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TITLE: Opioid prescribing for cancer patients in the last year of life: a longitudinal population cohort study.

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INTRODUCTION

An estimated 6.6 million people die from cancer each year across the world; about two thirds of these patients will experience pain and between 45 and 56% of all cancer patients will experience pain of moderate to severe intensity [22]. There is broad consensus that opioid-based pharmacotherapy is the first-line strategy for the treatment of moderate to severe cancer pain [5,18,16]. Yet despite advances associated with the increased availability and development of new opioids, under prescribing of analgesia in cancer remains prevalent with approximately one third of patients still not receiving pain medication proportional to their pain intensity [10] Effective cancer pain management in the community setting is particularly challenging, with pain reported to be well controlled for only 18% of those who die at home in the UK [24].

Whilst cancer-related pain remains a major public health problem worldwide [6] the problem exists in a context of growing concern about over prescribing of strong opioids in other patient groups, particularly in non-cancer chronic pain. The growth in strong opioid utilisation across the USA [26] and some European countries [3] has prompted fears of an international opioid prescribing epidemic.

The UK picture is similar; the growing use of buprenorphine, oxycodone hydrochloride and morphine sulphate in England increased annual costs for these drugs alone by over £10m between 2002 and 2013 [15]. Aggregated dispensing data reported by the UK National Health and Social Care Information Centre (NHSCIC) shows a 466% increase in opioid prescribing between 2000 and 2010. However, for cancer patients, opioid prescribing has not increased to the same extent and still represents only 16.1% of all opioid prescriptions issued in the UK [15].

In order to improve the management of cancer pain a number of important barriers need to be overcome [17] one of which is enabling more appropriate patient access to strong opioid treatment. In this study we determine the extent and duration of strong opioid prescribing in a cohort of cancer patients before death and the factors that influence prescribing to determine the scope for earlier intervention.

METHODS

Research Question

What is the extent and duration of strong opioid prescribing for cancer patients before death and what are the factors that influence prescribing?

Data and Patients

We obtained ethical approval to link UK Cancer Registry data with the corresponding electronic primary care medical records of adult patients (at least 18 years of age at time of death) who died from cancer (verified by death certification) over a seven year period (2005 to 2012) in a large UK city (Leeds). Cause of death, demographic information including Index of Multiple Deprivation (IMD), date of diagnosis and cancer site and stage, treatment history and place of death is most reliably recorded by the Cancer Registry. This registry is part of Public Health England and records every new cancer diagnosis within the UK and has a long-term role in monitoring trends in cancer incidence and survival. The Cancer Registry maximises dataset completeness by obtaining data from multiple sources including the Office of National Statistics, medical records, histopathology services and death certification.

Analgesic prescribing history is most reliably recorded within SystmOne which records all prescriptions issued in General Practice (Primary Care) and is the most reliable means of charting analgesic prescribing over time. Data on pain intensity is not routinely recorded within UK electronic patient care records and so was not available for analysis. The linkage of the two data sources was undertaken using an Open Pseudonymiser system which creates an encrypted code based on NHS number, patient sex and year of birth. We extracted all prescriptions for analgesics issued to each patient in the linked cohort during the 12 months prior to death. (See Appendix 1 for list of analgesics).

Leeds is the third largest city in the UK with a population of 750,000, 85% of which are white, 6% Asian, and 3.5 % black. Within Leeds, there are 545 general practitioners (family physicians) working in 109 general practices. Our data represents community prescribing activity from all General Practices in the city during this period (2005-2012).

Statistical Analysis

Patients were stratified into one of three analgesic groups: Group 1, no prescription group: patients who had received no analgesic prescriptions within the last year of life. Group 2, non-opioids / weak opioids: patients who had received at least one prescription for either a non-opioid or weak opioid but had not received a prescription for a strong opioid within the last year of life. Group 3, strong opioid: patients who had received at least one prescription for a strong opioid within the last year of life.

