U.S. Opioid Prescribing Trends for Adolescent and Young Adult Cancer Patients in Last Year of Life, 2002 – 2016: A Study from the Clare Project

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A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2018

Committee:

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Program Authorized to Offer Degree:

School of Public Health, Health Services

University of Washington

Abstract

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Research Objective/Background: Moderate to severe cancer pain affects most cancer patients, including >70,000 adolescent and young adult (AYA) cancer patients diagnosed annually between the ages of 15 – 39. Opioid medications are often used to treat cancer-related pain, especially in the last year of life. Yet, limited pain management research at end of life for AYA populations is available on a national scale to understand variation and trends, especially for opioid prescription patterns.

Study Design: We conducted a retrospective cohort study of AYAs with a cancer claim at ages 15– 39 years from 2002– 2016 who were enrolled in a health insurance plan for at least 365 days before death. All patients were commercially insured by one of the largest US health insurers, and in Optum administrative data, a purchased dataset. Data included medical service claims,

outpatient pharmacy services and patient information. We extracted data on all filled prescriptions for opioid and opioid partial analgesics based on National Drug Classification codes for every deceased patient during the 30 and 365 days prior to death and describe opioid prescription patterns and trends. We classified opioid prescriptions using the following established categories to examine prescriptions by type and strength: (1) Extended Release/Long Acting (ER/LA) Schedule II opioid, (2) short-acting Schedule II opioid, and (3) short-acting non-Schedule II opioid.

Principal Findings: Our cohort included 4,217 deceased AYA cancer patients; we excluded individuals who were not enrolled for the entire year prior to death (n=989) and individuals with no prescription records (n=189). Mean age at death was 33.6 years and 51% were women. In the last year of life, 30.5% of patients were prescribed ≥ 1 or more ER/LA opioid, 54.1% were prescribed ≥ 1 Schedule II opioid and 24.6% were prescribed ≥ 1 non-Schedule II opioid. ER/LA opioids, considered the strongest opioid category, were prescribed closer to death than other opioid categories; for patients who received at least 1 ER/LA opioid prescription, the median interval between first prescription during the last year of life and death was 22.3 weeks (IQR 10.7 – 41.9). Age at death was significantly related to a later (closer to death) first ER/LA opioid prescription, $p = .004$. Compared to patients age 15-19 at death, patients who were older at death (35-39 and 40-52) tended to receive an earlier first ER/LA prescription in the year before death. Results were similar for Schedule II opioids, where patients who were older at death tended to receive an earlier first Schedule II opioid prescription, $p<0.014$.

Conclusions: Our findings suggest that a high proportion of AYA patients are receiving an opioid in the last year of life, and the proportion with a filled prescription is correlated to age at

death. Our results provide a first look at opioid prescription use among deceased AYA cancer patients in the US, including frequency of opioid prescriptions filled.

Implications for Policy or Practice: Proper pain management using opioids for cancer patients experiencing moderate to severe pain in their last year of life is crucial for maintaining quality of life. AYA cancer patients have specific opioid needs and considerations than people with chronic non-cancer pain, and research, policies and practices should reflect these differences.

1. Introduction

For all cancer patients, including adolescent and young adult (AYA) cancer patients in the US who are diagnosed between the ages of 15 – 39, pain is a common and incredibly complex symptom. (Greco et al., 2014; Deandrea, Montanari, Moja & Apolone, 2008). Cancer pain affects at least 50% of all patients and about 75% of patients with advanced disease (Greco et al., 2014). Research suggests pain increases in advanced stages of cancer due to compounding biological, psychological and social factors, including tumor growth, organ failure, tissue damage, treatment side effects, and more (Davis & Walsh, 2004). A recent Australian retrospective cohort study reported that in a single AYA palliative care center, 91% of all AYA cancer patients reported pain, with 36% reporting severe pain, 33% reporting moderate pain and 21% reporting mild pain (Hughes et al., 2015). These numbers are particularly concerning as these are AYA patients in palliative care, a health services specialty approach that focuses on improving quality of life of patients with life-threatening illness and providing relief of at the end of life ("World Health Organization," n.d.).

