to use technology to dynamically understand patient and caregiver needs and target education to their specific questions and concerns.

As we aim to center all we do around our patients with serious illness and their caregivers, we strongly urge our field to strengthen its efforts to educate, engage, and prepare patients about palliative care services. More research is needed to shift toward consumer-facing engagement, particularly in developing low-cost, scalable methods that impact patient perceptions of palliative care, increase their readiness to engage with services, and provide them the language to share their positive experiences with other loved ones with serious illness. Technology-based platforms are ideal to educate and engage patients, as they are 1) agile enough to be updated continuously (i.e., compare to paper pamphlets); 2) support scalable dissemination (e.g., national roll-out of a mobile health application); 3) provide a personalized patient experience (e.g., content delivered based on how patients identify themselves or their needs); and 4) have low variable (i.e., based on number of users) costs after initial development. Well-recognized examples of using technology to engage patients in palliative care exist,[10,11] and we believe the potential is much larger. A future where patients not only understand palliative care but also demand its integration into usual care is not far off if we invest in impactful research that put patients' demand for knowledge and engagement at the center.

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Frequency of Concomitant Use of Opioids and Psychoactive Medications Among Cancer Patients Referred to Outpatient Palliative Care

Dear Editor,

Patients with cancer suffer from multiple complex symptoms.[1] These patients are often on multiple medications (polypharmacy) including opioids.[2] These combinations may be necessary for adequate control of symptoms. However, there are potentially severe effects when patients taking opioids receive other

A. A. and A. H. contributed equally to this article.

psychoactive medications, such as benzodiazepines and other central nervous system (CNS) depressants, increasing the risk of emergency room visits or inpatient admissions [3] due to severe sedation or respiratory depression.[4] Benzodiazepine use has been linked with more than 30% of opioid overdose deaths, whereas opioid use has been linked with over 77% of benzodiazepine overdose deaths.[5] Center for Disease Control guidelines identify the use of benzodiazepines with opioids in treatment of chronic noncancer pain as a major risk factor and recommend avoiding co-prescription of opioids and benzodiazepines.[6] Moreover, the surgeon general's report highlights the psychoactive drugs as conveying a higher risk of serious toxicity or potential death when used concomitantly with opioids.[7] In a recent letter, U.S. surgeon general highlighted that, since 1999, opioid overdose deaths have quadrupled and appealed to the physician community to "*educate ourselves to treat pain safely and effectively.*"[8]

To our knowledge there are limited reports on the frequency and type of psychoactive medications prescribed in combinations with opioids in patients with cancer.[2] The purpose of this study was to determine the frequency of concomitant use of opioids along with psychoactive medications in patients with cancer referred to our outpatient supportive care center (SCC).

Methods

This retrospective study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. During the study period from September 1, 2013, to August 31, 2014, retrospective data were extracted from chart review by palliative medicine specialists (A. A. and A. H.) and a physician (S. M. A. N.), who was especially trained for chart review for the purposes of this study. In all cases, data were collected from new patients ($n = 544$) referred to our outpatient SCC for their first visit and was analyzed to determine the frequency of patients on opioids alone (OA) versus concomitant opioids and psychoactive medications. The study was aimed at reviewing patients taking opioids either alone or in combination with psychoactive medications. Patients not taking opioids (i.e., on psychoactive medications alone) were not eligible to be included in this study.

For each patient initial consult, the following data were collected: patient demographics including age, sex, ethnicity, marital status, type of cancer, Edmonton Symptom Assessment Scale (ESAS) scores, dose of opioid used as morphine equivalent daily dose (MEDD), as well as use of psychoactive (benzodiazepine and antidepressant) medications.

Association of the type of medication with demographics and baseline characteristics was evaluated by Wilcoxon rank sum test for continuous variables and chi-square (Fisher's exact) test for categorical variables. All tests were performed two-sided and at 0.05 nominal significance level. All computations were carried out in Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Data from 541 of 544 newly referred patients to the outpatient SCC were evaluable. Of these 541 patients, 365 (67%) patients were taking opioids at the time of referral; 209 (57%) were on OA, whereas 156 (43%) were on concomitant opioids and psychoactive medications (69 [44%] were on opioid plus benzodiazepine, 46 [30%] were on opioid plus antidepressants, and 41 [26%] were on both). The proportion of patients taking antipsychotic medications was less than 1%.

