2003).

Pain's level of interference with function was evaluated using the interference items from the BPI (Daut et al. 1983). This 8 item scale asked patients to evaluate, using 0 (does not interfere) to 10 (completely interferes) NRSs, how during the past week, pain interfered with a variety of activities (e.g., general activity). Scores on the individual items are summed and divided by 8 to obtain a total interference score that ranges from 0 to 10. The α reliability for the scale ranges from 0.91 to 0.95 (Serlin et al. 1995; Cleeland et al. 1996).

2.4. Statistical analysis

Descriptive statistics and frequency distributions were generated for the patient's demographic and disease-related characteristics. Daily pain intensity ratings of average and worst pain were averaged on a weekly basis.

In order to perform the initial responder analysis, patients in the PRO-SELF© intervention and standard care groups were categorized as responders, partial responders, or non-responders based on their mean percent change in average and worst pain from the beginning to the end of the study. Percentage changes in average and worst pain, from the beginning to the end of the study, were averaged to obtain an overall percent change score in order to account for changes in persistent pain (i.e., average pain scores) and breakthrough pain (i.e., worst pain scores). Because clinically meaningful changes in chronic pain have been shown to correspond to a decrease of $\geq 30\%$ (Farrar 2000; Farrar et al. 2000; Farrar et al. 2001), patients with a $\geq 30\%$ decrease in pain intensity were categorized as responders; those with a decrease of between 1% and 29% were categorized as partial responders; and those with no change or an increase in pain were categorized as non-responders. Subsequent responder analyses were done only with patients in the PRO-SELF© group (i.e., PRO-SELF© responder analyses).

Differences in baseline demographic; disease and treatment characteristics; and percentages of patients within each responder group between the standard care and PRO-SELF© groups and among the three responder groups who received the PRO-SELF© intervention, were evaluated using Independent Student's t-tests, one way analyses of variance (ANOVAs), and Chi Square analyses. Analyses of covariance were performed to evaluate for differences in mood states, QOL, and pain's level of interference with function at the end of the study, between

patients in the standard care and PRO-SELF© groups, as well as among the three responder groups. This procedure allows for an evaluation of the end of study outcomes while controlling for these same outcomes at baseline. The examination of differences among groups in end of study outcomes, with baseline measurements of those outcomes covaried out, is often a preferred method for examining changes in outcome measures from the beginning to the end of a study (Cohen et al. 2003).

All calculations used actual values. Adjustments were not made for missing data. Therefore, the cohort for each analysis was dependent on the largest set of data across groups. If the overall analysis of covariance for a particular outcome indicated differences among the three responder groups, pairwise contrasts were conducted to determine where the differences were. The Bonferroni procedure was used to distribute a family alpha of .05 across the three pairwise contrasts. All p-values have been adjusted so that values of < .05 are considered statistically significant.

3. Results

3.1. Sample demographics

One hundred and seventy-four oncology outpatients with pain from bone metastasis completed the study. Thirty-eight patients (i.e., 22 in the PRO-SELF© group and 16 in the standard care group) did not complete the entire study for a variety of reasons, including: increased severity of illness or intervening cancer treatments that required hospitalization (n=28; 16 in the PRO-SELF© group and 12 in the standard care group) and death (n=10; six in the PRO-SELF© group and four in the standard care group). No differences were found in any of the demographic, disease, or baseline pain characteristics between patients who did and did not complete the study. The percentage of patients who did not complete the entire study did not differ significantly by treatment group (i.e., 19% in the PRO-SELF© group and 17% in the standard care group).

For the various analyses in this paper, complete data on both average and worst pain intensity scores, which were needed for the responder analysis were available on 167 patients (78 in the standard care group and 89 in the PRO-SELF© group). The demographic and disease characteristics of the patients in the standard care, PRO-SELF©, and responder groups are summarized in Table 1. No significant differences were found in any of the demographic or disease characteristics between patients in the standard care and PRO-SELF© groups or among the patients in the three responder groups.