Demographic characteristics as well as clinical and treatment factors were described for all patients stratified by the three analgesic groups. Differences in demographic, clinical and treatment factors across the three analgesic groups were derived from

univariate multinomial logistic regression models. Data from these models are presented as relative risk ratios (RRR) with 95% confidence intervals. Survival since diagnosis is described in terms of the number of weeks that elapsed between diagnosis and death and was stratified by cancer type. Frequencies (%) of prescriptions, number (%) of patients receiving at least one prescription, and median (IQR) prescriptions per patient are presented stratified by analgesic group. Timing of prescriptions prior to death is presented as median (IQR) weeks between first prescription and death stratified by analgesic group. The final analysis was to explore the factors associated with receiving an early or late prescription for a strong opioid. The median weeks before death that a first strong opioid was prescribed was used as a cut point to dichotomize the sample between those who received an early prescription of a strong opioid (≥10 weeks before death), and those who received a late prescription for a strong opioid (≤ 9 weeks before death). For those individuals who received at least one strong opioid prescription a multivariable logistic regression analysis was used to model the association between demographic, clinical and treatment factors and the risk of receiving an early or late strong opioid prescription. Data from this model are presented as odds ratios (OR) with 95% confidence intervals.

RESULTS

Sample characteristics

The study included 6,080 cancer patients who died between December 2005 and February 2012, of whom 4610 (75.8%) had received one or more prescriptions for analgesics. Patient characteristics are described in Table 1. Our cohort was

representative of all UK cancer patients [4] in relation to cancer prevalence and mortality. Of those who had received some form of cancer treatment (93.9%), the most common were chemotherapy (42.6%), surgery (38.3%), radiotherapy (35.1%) or hormone therapy (14.3%). Ethnicity data was unavailable for 34.7% and limited in detail for the remainder, of whom 63.1% were classified as White and 2.2 % other. An Index of Multiple Deprivation (IMD) was extracted for all patients. Over half (52.5%) had an IMD rank of 1 or 2 indicating a high level of deprivation and a minority (12.3%) fell within IMD rank 5 'least deprived'. Place of death was split between hospital (32.1%) hospice (31.7%) and home (26.6%). This pattern is broadly similar to UK national data on place of death for cancer patients [20] but reflects relatively good provision of palliative care services in Leeds. Nationally there are slightly more deaths in hospital (37.8%), and at home (29.6%), and fewer deaths in hospice (17.8%).

Median survival from diagnosis for the whole cohort was 60 weeks (IQR 22-147). Survival from diagnosis by cancer type was as expected: shortest in patients with primary of unknown origin, brain and neurological cancers, and lung cancer, and longest for patients with breast or prostate cancer.

Extent of analgesic prescribing

We found 96,810 analgesic prescriptions were issued to 4,610 patients; 31.5% of all prescriptions were for non opioids, 25.2% weak opioids and 43.3% strong opioids. Forty eight percent of patients received at least one prescription for a strong opioid. Over one third (36.7%) of all strong opioid prescriptions issued were for morphine, followed by diamorphine (15.9%) oxycodone (11.2%), fentanyl (10.4%),

buprenorphine (3.7%) and other (0.3%) (Figure 1). The median number of prescriptions for a strong opioid per patient was 4 (IQR 2-12).

Strong opioid prescriptions

Forty eight percent (95% CI 47-49%) of people who died of cancer received at least one prescription of strong opioid in the last year of life. Multivariable logistic regression models revealed no differences in the chance of receiving a strong opioid with age or sex, however compared to dying in a hospice, individuals dying in the hospital were 60% less likely to receive a strong opioid in the community in the last year of life (RRR 0.4, CI 0.3-0.5,P<0.001). Conversely patients who had received chemotherapy treatment in the last year of life were 30% more likely to have received a strong opioid compared to those who did not have chemotherapy treatment (RRR 1.3, CI1.1-1.6, P<1.1-1.6)

