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Patient-Reported Outcomes and Opioid Use by Outpatient Cancer Patients

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Abstract

The Memorial Sloan-Kettering Pain Registry contains patient characteristics, treatments, and outcomes for a prospective cohort of 1534 chronic pain cancer patients who were seen at outpatient pain service clinics. Average pain intensity (Brief Pain Inventory) was reported as mild by 24.6% of patients, moderate by 41.5%, and severe by 33.9%. The patient's report of average percent pain relief and health state (EQ-5D) was inversely related to average pain intensity category, while measures of pain interference, number of worst pain locations, and physical and psychological distress were directly related to pain intensity category. Eighty-six percent of patients received an opioid at one or more clinic encounters. Regression analysis revealed that being a male or being younger (<=65 yrs. of age) was associated with a greater likelihood of an opioid ordered. Being male nearly doubled the likelihood of a higher dose being ordered than being female. Bivariate analysis found that patients receiving opioids reported significantly more pain relief than no opioid patients. However, patients receiving opioids had higher pain interference scores, lower index of health-state, and more physical distress than no opioid patients Our results identify the need to consider opioid use and dosage when attempting to understand patient reported outcomes (PROs) and factors affecting pain management.

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Keywords

chronic cancer pain; patient-reported outcomes; pain intensity; opioid analgesic use; sex; age; opioid dosage

Cancer patients receiving active treatment or palliative care experience multiple, co-occurring symptoms and adverse effects. Several reports have examined patient reported outcomes (PROs) of cancer patients and identified patient characteristics that are associated with co-occurring symptoms[3, 9, 12, 28, 35, 41, 42]. Subclass analysis of symptom occurrence identified 4 classes of patients and found that those patients with the highest probability of symptoms were younger, had lower functional status, higher comorbidity, and poorer Quality of Life (QoL) scores.[3, 9, 12, 35, 41, 42] Patients who report both cancer pain and co-occurring noncancer pain were significantly younger, more likely to be female, have a higher level of comorbidity, and poorer QoL than oncology patients without pain[12, 35, 41, 42]. The identification of patient and treatment factors associated with cancer pain and their impact on outcomes, including quality of life (QoL), provide clinicians with information that can improve both the assessment and management of cancer pain. Symptoms associated with cancer and its treatment can also initiate emergency department (ED) visits and hospital admissions[31]. Mayer et., al. 2011 found that the chief complaint driving an ED visit was pain[31]. In a randomized trial of adults receiving outpatient chemotherapy, Basch et., al. 2016 found that the systematic collection of PROs using the EQ-5D, together with clinician alerts resulted in better QoL, fewer ER visits, fewer hospitalizations, longer duration of palliative chemotherapy and superior quality adjusted survival[5]. These data support the value of monitoring PROs as part of routine clinical visits.

Cleeland et.al.,[15] identified a number of patient factors that predicted inadequate pain management including minority status, age over 70, and female sex. This important study estimated analgesic use with a pain management index but did not report on opioid dose levels. Posternak et. al.,[41] used self-reports of outcomes from cancer patients to identify pain types, associated symptoms, and pain levels, and the effect of the pain type by cancer patients on their quality of life. This study was limited in that the patients were disproportionally (79%) female, had one of the 4 major cancer types (breast, gastrointestinal, gynecological, or lung), and no information was provided on the type and amount of opioid use on pain and related symptoms.

In a prior report we presented the results of the analysis of PROs for chronic noncancer pain patients from an outpatient Pain Registry at the Weill Cornell Medical College.[52] Using the same outcome measures and over the same time interval of data collection as the report below, we found the report of average percent pain relief and health state (EQ-5D) of these noncancer patients was inversely related to average pain intensity category, while measures of pain interference, number of worst pain locations, and physical and psychological distress were directly related to pain intensity category. Regression analysis revealed that being male was associated with greater likelihood of an opioid ordered and higher average dosage than being female.[52]

The purpose of this report is to present a descriptive analysis of PROs and medical histories including opioid medications prescribed and used by outpatients with chronic pain due to cancer that comprise a subpopulation being treated at a US comprehensive cancer center. We also compare these data with noncancer chronic pain Registry patients and begin to identify patient characteristics that are associated with current pain management practices of opioid use and use of higher doses of opioids.

Methods

The Registry

The Registry is part of a tri-institutional comparative effectiveness project aimed at identifying patient characteristics and treatments that are associated with better or worse pain outcomes. The Registry was developed using a model of comparative effectiveness research called Practice-Based Evidence (PBE).[24, 25] PBE is a prospective, observational method for determining those patient characteristics and treatments that are associated with better or worse outcomes in "real world" patients (effectiveness), not in randomized controlled studies (efficacy).[24]

Patients and IRB Approval

All patients seen in outpatient clinics provided by the Anesthesia Pain and Palliative Medicine Services at two of MSKCC's ambulatory care sites in Manhattan between 11/2010 and 12/2014 were given the opportunity to participate in a longitudinal observational study that is part of a tri-institutional comparative effectiveness project. This activity was part of a quality improvement program and received an expedited IRB approval with a waiver of informed consent and HIPAA consent so that patient data could be collected under standard of care. A data use agreement was executed between MSKCC and the Health System Innovation and Research Division, University of Utah School of Medicine, Salt Lake City, UT, who performed data analysis. These clinics only accept internal referrals of patients who have already established care at MSKCC. Consequently, almost all the patients have a cancer diagnosis. Other than willingness to complete the questionnaires, there were no inclusion or exclusion criteria. During the study period from June 18, 2011 to December 10, 2014, 1917 patients provided survey data and 1534 of these patients provided a complete data set (i.e., survey, medication, and demographic data) for at least one clinic visit. These patients provided 4,818 surveys. Eleven of these patients (19 surveys) had an average pain score in the last 24 hours from all surveys equal to 0, so they were not included in the survey results analysis but were included in the regression analyses. The average number of surveys per patient was 3.1+/− 3.1 SD and ranged from 1 to 39.

