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ORIGINAL ARTICLE

Early supportive medication use and end-of-life care among Medicare beneficiaries with advanced breast cancer

Devon K. Check[1] · **Donald L. Rosenstein**[2,3] · **Stacie B. Dusetzina**[1,3,4]

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Abstract
Purpose A randomized controlled trial of cancer patients has linked early supportive care with improved hospice use and less-aggressive end-of-life care. In practice, the early use of supportive interventions and potential impact on end-of-life care are poorly understood. We sought to describe early use of medications to treat common breast cancer symptoms (pain, insomnia, anxiety, and depression) and to assess the relationship between early use of these treatments and end-of-life care.
Methods Secondary analysis of 2006–2012 SEER-Medicare data was performed. Women included had stage IV breast cancer and died within the observation period. We used modified Poisson regression to assess the relationship between supportive medication use in the 90 days post-diagnosis and several end-of-life care measures (hospice use, in-hospital death, chemotherapy receipt within 14 days of death, ICU admission, or >1 hospitalization or emergency department/ED visit 30 days before death).
Results Among the 947 women included, 68 % of women used at least one supportive medication in the 90 days following their diagnosis: 60.3 % used opioid pain medications and 28.3 % received non-opioid psychotropic medications. Early use of any supportive medications was not associated with end-of-life care. Similarly, we found no differences in end-of-life care between opioid pain medication users and non-users. However, we found that non-opioid psychotropic medication users were less likely to receive chemotherapy in the last 14 days of life (aRR 0.33, 95 % CI 0.12–0.88).
Conclusions Non-opioid psychotropic use was associated with some aspects of end-of-life care. Future research should consider alternative measures of palliative and supportive care use using administrative data sources.

Keywords Breast cancer · End-of-life care · Hospice use

Introduction

Integrating palliative care early in the course of treatment for patients with terminal cancer has gained attention in recent years as a promising strategy for improving patients' quality of life (QOL) [1, 2] and extending their survival [3]. In addition, early palliative care has been linked with measures of less-aggressive end-of-life care. In a randomized controlled trial (RCT) of an early palliative care intervention, researchers found that patients who received early palliative care integrated with standard oncologic care were less likely than patients who received standard oncologic care alone to receive chemotherapy within 14 days of death and were more likely to transition to hospice prior to death [4]. One plausible hypothesis for the observed relationship between early palliative care, hospice use, and less-intensive end-of-life care is that, in providing decisional support, palliative care providers may assist

✉ Stacie B. Dusetzina
stacie_dusetzina@med.unc.edu

[1] Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[2] Department of Psychiatry, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[3] UNC Lineberger Comprehensive Cancer Center, 101 Manning Dr, Chapel Hill, NC 27514, USA

[4] Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Kerr Hall, Room 2203, Chapel Hill, NC 27599, USA

both oncologists and patients in planning for the end of life. Such discussions may facilitate the transition from active treatment to palliative care and improve the quality of end-of-life care [4]. In addition, patients who receive palliative care, which emphasizes symptom control and quality of life, early in the cancer care trajectory may be more likely to prioritize quality of life and supportive over aggressive care throughout the treatment trajectory, including near the end of life.

Although patients, family members, and clinicians have expressed preferences for end-of-life care that emphasizes pain relief and symptom management and preparation for dying [5–8], advanced cancer patients' end-of-life care is increasingly aggressive. Over time, there has been an increase in the number of patients receiving multiple regimens of chemotherapy with ongoing administration near the end of life. Emergency department (ED) utilization and inpatient admissions in the final month of life are also rising [9]. Intensive end-of-life care is of questionable benefit in terms of lengthening the life of terminally ill patients [10], and may actually be detrimental to patients' mental health and QOL [11, 12] in addition to resulting in unnecessary health care expenditures [13]. As aggressive end-of-life care rises, hospice length has been decreasing; thus, patients are not receiving the full benefit of hospice services [9].

Early integration of palliative care services may be a promising strategy for improving quality of care at the end of life [4]. One key goal of palliative care interventions is to address symptoms and side effects of cancer and its treatment [14, 15]. Pain, depression, anxiety, and sleeplessness are common symptoms that are often addressed pharmacologically [16]. It is unclear whether early use of medications to treat these symptoms could be an indicator of patients' engagement with palliative care. Within a cohort of breast cancer patients, we sought to (1) describe the early use of supportive medications to treat pain, depression, anxiety, and sleeplessness and (2) assess whether the early use of these symptom-directed therapies is associated with patients' end-of-life care.

Methods

Data source

Data for this analysis came from the linkage of the National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER) database linked with Medicare fee-for-service administrative claims from 2006 to 2012. Medicare is a federal program that provides health insurance for persons age 65 and over in the USA. Approximately 97 % of aged adults are eligible for Medicare [17]. The SEER program collects data from population-based cancer registries, representing 28 % of the population with cancer. The data are further linked with the National Death Index to obtain date and cause of death. For this study, we utilized data from the prescription drug event (PDE) records, Medicare Provider Analysis and Review (MEDPAR) file for inpatient services, the Hospital Outpatient Standard Analytic file for outpatient facility services, 100 % Physician/Supplier file for physicians' services, and the Hospice file [18].