Appropriate pain management is a complex, iterative and individualized process dependent on several compounding factors such as disease stage and type, pain mechanism, treatment options and age (Nresesyan & Slavin, 2007; Greco et al., 2014). Widely accepted guidelines from the World Health Organization (WHO) suggest use of a stepped analgesic ladder by physicians to manage pain: non-opioid analgesics to manage low levels of pain, "weak" opioids for moderate pain, and then immediate or sustained release strong opioids for severe pain (Nresesyan & Slavin, 2007; Portenoy, Zankhana, & Ebtesam, 2010). The opioids suggested in this ladder are almost all Schedule II opioids, a US pharmacological category that identifies substances with highly addictive properties that are also approved for medical purposes ("United States Drug Enforcement Administration," n.d). Opioid-based pharmacotherapy therapy is among the most effective ways to provide adequate pain relief, as seen in 70% – 90% of patients for the treatment of moderate to severe pain in all stages of cancer (Ripamonti et al., 2012; Ziegler, Mulvey, Blenkinsopp, Petty, & Bennett, 2016). However, an estimated one-third of all cancer patients are undertreated for their cancer pain, or their pain medication is not proportional to their reported pain intensity (Greco et al., 2014; Ziegler et al., 2016; Deandra et al., 2008).

We know relatively little about AYA cancer patients' health outcomes, including pain management ("Adolescent and young adult," 2006; Hughes et al., 2015). Limited AYA-focused research is available due to the challenges of enrollment in research studies as AYAs are treated in both pediatric and adult settings, because of personal, family and work competing priorities, and due to the relative rarity of AYA cancers ("Adolescent and young adult," 2006; "National Cancer Institute," 2016). Lack of knowledge may be contributing to continued pain undertreatment. In addition to lack of AYA cancer research, there is also growing concern regarding the international opioid crisis, prompting fear of opioid addiction and abuse among non-cancer populations initiated by physicians (Kolodny et al., 2015). Many Americans place a large part of the opioid epidemic blame on physicians and as a result, medical professionals may be hyperaware of the impact of their actions as they write another opioid prescription (Baruch, 2017; Scott, 2017; "Harvard," 2016). Such fears associated with opioid prescribing may also contribute to undertreatment of AYA cancer pain.

To date, there is only one longitudinal study of opioid prescribing patterns in cancer patients (Ziegler et al., 2016). In 2016, Ziegler and colleagues linked prescription data with claims data among a cohort of UK cancer patients aged 18 and over with all cancer types who died from 2002 to 2013. Results indicated opioid use is of relatively short duration and late onset with a median of 9 weeks from first strong opioid prescription to death (Ziegler et al., 2016). The authors concluded that these findings support the hypothesis that many cancer patients are undertreated for their cancer pain. No previous study has looked at opioid prescribing patterns in AYA cancer patients in the US. In this study, we describe opioid prescribing among AYA cancer patients on a national scale to understand the current trends in the US.

2. Methods

2.1. Research questions

What is the onset, extent and duration of opioid prescribing patterns for AYA patients with cancer before death? What patterns and trends describe this cohort in the last year of life?

2.2. Data and study population

We conducted a retrospective cohort study of AYA patients from Optum data. We purchased and analyzed Optum administrative data from 2002 – 2016 for this study, which includes national claims-based data from commercially insured patients from one of the largest US health insurers ("Optum," n.d.). These claims data include de-identified patient characteristics (gender, age at death) and provider, procedure and medical service claims, including outpatient pharmacy service claims.

Our observational cohort includes patients with a cancer diagnosis, determined by emergence of an International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) code during the ages of 15 – 39. We restricted the cohort to 4,217 patients with an observed death who were enrolled at the time of death. Because only month and year of death were available, we used the last day of the month and year as a proxy for specific date of death. We excluded patients with no prescription records (n=189) and patients who were not enrolled under a health insurer for at least 365 days prior to death (n=989) to ensure an adequate period for analysis. With this restriction, our study cohort includes 3,039 deceased AYA patients with a cancer claim at ages 15 – 39 from years 2002 – 2016.