Study Variables and Measures

The first source of data was patients' self-reported outcomes (PROs). At each encounter patients were asked to complete four surveys prior to seeing their physician: the Brief Pain Inventory (BPI),[16] Condensed Memorial Symptom Assessment Scale (CMSAS),[11] EuroQOL five dimensions (EQ-5D),[6, 43] and in the case of those taking opioids, the Current Opioid Misuse Measure (COMM).[7] The COMM data will be the subject of a separate report. Patients could provide these data by using an iPad in the clinic or by email link from

home. Paper surveys were also available that were later transcribed to an iPad by a research assistant for uploading. The PRO survey data were uploaded to a secure server housed at Memorial Sloan-Kettering Cancer Center (Webcore).

The BPI is a validated tool in cancer patients designed to assess severity of pain and impact of pain on daily function.[16, 18, 19, 46] The BPI assesses severity of pain in the last 24 hours using a scale from 0 (no pain) to 10 (worst pain imaginable), impact of pain on daily function looking at seven aspects: general activity, mood, walking, normal work, relations with others, sleep, and enjoyment with life scoring them 0 (no interference) to 10 (completely interferes), in addition to percent pain relief and pain location.

The CMSAS is a 14-item PRO assessment tool that asks whether a symptom was present (yes or no) and if yes, uses a five-point rating scale to quantify the amount of distress (‘not at all’ through ‘very much’) caused by 11 physical symptoms (CMSAS Physical) during the past 7 days and how frequently (‘rarely’ through ‘almost constantly’) for 3 psychological symptoms (CMSAS Psychological). The CMSAS and related versions have been validated as measures of quality of life associated with physical and psychologic distress in cancer and palliative care patients.[10, 11, 40]

The EQ-5D consists of 2 parts - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).[6, 43] The EQ-5D descriptive system (Health State Index) comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The patient is asked to indicate his/her health state selecting the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The scores for each of the 5 dimensions are summed and the sum score is converted to a weighted index (the EQ-5D Health State Index) as described in the EQ-5D user guide, available to registered users at www.euroqol.org. The EQ VAS records the respondent’s self-rated health on a vertical, visual analogue scale where the endpoints are labelled ‘Best imaginable health state’ =100 and ‘Worst imaginable health state’ =0. This information can be used as a quantitative measure of health outcome as judged by the individual patient. Taken together these PROs include many of the domains related to pain and we consider them to comprise part of the common data elements for a minimum data set for chronic cancer pain Registry outcomes.

Data elements obtained from the MSKCC electronic health record (EHR) included patient factors (demographics such as age and sex); medical, surgical, and social histories; diagnostic billing codes; and process factors (treatments - both medications and interventions). The clinical diagnoses are based on diagnostic billing codes (ICD9). The age categorization was done based on prior studies of age and sex in pain.[8, 29]

Our collaborators at the Health System Innovation and Research Division of University of Utah School of Medicine, Salt Lake City, Utah (HSIR-Utah) host the database and merge coded patient-reported outcomes data captured in Webcore with coded clinical data captured in the EHR to form a complete coded data set for the Registry database.[33] Data from Webcore and the EHR were merged by having a common coded patient ID that linked them.

Although patient identifiers were removed, the data do contain encounter dates, and therefore the data represent a limited data set according to HIPAA Privacy Rules. Results of each survey were computer scored, summarized, and electronically entered into the EHR. The summarized report was available to the appropriate clinician and included a comparison of results of the current and prior survey encounters.[33]

Estimating Opioid Use, Dosage, and Duration

We abstracted the patient Health Information System (HIS) to obtain opioid medications for each survey encounter. For each survey encounter the HIS listed the opioid(s) and daily doses that the patient was taking (in use), and those that were prescribed. For each survey encounter we obtained opioid(s) prescriptions, dose, and total number of doses (basal and supplemental (PRN) doses) that the physician prescribed and we assumed the patient was taking. Therefore, opioid use was defined at the encounter level as “receiving” (ordered at a previous encounter and we assumed patient to be taking) or “ordered” (at the present encounter). The term “taking” refers to the patient and includes receiving and ordered encounters. The opioid variables we use are Opioid Use-Yes or No, Opioid Dose (as MEQs/day), Duration of Opioid Use, and Opioid Ordered (yes/no and/or MEQs/day). For supplemental “receiving” and “ordered” doses, we assumed the patient took the maximal 24 hour dosage prescribed including the maximal supplemental dosage as indicated in the HIS. Each total daily (24 hr.) opioid dose was converted to corresponding Morphine Equivalents dose (MEQ) using the conversion factors obtained from the tables and text of the Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain.[2] We excluded patients receiving intrathecal opioids from this analysis. Meghani et.al., (2014)[32] used a medication bottle cap with a microprocessor (MEMS) that records the occurrence and time of bottle opening in real time to measure dose adherence” (percentage of the total number of prescribed doses that were taken) by cancer patients, over an 88 day period. For Whites, overall adherence was 74 % compared to 53% for African Americans for WHO step 1 through 3 analgesics and 77% for Whites compared to 63% for African Americans for WHO step 3 opioids. As shown in Supplemental Table 1, Whites are the predominate group in the present study. These results are consistent with high rates (90%) of opioid adherence using patient reports, Nguyen et.al, 2013.[36]

Statistical Analysis

Descriptive statistics were performed for the patient factors and process factors. The total patient population was divided into three groups by average 24 hour pain intensity scores: mild (1–4), moderate (5–6), and severe (7–10).[46]

Bivariate analyses (2-sample t-tests, analysis of variance for continuous variables with the Duncan multiple range test for multiple comparisons, or chi-square tests, as appropriate) were performed to measure associations between average pain intensity levels and other PROs (pain interference with activities of daily living, physical symptoms, psychological symptoms, and health state). Multivariate logistic regression via general estimating equation (GEE) models to analyze longitudinal data were used to determine which patient characteristics were independently and significantly associated with use of opioids and use

of higher doses of opioids. Two-sided probabilities of <=0.05 were considered statistically significant.