Cohort

We identified patients with a first diagnosis of breast cancer during 2007–2011 who were ≥65 years old and who were not diagnosed at autopsy or death and not missing month of diagnosis (N = 104,629). From this group, we excluded patients who were not continuously enrolled in fee-for-service Medicare Parts A and B (inpatient and outpatient coverage, respectively) for 6 months before diagnosis and 3 months after diagnosis. We exclude patients enrolled in Medicare Advantage—privately managed health maintenance organization (HMO) plans—as we are unable to capture health care utilization for this subset of Medicare beneficiaries (n = 40, 875). We also excluded patients who were not enrolled in a stand-alone Medicare Part D plan for 3 months before and after diagnosis (n = 30,105) as well as men (n = 263) and women with end-stage renal disease (n = 220). Finally, we excluded women diagnosed with stage 0, I, II, or III disease (n = 31,767), those who were alive at the end of the study period (n = 321), those who died within 90 days of diagnosis (n = 108), and those who were enrolled in an HMO in the month before death (n = 23). The final cohort consisted of 947 women.

Outcomes

We created indicators for four end-of-life care measures that have been developed and measured in administrative data [9, 19]. These were as follows: (1) hospice use before death—including any use and the length of use among users; (2) terminal hospitalizations (in-hospital deaths); (3) receipt of chemotherapy within 14 days of death; and (4) high-cost health care utilization (ICU admission, ≥1 emergency department visit, or ≥1 hospitalization) in the last 30 days of life.

Independent variable

The primary independent variable—early supportive medication use—was defined as use of a prescribed medication to treat depression, anxiety, insomnia, or pain within 90 days [3] of a patient's breast cancer diagnosis. We identified relevant products using generic drug names in the Medicare Part D clams, including antidepressants, non-benzodiazepine anxiolytics and sleep aids, and opioid analgesics (see Appendix 1 for included medications). We were unable to capture use of benzodiazepines, which may be used to treat anxiety and

insomnia, as Medicare Part D did not cover the drugs during our study period.

Control variables

Covariates obtained from the SEER registry included age at diagnosis, race/ethnicity, marital status, year of diagnosis, and US region of residence. Registry data also included the extent of urbanization at patients' residences (from the Area Resource File), and 2000 census tract-level measures of socioeconomic status, including median income and proportion of adult residents with <12 years of education. We assessed comorbid illness using the Klabunde modification of the Charlson score based on patients' Medicare Part A and B claims during the 6 months before diagnosis [20]. Cancer-directed treatment variables (surgery, radiation, chemotherapy, endocrine therapy) were identified from inpatient, outpatient, and pharmacy claims (Medicare Parts A, B, and D) using International Classification of Diseases (ninth revision) (ICD9), Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes (NDCs), respectively. We also controlled for patients' history of any inpatient or outpatient mental health diagnosis (ICD9 codes 290.0–319.99) and prior use of the medications of interest.

Propensity score estimation and application

We estimated propensity scores by modeling the probability of using supportive medications (any supportive medications and individual categories of medications) in the 90 days following breast cancer diagnosis as a function of the control variables described above. Next, using the resulting propensity score, we created inverse probability of treatment weights (IPTW) for each patient, equal to $1/p$ (where p is the propensity score) for patients who used supportive medications and $1/(1-p)$ for patients who did not use supportive medications. We stabilized the propensity score weights by multiplying the IPTW by the marginal prevalence of the treatment actually received. This method of propensity score weighting provides an estimate of the treatment effect in the population (in this case, the effect of supportive medication use among stage IV breast cancer patients) [21].

Statistical analysis

We compared unadjusted baseline characteristics between patients grouped by early use of any supportive medications using Pearson chi-squared tests for categorical variables and Student t tests for continuous variables. Next, using the propensity score-weighted cohort, we estimated the risk of each end-of-life care outcome for patients who received supportive medications versus those who did not. Separate models were estimated for (1) any supportive treatments, (2) opioid pain medications, and (3) non-opioid psychotropic medications (antidepressants/anxiolytics, non-benzodiazepine sleep aids). We examined use of opioid pain medications and non-opioid psychotropic medications separately because we expect that post-surgical and tumor-related pain management may be well integrated into standard oncologic care. Psychosocial symptom management with non-opioid psychotropic medications, on the other hand, may better indicate patients' involvement with supportive care. Covariates that remained imbalanced among supportive treatment users and non-users after propensity score weighting were added to the outcome models as appropriate. We used generalized estimating equations with log links and Poisson distributions to estimate adjusted risks and risk ratios with 95 % confidence intervals for each outcome [22]. We used SAS 9.3 (Cary, NC) for all analyses.