2.3. Measurement of opioids

We extracted data on all prescriptions filled for opioids and partial opioid analgesics by every patient from 2002 – 2016, which were based on National Drug Classification (NDC) codes ("United States Food & Drug Administration," 2017).To examine patterns of opioid prescriptions by type and strength, we classified opioid prescriptions using the following established categories: (1) short-acting non-Schedule II opioid, (2) short-acting Schedule II opioid and (3) Extended Release/Long Acting (ER/LA) Schedule II opioid (Boudreau et al., 2009, Von Korff et al., 2008). "Short-acting" or rapid onset analgesics refer to pain medications that are used generally for the treatment of breakthrough pain, compared to "long-acting" which are used for continuous, round-the-clock pain treatment; in general, opioids that are more potent are categorized under long-acting analgesics (Boudreau et al., 2009). The strength of the opioid prescribed (non-Schedule II, Schedule II) further categorizes opioids based on a drug's medical uses as well as potential for abuse and dependency; Schedule II opioids are considered more potent and addictive than drugs categorized into other schedules ("United States Drug Enforcement Administration," n.d.). We also examined an any opioid category to look at all opioids overall.

2.4. Statistical analysis

We describe the characteristics of AYA cohort by age, sex, region and year of death. Descriptive analysis was conducted to examine opioid prescription of deceased AYA cancer patients by analgesic groups and temporal trends from 2002 – 2016 in the last year of life. Prescription frequencies, number of patients receiving ≥ 1 prescription, and median (Interquartile Range [IQR]) number of prescriptions by patient are described. Timing of prescription before death is presented as the median (IQR) time between the first of an opioid prescription event (in the last 365 days of life) and death to assess when cancer pain management using opioids was initiated in the last year of life.

To examine what kind of relationship existed between age groups at death and first opioid prescription in the year before death among all categories, we conducted linear regression analyses and likelihood ratio tests. In an alternative approach, we also conducted non-parametric tests for trend across ordered groups, as some opioid prescribing patterns were not normally distributed. Linear trend tests were also conducted to look more closely at how age at death was related to a first opioid prescription.

Table 1. Characteristics of deceased AYA patients in last year of life and opioid prescriptions filled in 2002 – 2016 in an insured US cohort

Characteristic	All patients, n = 3,039		1+ any opioid, n = 2, 602[a]		1+ ER/LA, n = 1, 643[b]		1+ Schedule II, n = 2,483[c]		1+ non-Schedule II, n = 747[d]	
Last prescription fill location[e]	No.	%	No.	%	No.	%	No.	%	No.	%
Midwest	804	26%	712	27%	469	29%	680	27%	210	28%
Northeast	268	9%	228	9%	134	8%	215	9%	57	8%
South	1,447	48%	1,223	47%	750	46%	1,168	47%	381	51%
West	513	17%	435	17%	287	17%	416	17%	97	13%
Gender										
Female	1, 543	51%	1,364	52%	894	54%	1,305	53%	424	57%
Age at death										
15 – 19	158	5%	128	5%	71	4%	111	4%	49	7%
20 – 24	182	6%	149	6%	91	6%	143	6%	42	6%
25 – 29	261	9%	227	9%	142	9%	220	9%	67	9%
30 – 34	607	20%	527	20%	345	21%	507	20%	155	21%
35 – 39	1,118	37%	973	37%	624	38%	931	37%	291	39%
40 – 52	713	23%	598	23%	370	23%	571	23%	143	19%

[a] Opioids includes opioid and opioid partial analgesics; multiple opioid prescriptions and types were written per person, e.g. there is overlap between the three opioid categories