3.2. Responder analysis

The initial responder analysis was performed on the 89 patients in the PRO-SELF© group and the 78 patients in the standard care group to determine the percentage of patients in each treatment group that could be categorized as responders (i.e., $\geq 30\%$ decrease in the mean of average and worst pain from the beginning to the end of the study), partial responders (i.e., 1% to 29% decrease), or non-responders (i.e., no change or an increase in pain). As shown in Figure 1A, significant differences were found between the PRO-SELF© and standard care groups in the percentage of patients categorized as responders (49.4% versus 15.4%), partial responders (24.7% versus 37.2%), and non-responders (25.8% versus 47.4%, respectively; $X^2 = 21.9$, $p < .0001$).

Figure 1B illustrates the percentages of patients in the PRO-SELF© group categorized as responders (54.9%, 49.4%), partial responders (19.8%, 21.3%), or non-responders (25.3%, 29.2%) based on their ratings of average and worst pain, respectively.

3.3. Changes in Profile of Mood States Scores

As shown in Table 2, after controlling for POMS scores at baseline, no significant differences were found, between the standard care and PRO-SELF© groups, in any of the subscale scores or in the TMD score of the POMS at the end of the study. However, significant differences were found, among the three PRO-SELF© responder groups in depression scores on the POMS ($p=.02$). Post hoc contrasts demonstrated that the partial responders had significantly lower depression scores at the end of the study, than the responders.

3.4. Changes in SF-36 Scores

As shown in Table 3, after controlling for SF-36 scores at baseline, significant differences were found, between the standard care and PRO-SELF© groups, in the BP subscale score at the end of the study; such that patients in the PRO-SELF© group reported significantly higher BP scores which indicates less pain ($p=.005$).

Significant differences were found, among the three PRO-SELF© responder groups in BP ($p<.0001$) and SF ($p=.019$) subscale scores of the SF-36, as well as in the standardized physical health ($p=.004$) and mental health ($p=.03$) component scores of the SF-36 (Table 3). Post hoc contrasts demonstrated that the responders reported significantly higher scores than the non-responders for these subscales.

3.5. Changes in Pain Interference Scores

As shown in Table 4, for each of the pain interference items, after controlling for the interference scores at baseline, no significant differences were found, between the standard care and PRO-SELF© groups, in any of the interference scores at the end of the study.

Significant differences were found, among the three PRO-SELF© responder groups in all of the pain interference items, except sexual activity (all $p\leq.02$; Table 4). In most cases, post hoc contrasts demonstrated that the responders reported significantly less pain interference with the various activities than the non-responders.

4. Discussion

This study is the first to use a responder analysis approach to evaluate for differences in secondary outcomes (i.e., mood states, QOL, pain interference with function) from a RCT of a psychoeducational intervention to improve cancer pain management. While statistically and clinically significant reductions in pain intensity scores, significant improvements in patients' knowledge about pain management, and significant improvements in the number of appropriate analgesic prescriptions did occur as a result of the intervention (Schumacher et al. 2002a; Schumacher et al. 2002b; Kim et al. 2004; Miaskowski et al. 2004), initial analyses of the overall effectiveness of the intervention in improving mood and QOL and decreasing levels of pain interference with function failed to demonstrate significant differences between the intervention and the standard care groups on the majority of the outcome measures. Possible explanations for the lack of an overall treatment effect on these important clinical outcomes could include the fact that the instruments chosen to measure these outcomes were not sensitive enough to detect treatment effects; that it was unrealistic to expect that a unidimensional psychoeducational intervention targeted at pain would have effects on mood or QOL; that decreases in pain intensity were associated with increases in analgesic side effects which may have dampened improvements in QOL; and/or that these outcome measures may change more slowly than measures of pain intensity and therefore could not be detected during this brief, six week study.