Timing and duration of strong opioid prescriptions

We examined the timing of strong opioid prescribing by calculating the interval in weeks between the first prescription event (by prescription type described in Appendix 1) and death. For those patients who had received a strong opioid, the median interval between first prescription for any strong opioid and death was 9 weeks (IQR 3-23). The median interval between first prescription and death for the specific opioids morphine, oxycodone or fentanyl was slightly longer than the overall median, 11 weeks (IQR 4-24 and 4-29 respectively) (Table 2). Diamorphine was the opioid prescribed closest to death with a median interval before death of 1 week

(IQR1-3) which is consistent with its typical clinical use in the UK as a subcutaneous infusion in the last days of life. Figure 2 shows a rapid increase in strong opioid prescriptions issued in the last 3 months of life. However, at 6 weeks before death only 30% of cancer patients had been prescribed a strong opioid.

To investigate the factors associated with receiving an early or late first prescription for a strong opioid we dichotomized the group based on the timing of each persons' first strong opioid prescription: early group ≥ 10 weeks before death, late group ≤9 weeks before death. Table 3 summarises a multivariable logistic regression model that quantifies the relationship between early or late prescription of strong opioid and patient's demographic and treatment variables. This model reveals that compared to being under 50 years of age, those 60 years and over were between 1.7 (1.2-2.4) and 4.3 (1.9-9.7) times more likely to receive a late prescription for a strong opioid. Figure 3 shows the decreasing proportion of early first prescriptions for a strong opioid with increasing age.

Compared to patients who died in a hospice, those who died in a hospital were 40% more likely to receive a late prescription in the community for a strong opioid (RRR 1.4, 95% CI 1.1-1.7,P<0.01). Patients who died in their own home or a care home were 2.6 and 2.8 times respectively more likely to receive a late prescription for a strong opioid. Further analysis on those individuals who died in their own home or a care home revealed that although they were just as likely to receive at least one strong opioid prior to death as those dying in hospice, they were 7.5 (4.5-12.1) and 4.1 (1.9-8.6) times more likely to receive diamorphine as their first strong opioid prescription which in 75% of cases was prescribed 3 weeks or less prior to death.

Patients who had surgery were 40% more likely to receive a late prescription for a strong opioid compared to patients who did not have surgery. In contrast, patients who received chemotherapy and/or radiotherapy were 30% more likely to have received an early prescription for a strong opioid compared to patients who had not received these treatments.

DISCUSSION

There are very few longitudinal population level studies of opioid prescribing in patients dying of cancer. Previous studies chart opioid prescribing over the last 3 months of life [11,2] sum total opioid dosage over a designated period [13] or report dose at specific time points [2]. This study is the first to accurately determine the median interval between first prescription of a strong opioid and death in a large population by charting analgesic prescribing daily over the last year of life.

Almost half (48%) of all patients in our study received a strong opioid before death, though only 30% had received a strong opioid at 6 weeks before death. These figures are consistent with a recent (2012) UK study [11] which reported 43.6% of cancer patients receive an opioid in the last three months of life and two studies based in the Netherlands [2] and Denmark [12] which report the proportion of cancer patients prescribed an opioid in the last 12 months of life to be 51% and 54% respectively. In the context of the evidence on pain prevalence in advanced cancer (estimated to be between 62 and 86% [22,23]) our data supports the hypothesis of potential under treatment of cancer pain and suggests that many more patients with advanced cancer and pain may benefit from a strong opioid analgesic.

Of those who did receive a strong opioid, the median interval between first prescription and death was short (9 weeks). This does not correspond to the

evidence on the onset of severe pain in this patient group [22,3,23] which for many patients occurs much earlier in the cancer trajectory. We examined whether late diagnosis could account for this but median survival for our sample from diagnosis was 60 weeks suggesting that most opioid prescribing in fact occurred late in the trajectory between diagnosis and death, regardless of cancer duration. Additionally over 90% of all patients in the cohort had received some form of cancer treatment therefore it was not the absence of a cancer diagnosis or poor engagement with cancer services that hindered timely access to an opioid. The association between treatment with chemotherapy or radiotherapy and earlier opioid prescription suggests that more active oncology management provides opportunities to identify pain. Overall, less than half of all patients that die from cancer receive a strong opioid, and in those that did, an average of four prescriptions were issued over a median duration of 9 weeks before death.