[b] Opioid categories, ER/LA: includes Extended-Release/Long-Acting opioid analgesics such as Morphine sustained release/long acting, Fentanyl transdermal, Tramadol ER, Oxycodone HCL controlled release, Methadone, Hydromorphone HCL ER, Oxymorphone HCL ER, Buprrenorphine, Tapentadol hydrochloride (sustained, extended, multiphasic release), Hydrocodone (no acetaminophen, aspirin, or ibuprofen)

[c] Opioid categories, Schedule II opioid analgesics: includes Hydrocodone (with acetaminophen, apap, ibuprofen or aspirin), non-ER/LA Morphine, Codeine or Codeine sulfate, Oxycodone, Buprenorphone (short acting formulations), Hydromorphone HCL, Meperidxine hydrochloride, Fentanyl citrate transmucosal, Oxymorphone HCL, Tapentadol hydrochloride (Nucynta), Levorphanol with/without tartrate, Hydrocodone

[d] Opioid categories, non-Schedule II opioid analgesics: includes Propoxyphene, Codeine with acetaminophen, Tramadol (with or without aspirin), Pentazocine, Codeine with carisoprodol, Butorphanol (with or without tartrate)

[e] US Census Regions

Lastly, we examined how many patients in our cohort received an early or late ER/LA prescription following Ziegler et al.'s methodology of strong opioid analysis, using our cohort's median number of weeks from first ER/LA prescription to death as a cut-off point in the last year for comparison. We also evaluated different age at death groups, since AYA cancer populations can be treated in both pediatric and adult settings. Stata Statistical Software 15.1 was used in this analysis ("StataCorp," 2017). Statistical tests were 2-sided and conducted at a $p < .05$ significance level.

3. Results

3.1. Sample characteristics

In our cohort of 3,039 AYA patients, patients resided in all 50 states, with a majority of patients from US Census region South (47%) **(Table 1)**. Our cohort was also evenly split by gender with 51% female. Most deaths in this AYA cohort were among patients who were age 30 or older, with the highest number if deaths in age group 35 – 39 **(Table 1)**.

3.3 Extent of analgesic prescribing

We found that 49,511 opioid prescriptions were filled among the 3,039 patients in our analysis; 30.5% of patients were prescribed ≥ 1ER/LA opioid, 54.1% of patients were prescribed ≥ 1 Schedule II opioid, and 24.6% of patients were prescribed ≥ 1 non-Schedule II opioid. In our cohort, about 2,602 (86.5%) had filled one or more opioid prescription in the last year of life. The median number of prescriptions per patient was 8 (IQR 1 – 12) and the mean was 8.7. The majority of cohort patients received multiple opioid prescriptions; 2,717 patients had at least 2 opioid prescription types and 466 patients were prescribed all 3 opioid types in their last year of life.

3.4. Timing and duration of strong opioid prescriptions

Schedule II opioids was the earliest prescription type, on average **(Table 2)**; for patients who received at least 1 Schedule II opioid, the median interval between first prescription and death was 36.7 weeks (IQR 21.6 – 47.7) followed by non-Schedule II opioids with a median of 31.7 weeks from first prescription to death (IQR 18 – 43.7). ER/LA opioids, which are considered the strongest opioid category, was prescribed the latest in the timeline during last year of life; for patients who received at least 1 ER/LA opioid prescription, the median interval between first prescription and death was 22.3 weeks (IQR 10.7 – 41.9). Slightly more than half of ER/LA prescriptions are started in the last 6 months of life while short-acting Schedule II and non-Schedule II prescriptions are more commonly initiated prior to the last 6 months **(Table 3)**.