Results

Patient Characteristics

We divided the patients into 4 age groups: 1.4% were less than 25 years old, 13.4% were 25 to 44 years old, 49.9% were 45 to 64 years old, and 35.3% were greater than or equal to 65 years of age. There were more women than men (57.2 to 42.8%). Race and ethnicity data are shown in Supplemental Table 1. Eighty percent of the Registry patients identified their race as white and 89.8 % identified their ethnicity as Not Hispanic or Latino. We identified 1668 cancer ICD-10 codes associated with the 1534 Registry patients and 105 patients with no cancer diagnosis listed (Supplemental Table 2). The ICD-10 codes were converted to cancer sites using the list of leading sites of new cancer cases and deaths, estimated by the American Cancer Society (ACS) for 2015.[1] Breast cancer was the most frequent diagnosis, followed by lung, colon and rectum, and prostate. Some patients without active cancer or a documented history of cancer are referred to the MSKCC pain services outpatient clinics. Since we include all clinic attendees who complete a survey in the Registry, we had 105 of these noncancer identified patients in this analysis. However, results of the analyses presented below remained the same when these patients were excluded.

Patient-Reported Outcomes-Univariate Analysis

Table 1 shows the patient-reported pain intensity and pain relief outcomes, pain interference, CMSAS physical and psychological symptoms, health status and number of unique pain locations, and worst pain locations. For comparative purposes, we divided the patients into three categories of increasing pain intensity (Mild, Moderate, or Severe) based on their average pain intensity scores (BPI) in the 24 hours prior to the survey and then averaged over all their visits. We selected the average pain intensity scores to define the 3 pain categories. Approximately 95% of survey patients provided a score for average pain, the first pain intensity score in our BPI survey. This response rate was higher than the other pain intensity scores. We also found that the 5% of surveys that did not provide an average pain score almost always had more other scores missing and therefore we rejected any survey that did not have an average pain score. In patients with chronic noncancer pain we found that pain interference, number of worst pain locations, and physical and psychological distress were directly related to the average pain intensity categories while average percent pain relief and health state (EuroQOL 5 Dimensions) was inversely related to the average pain intensity categories.[52] Chiu et.al., 2016 [13] in a study of patients experiencing taxane-induced arthralgia and myalgia found that average pain scores correlated best with all BPI interference responses. Three hundred and seventy-four (24.6%) of the patients reported their average pain was Mild (mean score =3.2, range 1 to 4), 632 (41.5%) reported their average pain was Moderate (mean=5.5, range 5 to 6), and 517 (33.9%) reported their average pain was Severe (mean 7.8, range 7 to 10).

From Table 1 the significant (p<.0001) progressive relationship of the other pain intensity scores to the mean average pain scores can be seen. Patients who reported their average pain

as Mild had a lower mean worst pain score than those patients whose average pain was Moderate, and those with Moderate average pain had a lower mean worse pain score than those with Severe pain (Table 1). Likewise, patients with Mild average pain had a significantly ($p<.0001$) lower mean least pain score than those patients whose average pain was Moderate or Severe. For each of these pain intensity groups, the patient's report of average percent pain relief in the past 24 hours was inversely related to the average pain intensity categories: 61.0% average pain relief for those patients with average pain that was mild, 53.7% for those with average pain that was moderate, and 45.5% for those with average pain that was severe.

The mean pain interference subscale score was also related to the average pain categories shown in Table 1. Those patients in the Mild average pain category had an average BPI Pain interference subscale score of 3.9 while those in the Moderate average pain category had an average BPI Pain interference subscale score of 5.6, and for those in the Severe average pain intensity category the score was 7.0 ($p <.0001$).

The mean score for each of the items that comprise the pain interference subscale (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) were significantly increased ($p<.0001$) as the average pain intensity category increased from Mild to Severe. Progressively as the average pain intensity category increased, the highest scores (greatest interference) were found with enjoyment of life followed by general activity, normal work, mood, sleep, walking ability, and relations with other people (Table 1).

The mean CMSAS-Physical Distress subscale score increased as the average pain intensity category progressively increased (Table 1), from 1.4 for those with Mild pain, to 1.6 for those with Moderate pain, to 1.9 for those with Severe pain ($p<.0001$). For the items that comprise the CMSAS-Physical Distress subscale, pain, lack of energy, and difficulty sleeping had the highest mean scores, while shortness of breath, nausea, and weight loss had the lowest mean scores.

The mean CMSAS-Psychological Distress subscale score increased as the average pain intensity category increased (Table 1), from 1.3 for those with Mild pain, to 1.6 for those with Moderate pain, to 2.0 for those with Severe pain ($p<.0001$). For the items that comprise the CMSAS-Psychological Distress subscale, worrying had the highest mean scores, followed by feeling sad, and feeling nervous. The CMSAS Number of Symptoms (NS) measure is the average number of Physical plus Psychological CMSAS symptom scores. The CMSAS NS progressively increased from 7.1 for those with Mild pain, to 7.9 for those with Moderate pain, and to 8.5 for those with Severe pain ($p<.0001$).