However, when the PRO-SELF© group was categorized based on pre-specified outcomes (e.g., $\geq 30\%$ decrease in mean of average and worst pain from the beginning to the end of the study), differences in these outcome measures were observed among the responders, partial responders, and non-responders. Even with the relatively small sample sizes, significant differences in the expected directions occurred with various aspects of QOL as measured by the SF-36 and with pain's level of interference with function. The majority of these differences were found between the responders and the non-responders. These findings point to the need to evaluate for differences in primary and secondary outcomes at the level of the individual or groups of individuals. As noted by Dionne et al (Dionne et al. 2005) and demonstrated in this study, the use of responder approaches in analgesic studies may offer another valid, reliable, and clinically meaningful way to evaluate for changes in outcome measures following a pain management intervention.

The scores on the various subscales of the POMS, as well as the TMD score, are comparable to scores obtained from patients with various types of cancer pain in the United States (Glover et al. 1995; Miaskowski et al. 1997) and Taiwan (Ahles et al. 1984; Lin et al. 2003). While not significantly different, patients in the non-responder group reported less vigor and higher mood disturbance scores than the other two groups. It is not clear why patients in the partial responder group reported significantly lower depression scores than patients in the responder group. An examination of the other POMS subscale scores on Table 2 demonstrates a similar pattern for anger, fatigue, confusion, and TMD. It is unlikely that disease or treatment characteristics contributed to these differences because these characteristics were similar across the three PRO-SELF© responder groups. This finding warrants additional investigation because of the small sample sizes and the multiplicity of tests. The use of more specific mood (e.g., Center for Epidemiological Studies – Depression Scale; (Radloff 1977); Spilberger State Anxiety Scale (Johnson and Spielberger 1968)) and fatigue (e.g., Lee Fatigue Scale (Lee et al. 1994)) measures with established cutoff scores may provide important information on the ability of a psychoeducational intervention to improve patients' mood states.

As shown in Table 3, a comparison of the patients' SF-36 subscale scores, as well as the PCS and MCS scores to the average scores for the general population in the United States (Ware 2000), indicates that these patients had significant limitations in all aspects of physical and mental function that were evaluated using the SF-36. This finding is not unexpected given the fact that all of these patients were experiencing pain from bone metastasis and that over 50% of the patients had been in pain for greater than 6 months (Miaskowski et al. 2004).

As noted by Ware and colleagues ((Ware 2000; Ware and Kosinski 2001), the PCS and MCS scores were developed as summary measures from numerous studies. These two summary scores undergo linear transformations so that they can be compared to the mean of 50 and standard deviation of 10, in the general population in the United States (US). In this study, the PCS score was almost 20 points lower and the MCS score was about 5 points lower than in the general US population. However, it is interesting to note, that at the end of the intervention study, patients in the responder group had significant improvements in both the PCS and MCS scores compared to those in the non-responder group.

While statistically significant differences in the PCS and MCS were found, it is important to determine whether these differences are clinically meaningful. Several reports in the QOL literature suggest that minimally important and clinically meaningful differences in QOL are in the range of 0.2 to 0.5 standard deviation units (Osoba 1999; Guyatt et al. 2002; Norman et al. 2003). Therefore, effect sizes were calculated for the differences in the PCS and MCS scores between the responder and the non-responder groups. The effect sizes were within the moderate to large range (i.e., 0.63 for the PCS and 0.79 for the MCS; (Cohen 1988)) which suggests clinically meaningful differences.

It was reasonable to expect that an intervention targeted at improving cancer pain management would result in significant differences in pain's level of interference with the various activities evaluated using the BPI. However, no differences in any of the interference items were found between the intervention and standard care groups. In contrast, when the PRO-SELF[®] responder analysis was done, significant decreases in pain interference with general activity, mood, walking ability, and enjoyment with life were reported by patients in the responder group compared to the non-responder group. In addition, pain's level of interference with normal work and sleep, as well as the total interference score were significantly reduced in the responders compared to both the partial and the non-responders. Again, effect sizes were within the moderate to large range (i.e., 0.53 to 0.83; (Cohen 1988)) which suggests clinically meaningful differences occurred in the various interference items as a result of the psychoeducational intervention for a subgroup of patients.