Table 2. Number of weeks between first prescription event and death in the last 365 days of life among AYA patients, 2002 – 2016

Prescription type	Median weeks (IQR)[a] from 1st Rx to death	Mean weeks from 1st Rx to death
Any opioid (n=2,602)	39.6 (24.3 – 48.9)	35.6
ER/LA (n=1, 643)	22.3 (10.7 – 41.9)	25.6
Schedule II (n=2,483)	36.7 (21.6 – 47.7)	33.8
Non-Schedule II (n=747)	31.7 (18.0 – 43.7)	30.5

[a] Interquartile range, or IQR, refers to the 25th percentile and 75th percentile

Table 3. Frequency of 1st opioid prescription filled in the last year of life by time period								
Time before death when 1st opioid was filled	**Any opioid, n= 2,602**		**ER/LA, n = 1,643**		**Schedule II, n = 2,483**		**Non-Schedule II, n = 747**	
	No.	%	No.	%	No.	%	No.	%
Last 0 – 30 days	143	5.5%	301	18.3%	167	6.7%	66	8.8%
Last 31 – 90 days	140	5.4%	203	12.4%	147	6%	54	7.2%
Last 91 – 180 days	433	16.6%	406	24.7%	465	18.7%	162	21.7%
Last 181 – 365 days	1, 886	72.5%	733	44.6%	1,704	68.6%	465	62.3%

Looking at median weeks between first opioid prescription event and death in the last year of life, we saw different patterns based on age at death groups **(Table 4).** We found that age at death by group was significantly related to a later (closer to death) first ER/LA opioid prescription in the year before death (p = .004). Compared with AYA cancer patients aged 15 – 19 years at death, those who were older at death tended to receive a first ER/LA prescription earlier in the year before death **(Table 5).** Patients who died at age 35 – 39 received a first ER/LA prescription 5.0 weeks earlier on average than patients who died at 15 – 19 (95% Confidence Interval [CI], 0.9 – 8.9); patients who died at 40-52 received a first prescription 7.0 weeks earlier than those who died at 15 – 19 (CI, 2.9-11.2); the other comparisons were not significant. Using non-parametric testing to look at age at death by groups (15 – 19, 20 – 24, 25 – 29, 30 – 34, 35 – 39 and 40 – 52), we also found that older age group at death was associated with an earlier first overall opioid prescription during the last year of life (p < .001).

Continuous age at death was significantly related to time from the first ER/LA prescription to death, with an additional 0.22 weeks per additional year of age at death (regression coefficient 0.22 (95% CI, [0.1 – 0.3], p = .0003). Another way to interpret this finding is that for every additional 10 years, age at death was associated with a first ER/LA opioid almost 2 weeks earlier compared to the youngest group.

Table 4. Median (Interquartile range) number of weeks between 1st opioid prescription fill and death in the last 365 days of life, by age at death				
Variable	**1+ any opioid, n= 2,602 (Q1 – Q4)**	**1+ ER/LA, n = 1,643 (Q1 – Q4)**	**1+ Schedule II, n = 2,483 (Q1 – Q4)**	**1+ non-Schedule II, n = 747 (Q1 – Q4)**
Age at death				
15-19	34.7 (16.8 – 45.0)	16 (5.1 – 31.1)	31.1 (18.3 – 43.6)	32.4 (15 – 40.9)
20-24	37.8 (24.6 – 48.9)	18.7 (9.9 – 37.4)	35 (20.9 – 47.7)	30.4 (19.4 – 45.4)
25-29	40.6 (27.7 – 48.1)	20.9 (10.7 – 43.1)	37.5 (25.8 – 50.4)	35.7 (22.1 – 43.3)
30-34	39.1 (23.9 – 48.6)	19.6 (10 – 37.4)	36.7 (21.4 – 47.7)	31.7 (18.1 – 44.6)
35-39	39.4 (23.9 – 49.4)	22.9 (10.4 – 42.9)	36.2 (20.4 – 48.3)	32 (18 – 43.9)
40-52	41.1 (24.9 – 49.0)	25.5 (13.4 – 45.4)	38.9 (23.1 – 47.9)	30.1 (17.1 – 43.9)

Younger age at death was also significantly associated with a later first Schedule II opioid prescription during the year before death (p = 0.014) **(Table 5).** Using age group 15 – 19 as the comparison, older patients were overall more likely to have received a first Schedule II prescription earlier, though the association was not significant for ages 20-24. For example, patients who died between ages 40 – 52 received a first Schedule II prescription about 5.2 weeks (95% CI, 2.2 – 8.2) earlier, on average.