Table 1 summarizes the demographic and clinical baseline characteristics as well as ESAS scores for the two groups (209 [57%] patients on OA and 156 [43%] on concomitant opioids and psychoactive medications). Median age was 60 years, whereas almost two-thirds of patients were married, in both groups. Most patients in both groups were Caucasians, more in the concomitant groups (82%) than in OA group (58%, $P < 0.001$). There was no statistically significant association of prescription pattern with cancer types or reason for the referral, although majority of the referrals overall (approx. 82%) were for uncontrolled symptoms.

Patients in the concomitant group were on higher MEDD ($P = 0.003$, Table 1). These patients had statistically significant higher ESAS scores for anxiety ($P < 0.001$) and depression ($P < 0.001$), and a trend toward high spiritual pain ($P = 0.056$). They also reported clinically significant higher scores for fatigue, nausea, and financial distress (minimal clinically important difference for ESAS scores being 1 point for individual score; Table 1).

Discussion

Concomitant use of opioids with CNS depressants such as benzodiazepines remains prevalent despite widespread concerns of long-term cognitive defects and overdose-related deaths.[3–5,7] U.S. Food and Drug Administration has also emphasized enhancing the safety information on opioid labeling, highlighting risks of interactions with CNS depressants.[9] In this retrospective study, we found that 43% of patients with cancer were on combinations of opioids and other psychoactive medications (benzodiazepines and antidepressants) at the time of referral to the SCC. This

Table 1
Demographics, Baseline Characteristics, and ESAS Scores for Patients on Opioids vs. Opioids Plus Psychoactive Medications

Variable	Opioids Only	Opioids Plus Psychoactive	*P*-value
Patients, n (%)	209 (57)	156 (43)	
Median age (range)	60 (24, 89)	60 (25, 86)	0.924
Race, n (%)			
White	120 (58)	127 (82)	<0.001
Hispanic	36 (17)	14 (9)	
Black	38 (18)	12 (8)	
Asian	14 (7)	2 (1)	
Sex, n (%)			
Female	92 (44)	82 (53)	0.106
Marital status, n (%)			
Married	137 (66)	105 (68)	0.539
Other	72 (34)	50 (32)	
Cancer type, n (%)			
Breast	23 (11)	18 (12)	0.869
Gastrointestinal	54 (26)	40 (26)	
Genitourinary	15 (7)	15 (10)	
Gynecological	18 (9)	9 (5)	
Head and neck	23 (11)	19 (12)	
Hematological	6 (3)	7 (5)	
Other	10 (5)	10 (6)	
Sarcoma	11 (5)	9 (5)	
Thoracic	49 (23)	29 (19)	
Reason of visit; n (%)			
Uncontrolled symptoms	176 (84)	123 (79)	0.351
Symptoms and counseling	31 (15)	32 (20)	
Counseling	2 (1)	1 (1)	
CAGE; n (%)			
Positive	48 (60)	32 (40)	0.611
Negative	161 (57)	123 (43)	
Median MEDD (range)	60 (5, 1580)	90 (4, 960)	0.003
Pain	7 (0.0, 10.0)	7 (0.0, 10.0)	0.644
Fatigue	6 (0.0, 10.0)	7 (0.0, 10.0)	0.345
Nausea	1 (0.0, 10.0)	2 (0.0, 10.0)	0.209
Depression	2 (0.0, 10.0)	4 (0.0, 10.0)	<0.001
Anxiety	2 (0.0, 10.0)	5 (0.0, 10.0)	<0.001
Drowsiness	4 (0.0, 10.0)	4 (0.0, 10.0)	0.146
Shortness of breath	3 (0.0, 10.0)	3 (0.0, 10.0)	0.672
Appetite	5 (0.0, 10.0)	5 (0.0, 10.0)	0.334
Feeling of wellbeing	5 (0.0, 10.0)	5 (0.0, 10.0)	0.726
Sleep	6 (0.0, 10.0)	6 (0.0, 10.0)	0.924
Financial distress	1 (0.0, 10.0)	2 (0.0, 10.0)	0.165
Spiritual pain	0 (0.0, 10.0)	1 (0.0, 10.0)	0.056

MEDD = morphine equivalent daily dose; ESAS = edmonton symptom assessment scale; CAGE = cut down, annoyed, guilty, eye-opener.
All ESAS scores are in median (range). CAGE questionnaire (≥2 for all female patients and ≥1 for male patients).

is a very high number for such a high-risk population for the development of delirium and serious toxicity.