For patient-reported outcomes for Health State and the number of unique Pain Locations, as average pain categories increased, the EQ-5D Health State Visual Analogue Scale (VAS) scores decreased and the EQ-5D Health State Index also decreased; both trends are indicative of a lower self-report of health state by these patients. The average number of Unique Pain Locations increased as the average pain intensity category increased, from 4.4

for those with Mild pain, to 6.0 for those with Moderate pain, to 6.9 for those with Severe pain (p<.0001), (Table 1).

The patient-reported sites of the most frequent worst pain location per patient by average pain category are listed at the end of Table 1. Patient reports of Abdomen-Chest as the worst pain location significantly decreased as average pain severity increased. No other trends were observed for this outcome.

For all outcomes listed in Table 1, based on the Duncan's post-hoc Multiple Range test, the measurement values were significantly different by average pain intensity of Mild, Moderate, and Severe except for CMSAS physical symptoms of feeling drowsy, shortness of breath, and constipation, and most of the worst pain locations. For the three CMSAS physical symptoms, those with mild pain intensity were significantly different from those with moderate pain intensity for constipation and those with moderate pain intensity were significantly different from those with severe pain intensity for feeling drowsy and shortness of breath.

Most MSKCC Registry patients (85.6%) were taking an opioid (opioid – yes) at one or more of the survey encounters. The mean Morphine Equivalents dose (MEQs) in mg/day was 219 +/− 335 SD, while the median MEQ dose was 109 mg/day with a range from 0.4 to 3960 MEQs.

Table 2 shows the demographic data (age ranges and sex) by opioid status. A higher percentage of patients age 45–64 were taking opioids compared to age >=65 yrs. of age (p=0.014). Also, a higher percentage of males were taking opioids than females (p=0.002). When age range by sex was compared, the percentage of males taking opioids exceeded the percentage of females taking opioids by a small percentage at each age range and the difference was significant for males age >= 65 (p=0.0397).

Table 3 compares the patient-reported outcome (patient level analysis) for patients that were (opioid use-yes) or were not (opioid use-no) taking an opioid. The average BPI Percent Pain Relief was greater for opioid use patients (p<.0001). The average BPI Pain Interference score and average CMSAS Physical subscale scores were higher while the average EQ-5D index score was lower for the opioid use patients compared to no opioids. The average Pain 24hrs pain intensity score and the mean CMSAS Psychological subscale scores were not significantly different for the opioid use patients compared to no opioids.

Patient-Reported Outcomes-Regression Analysis

Table 4 presents the results of the regression analyses used to determine what factors (demographics, patient-reported outcomes, or selected clinical diagnoses) were associated with (i.e., predictors of) opioid use and a higher opioid dose being ordered. The higher dose selected was ≥120 MEQs/per day. The Washington State Interagency Guideline on Prescribing Opioids for Pain[50] recommend 120 mg daily MEQ as a "yellow flag" dose for a strategy to prevent adverse events and overdose by advising providers to seek consultation with a pain specialist. We selected 120 mg daily MEQ dose as the higher dose variable in the regression analyses presented in Table 4.

Table 4 shows the findings when analyzing the data with encounter as the unit of analysis. This methodology and statistical significance of the results take into account the fact that there is correlation among the multiple encounters for a single patient. The cell size number of encounters that is shown in Table 4 for each predictor variable is the number that answered no or yes or had a lower or higher dosage for that outcome. Both numbers are taken into account along with the number of patients/cell when determining significance of the predictor variable for that outcome when all other variables are controlled for. As appropriate, for continuous variables, e.g., Average Pain 24hrs, only the total number of encounters is presented. The smallest number of patients/cell for a predictor variable on which an analysis is based is 35 for Tobacco Use Disorder and 48 for Substance Use. As can be seen (Table 4), all the others are based on more total patients/cell. We feel comfortable in including these two predictor variables in the analyses and letting the reader determine the importance of the associations, if any (see also below-limitations).

Being a patient aged >= 65 was associated with less likelihood of an opioid being ordered and less likelihood of a higher opioid dose ordered (>120 MEQs) than being a patient age 45 to 64. Males were 1.66 times more likely to have an opioid ordered than females and being a male doubles the likelihood of a higher opioid dose being ordered (Table 4). A patient-reported outcome of worst pain location as abdomen, face-head-neck, or hip was associated with less likelihood of an opioid ordered than reporting back pain. These worst pain locations were not associated with a higher opioid dose ordered. The self-report of greater percent pain relief or more physical distress (CMSAS physical) was associated with greater likelihood of an opioid ordered and a higher opioid dose ordered. Self-reporting more psychological distress (CMSAS Psychological) or a better health state was associated with less likelihood of opioid ordered and less likelihood of a higher opioid dose ordered.

The psychiatric clinical diagnoses of anxiety, depression, or substance abuse were not significantly associated with an opioid ordered, while a diagnosis of tobacco use disorder was associated with a lower likelihood of an opioid being ordered. Even though a Registry patient with a diagnosis of depression was not significantly associated with an opioid being ordered after controlling for other covariates, if the patient with depression did have an opioid ordered, that patient was 1.55 times more likely to have a higher opioid dose ordered than a patient without this diagnosis (Table 4).