***Table 5**. Age at death and time since first opioid prescription filled during the year before death among AYA patients with cancer: linear regression results*

	ER/LA, n = 1,643		Schedule II, n = 2, 483	
	Coefficient[a]	**95% Confidence Interval**	**Coefficient**	**95% Confidence Interval**
Age at death				
15-19	Comparison Group			
20-24	3.0	-2.0 to 8.0	3.2	-0.4 to 6.9
25-29	4.5	-0.1 to 9.1	5.5	2.1 to 8.9
30-34	3.1	-0.9 to 7.3	4.1	1.1 to 7.2
35-39	5.0	0.9 to 8.9	3.9	1.0 to 1.0
40-52	7.0	2.9 to 11.1	5.2	2.2 to 8.2

[a] Coefficient from linear regression, representing the additional number of weeks to death in the age group, compared to ages 15-19

The non-parametric trend test for Schedule II opioids by age at death groups was also significant ($p < 0.001$). The trend test with age at death as a continuous variable was significant ($p = 0.018$) with a coefficient of 0.11, representing an additional 0.11 weeks from first prescription to death for each additional year of age at death.

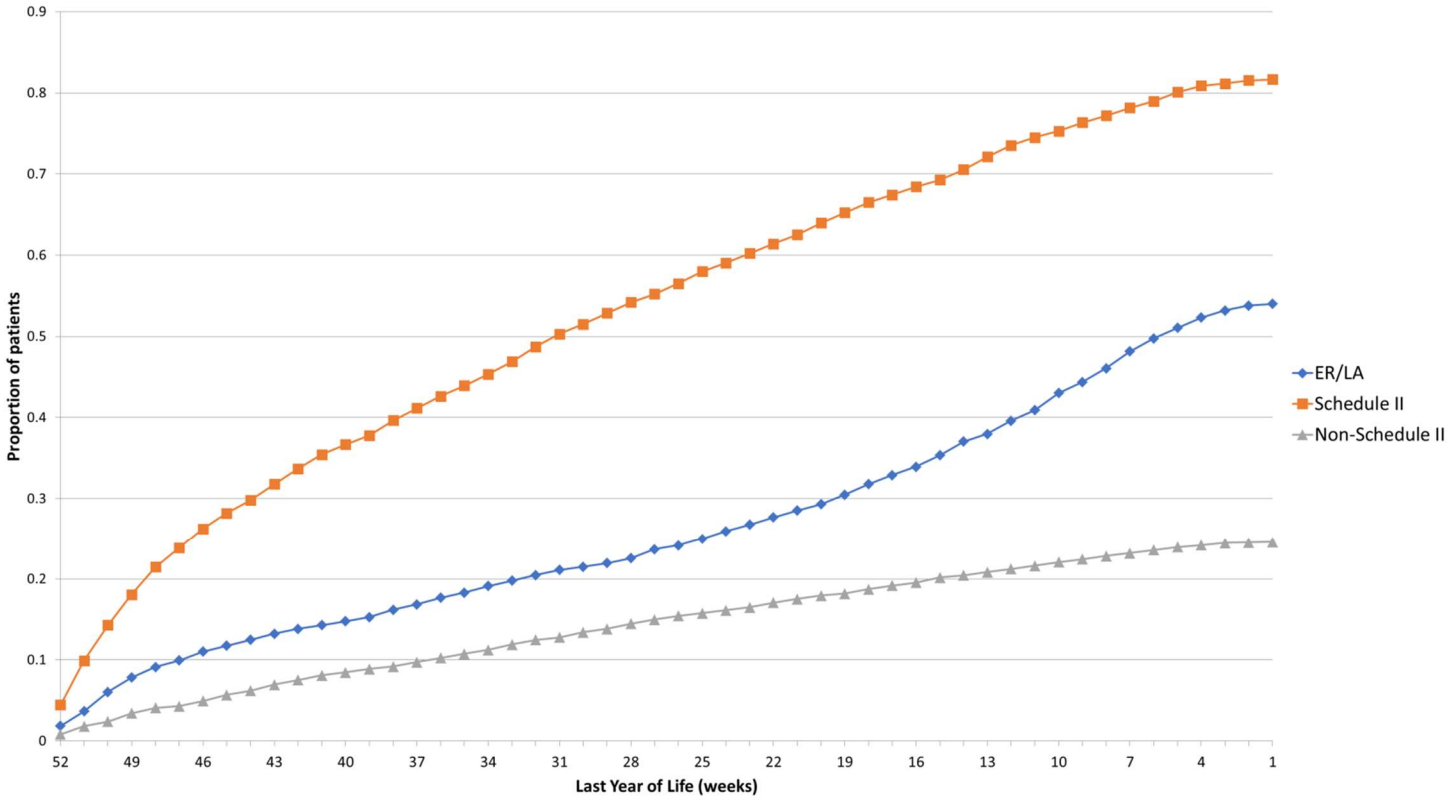
Lastly, the median number of weeks before death of a first ER/LA prescription was 22 weeks, or about 5 months. At 22 weeks prior to death, about 50% of patients had an early ER/LA prescription; **Figure 1** shows this increase at about the midpoint in the last year of life in the AYA cohort.