Sensitivity analyses

We performed a sensitivity analysis to consider the effect of restricting the analytic sample to patients whose cause of death was listed as breast cancer. We also considered an alternative definition of supportive medication use that included use of antipsychotics, which may be used to treat depression.

Results

There were 947 women who met our eligibility criteria. Mean and median survival from diagnosis was 634 (SD 503) and 478 (IQR 705) days, respectively. The mean age at diagnosis was 77 (SD 7.6). Most patients were unmarried (widowed, divorced, or never married) (70.6 %) and white (79.4 %). About 85 % of patients received treatment for their cancer: 24.6 % had surgery, 34.6 % received radiation, 60.3 % received endocrine therapy, and 43.9 % received chemotherapy.

Approximately 68 % of women used supportive medication in the 90 days following their diagnosis: 60.3 % used opioid pain medications and 28.3 % received non-opioid psychotropic medications. Among those who received supportive medications, 20.6 % of women used both opioids and non-opioid psychotropics. When comparing women who did and did not receive any supportive therapies prior to propensity score weighting, we found differences in age at diagnosis, marital status, region of residence, metropolitan versus non-metropolitan residence, median census tract income, previous mental health diagnosis, previous use of supportive medications, receipt of any cancer treatment, and receipt of surgery, radiation, and chemotherapy. After propensity score weighting, characteristics between the two groups were well balanced, with the exception of metropolitan versus non-metropolitan residence (Table 1). Comparisons of women's characteristics across three medication use groups (opioid pain

Table 1 Sample characteristics, by any use of supportive medications, before and after propensity score weighting

	Before propensity score weighting			After propensity weighting		
	Non-users	Users	*p* value	Non-users	Users	*p* value
Number of patients	303	644		300.27	644.14	
Demographic characteristics						
Age at cancer diagnosis—mean (SD)	76.34	78.90	*<0.0001*	77.04	77.14	0.85
Marital status at diagnosis, % married/partnered	20.46	26.86	0.05	24.95	26.09	0.41
Race						
White	76.57	80.75	0.32	76.73	80.83	0.28
Black	15.51	13.04		16.46	14.53	
Others	7.92	6.21		6.81	12.74	
Hispanic ethnicity						
Yes	7.92	7.61	0.19	8.77	7.15	0.08
No	92.08	91.30		91.23	91.41	
Median household income in census tract of residence						
$5299–26,387	18.48	27.80	*0.01*	21.57	25.94	0.27
$26,388–36,095	23.76	25.78		24.51	24.11	
$36,096–50,560	28.71	23.14		30.25	24.22	
$50,561–200,014	29.04	23.14		23.67	25.59	
Proportion of residents with no high school degree in census tract of residence (%)						
0.53–8.98	25.08	24.53	0.25	20.16	24.86	0.23
8.99–16.50	29.37	23.29		30.90	25.08	
16.51–27.60	23.43	25.62		23.11	25.58	
27.61–79.99	22.11	26.40		25.83	24.35	
Residence						
Metropolitan county	87.13	78.57	*<0.01*	86.31	79.90	*0.002*
Non-metropolitan county	12.87	21.43		13.69	20.10	
US region						
Northeast	33.99	20.81	*<0.0001*	26.37	25.49	0.99
Midwest	16.17	14.29		15.73	15.42	
South	32.67	34.47		32.00	32.99	
West	17.16	30.43		25.90	26.10	
Clinical characteristics						
Year of cancer diagnosis						
2007	29.37	21.89	0.12	27.39	24.35	0.99
2008	18.15	22.36		20.16	21.05	
2009	21.45	21.12		23.08	21.57	
2010	16.83	18.63		15.66	17.95	
2011	14.19	15.99		13.71	15.08	
Charlson Comorbidity Score						
0	78.22	67.70	0.002	74.54	69.44	0.26
1	16.50	21.58		17.73	20.68	
2+	5.28	10.71		7.73	9.87	
Cancer treatment (any)	80.20	87.27	*<0.01*	81.94	85.55	0.15
Surgery	19.80	26.86	*<0.05*	23.69	24.60	0.76
Radiation	29.70	36.96	*<0.05*	32.02	36.71	0.16
Chemotherapy	36.30	47.52	*0.001*	42.39	43.79	0.68
Endocrine Therapy	61.06	59.94	0.74	59.48	59.92	0.90
Previous mental health diagnosis	10.56	19.41	*< 0.001*	12.97	17.51	0.08
Previous supportive medication use (any)	12.21	45.81	*< 0.0001*	34.65	35.12	0.89

Some patients were missing information on marital status at diagnosis, Hispanic ethnicity, and census tract information, and dummy variables were included in the models so that these patients were not excluded from analyses. Values in italic are statistically significant

medications, non-opioid psychotropic medications, neither type of medication) are displayed in Appendix 2.