We found older patients were equally likely to receive an opioid as younger patients, though if they did receive an opioid, it was significantly later than in younger patients with a clear relationship between increasing age and shorter treatment duration. Inequity of access to opioids among older patients has been highlighted in previous studies [11,7] although the reasons for this remains unclear. A meta-analysis of 46 studies on cancer pain prevalence found no differences between younger and older cancer patients in terms of pain severity [22]. Therefore further research is needed to explore why later opioid prescribing exists in older cancer patients.

This is the first study to explore the relationship between opioid prescribing for cancer pain in relation to place of death. Patients who died in hospital were 60% less likely to receive a strong opioid in the community in the year before death than patients who died in a hospice. We considered whether this finding could be

attributable to our dataset being derived exclusively from community issued prescriptions. However given that for most cancer patients 90% of the last year of life is spent at home (the average length of a cancer inpatient stay in the UK is 8 days and the average number of admissions in the last year of life is 5) [19] it is highly unlikely that missed hospital issued prescriptions would alter this finding. We therefore hypothesise that the association between hospital deaths and lower levels and later prescribing of a strong opioid might reflect poor pain control as a reason for admission. Possible contributory factors to dying in hospital may be poor planning, and a lack of coordinated care or specialist palliative care involvement. Although patients who died at home or in a care home were equally likely to receive an opioid as those who die in a hospice, the first opioid prescription was issued much later and in 75% of cases was for diamorphine, a drug typically used in the last days of life. We hypothesise that although deaths at home may be associated with lower prevalence of complex problems or symptoms that would otherwise trigger hospital or hospice admission, the timing and nature of prescribing could indicate under treatment within this group. Earlier integration of specialist palliative care may be one solution to this; A multi- centre study of 1,450 patients with cancer pain comparing oncology care alone to early integration of palliative care alongside oncology care found that early access was associated with a 31% reduced risk of suffering from severe pain [7]. This may be largely attributable to the enhanced opportunity for pain monitoring and screening. The potential impact of improving the opportunities for screening for cancer pain on prescribing should not be underestimated. A recent study demonstrated a 179% increase in the use of opioids in patients dying of cancer after the introduction of a daily pain measurement using a numerical rating scale [19].

This study has limitations. Firstly, the population is derived from a single UK city, and whilst we have been able to determine the population is broadly representative of the UK cancer population in terms of prevalence of cancer type, age, sex and survival, the extent to which opioid prescribing is representative of national and international activity is harder to determine. The prescribing activity is derived from 545 general practitioners (family physicians) working within 109 general practices so it represents a large number of prescribers. The higher rates of death at home or in hospice in Leeds compared to UK national data probably reflect a good provision of community palliative care. It is possible that our data may represent an over-estimate of strong opioid prescribing practice than in the UK in general. Secondly, we have used cause of death data derived from death certification to identify a cohort who have died from cancer. Previous cancer mortality studies exploring analgesic prescribing report on populations who have died with a diagnosis of cancer rather died of cancer. We acknowledge cause of death recording on death certification is imperfect, however two recent studies [20,9] suggest the level of inaccuracy is overstated and is in fact as low as 4%. We acknowledge a margin of error exists and is likely to be evident in our dataset however we are confident it does not undermine our attempt to make methodological progress by defining a cohort who have died from, rather than with, cancer. The data used in this study is derived from a live clinical system and as such is likely to represent errors or omissions inherent within that system. We also acknowledge that the data on analgesic prescribing is restricted to community issued prescriptions and whilst this is the most appropriate source to capture longitudinal prescribing data over a 12 month period it cannot capture prescribing during inpatient admissions to hospices or acute hospitals (although to some extent prescribing that continues following discharge may reflect inpatient activity).