4. Discussion

In our cohort of AYA decedents, pain management using opioids begins early, specifically with Schedule II opioids at 37 weeks prior to death followed by strong ER/LA opioids at 22 weeks prior to death. Unfortunately, there are no national studies in the US of AYA cancer decedents or even all cancer decedents to compare to. We can only compare our findings to one other study done with older patients in another western country. Ziegler and colleagues evaluated similar questions about opioid prescribing in adults 18 years or older with cancer and subsequent death. In our cohort, nearly all (86%) AYA cancer patients were prescribed at least one opioid analgesic in their last year of life, as compared to 75.8% in the UK (Ziegler et al., 2016). The cohort in Ziegler's study had a higher proportion of cancer patients without any recorded prescription (24.2%) compared to our study (4.5%). However, there could also be different cultural preferences and practices at play, especially with older adults; older and younger patients in the study were equally likely to receive an opioid prescription, whereas in our US cohort, patients were more likely to be on a stronger opioid as they aged. It is also possible that US cancer patients are prescribed more opioids than in the UK or that clinical practices vary greatly between the two countries, though a one-to-one comparison is not possible.

An interesting comparison is to look at the initiation of opioids that are considered the most potent analgesic: UK's Strong opioid category and US' ER/LA opioid category. There is a large difference in time from first powerful opioid prescription to death; 9 weeks (IQR 3 – 23) in the UK and 22 weeks (IQR 10.7 – 41.9) in the US. Looking at this information independently, it appears US medical professionals prescribe a first ER/LA or strong opioid much earlier among cancer patients in the last year of life. Of course, Ziegler's cohort includes only cancer patients of 18 years or older, however, it is still interesting to examine UK and US differences in opioid prescription onset for cancer patients given the growing global concern about overprescribing opioids to different patient groups.

Figure 1. *Cumulative proportion of patients prescribed their 1st opioid analgesic over time during the last year of life* [a]



[a] Last week of life (week 52) includes 8 days because a full year cannot be divided into exactly 52 weeks

We also found that opioid prescribing patterns in the US for AYA cancer patients for different opioid types seem to be reflective of common physician practices and onset of different types of the first prescription are clinically reasonable. We see reflected in this cohort the analgesic ladder approach recommended by the WHO cancer pain management guidelines (Ripamonti et al., 2012; Portenoy et al., 2010; Jadad & Browman, 1995). This stepwise strategy suggests that patients who report mild pain should be started on non-opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), and as a patient reports higher severity of pain they should be prescribed strong opioids and assumes pain increases as patients get closer to end of life (Ripamonti et al., 2012; Portenoy et al., 2010; Jadad & Browman, 1995). Cancer patients commonly report pain, which increases as cancer progresses and according to the Whitecar et. al, "worsening pain is often a sign of worsening disease (p. 5);" we see in the data that a higher overall proportion of first ER/LA opioids are prescribed in the last months of life (Whitecar, Jonas & Clasen, 2000).