In our sample, 68–69 % of patients used hospice; 11 % entered hospice within 3 days of death; 24–25 % died in the hospital; 5 % received chemotherapy within 14 days of death; and between 29 and 35 % had an ICU admission, >1 ED visit, or >1 hospitalization in the last 30 days of life. When considering all supportive treatments together (i.e., use of any supportive medications), we found no differences between medication

users and non-users in terms of likelihood of experiencing any of the end-of-life care outcomes (Table 2).

When considering medication categories separately, in unadjusted analyses, opioid pain medication users had a 150 % increased risk of receiving chemotherapy within 14 days of death, compared to patients who did not use opioid pain medications (RR 2.50, 95 % CI 1.26–4.97). In contrast, non-opioid psychotropic medication users had a 57 % decreased risk of receiving chemotherapy within 14 days of death compared to patients who did not use these medications (RR 0.43, 95 % CI 0.20–0.95) (Table 3).

In adjusted analyses, there were few differences in end-of-life care by supportive medication use status. However, the relationship between non-opioid psychotropic use and receipt of chemotherapy within 14 days of death persisted with medication users having a 67 % decreased risk of receiving chemotherapy within 14 days of death (aRR 0.33, 95 % CI 0.12–0.88). The risk of end-of-life chemotherapy receipt was 0.02 among non-opioid psychotropic users and 0.06 among non-users. Early use of opioid pain medications was no longer statistically significantly associated with receipt of chemotherapy at the end of life after adjustment.

In a sensitivity analysis restricting to patients who died of breast cancer (n = 645), there were similarly no significant relationships between any supportive medication use or opioid pain medication use and end-of-life care measures. The effect of non-opioid psychotropic medication use on risk of receiving chemotherapy within 14 days of death became larger (aRR 0.24, 95 % CI 0.06–0.95). Further, although there was no significant difference between non-opioid psychotropic users and non-users in risk of using hospice services, the relationship between non-opioid psychotropic use and risk of entering hospice within 3 days of death became marginally statistically significant (aRR 0.39, 95 % CI 0.15–1.00). In an additional sensitivity analysis using an alternative definition of non-opioid psychotropic medication that included first- and second-generation antipsychotics, results were consistent with our primary adjusted models.

Discussion

Based on results from an RCT of an early palliative care intervention, we hypothesized that patients' use of supportive medications may be associated with their end-of-life care. Overall, in our sample, use of any supportive medications was not associated with hospice use or intensity of end-of-life care. When considering medication groups separately, however, we found that non-opioid psychotropic medication use was associated with a decreased risk of receiving chemotherapy within 14 days of death. Across all analyses, we observed no significant relationships between early opioid pain medication use and end-of-life care outcomes.

One possible explanation for our lack of an observed relationship between opioid pain medication use and end-of-life care is that pain management, compared to comprehensive supportive and psychosocial care, may be better integrated into standard oncologic care [23, 24]. In addition, a large proportion of opioid users in our sample appeared to be receiving these drugs post-surgery (among opioid users, nearly 30 % had surgery). Opioid use for post-surgical pain, in particular, may not be indicative of a patient's engagement with other aspects of supportive care.

Receipt of non-opioid psychotropic medications that are often used to treat depression, anxiety, and sleeplessness may be a better indicator of a patient's interaction with more comprehensive supportive care and/or a provider serving in a supportive capacity (e.g., a mental health or primary care provider). If this is the case, patients receiving non-opioid psychotropic medications may also be more likely than non-recipients to receive decisional support and assistance in planning for the end of life. These aspects of supportive care may help facilitate the transition from active treatment to palliative care [4], although the results of our primary analysis did not suggest that non-opioid psychotropic medication use is associated with earlier or increased hospice use. We did find a reduced use of chemotherapy in the 14 days prior to death among non-opioid psychotropic users, which may indicate more intentional end-of-life care planning. Alternatively, this finding could also be the result of selection bias if, for example, patients experiencing depression or anxiety are less motivated to continue cancer treatment.

Our lack of an observed relationship between supportive medication use and other aspects of end-of-life care, including hospice use and length of use, in our primary analysis could be because pharmacologic symptom management, although measurable in administrative claims data, is an insufficient indicator of patients' engagement with supportive care. Although use of medications to treat pain and, in particular, depression, anxiety, and sleeplessness may reflect the involvement of mental health care and/or other supportive providers in patients' cancer care, other aspects of supportive or palliative care that patients receive are likely highly variable [25]. The one study of an outpatient palliative care intervention that has demonstrated an effect on end-of-life care [4] included multiple components. In that RCT, although palliative care clinicians were allowed the flexibility to address individual patient needs, they were encouraged to follow palliative care visit guidelines adapted from the National Consensus Project for Quality Palliative Care [26]. Retrospective chart reviews