Discussion

We used PBE methodology to define patient characteristics, treatments, and patient-reported outcomes that constitute the Registry database.[25, 33] Our modal age group was between 45 and 64 yrs. old; 85.2% were over the age of 45. Our patient population had more women (57.2%) than men (42.8%). These age and sex distributions are similar to other demographic reports of cancer patients [17, 44, 49], literature on sex differences, [4] and noncancer chronic pain patients in our Registry database.[51] Our patients' cancer diagnoses are consistent with the ACS estimates: breast (females), prostate (males), lung and bronchus, and colorectal (both sexes) were the leading sites of new cancer cases in 2015.[1]

A recent meta-analysis of 52 studies on pain severity (n=32,261) showed that among all patients with cancer, moderate to severe pain (numerical rating scale score ≥5) was reported by 38% of patients and 51.9% of cancer patients with advanced, metastatic, or terminal disease.[41] For our Registry patients, average pain was reported as moderate or severe by 75.4% (Table 1). As uncontrolled pain and dose limiting side effects are the two most common reasons for a referral to our outpatient pain services, it is not surprising that our patient sample had higher prevalence of patients with moderate to severe pain than has been reported for cancer patients in general surveys. For the noncancer Registry patients, 77.7% report average pain moderate or severe, an indication that these levels of pain intensity may reflect the tertiary pain clinic population independent of the type of pain.[52]

The report of average percent pain relief in the past 24 hours was inversely related to average pain intensity categories: 61.0% for patients with mild average pain, 53.7% for those with moderate average pain, and 45.5% for those with severe average pain (Table 1). Our Registry data do not include a placebo group and therefore are not directly comparable with outcomes of RCTs.[20] Defining clinically meaningful pain relief is a multifactorial process.[20, 21] A consensus review suggests that a report of 30%–50% pain relief is meaningful.[20] By these criteria our patients report clinically meaningful pain relief at each pain category with the most relief for those reporting mild average pain scores and least for those reporting severe average pain scores (Table 1).

Measurement of pain intensity and its impact on activities of daily living (interference) has been recommended to be included in all chronic pain clinical trials.[47] Pain experience and physical function/disability are closely tied constructs within the broader biopsychosocial context of pain. Clinical literature supports the concept that these two domains are highly interdependent: pain can reduce physical and emotional function, and improving physical and emotional function can reduce reports of pain and disability.[37] Our mean pain interference subscale score was, accordingly, related to increased pain intensity represented by average pain categories shown in Table 1. The mean score for each item in the pain interference subscale significantly increased ($p<.0001$) as average pain intensity category increased. For patients with severe average pain, highest interference scores were found with enjoyment of life, general activity, and normal work, followed by mood, sleep, walking ability, and relations with other people.

Interpretation of PROs can be aided by estimation of the Minimally Important Difference (MID), i.e., the smallest difference in the PRO that the patient would consider meaningful, either beneficial or detrimental.[14, 27, 30] Mathias,[30] using several methods to estimate the MID with a data set from a randomized controlled drug trial in breast cancer patients, concluded that a 2 point change from baseline in the BPI worst pain report was a representative MID. Given all of the caveats associated with MID estimation for individual or group PROs,[20, 27] for patients reporting their worst pain, we found a 3.2 point difference between those with mild compared to severe worst pain (Table 1).

A common distribution-based approach to determining MID is to use one-half of the standard deviation for the measure.[14, 20] Applying this estimate, we find that each of the MID differences would be meaningful for each of the average pain intensity measures and

between the average percent relief for mild and severe pain (Table 1). For the average pain inference scores for each of the group PROs, the mild, moderate, or severe average scores are different and meaningful, except for walking ability between moderate and severe pain categories.

It is well-established that cancer patients report a high prevalence of physical and psychological symptoms and that these symptoms are significantly related to impairment in performance status, psychological distress, and overall quality of life.[39, 40] Recently, NCI suggested that clinical trials using PROs use a core set of 12 symptoms.[44] Although the development of our Registry preceded this publication, our patient-reported symptom assessments include 10 of the 12 symptoms recommended by the NCI (see Table 1). Not included are numbness/tingling and diarrhea.

While we did not conduct a latent class or subgroup analysis and therfore can not comment directly on the presecnce or absence of the symptom subgroups others have identified [3, 9, 12, 35, 41, 42] we did find that as the PRO of average pain intensity increased, both Physical and Psychological distress as measured by the CMSAS were increased (Table 1). Both the average CMSAS Physical and Psychological scores increased by approximately the same amount as average pain intensity increased from Mild to Severe (Table 1). An increase in CMSAS score is indicative of an increase in symptom burden.[11] In a Veterans Administration cancer patient population the symptoms assessed by the CMSAS-Physical and Psychological subscales have been found to be important for quality of life and the CMSAS-Psychological predicts survival independent of stage of the disease.[11]

The EQ-5D is a frequently applied general health state measure that is used often as a complement to disease-specific outcome measures. While it is common to include health-related quality-of-life (QOL) measures such as the EQ-5D in clinical trials in oncology, only rarely have these assessments been combined with BPI pain intensity and interference measures. Sandblom et.al.[45] found that in men with prostate cancer, in the year before death, both pain and subsequent death were found to predict decreased quality of life as measured by the EQ-5D. Mendoza et.al,[34] compared the BPI and EQ-5D scores of patients with breast, prostate, and multiple myeloma and concluded that pain severity and pain interference may predict EQ-5D scores in these patients. We found a clinically meaningful difference[38] in the EQ-5D index and Health State VAS scores as a function of the PRO report of mild, moderate, or severe pain (Table 1). Also, patients that used opioids had a significantly lower average EQ-5D index score compared to no opioid patients (Table 3).

While the number of pain sites reported by cancer patients varies, 12 to 34% report 3 or more pain locations.[22, 23, 48] We found that patient reports of number of unique pain locations (Table 1) increase as average pain severity increases and patient reports of Abdomen-Chest as the worst pain location appear to decrease as average pain severity increases. Thus, the number of patient-reported pain locations appears to be a useful assessment.