It is interesting to speculate why our psychoeducational intervention was more effective for one subset of patients. As with a pharmacologic intervention, the dose and duration of the therapy has an impact on a variety of patient outcomes. One plausible hypothesis is that the patients in the partial and non-responder groups did not receive a high enough dose of the intervention; that averaged about 4.5 hours in this RCT. In two recent reviews, Miaskowski (Miaskowski 2003;2004) noted that neither the optimal dose (i.e., number of minutes or hours) nor the optimal duration (i.e., total number of weeks) of a psychoeducational intervention for cancer pain management is known. In contrast, work by Howard and colleagues (Howard et al. 1986;Lutz et al. 2001;Lutz 2003) found that the optimal dose of a psychotherapy intervention was 8 hours for 50% of the patients studied regardless of their specific psychiatric diagnoses. The remaining 50% of these patients needed a higher dose of psychotherapy defined as more time with the therapist. An equally plausible explanation for the failure to achieve a 30% reduction in pain intensity scores in 50% of the patients in the PRO-SELF[®] intervention group is that this was the “wrong” intervention for some patients. A RCT is planned to test the “dose response” hypothesis first.

Several limitations of the RCT are worth noting that may have affected the outcomes of this responder analysis. The majority of patients was white and well educated which limits the generalizability of the study findings. In addition, the sample sizes for the responder analysis were relatively small and may have limited our ability to detect some differences. Despite these limitations, this responder analysis provides important new information on the effectiveness of a psychoeducational intervention for cancer pain management. In addition, it provides direction for subsequent analyses of analgesic trials with both pharmacologic and nonpharmacologic interventions that may allow us to determine clinically meaningful inter-individual differences in patient outcomes.

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References

- Ahles TA, Ruckdeschel JC, Blanchard EB. Cancer-related pain--I. Prevalence in an outpatient setting as a function of stage of disease and type of cancer. *J Psychosom Res* 1984;28(2):115–119. [PubMed: 6610747]
- Allard P, Maunsell E, Labbe J, Dorval M. Educational interventions to improve cancer pain control: a systematic review. *J Palliat Med* 2001;4(2):191–203. [PubMed: 11441627]
- Avorn J, Soumerai SB. Improving drug-therapy decisions through educational outreach. A randomized controlled trial of academically based “detailing”. *N Engl J Med* 1983;308(24):1457–1463. [PubMed: 6406886]