Finally, and in common with other retrospective cohort studies of this type [2, 7,11, 12] we were not able to directly match level of analgesic prescription with the level of patient reported pain intensity as the latter data are not routinely recorded in electronic patient records. We recognise the lack of pain assessment is a limiting factor in assessing the effectiveness of pain management but the purpose of this study is to capture prescribing practice in the context of routine care and identify factors that are associated with poorer access to strong opioids.

CONCLUSIONS

We have identified for the first time the relatively late onset and short duration of strong opioid treatment in cancer patients prior to death. This pattern of prescribing does not match epidemiological data which points to earlier onset of pain that is moderate to severe in intensity for half of all patients with cancer. The clinical implications of this study are clear; within the advanced cancer population there is a need to develop mechanisms to improve pain assessment and initiate a more proactive approach to prescribing, particularly for older patients. One mechanism to achieve this is through earlier integration of palliative care to improve pain control and begin to address the inequalities evidenced here.

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Contributors

LZ, MB, MM, DP and AB, all contributed to study design. MM led the data analysis and DP led the data validation. LZ, MB, MM, DP and AB all contributed to the data interpretation and writing of this paper.

Declaration of interests

All authors LZ, MB, MM, DP and AB have completed the Unified Competing Interest form (www.icmje.org/coi_disclosure.pdf available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

Transparency declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted; and that there have been no deviations from the study protocol

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Figure and Table Legends

Figure 1 legend:

Data presented are the proportion of patients receiving at one prescription event for each of the strong opioid drugs in the last year of life.

*Proportion of 'Any' strong opioid is calculated as the number of patients receiving at least one strong opioid divided by the total number of patients in the dataset (n=6080).

** Other strong opioids were: Rapid release fentanyl, Dipipanone, Dipinanone Meptazinol, Pethadin

Table 1 legend:

Data are presented as n(%) except survival which is median (IQR). Proportions are calculated as row proportions of the 'All' column.

* all p values are derived from chi-squared comparisons (not including the 'All' column) except for survival which is derived from Kurskal Wallis equality-of-populations rank test.† 1=most deprived, 5=least deprived.

Table 2 legend:

* Other strong opioids were: Rapid release fentanyl, Dipipanone, Meptazinol, Pethidine.

Data presented here does not include patients with no prescription events (n=1470).

Data are presented as median (IQR).

Table 3 legend:

All data are presented as odds ratios (95% CI). The early prescription group were the referent category, therefore the model was predicting the odds or receiving a late opioid prescription