Our report identifies associations of patient characteristics and PRO symptoms with opioid use and dosage in cancer patients. In our sample, being younger (<=65 yrs. of age) and

being a male were associated with higher probability of opioid use (Table 2). Being male doubled the likelihood of higher dose being ordered than being female (Table 4). While patients in the opioid group reported significantly higher pain relief (Average BPI Percent Pain Relief) than patients not prescribed opioids, patients in the opioid group reported more physical symptoms, higher pain interference score, lower index of health-related quality of life, and more physical distress (Table 3). The mean BPI Pain in the last 24hrs score and the mean CMSAS Psychological subscale scores were not different between the groups (Table 3). These results extend previous analyses of symptom occurrence in cancer patients [3, 9, 12, 35, 41, 42] and age and gender differences in pain management [15]. Findings from our multivariate logistic regression analyses (Table 4) demonstrate that most of the bivariate findings in Tables 1–3 remain when controlling for other factors, adding overall strength to these findings.

Our data do not provide an explanation for these differences, rather they identify the need to consider opioid use and dosage when attempting to understand PROs and factors affecting pain management. The primacy of including opioid use/dosage in these analysis is further illustrated by our report of similar associations with opioid use with age and sex-dependent pain relief and adverse effects in noncancer pain Registry patients.[51, 52]

This report has several limitations. The observational nature of our data precludes inferences about temporal causality. We did not measure the medication adherence of our patients (see Results). Pain management with or without opioids requires individualization of treatment that the analyses presented here do not capture. Future studies will employ episodic longitudinal analysis to capture this aspect of treatment. We also need to examine specific pain states in more detail. A few predictor variables had relatively small patient numbers (Table 9) and the reader should decide the clinical significance of these results. As the Registry grows we will revisit these variables. Based on census data at MSKCC from 2012 to 2015 Malhotra (Malhotra, 2017) estimated that no more than 1.3% of patients seek specialty Pain Management within the center. There were small but significant differences in age and the frequency of Breast, Genitourinary, Gynecologic, and Endocrine tumors and leukemia and lymphoma in the Pain Clinic patients compared to the MSKCC patients as a whole. Therefore, the generalizability of our finds may be limited. However, in contrast to most randomized controlled trials of pain treatments, our Pain Clinic patients are certainly representative of “real world” patients with comorbidities. With the increase in life expectancy of cancer pain patients and increase in the number of survivors with significant pain requiring ongoing opioid therapy, specialized outpatient cancer pain clinics have been growing as an integral part of cancer care at specialized cancer centers. A recent survey of cancer centers in the USA showed that inpatient consultation teams, outpatient palliative-care clinics, acute palliative-care units, and institution-run hospices were present in 92%, 59%, 26%, and 31% of National Cancer Institute (NCI)-designated cancer centers, and 56%, 22%, 20%, and 42% of non-NCI-designated cancer centers, respectively. [26] Further research comparing patient characteristics, interventions, and outcomes among patients seen at tertiary cancer anesthesia pain, supportive, and palliative clinics as compared to patients with pain seen exclusively in general oncology settings are needed and can be done using our database and the larger institutional database.

We have documented that our Registry can collect information on many patient characteristics, treatments, and outcomes of interest. Importantly, pain registries that collect the same information from cancer and noncancer patients allow the results of the analysis to identify common predictors that can supersede classification barrier of cancer vs noncancer. In this report and a previous report[52], we found that sex and age are predictors of opioid use and are critical in attempting to understand PROs and their relationship to pain management. Reliable data allow clinicians to view results of treatments in the broader context of clinic-level population pain management. Ultimately, the Registry can be used to identify best practices, which have the potential to benefit many chronic pain patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- A Registry with patient characteristics, treatments, and outcomes of cancer patients
- Average pain intensity was mild for 24.6%, moderate for 41.5%, and severe for 33.9%
- Median daily opioid dose in morphine equivalents was 109 (range 0.4 to 3960 MEQs)
- Males are twice as likely as females to have an opioid ordered at a higher dosage
- Opioid use and dosage are essential to understand patient reported outcomes

Perspective

This report describes the results of the analyses of PROs and patient-related electronic health record data collected under standard of care from cancer patients at outpatient pain management clinics of Anesthesiology and Palliative Care at the Memorial Sloan–Kettering Cancer Center. Consideration of sex and age as predictors of opioid use is critical in attempting to understand PROs and their relationship to pain management.

Table 1

Patient-Reported Outcomes by Average BPI 24-hour Pain Score of Mild, Moderate, and Severe for MSKCC Pain Registry Patients