- Baker F, Denniston M, Zabora J, Polland A, Dudley WN. A POMS short form for cancer patients: psychometric and structural evaluation. *Psychooncology* 2002;11(4):273–281. [PubMed: 12203741]
- Burrows M, Dibble SL, Miaskowski C. Differences in outcomes among patients experiencing different types of cancer-related pain. *Oncol Nurs Forum* 1998;25(4):735–741. [PubMed: 9599356]
- Cleeland CS. Undertreatment of cancer pain in elderly patients. *JAMA* 1998;279(23):1914–1915. [PubMed: 9634265]
- Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med* 1994;330(9):592–596. [PubMed: 7508092]
- Cleeland CS, Nakamura Y, Mendoza TR, Edwards KR, Douglas J, Serlin RC. Dimensions of the impact of cancer pain in a four country sample: new information from multidimensional scaling. *Pain* 1996;67(23):267–273. [PubMed: 8951920]
- Cohen, J. Statistical power analysis for the behavioral sciences. Lawrence Erlbaum Associates; Hillsdale, NJ: 1988.
- Cohen, J.; Cohen, P.; West, S.; Aiken, L. Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences. Lawrence Erlbaum Associates; Hillsdale, New Jersey: 2003.
- 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. [PubMed: 6646795]
- Dionne RA, Bartoshuk L, Mogil J, Witter J. Individual responder analyses for pain: does one pain scale fit all? *Trends Pharmacol Sci* 2005;26(3):125–130. [PubMed: 15749157]
- Farrar JT. What is clinically meaningful: outcome measures in pain clinical trials. *Clin J Pain* 2000;16(2 Suppl):S106–112. [PubMed: 10870749]
- Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain* 2000;88(3):287–294. [PubMed: 11068116]
- Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94(2):149–158. [PubMed: 11690728]
- Ferrell B, Rhiner M, Rivera LM. Development and evaluation of the family pain questionnaire. *Journal of Psychosocial Oncology* 1993;10:21–35.
- Glover J, Dibble SL, Dodd MJ, Miaskowski C. Mood states of oncology outpatients: does pain make a difference? *J Pain Symptom Manage* 1995;10(2):120–128. [PubMed: 7730684]
- Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002;77(4):371–383. [PubMed: 11936935]
- Howard KI, Kopta SM, Krause MS, Orlinsky DE. The dose-effect relationship in psychotherapy. *Am Psychol* 1986;41(2):159–164. [PubMed: 3516036]
- Jacox, A.; Carr, DB.; Payne, R. Agency for Health Care Policy and Research, U. S. Department of Health and Human Services, Public Health Service; Rockville, MD: 1994. Management of Cancer Pain. Clinical Practice Guideline 9. AHCPR Publication 94-0592
- Johnson DT, Spielberger CD. The effects of relaxation training and the passage of time on measures of state- and trait-anxiety. *J Clin Psychol* 1968;24(1):20–23. [PubMed: 4384306]
- Karnofsky, D. Performance scale. In: Kennealey, GT.; Mitchell, MS., editors. *Factors that Influence the Therapeutic Response in Cancer: A Comprehensive Treatise*. Plenum Press; New York: 1977.
- Kim JE, Dodd M, West C, Paul S, Facione N, Schumacher K, Tripathy D, Koo P, Miaskowski C. The PRO-SELF pain control program improves patients' knowledge of cancer pain management. *Oncol Nurs Forum* 2004;31(6):1137–1143. [PubMed: 15547636]
- Lee KA, Lentz MJ, Taylor DL, Mitchell ES, Woods NF. Fatigue as a response to environmental demands in women's lives. *Image J Nurs Sch* 1994;26(2):149–154. [PubMed: 8063323]
- Lin CC, Lai YL, Ward SE. Effect of cancer pain on performance status, mood states, and level of hope among Taiwanese cancer patients. *J Pain Symptom Manage* 2003;25(1):29–37. [PubMed: 12565186]
- Lutz W. Efficacy, effectiveness, and expected treatment response in psychotherapy. *J Clin Psychol* 2003;59(7):745–750. [PubMed: 12808581]
- Lutz W, Lowry J, Kopta SM, Einstein DA, Howard KI. Prediction of dose-response relations based on patient characteristics. *J Clin Psychol* 2001;57(7):889–900. [PubMed: 11406802]