Table 2 Risk of hospice use and aggressive end-of-life care, by supportive medication use

	Hospice use		≤3 days hospice		Terminal hospitalization		Chemotherapy in last 14 days of life		ICU admission or >1 ED visit or hospitalization in last 30 days of life	
	Risk (95 % CI) Users	Risk (95 % CI) Non-users	Risk (95 % CI) Users	Risk (95 % CI) Non-users	Risk (95 % CI) Users	Risk (95 % CI) Non-users	Risk (95 % CI) Users	Risk (95 % CI) Non-users	Risk (95 % CI) Users	Risk (95 % CI) Non-users
Unadjusted results										
Any supportive medications	0.68 (0.65–0.72)	0.68 (0.63–0.73)	0.11 (0.09–0.15)	0.11 (0.07–0.16)	0.25 (0.22–0.29)	0.25 (0.20–0.30)	0.06 (0.04–0.08)	0.03 (0.02–0.06)	0.31 (0.27–0.35)	0.31 (0.26–0.36)
Opioid pain medications	0.68 (0.65–0.72)	0.68 (0.64–0.73)	0.12 (0.09–0.15)	0.10 (0.07–0.15)	0.25 (0.22–0.29)	0.24 (0.20–0.29)	0.07 (0.05–0.09)	0.03 (0.01–0.05)	0.31 (0.22–0.33)	0.31 (0.27–0.36)
Non-opioid psychotropic medications	0.70 (0.65–0.76)	0.68 (0.64–0.71)	0.09 (0.06–0.14)	0.12 (0.09–0.15)	0.23 (0.19–0.29)	0.26 (0.23–0.29)	0.03 (0.01–0.05)	0.06 (0.04–0.08)	0.34 (0.28–0.40)	0.30 (0.26–0.33)
Propensity score-weighted results										
Any supportive medications	0.68 (0.65–0.72)	0.69 (0.62–0.76)	0.11 (0.08–0.14)	0.11 (0.07–0.17)	0.25 (0.22–0.29)	0.24 (0.18–0.31)	0.05 (0.04–0.07)	0.05 (0.02–0.12)	0.29 (0.26–0.33)	0.35 (0.28–0.43)
Opioid pain medications	0.69 (0.65–0.73)	0.67 (0.61–0.73)	0.11 (0.08–0.14)	0.09 (0.06–0.15)	0.25 (0.22–0.30)	0.26 (0.21–0.32)	0.06 (0.04–0.08)	0.04 (0.02–0.09)	0.29 (0.25–0.33)	0.35 (0.30–0.42)
Non-opioid psychotropic medications	0.68 (0.60–0.76)	0.68 (0.64–0.73)	0.09 (0.06–0.18)	0.11 (0.08–0.15)	0.27 (0.20–0.36)	0.24 (0.21–0.29)	0.02 (0.01–0.06)	0.06 (0.04–0.09)	0.37 (0.29–0.46)	0.30 (0.25–0.34)

Table 3 Risk ratio of hospice use and aggressive end-of-life care, supportive medication users compared to non-users

	Hospice use		≤3 days hospice		Terminal hospitalization		Chemotherapy in last 14 days of life		ICU admission or >1 ED visit or hospitalization in last 30 days of life	
	Risk ratio	95 % CI	Risk ratio	95 % CI	Risk ratio	95 % CI	Risk ratio	95 % CI	Risk ratio	95 % CI
Unadjusted results										
Any supportive medications	1.00	0.95–1.10	1.04	0.65–1.68	1.01	0.80–1.28	2.04	1.00–4.15	1.00	0.82–1.23
Opioid pain medications	1.00	0.92–1.10	1.14	0.72–1.80	1.03	0.82–1.30	*2.50*	*1.26–4.97*	0.99	0.82–1.21
Non-opioid psychotropic medications	1.03	0.94–1.13	0.77	0.46–1.30	0.90	0.70–1.16	*0.43*	*0.20–0.95*	1.13	0.92–1.39
Propensity score-weighted results										
Any supportive medications	0.99	0.89–1.11	1.02	0.59–1.78	1.08	0.80–1.44	1.22	0.48–3.10	0.85	0.67–1.08
Opioid pain medications	1.04	0.93–1.16	1.12	0.67–1.88	0.98	0.75–1.27	1.60	0.65–3.84	0.83	0.67–1.03
Non-opioid psychotropic medications	0.99	0.86–1.14	0.93	0.48–1.81	1.10	0.79–1.55	*0.33*	*0.12–0.88*	1.23	0.93–1.64

Values in italic are statistically significant

from the trial revealed that palliative care consultations focused primarily on symptom management, patient and family coping, and illness understanding and education [15]. Apart from symptom management, these components of palliative care are difficult if not infeasible to measure using existing data sources. Thus, accurately capturing patients' use of palliative care services in practice is challenging.