Patient-Reported Outcome	Mild (1–4) Mean score (SD)	Moderate (5–6) Mean score (SD)	Severe (7–10) Mean score (SD)	Significant Differences
Pain Intensity and Pain Relief (BPI)	N=374 (24.6%)	N=632 (41.5%)	N=517 (33.9%)	
Average Pain last 24 hrs.	3.2^{C} (0.8)	5.5^{B} (0.5)	7.8^{A} (0.9)	A>B>C * p<.0001
Average Worst Pain last 24 hrs.	5.2^{C} (2.0)	7.1^{B} (1.4)	8.4^{A} (1.2)	A>B>C * p<.0001
Average Least pain last 24 hrs.	1.9^{C} (1.4)	3.6^{B} (1.6)	6.0^{A} (2.1)	A>B>C * p<.0001
Average Percent Relief last 24 hrs.	61.0^{C} (26.7)	53.7^{B} (22.0)	45.5^{A} (24.5)	A<B<C * p<.0001
Patients Pain Interference (BPI)	N=368 (24.6%)	N=624 (41.6%)	N=506 (33.8%)	
Average Pain Interference score	3.9^{C} (2.2)	5.6^{B} (1.9)	7.0^{A} (1.8)	A>B>C * p<.0001
General Activity	4.2^{C} (2.6)	6.1^{B} (2.2)	7.5^{A} (1.9)	A>B>C * p<.0001
Mood	3.8^{C} (2.4)	5.6^{B} (2.4)	7.0^{A} (2.2)	A>B>C * p<.0001
Walking Ability	3.5^{C} (2.9)	5.2^{B} (2.7)	6.4^{A} (2.9)	A>B>C * p<.0001
Normal Work	4.4^{C} (2.8)	6.1^{B} (2.5)	7.4^{A} (2.2)	A>B>C * p<.0001
Relation with Other People	2.8^{C} (2.4)	4.3^{B} (2.6)	5.7^{A} (2.7)	A>B>C * p<.0001
Sleep	3.7 ^{C} (2.6)	5.5 ^{B} (2.5)	6.9^{A} (2.6)	A>B>C * p<.0001
Enjoyment of Life	4.6^{C} (2.7)	6.4^{B} (2.3)	7.7^{A} (2.2)	A>B>C * p<.0001
CMSAS Physical Symptoms in past 7 days	N=368 (24.8%)	N=618 (41.7%)	N=496 (33.5%)	
Average CMSAS Physical score	1.4^{C} (0.7)	1.6^{B} (0.7)	1.9^{A} (0.7)	A>B>C * p<.0001
Lack of energy	2.0^{C} (1.2)	2.3^{B} (1.1)	2.6^{A} (1.1)	A>B>C * p<.0001
Lack of Appetite	1.1^{B} (1.2)	1.2^{B} (1.2)	1.5^{A} (1.3)	A>B * p<.0001
Pain	2.4^{C} (0.9)	3.0^{B} (0.7)	3.5^{A} (0.6)	A>B>C * p<.0001
Dry Mouth	1.0^{C} (1.1)	1.2^{B} (1.2)	1.5^{A} (1.4)	A>B>C * p<.0001
Weight Loss	0.6^{B} (1.1)	0.7^{B} (1.0)	1.0^{A} (1.3)	A>B * p<.0001

Patient-Reported Outcome	Mild (1–4) Mean score (SD)	Moderate (5–6) Mean score (SD)	Severe (7–10) Mean score (SD)	Significant Differences
Feeling Drowsy	1.3[B] (1.2)	1.4[B,A] (1.2)	1.6[A] (1.3)	A>B * p=0.025
Shortness of Breath	0.7[B] (1.1)	0.7[B] (1.0)	0.9[A] (1.2)	A>B * p=0.003
Constipation	1.0[B] (1.2)	1.2[A] (1.3)	1.3[A] (1.3)	A>B * p=0.018
Difficulty Sleeping	1.4[C] (1.2)	1.9[B] (1.3)	2.3[A] (1.3)	A>B>C * p<.0001
Nausea	0.5[C] (0.9)	0.7[B] (1.0)	0.9[A] (1.1)	A>B>C * p<.0001
CMSAS Psychological Symptoms in past 7 days	N=363 (24.6%)	N=617 (41.8%)	N=497 (33.6%)	
Average CMSAS Psychological score	1.3[C] (1.0)	1.6[B] (1.1)	2.0[A] (1.2)	A>B>C * p<.0001
Worrying	1.6[C] (1.2)	1.9[B] (1.3)	2.3[A] (1.3)	A>B>C * p<.0001
Feeling Sad	1.2[C] (1.1)	1.6[B] (1.2)	1.9[A] (1.3)	A>B>C * p<.0001
Feeling Nervous	1.1[C] (1.1)	1.4[B] (1.2)	1.8[A] (1.3)	A>B>C * p<.0001
Patients Health State and	N=360 (24.8%)	N=611 (42.1%)	N=481 (33.1%)	
Health State VAS 100 to 0 (best to worst)	58.9[C] (19.4)	55.4[B] (17.4)	48.7[A] (20.1)	A<B<C * p<.0001
EQ-5D Health State Index, 1.1 to 0 (best to worst)	0.7[C] (0.2)	0.6[B] (0.2)	0.5[A] (0.2)	A<B<C * p<.0001
Number of Unique Pain Locations	N=374 (24.6%)	N=632 (41.5%)	N=517 (33.9%)	
Average Number of Unique Pain Locations	4.4[C] (3.5)	6.0[B] (4.6)	6.9[A] (5.2)	A>B>C * p<.0001
Percent of Patients Identifying Site as Worst Pain Locations	**Percent of Patients**	**Percent of Patients**	**Percent of Patients**	
Abdomen-Chest	26.2	19.9	15.9	p<0.001 **
Back	21.1	21.2	23.6	NS
Buttock	5.6	4.7	5.6	NS
Extremities	15.4	21.5	16.3	NS
Face-Head-Neck	8.6	10.3	7.4	NS
Hip	5.3	6.0	5.6	NS
Missing	17.6	16.5	25.7	NS

* Probability based on Analysis of Variance test and Duncan's Multiple Range test differences

** Cochran-Armitage Trend Test; NS=not significant

Table 2

Demographic Characteristics Associated with Opioid Use for MSKCC Pain Registry Patients

Variable	Number	Opioid Use-No (Percent of Total Number)	Opioid Use-Yes (Percent of Total Number)	p-value Pearson χ^2
Age<25 yrs	21	38.1	61.9	
Age 25–44 yrs	206	11.2	88.8	
Age 45–64 yrs	766	12.5	87.5	*p=0.014
Age >=65 yrs	541	17.4	82.6	
Males	656	11.1	88.9	**p=0.002
Females	878	16.9	83.1	
Age 25–44 yrs-Males	97	8.2	91.8	p=0.2097
Age 25–44 yrs-Females	109	13.8	86.2	
Age 45–64 yrs-Males	319	10.0	90.0	p=0.0773
Age 45–64 yrs-Females	447	14.3	85.7	
Age >=65 yrs-Males	230	13.5	86.5	†p=0.0397
Age >=65 yrs-Females	311	20.3	79.7	