- McNair, DM.; Lorr, M.; Droppleman, LF. EDITS Manual for the Profile of Mood States. Educational and Industrial Testing Service; San Diego, CA: 1971.
- Miaskowski, C. Pain Management. In: Given, CW.; Given, B.; Champion, VL.; Kozachik, S.; DeVoss, DN., editors. *Evidenced-based Cancer Care and Prevention: Behavioral Interventions*. Springer Publishing Company; New York: 2003. p. 274-291.
- Miaskowski C. Psychoeducational interventions for cancer pain serve as a model for behavioral research. *Commun Nurs Res* 2004;37:51, 53–71. [PubMed: 15320538]
- Miaskowski, C.; Cleary, J.; Burney, R.; Coyne, P.; Finley, R.; Foster, R.; Grossman, S.; Janjan, N.; Ray, J.; Syrjala, K.; Weisman, S.; Zahrbock, C. Guideline for the Management of Cancer Pain in Adults and Children. 3. American Pain Society; Glenview, IL: 2005.
- Miaskowski C, Dodd M, West C, Schumacher K, Paul SM, Tripathy D, Koo P. Randomized clinical trial of the effectiveness of a self-care intervention to improve cancer pain management. *J Clin Oncol* 2004;22(9):1713–1720. [PubMed: 15117994]
- Miaskowski C, Zimmer EF, Barrett KM, Dibble SL, Wallhagen M. Differences in patients' and family caregivers' perceptions of the pain experience influence patient and caregiver outcomes. *Pain* 1997;72(12):217–226. [PubMed: 9272806]
- Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003;41(5):582–592. [PubMed: 12719681]
- Osoba D. Interpreting the meaningfulness of changes in health-related quality of life scores: lessons from studies in adults. *Int J Cancer Suppl* 1999;12:132–137. [PubMed: 10679884]
- Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement* 1977;1(3):385–401.
- Schumacher KL, Koresawa S, West C, Dodd M, Paul SM, Tripathy D, Koo P, Miaskowski C. The usefulness of a daily pain management diary for outpatients with cancer-related pain. *Oncol Nurs Forum* 2002a;29(9):1304–1313. [PubMed: 12370700]
- Schumacher KL, Koresawa S, West C, Hawkins C, Johnson C, Wais E, Dodd M, Paul SM, Tripathy D, Koo P, Miaskowski C. Putting cancer pain management regimens into practice at home. *J Pain Symptom Manage* 2002b;23(5):369–382. [PubMed: 12007755]
- Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain* 1995;61(2):277–284. [PubMed: 7659438]
- Shacham S. A shortened version of the Profile of Mood States. *J Pers Assess* 1983;47(3):305–306. [PubMed: 6886962]
- Soumerai SB, Avorn J. Principles of educational outreach ('academic detailing') to improve clinical decision making. *JAMA* 1990;263(4):549–556. [PubMed: 2104640]
- Turk DC, Dworkin RH. What should be the core outcomes in chronic pain clinical trials? *Arthritis Res Ther* 2004;6(4):151–154. [PubMed: 15225358]
- Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS, Hewitt DJ, Jadad AR, Katz NP, Kramer LD, Manning DC, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robinson JP, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Witter J. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003;106(3):337–345. [PubMed: 14659516]
- Ware JE Jr. SF-36 health survey update. *Spine* 2000;25(24):3130–3139. [PubMed: 11124729]
- Ware JE Jr. Conceptualization and measurement of health-related quality of life: comments on an evolving field. *Arch Phys Med Rehabil* 2003;84(4 Suppl 2):S43–51. [PubMed: 12692771]
- Ware JE Jr, Gandek B, Kosinski M, Aaronson NK, Apolone G, Brazier J, Bullinger M, Kaasa S, Lepke A, Prieto L, Sullivan M, Thunedborg K. The equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in 10 countries: results from the IQOLA Project. *International Quality of Life Assessment*. *J Clin Epidemiol* 1998a;51(11):1167–1170. [PubMed: 9817134]
- Ware JE Jr, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of

results from the Medical Outcomes Study. *Med Care* 1995;33(4 Suppl):AS264–279. [PubMed: 7723455]

Ware JE Jr, Kosinski M, Gandek B, Aaronson NK, Apolone G, Bech P, Brazier J, Bullinger M, Kaasa S, Leplege A, Prieto L, Sullivan M. The factor structure of the SF-36 Health Survey in 10 countries: results from the IQOLA Project. *International Quality of Life Assessment. J Clin Epidemiol* 1998b; 51(11):1159–1165. [PubMed: 9817133]

Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. *Qual Life Res* 2001;10 (5):405–413. [PubMed: 11763203]discussion 415–420

West CM, Dodd MJ, Paul SM, Schumacher K, Tripathy D, Koo P, Miaskowski C. The PRO-SELF(c): Pain Control Program--an effective approach for cancer pain management. *Oncol Nurs Forum* 2003;30(1):65–73. [PubMed: 12515985]

Figure 1.

Figure 1A – Percentage of patients in the PRO-SELF© (n=89) and standard care (n=78) groups who were categorized as a non-responder, partial responder, or responder.

Figure 1B - Percentage of patients in the PRO-SELF© (n=89) who were categorized as a non-responder, partial responder, or responder based on their ratings of average and worst pain.