Our results also show that age at death is associated with first ER/LA opioid prescription, such that younger AYA patients received their prescriptions later than older AYA patients, indicating a delay in the start of stronger opioids. This disparity may be an indication of undertreatment of younger AYA cancer patients, though it is difficult to conclude definitively using Optum administrative data. There could be a number of reasons for older AYA patients to get earlier opioid prescriptions as compared to younger patients, especially when comparing between age at death groups 40 – 52 and 15 – 19. Doctors may be more concerned about prescribing ER/LA opioids, which are incredibly strong, highly controlled, Schedule II drugs with high potential for abuse and

dependence, to younger cancer patients out of hope they will go into remission (Nersesyan & Slavin 2007). Differences between pediatric and adult oncology provider practices may also play a role; for example some providers may focus on treatment and cure and some on palliative, long-term care depending on the age of the patient and setting where the patient is first diagnosed and/or treated. We found similar results when looking at age at death groups by first Schedule-II opioid prescription, which can be interpreted in a similar fashion. Findings such as this reinforce existing literature that suggests AYA cancer patients need more careful and specific oncology treatment, and should be treated as a specific group rather than lumped in with either pediatric oncology or adult oncology patients ("National Cancer Institute, 2018; "Stupid cancer," n.d.; "Critical mass," n.d.).

5. Conclusions

Our study suggests that the onset of analgesic pain management using opioids, and its timeline in the last year of life for US AYA cancer patients, is clinically reasonable, and that pain management in this population starts early in the last year of life in the United States. In particular, about half of AYA patients in our cohort received their first ER/LA prescription at about 22 weeks, or about 5.5 months, before death. However, since we only focused on first prescription fills in the last year of life, we are unable to comment on whether follow-up pain management is adequate. We suggest that further researchers look at other aspects of pain management such as analgesic refills, renewing opioid prescriptions, etc., among AYA cancer patients at end of life. We can report on initiation of opioid therapies for pain in the last year of life; it is important for physicians to support AYA research and align clinical guidelines with patient need in the management of cancer pain.

Our results provide the groundwork for research by describing the current state of opioid pain medication in AYA patients who have died and highlight the need for continued and in-depth health services research within the AYA population, in particular on the topic of end of life care and pain management ("National Cancer Institute, 2018; "Stupid cancer," n.d.; "Critical mass," n.d.) Challenges to controlling patient pain include guidelines that have not kept pace with changes in cancer and pain research, high incidences of cancer, lack of good clinical trials, and specialized needs for certain undertreated populations, such as AYA patients. Understanding this clinical gap is especially important in the current US context where politicians, doctors and the public are concerned about opioid addiction and opioid overprescribing in non-cancer populations (Ziegler et al., 2016; Greco et al., 2014; "Centers for Disease Control," 2017).

6. Strengths and Limitations

This study is one of the first to look at US AYA cancer patients' opioid prescription profile in a large cohort spanning 15 years with patients in all 50 states. Limitations of using Optum administrative data for analysis include the need to use a proxy for death date, lack of data on age at diagnosis, and limited data on patient characteristics. However, despite these limitations, our results provide descriptive analyses of prescribing patterns in the AYA cancer population that were not available previously. Proper pain management for cancer patients in their last year of life is crucial for improving quality of life, and AYA cancer patients have different opioid needs and considerations than people with chronic non-cancer pain (Hughes et al., 2015; "Adolescent and young adult," 2006) or older cancer patients. This first look provides a foundation of knowledge about pain management among AYA cancer patients in their last year of life and has implications for the development of more effective and tailored control of cancer pain for an often overlooked cancer population.

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