*p<0.01, **0<0.001

Table 1 Patient Characteristics

Variable	All n=6080	Prescription Level: No pres' n=1470 (24.2)	Non-opioid / weak opioid n=1691 (27.8)	Strong Opioid n=2919 (48.0)	P*
Age at diagnosis					
<50	414 (6.8)	111 (26.8)	73 (17.6)	230 (55.6)	<0.001
50-59	794 (12.6)	174 (21.9)	172 (21.7)	448 (56.4)	
60-69	1570 (25.8)	358 (22.8)	392 (25)	820 (52.2)	
70-79	2000 (32.9)	500 (25)	585 (29.3)	915 (45.8)	
80-89	1168 (19.2)	294 (25.2)	413 (35.4)	461 (39.5)	
>90	134 (2.2)	33 (24.6)	56 (41.8)	45 (33.6)	
Sex					
Male	3253	783 (24.1)	901 (27.7)	1569 (48.2)	0.933
Female	2827	689 (24.3)	791 (27.9)	1350 (47.8)	
Ethnic description					
White	3836	954 (24.9)	1075 (28.0)	1807 (47.1)	0.01
Not known	2112	476 (22.5)	593 (28.1)	1043 (49.4)	
Other	132	40 (30.3)	23 (17.4)	69 (52.7)	
IMD rank†					
1	1945	436 (22.4)	519 (32.7)	990 (50.9)	<0.01
2	1247	329 (26.4)	334 (26.8)	584 (46.8)	
3	905	241 (26.6)	275 (30.4)	389 (43.0)	
4	1232	292 (23.7)	350 (28.4)	590 (47.9)	
5	748	171 (22.8)	213 (28.5)	364 (48.7)	
Place of death					
Hospital	1949	508 (26.1)	877 (45.0)	564 (28.9)	<0.001
Hospice	1930	395 (20.5)	476 (24.5)	1059 (54.9)	
Patient's home	1619	415 (25.6)	203 (12.5)	1001 (61.8)	
Care home	496	123 (24.8)	120 (24.2)	253 (51.0)	
Other	86	29 (33.7)	12 (17.4)	42 (48.8)	
Cancer site					
Lung	1668	413 (24.8)	400 (24.0)	855 (51.3)	<0.001
Upper GI	933	237 (25.4)	239 (25.6)	457 (49.0)	
Colorectal	796	191 (24.0)	224 (28.1)	381 (47.9)	
Breast	612	131 (20.4)	200 (32.7)	281 (45.9)	
Prostate	579	118 (20.4)	182 (31.4)	279 (48.2)	
Urological	445	104 (23.4)	158 (35.5)	183 (41.1)	
Gynaecological	349	88 (25.2)	100 (28.7)	161 (46.1)	
Head & Neck	252	72 (28.6)	61 (24.2)	119 (47.2)	
Brain & Neurological	144	48 (33.3)	46 (31.9)	50 (34.7)	
Primary Unknown	60	11 (18.3)	14 (23.3)	35 (58.3)	
Other	242	57 (23.6)	67 (27.7)	118 (48.8)	
Survival					
Diagnosis to death (months)	14 (6-34)	13 (5-31)	12 (4-32)	15 (7-37)	<0.001
Oncology treatment					
Surgery					
No	3750	926 (24.7)	947 (25.3)	1877 (50.1)	<0.001
Yes	2330	554 (23.4)	744 (31.9)	1042 (44.7)	
Radiotherapy					
No	3945	931 (23.6)	1166 (29.6)	1848 (46.8)	<0.001
Yes	2315	359 (25.3)	525 (24.6)	1071 (50.2)	
Chemotherapy					
No	3487	876 (25.1)	1088 (31.2)	1523 (43.7)	<0.001
Yes	2593	594 (22.9)	603 (25.3)	1396 (48.01)	
Hormone therapy					
No	5213	1296 (24.9)	1401 (26.9)	2516 (48.3)	<0.001
Yes	867	174 (20.1)	290 (33.5)	403 (46.5))	

Table 2 Median (IQR) weeks elapsed between first prescription event and death.

Variable	Weeks between first prescription event and death
Any prescription type	21 (7-42)
Prescription type	
Non opioids	38 (19-48)
Weak opioids	29 (13-47)
Strong opioids	9 (3-23)
Strong opioids	
Morphine	11 (4-24)
Oxycodone	11 (4-29)
Fentanyl	12 (4-23)
Burpenorphine	16 (5-32)
Diamorphone	1 (1-3)
Other*	24 (9-44)

Table 3

Variable	Predicting late strong opioid prescription
Age at diagnosis	
<50	-
50-59	1.4 (0.9-2)
60-69	1.7 (1.2)**
70-79	2.1 (1.5-2.9)**
80-89	2.7 (1.9-4)**
>90	4.3 (1.9-9.7)**
Sex	
Male	-
Female	0.9 (0.7-1.1)
Ethnic description	
Other	-
White	1.2 (0.7-2)
Not known	1.1 (0.6-1.9)
IMD rank†	
1	-
2	1.1 (0.9-1.3)
3	1.2 (0.9-1.6)
4	0.9 (0.7-1.2)
5	1.3 (1-1.7)
Place of death	
Hospice	-
Hospital	1.4 (1.1-1.7)*
Patient's home	2.6 (2.1-3.1)**
Care home	2.8 (2.1-3.9)**
Other	1.7 (0.9-3.2)
Cancer site	
Lung	-
Upper GI	1.2 (0.9-1.6)
Colorectal	1.2 (0.9-1.6)
Breast	1.3 (0.9-2)
Prostate	0.5 (0.3-0.8)**
Urological	0.9 (0.6-1.3)
Gynaecological	1 (0.7-1.5)