Table 1
Differences in demographic and disease characteristics between patients in the standard care and PRO-SELF[®] groups and among the three PRO-SELF[®] responder groups

Characteristic	Intervention Study		PRO-SELF® Responder Analysis				
	Standard Care N = 78	PRO-SELF® N = 89	Significance	Responder (1) N = 44	Partial Responder (2) N = 22	Non-responder (3) N = 23	Significance
Age (years)							
Mean (SD)	58.5 (13.1)	59.8 (11.6)	NS	57.5 (11.0)	61.4 (11.5)	63.2 (12.5)	NS
Education (years)							
Mean (SD)	14.9 (3.3)	14.7 (3.2)	NS	14.5 (3.0)	15.3 (2.9)	14.1 (3.5)	NS
KPS score							
Mean (SD)	71.9 (12.2)	68.7 (11.4)	NS	71.3 (10.4)	66.2 (13.6)	66.3 (10.1)	NS
Gender (%)							
Male	25.6	31.5	NS	27.3	40.9	31.8	NS
Female	74.4	68.5		72.7	59.1	68.2	
Lives alone (%)	19.5	34.1	NS	37.2	22.7	36.4	NS
Marital status (%)							
Married/partnered	61.0	49.4	NS	47.7	54.5	50.0	NS
Never married	5.2	10.1		11.4	9.1	4.5	
Other	33.8	40.5		40.9	36.4	45.5	
Ethnicity (%)			NS				NS
White	88.5	80.7		84.1	81.0	72.7	
Non-white	11.5	19.3		15.9	19.0	27.3	
Employment (%)			NS				NS
Full time	6.7	9.1		9.1	4.5	0.0	
Disability	24.7	34.8		38.6	31.8	31.8	
Retired	40.3	33.7		29.5	31.8	45.5	
Other	28.3	31.5		31.9	31.9	22.7	
Diagnosis (%)			NS				NS
Breast	53.2	53.9		59.1	50.0	45.5	
Prostate	13.0	12.4		9.1	9.1	22.7	
Lung	14.3	10.1		6.8	4.5	22.7	
Other	19.5	23.6		25.0	36.4	9.1	
Current therapy* (%)			NS				NS
Chemotherapy	45.5	48.3		54.5	45.5	40.9	
Hormonal therapy	31.2	32.6		34.1	31.8	27.3	
Radiation therapy	14.3	16.9		22.7	9.1	13.6	
Biotherapy	1.3	1.1		0.0	4.5	0.0	
No treatment	14.7	10.3		9.3	4.5	19.0	

Abbreviations: KPS = Karnofsky Performance Status; NS = not significant; SD = standard deviation

* Patients could be receiving more than one type of treatment simultaneously

Table 2

Differences in Profile of Mood States scores^{*}, at the end of the study, between patients in the standard care and PRO-SELF© groups and among the three PRO-SELF© responder groups

POMS scores	Intervention Study		Significance ^{**}	PRO-SELF© Responder Analysis		
	Standard Care N = 78	PRO-SELF© N = 89		Responder (1) N = 44	Partial Responder (2) N = 22	Non-responder (3) N = 23
Tension	4.4 (3.8)	4.8 (4.5)	NS	4.6 (4.4)	4.6 (4.4)	5.6 (4.7)
Depression	3.8 (4.2)	4.3 (4.4)	NS	4.4 (4.3)	2.7 (3.0)	6.0 (5.3)
Anger	3.3 (3.7)	3.5 (4.3)	NS	3.5 (4.5)	3.2 (4.7)	3.9 (3.7)
Vigor ^{***}	5.7 (4.4)	4.7 (4.1)	NS	5.4 (4.2)	4.7 (4.8)	3.3 (3.0)
Fatigue	8.3 (4.8)	7.7 (4.7)	NS	7.8 (4.8)	6.9 (5.4)	8.3 (3.5)
Confusion	5.0 (3.4)	5.2 (3.5)	NS	5.0 (3.2)	4.3 (3.7)	6.6 (3.7)
TMD score	19.1 (18.2)	21.0 (19.3)	NS	19.8 (18.7)	16.9 (21.4)	27.2 (17.7)

^{*} All values are expressed as actual means and standard deviations

^{**} Reported significance levels are based on end of study values after controlling for baseline values

^{***} Higher scores indicate more vigor

Table 3

Differences in SF-36 scores *, at the end of the study, between patients in the standard care and PRO-SELF© groups and among the three PRO-SELF© responder groups