*Comparing age 45–64 yrs. (Opioid Use-Yes) with age >=65 yrs. (Opioid Use-Yes). Pearson $\chi 1^2$ =5.9848, p=0.014

**Comparing Males (Opioid Use-Yes) with Females (Opioid Use-Yes). Pearson $\chi 1^2$ =9.9917, p=0.002

†Comparing Males age >=65 yrs with Females age >=65 yrs. Pearson $\chi 1^2$ = 4.2323, p=0.0397

Table 3

Patient-Reported Outcomes of Opioid Use-No or Opioid Use-Yes for MSKCC Pain Registry Patients

Patient-Reported Outcome	Opioid Use-No Mean (SD)	Opioid Use-Yes Mean (SD)	2 sided t-test P value
Average Pain 24 hrs. score	5.62 (2.24)	5.68 (1.87)	NS
Average BPI Percent Pain Relief	34.81 (26.29)	55.61 (23.40)	<0.0001
Average BPI pain interference Score	5.18 (2.57)	5.66 (2.23)	0.01
Average CMSAS Physical subscale score	1.33 (0.70)	1.71 (0.72)	<0.0001
Average CMSAS Psychological subscale score	1.62 (1.22)	1.67 (1.12)	NS
Average EQ-5D Index	0.63 (0.20)	0.56 (0.20)	<0.0001
	Percent	Percent	
Average Pain 24 hrs-Mild	15.2	84.8	
Average Pain 24 hrs-Moderate	12.3	87.7	
Average Pain 24 hrs-Severe	15.3	84.7	
Number of Patients	221	1313	

Table 4

Demographics, Patient-Reported Outcomes, and Clinical Diagnosis as Predictors of Opioid Ordered or Higher Opioid Dosage (>120 MEQs/day) Ordered for MSKCC Pain Registry Patients (Encounter level analyses).

	Number of Encounters with specified outcome for that predictor used in the Regression Analysis: No/Yes (Number of Patients/analysis cell)	**Opioid Ordered†**		**Number of Encounters with specified outcome for that predictor used in the Regression Analysis: Lower/Higher dosage (Number of Patients/analysis cell)**	**Higher Opioid Dosage (>120 MEQs/day) Ordered†**	
Variable		**Odds ratio**	**95% Confidence Interval**		**Odds ratio**	**95% Confidence Interval**
Demographics						
Age Group: >=65 vs 45–64	>=65: 354/831 (577) 45–64: 493/1723 (892)	0.74 *	(0.58,0.95)#	>=65: 430/401 (380) 45–64: 690/1033 (634)	0.56 **	(0.40,0.79)
Sex: Male vs Female	Male: 353/1427 (765) Female: 667/1602 (997)	1.66 ***	(1.34,2.04)	Male: 510/917 (565) Female: 799/803 (647)	2.04 ***	(1.51,2.75)
Patient-Reported Outcomes						
Worst Pain Location: Abdomen vs Back	Abdomen: 155/447 (363) Back: 171/670 (464)	0.59 ***	(0.43,0.81)	Abdomen: 185/262 (265) Back: 279/391 (350)	0.89	(0.59,1.34)
Worst Pain Location: Face/Head/Neck vs Back	Face/Head/Neck: 97/245 (183) Back: 171/670 (464)	0.65 *	(0.43,0.97)	Face/Head/Neck: 107/138 (133) Back: 279/391 (350)	1.0	(0.60,1.67)
Worst Pain Location: Hip vs Back	Hip: 62/152 (136) Back: 171/670 (464)	0.64 *	(0.42,0.97)	Hip: 81/71 (91) Back: 279/391 (350)	0.6	(0.34,1.06)
Average Pain 24 HRS	4049 (1389)	1.02	(0.97,1.08)	3029 (1082)	1.04	(0.96,1.12)
Percent Pain Relief	4049 (1389)	1.02 ***	(1.01,1.02)	3029 (1082)	1.01 ***	(1.01,1.02)
Pain Interference	4049 (1389)	1.0	(0.95,1.05)	3029 (1082)	0.97	(0.91,1.03)
CMSAS Physical subscale	4049 (1389)	1.18 *	(1.01,1.38)	3029 (1082)	1.29 **	(1.06,1.56)
CMSAS Psychological subscale	4049 (1389)	0.84 ***	(0.77,0.92)	3029 (1082)	0.97	(0.87,1.09)
EQ-5D Index	4049 (1389)	0.54 *	(0.32,0.93)	3029 (1082)	0.27 ***	(0.14,0.52)
Clinical Diagnosis						
Anxiety	486/1557 (872)	1.11	(0.87,1.42)	650/907 (626)	0.84	(0.61,1.17)
Depression	478/1419 (764)	1.03	(0.81,1.32)	548/871 (529)	1.55 **	(1.11,2.17)
Substance Abuse	17/68 (60)	1.12	(0.64,1.98)	27/41 (48)	0.70	(0.34,1.42)

	Number of Encounters with specified outcome for that predictor used in the Regression Analysis: No/Yes (Number of Patients/analysis cell)	Opioid Ordered†		Number of Encounters with specified outcome for that predictor used in the Regression Analysis: Lower/Higher dosage (Number of Patients/analysis cell)	Higher Opioid Dosage (>120 MEQs/day) Ordered†	
Variable		**Odds ratio**	**95% Confidence Interval**		**Odds ratio**	**95% Confidence Interval**
Tobacco Use Disorder	22/45 (56)	0.50 **	(0.29,0.84)	19/26 (35)	0.67	(0.29,1.54)

* 0.01<p<0.05;

** 0.001<p<=0.01;

*** p<=0.001;

† Odds ratio and confidence intervals from general estimating equation models.