Our data also show that patients taking opioids concomitantly with psychoactive medications had significantly higher MEDD, which raises further concerns about potential for serious toxicity. Such patients at their first presentation to our clinic also reported statistically significant high anxiety and depression on ESAS with a trend toward higher spiritual pain. They also reported clinically significant higher scores for fatigue, nausea, and financial distress. Hence, it is imperative that clinicians remain mindful of avoiding such co-prescriptions and limit these to only selected cases managed under careful supervision.

Our study found that Caucasian patients were more likely to receive opioids and concomitant psychoactive medications than other ethnic groups. This disparity needs further investigation. Other studies have observed that non-Caucasians patients receive different pharmacological interventions for pain and symptom management including opioids and other medications.[10] Our study by its nature does not allow us to understand the reason for such a different prescription pattern. More research is needed in this area.

Our study is limited in collecting data from only one cancer center. It also looks at patients who have been referred to the palliative care team and likely to have higher symptom burden, possibly overrepresenting polypharmacy. We also did not review the details of doses and type of psychoactive medications and whether these medications were provided by one particular physician or team of different clinicians. It is common for patients with cancer to see multiple specialists. Also, we did not review for how much duration the patients were taking the psychoactive medications especially antidepressants either chronically, predating the diagnosis of life-limiting illness, or intermittently, like benzodiazepines, as premedication before an intervention or procedure, or as a part of a treatment protocol for symptom control, such as nausea or anxiety with chemotherapy. At our institution, we have observed that most of the patients are placed on a more continuous regimen of benzodiazepines before referral to our team. In certain situations, such as chronic anxiety state or mood disorder requiring medication(s) and then being diagnosed with cancer, the combined use of opioids and psychoactive medications may also be unavoidable, requiring opioids for cancer-related pain. However, our study shows that patients who were prescribed benzodiazepines and antidepressants along with opioids were still reporting higher scores for anxiety and depression.

We did not have specific data on percentage of patients receiving psychotherapy or other nonpharmacological interventions for mood-related issues, before being referred to our center. However, vast majority of patients being referred to our center have not received this support before and during our first and subsequent encounters almost all our patients receive counseling either from our palliative trained physicians and nurses or from specially trained palliative care counselors. However, the prescription pattern studied in this study is from before visit to our center.

Cut down, Annoyed, Guilty, Eye-opener (CAGE) screening questionnaire is used in our clinic to asses

risk for chemical coping and aberrant drug behavior. Our study showed no significant difference between the two groups for CAGE score (Table 1). We, however, did not have information on patients' use of marijuana for possible medical purposes. Future studies should aim to explore these associations.

Data in this study date to four years ago, and owing to the evolving nature of our understanding of opioid interactions, clinical practices may have changed in more recent cohorts. Therefore, more research is needed to study the trends in prescription patterns as well as role of the palliative care team in providing the education and support in limiting concomitant use of different psychoactive medications with opioids, particularly in patients with cancer.

Conclusion

A large proportion (156, 43%) of patients with cancer newly referred to outpatient palliative care was on concomitant opioids and psychoactive medications. These patients were on higher doses of opioids and exhibited higher psychosocial and spiritual distress at the time of first presentation to the outpatient SCC. Further studies are required to assess patient characteristics and highlight predictors, which may help with early recognition of such risky prescribing practice. There is also the need to explore how many of such patients continue to take similar medication combinations after the palliative care clinic visits, with focus on ability of palliative care teams in reducing polypharmacy and what are the long-term implications of such concomitant use on patient with cancer morbidity and/or mortality.

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