Interestingly, our sensitivity analyses did reveal a significant relationship between early use of non-opioid psychotropic medications and earlier hospice use when restricting to patients who died of their breast cancer. Women who died from cancer during the study period might have distinct supportive care needs and may benefit the most from both symptom management and advance care planning aspects of supportive care. This may explain why, in this sample, patients who used non-opioid psychotropics were less likely to enter hospice very near death. This may also explain why the negative effect of non-opioid psychotropic use on risk of receiving chemotherapy within 14 days of death was larger in this restricted sample than in our main analysis.

The interpretation of our findings is limited by a number of factors. The first concerns external generalizability, as our study was limited to fee-for-service Medicare beneficiaries with advanced breast cancer; excluding patients enrolled in Medicare HMO plans. However, fee-for-service enrollees represent over 70 % of all Medicare beneficiaries during our study period [27].

It is unclear whether our findings extend to patients with other cancers and/or other (or no) insurance coverages. Second, following previous studies [3], our measures of early supportive care consisted of binary indicators of medication use in the 90 days following breast cancer diagnosis. Thus, we did not capture the specific timing or intensity of patients' use of supportive services. Third, we likely underestimated use of non-opioid psychotropic medications as we were unable to capture use of benzodiazepines, which may be used to treat anxiety and insomnia. Medicare Part D did not cover benzodiazepines until 2013, after our study period. Fourth, we were unable to control for unmeasured patient-level factors that may confound the relationship between early supportive medication use and different aspects of end-of-life care. Thus, we cannot infer causality from our observed relationships between medication use and some aspects of end-of-life care. Finally, it is important to note that our study and others that do not account for patients' and caregivers' preferences for and experiences with end-of-life care cannot draw conclusions about quality of end-of-life care.

Our study expands upon existing RCT evidence about the role of early supportive cancer care by providing novel observational data about the early use of medications to control symptoms in practice and the relationship between use of these services and patterns of care at the end of life. Specifically, our study found that women who received non-opioid psychotropic medications had a decreased risk of receiving chemotherapy within 14 days of death. In the context of increasingly aggressive EOL care that may be inconsistent with patients' preferences in general [5–8, 28], the results of our study and others suggest that early engagement with supportive care may be a promising strategy for reducing aggressiveness of care very near death. However, assessing whether less-aggressive care at the end of life is consistent with good quality care requires the inclusion of data on patients' and caregivers' specific preferences for and experiences with EOL care. Future research should also consider alternative measures of palliative and supportive care use using administrative and other data sources. For example, it may be possible to isolate opioid use not related to surgery by restricting the dates on which opioid prescriptions were filled to those not proximate to surgery. Separate from supportive medication use, researchers might consider measuring claims for services provided by non-oncology providers who may serve in a supportive capacity (e.g., primary care or mental health providers). Encounters for patient counseling and decision support are also important aspects of supportive care; however, such encounters may be under-coded in claims data and better captured by clinical records.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Appendix 1

Table 4. Sample characteristics by use of opioid pain medications and non-opioid psychotropic medications, before propensity score weighting

	Opioid pain medications			Non-opioid psychotropic medications		
	Non-users	Users	*p* value	Non-users	Users	*p* value
Number of patients	376	571		679	268	
Demographic characteristics						
Age at cancer diagnosis—mean (SD)	78.99	75.95	*<0.0001*	77.32	76.74	0.2881
Marital status at diagnosis, % married/ partnered	20.48	237.67	*<0.05*	24.74	25.00	0.9208
Race						
White	78.72	79.86	0.6722	75.85	88.43	*<0.0001*
Non-white	21.28	20.14		24.15	11.57	
Hispanic ethnicity						
Yes	7.18	8.06	0.0844	8.25	6.34	0.6128
No	92.82	90.72		91.02	92.91	
Median household income in census tract of residence						
$5299–26,387	19.41	28.37	0.9232	24.01	26.87	0.3615
$26,388–36,095	22.07	27.15		26.07	22.76	
$36,096–50,560	27.93	22.94		25.33	23.88	
$50,561–200,014	48.10	51.90		24.59	26.12	
Proportion of residents with no high school degree in census tract of residence (%)						
0.53–8.98	26.33	23.64	*<0.05*	23.56	27.61	0.0944
8.99–16.50	28.99	22.77		27.25	20.15	
16.51–27.60	23.40	25.92		24.59	25.75	
27.61–79.99	21.01	27.67		24.59	26.12	
Residence						
Metropolitan county	86.70	77.76	*<0.001*	81.59	80.60	0.7239
Non-metropolitan county	13.30	22.24		18.41	19.40	
US region						
Northeast	33.24	19.61	*<0.0001*	27.39	19.03	*<0.05*
Midwest	14.63	15.06		15.32	23.81	
South	33.24	34.33		33.28	35.45	
West	18.88	31.00		24.01	31.72	
Clinical characteristics						
Year of cancer diagnosis						
2007	28.72	21.37	0.1086	25.33	21.64	0.5506
2008	18.35	22.27		20.47	22.39	
2009	20.21	21.89		21.21	21.27	
2010	17.55	18.39		17.08	20.52	
2011	15.16	15.59		15.91	14.18	
Charlson Comorbidity Score						
0	75.53	68.13	0.05	75,26	60.45	*<0.0001*
1	17.02	21.89		17.23	26.87	
2+	7.45	9.98		7.51	12.69	
Cancer treatment (any)	81.12	87.57	*<0.01*	84.98	85.07	0.9700
Surgery	18.62	28.55	*<0.001*	23.56	27.24	0.2369
Radiation	29.26	38.18	*<0.01*	36.67	29.48	0.0361
Chemotherapy	37.23	48.34	*<0.001*	44.48	42.54	0.5879
Endocrine therapy	60.64	60.07	0.8612	59.94	61.19	0.7226
Previous mental health diagnosis	16.49	16.64	0.9522	10.31	32.46	*<0.0001*
Previous supportive medication use (any)	23.94	42.38	*<0.0001*	20.77	71.27	*<0.0001*
Previous opioid use	8.78	31.35	*<0.0001*	17.67	34.33	*<0.0001*
Previous non-opioid psychotropic use	17.02	23.47	*<0.05*	4.42	62.69	*<0.0001*