SF-36 subscales Average scores for the general population in the United States	Intervention Study		Significance	PRO-SELF© Responder Analysis		
	Standard Care N = 78	PRO-SELF© N = 89		Responder (1) N = 44	Partial Responder (2) N = 22	Non-responder (3) N = 23
General health 71.9 (20.3)	40.6 (20.2)	40.9 (19.4)	NS	42.4 (18.9)	43.7 (21.4)	34.6 (17.7)
Physical functioning 84.2 (23.3)	42.8 (26.0)	40.9 (25.5)	NS	46.1 (25.5)	40.0 (26.8)	32.0 (19.3)
Role limitations – physical 80.9 (34.0)	15.0 (26.9)	16.9 (30.8)	NS	20.3 (32.4)	18.2 (32.0)	10.7 (28.0)
Bodily pain 75.2 (23.7)	39.6 (19.8)	46.8 (22.1)	p=0.005	55.5 (20.3)	44.1 (22.1)	33.5 (15.8)
Vitality 60.0 (20.9)	38.6 (18.8)	39.9 (19.6)	NS	45.2 (17.9)	38.4 (23.1)	32.4 (16.0)
Mental health 74.7 (18.1)	68.1 (19.0)	67.6 (18.5)	NS	70.5 (15.5)	73.8 (18.0)	58.3 (18.9)
Role limitations – emotional 81.3 (33.0)	42.1 (42.9)	44.1 (44.8)	NS	52.8 (45.3)	50.0 (46.9)	22.2 (33.9)
Social functioning 83.3 (22.7)	60.1 (26.3)	56.6 (27.1)	NS	62.2 (25.9)	61.9 (27.4)	44.0 (23.9)
Physical component summary score 50.0 (10.0)	32.4 (7.7)	33.2 (7.6)	NS	35.4 (7.8)	31.8 (7.8)	30.6 (5.9)
Mental component summary score 50.0 (10.0)	45.2 (10.6)	44.9 (11.2)	NS	47.0 (10.1)	48.0 (11.7)	38.8 (9.7)

* All values are expressed as actual means and standard deviations

** Reported significance levels are based on end of study values after controlling for baseline values

*** Higher scores indicated less pain

Table 4

Differences in interference item scores *, at the end of the study, between patients in the standard care and PRO-SELF© groups and among the three PRO-SELF© responder groups

Interference items	Intervention Study		PRO-SELF© Responder Analysis			
	Standard Care N = 78	PRO-SELF© N = 89	Statistic	Responder (1) N = 44	Partial Responder (2) N = 22	Non-responder (3) N = 23
General activity	4.9 (2.9)	4.3 (2.9)	NS	3.4 (3.0)	4.6 (2.5)	5.6 (2.8)
Mood	3.9 (2.8)	3.9 (3.0)	NS	2.9 (2.9)	4.7 (3.2)	5.1 (2.4)
Walking ability	4.8 (3.2)	4.7 (3.0)	NS	4.1 (3.2)	4.9 (2.9)	5.7 (2.5)
Normal work	5.8 (3.0)	5.4 (3.0)	NS	4.4 (3.1)	6.4 (2.8)	6.6 (2.2)
Relations with others	3.3 (3.1)	3.4 (2.8)	NS	2.5 (2.8)	4.5 (2.8)	3.9 (2.2)
Sleep	4.1 (3.3)	3.3 (2.8)	NS	2.2 (2.4)	4.5 (3.0)	4.1 (2.7)
Enjoyment of life	4.7 (3.1)	4.3 (2.9)	NS	3.4 (2.9)	5.4 (3.0)	4.9 (2.2)
Sexual activity	5.0 (3.8)	4.3 (4.2)	NS	3.2 (4.1)	5.7 (3.9)	5.3 (4.3)
Total interference score	4.6 (2.4)	4.2 (2.4)	NS	3.2 (2.5)	5.0 (2.2)	5.2 (1.5)

* All values are expressed as actual means and standard deviations

** Reported significance levels are based on end of study values after controlling for baseline values