Variable	Predicting late strong opioid prescription
Head & Neck	1.2 (0.8-1.8)
Brain & Neurological	4 (1.9-8.5)
Primary Unknown	2.1 (0.9-4.4)
Other	1 (0.7-1.6)
Survival	
Diagnosis to death (months)	0.9 (0.9-0.9)**
Oncology treatment	
Surgery	
No	-
Yes	1.4 (1.1-1.7)*
Radiotherapy	
No	-
Yes	0.7 (0.6-0.9)**
Chemotherapy	
No	-
Yes	0.7 (0.6-0.8)**
Hormone therapy	
No	-
Yes	0.9 (0.6-1.5)

Figure 1 Proportion of patients receiving at least one prescription event by strong opioid category

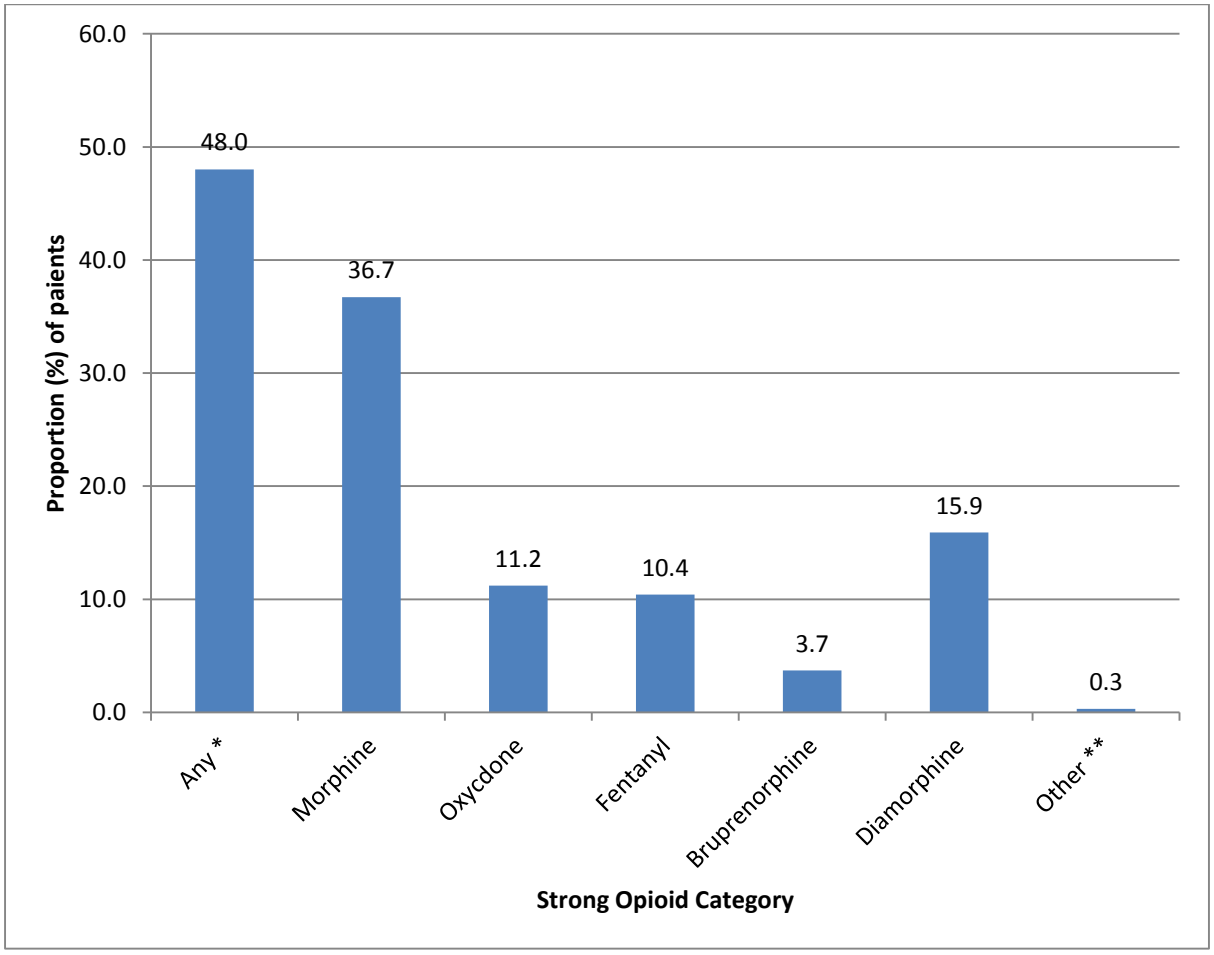

Figure 2 Cumulative proportion of patients prescribed analgesics week by week for the last year of life

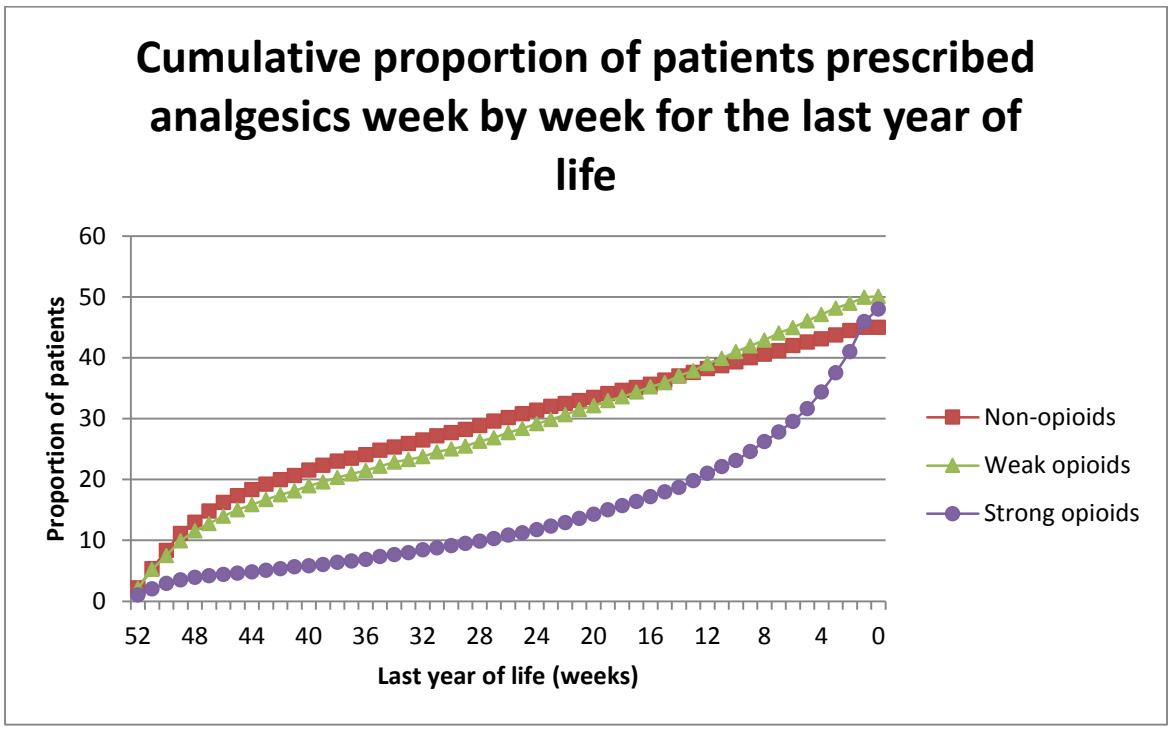

Figure 3
Proportion of patients (%) who receive an early or late strong opioid prescription by age at diagnosis.