Forty-three patients were missing information on marital status at diagnosis, seven were missing information on Hispanic ethnicity, one was missing census tract information, and dummy variables were included in the models so that these patients were not excluded from analyses. Values in italic are statistically significant. The "Black" and "Other Race" categories were collapsed for the purposes of the table to protect patients' identities

Appendix 2

Table 5. Generic names of medications included in analysis

Supportive medication category	Generic drug names
Opioid pain medications	Buprenorphine
	Fentanyl
	Hydrocodone
	Hydromorphone
	Levorphanol
	Meperidine
	Methadone
	Morphine
	Nalbuphine
	Oxycodone
	Oxymorphone
	Propoxyphene
	Tapentadol
	Tramadol
Non-opioid psychotropic medications	Antidepressants
	Amitriptyline
	Amoxapine
	Bupropion
	Citalopram
	Clomipramine
	Desipramine
	Desvenlafaxine
	Doxepin
	Duloxetine
	Escitalopram
	Fluoxetine
	Fluvoxamine
	Imipramine
	Isocarboxazid
	Maprotiline
	Milnacipran
	Mirtazapine
	Nefazodone
	Nortriptyline
	Paroxetine
	Phenelzine
	Protryptyline
	Sertraline
	Tranylcypromine
	Trazodone
	Trimipramine
	Venlafaxine
	Vilazodone
	Non-benzodiazepine sleep aids
	Hydroxyzine
	Pregabalin
	Buspirone
	Zolpidem
	Eszopiclone
	Zaleplon
	Antipsychotics
	Apriprazole
	Asenapine
	Chlorpromazine
	Clozapine
	Fluphenazine
	Haloperidol
	Iloperidone
	Loxapine
	Lurasidone
	Olanzapine
	Paliperidone
	Perphenazine
	Pimozide
	Quetiapine
	Risperidone
	Thiothixene
	Trifluoperazine
	Ziprasadone

References

1. Bakitas M, Lyons KD, Hegel MT, Balan S, Brokaw FC, Seville J, Hull JG, Li Z, Tosteson TD, Byock IR, Ahles TA (2009) Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA 302(7):741–749. doi:10.1001/jama.2009.1198
2. Rabow MW, Dibble SL, Pantilat SZ, McPhee SJ (2004) The comprehensive care team: a controlled trial of outpatient palliative medicine consultation. Arch Intern Med 164(1):83–91. doi:10.1001/archinte.164.1.83
3. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ (2010) Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363(8):733–742. doi:10.1056/NEJMoa1000678
4. Greer JA, Pirl WF, Jackson VA, Muzikansky A, Lennes IT, Heist RS, Gallagher ER, Temel JS (2012) Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. J Clin Oncol Off J Am Soc Clin Oncol 30(4):394–400. doi:10.1200/JCO.2011.35.7996
5. Steinhauser KE, Christakis NA, Clipp EC, McNeilly M, Grambow S, Parker J, Tulsky JA (2001) Preparing for the end of life: preferences of patients, families, physicians, and other care providers. J Pain Symptom Manag 22(3):727–737
6. Steinhauser KE, Clipp EC, McNeilly M, Christakis NA, McIntyre LM, Tulsky JA (2000) In search of a good death: observations of patients, families, and providers. Ann Intern Med 132(10):825–832
7. Singer PA, Martin DK, Kelner M (1999) Quality end-of-life care: patients' perspectives. JAMA 281(2):163–168
8. Voogt E, van der Heide A, Rietjens JA, van Leeuwen AF, Visser AP, van der Rijt CC, van der Maas PJ (2005) Attitudes of patients with incurable cancer toward medical treatment in the last phase of life. J Clin Oncol Off J Am Soc Clin Oncol 23(9):2012–2019. doi:10.1200/JCO.2005.07.104
9. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC (2004) Trends in the aggressiveness of cancer care near the end of life. J Clin Oncol Off J Am Soc Clin Oncol 22(2):315–321. doi:10.1200/JCO.2004.08.136
10. Rose JH, O'Toole EE, Dawson NV, Lawrence R, Gurley D, Thomas C, Hamel MB, Cohen HJ (2004) Perspectives, preferences, care practices, and outcomes among older and middle-aged patients with

late-stage cancer. J Clin Oncol Off J Am Soc Clin Oncol 22(24): 4907–4917. doi:10.1200/JCO.2004.06.050

11. Wright AA, Keating NL, Balboni TA, Matulonis UA, Block SD, Prigerson HG (2010) Place of death: correlations with quality of life of patients with cancer and predictors of bereaved caregivers' mental health. J Clin Oncol Off J Am Soc Clin Oncol 28(29):4457–4464. doi:10.1200/JCO.2009.26.3863
12. Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, Mitchell SL, Jackson VA, Block SD, Maciejewski PK, Prigerson HG (2008) Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA 300(14):1665–1673. doi:10.1001/jama.300.14.1665
13. Levit L BE, Nass S, Ganz PA (2013) Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis.
14. The National Cancer Institute (2010). Palliat Care Cancer http://www.cancer.gov/cancertopics/advanced-cancer/care-choices/palliative-care-fact-sheet. Accessed 31 August 2015.
15. Jacobsen J, Jackson V, Dahlin C, Greer J, Perez-Cruz P, Billings JA, Pirl W, Temel J (2011) Components of early outpatient palliative care consultation in patients with metastatic nonsmall cell lung cancer. J Palliat Med 14(4):459–464. doi:10.1089/jpm.2010.0382
16. Bower JE (2008) Behavioral symptoms in patients with breast cancer and survivors. J Clin Oncol Off J Am Soc Clin Oncol 26(5): 768–777. doi:10.1200/JCO.2007.14.3248
17. The National Cancer Institute. SEER-Medicare: Medicare Enrollment and Claims Data. http://healthcaredelivery.cancer.gov/seermedicare/medicare/. Accessed 25 January 2016.
18. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF (2002) Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 40(8 Suppl):IV–3-18. doi:10.1097/01.MLR.0000020942.47004.03
19. Earle CC, Neville BA, Landrum MB, Souza JM, Weeks JC, Block SD, Grunfeld E, Ayanian JZ (2005) Evaluating claims-based indicators of the intensity of end-of-life cancer care. Int J Qual Health Care: J Int Soc Qual Health Care/ISQua 17(6):505–509. doi:10.1093/intqhc/mzi061
20. Klabunde CN, Potosky AL, Legler JM, Warren JL (2000) Development of a comorbidity index using physician claims data. J Clin Epidemiol 53(12):1258–1267
21. Sturmer T, Rothman KJ, Glynn RJ (2006) Insights into different results from different causal contrasts in the presence of effect-measure modification. Pharmacoepidemiol Drug Saf 15(10):698–709. doi:10.1002/pds.1231
22. Zou G (2004) A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 159(7):702–706
23. Levy MH (1989) Integration of pain management into comprehensive cancer care. Cancer 63(11 Suppl):2328–2335
24. Gordon DB, Dahl JL, Miaskowski C, McCarberg B, Todd KH, Paice JA, Lipman AG, Bookbinder M, Sanders SH, Turk DC, Carr DB (2005) American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. Arch Intern Med 165(14):1574–1580. doi:10.1001/archinte.165.14.1574
25. Hui D, Elsayem A, De la Cruz M, Berger A, Zhukovsky DS, Palla S, Evans A, Fadul N, Palmer JL, Bruera E (2010) Availability and integration of palliative care at US cancer centers. JAMA 303(11): 1054–1061. doi:10.1001/jama.2010.258
26. The National Consensus Project for Quality Palliative Care. Clinical Practice Guidelines for Quality Palliative Care 3rd edition 2013. http://www.nationalconsensusproject.org/Guidelines_Download2.aspx. Accessed 31 August 2015.
27. Kaiser Family Foundation. Medicare Advantage. http://kff.org/medicare/fact-sheet/medicare-advantage/. Accessed 25 January 2016.
28. Wright AA, Keating NL, Ayanian JZ, Chrischilles EA, Kahn KL, Ritchie CS, Weeks JC, Earle CC, Landrum MB (2016) Family perspectives on aggressive cancer care near the end of life. J Am Med Assoc 315(3):284–292. doi:10.1001/jama.2015.18604