Medication Changes Initiated after Palliative Care Consult in Hospitalized Patients: A Focus on Changes in Analgesic and Chronic Disease Medication Regimens

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Abstract: Literature guiding clinicians on appropriate prescribing as death nears is scarce. The aim of this study was to retrospectively evaluate medication changes implemented after palliative care consultations at two VA (veterans affairs) end-of-life care units. Analysis focused on the change in analgesic and chronic disease medication regimens, including administration route. Sixty patients who received an inpatient palliative care consult and subsequently passed away on the either VA end-of-life care unit between June 30, 2010 and June 30, 2011 were included for analysis. Opioid and non-opioid analgesic medications were distinguished in this study. Medication name and route of administration were documented from inpatient electronic medication profiles up to one week prior to the inpatient palliative care consult (T_{prior}), the day after consult (T_{+1}), and the day of death (T_{death}). Opioid analgesic medications prescribed increased from 0.95 per patient prior to consult to 1.87 at death. Investigators observed a shift away from oral opioid analgesic formulations to intravenous and subcutaneous push as the preferred routes of administration at time of death. Chronic medications decreased from 5.15 per patient prior to consult to 1.23 at death. The overall increase in analgesic medications at time of death reflects a focus on symptom management and comfort care in this special population. Trimming of non-essential medications is a patient-specific art and continued efforts should be made to reduce pill burden by removing medications that are not directly related to comfort-care in the palliative patient as death approaches.

Key words: Opioid, analgesic, medication, palliative care, hospice, end-of-life, de-prescribing, subcutaneous.

1. Introduction

Hospice and palliative care are unique approaches for patients whose goals are no longer curative in nature, shifting the focus from interventional medical techniques to pain relief, comfort, and enhancing quality of life [1]. While palliative programs have been shown to improve end-of-life care, literature for appropriate medication prescribing in patients nearing death is scarce. Terminally ill patients are frequently

continued on standard medical care, an effort that may inadvertently worsen end of life issues [2]. There is little discussion of rational prescribing at the end-of-life in such patients and guidelines in chronic disease care with less stringent treatment targets as death approaches are lacking [3, 4]. When a palliative care approach is chosen, the patient's estimated remaining life expectancy should be weighed against the time until drug risk and time until drug benefit for both chronic and symptom-specific medications. Indeed, hospice and palliative care programs can offer a "good death" and have been shown to improve the patient's quality of care and lead to higher family

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satisfaction [5, 6].

The purpose of this study was to retrospectively evaluate medication changes implemented after inpatient palliative care consultations within the NF/SG VHS (North Florida/South Georgia Veterans Health System). Within this health system are two well-respected inpatient end-of-life care units, Starlight Way Palliative Care Unit at the Malcom Randall VAMC (veterans affairs medical center) and Serenity Place Hospice Unit at the Lake City VAMC. At time of data collection and analysis, the end-of-life care units combined for a total of 28 beds. Medication analysis specifically focused on documenting changes in analgesic and chronic disease state medication regimens (including route of administration) as death neared for hospitalized patients who accepted a palliative care treatment approach and were subsequently transferred to either inpatient care unit. Study investigators hypothesized a marked decrease in the number of chronic disease medications utilized (also termed “trimming” of non-essential medications) as death approached as well as a marked increase in the number of analgesic medications employed for symptom management of this special population.

2. Patients and Methods

This work was supported by resources provided by the NF/SG VHS (North Florida/ South Georgia Veterans Health System). Specifically, the study protocol was approved by the Veterans Affairs Research and Development committee as well as the University of Florida Institutional Review Board. The study population was selected from deceased end-of-life care unit patients at the Malcom Randall

VAMC Palliative Care Unit and Lake City VAMC Hospice Unit. In order to be eligible for the study, the patient must have received an inpatient palliative care consult, been transferred to either inpatient end-of-life care unit, and passed away on the unit between June 30, 2010 and June 30, 2011. Outpatient hospice and palliative care consults were excluded as actual medication administration/real-time prescribing is not as easily evaluated in this population. For the same reason, patients who received inpatient palliative care consults and were subsequently discharged to home hospice or other non-VA end-of-life care unit were also excluded. Thirty patients from each end-of-life care unit who met study criteria were randomly selected for review.

The patients’ medication changes were evaluated by recording active analgesic and chronic medications up to one week prior to the palliative care consult (T_{prior}), the day after palliative care consult (T_{+1}), and the last day of life (T_{death}). Medication administration records were retrospectively evaluated through evaluation of electronic medical records readily available in this health system. Patients’ age at death, terminal diagnoses, and gender were also recorded (See Table 1). Data collection included the name of medication, route of administration, and indication (whether for chronic disease, disease prevention/prophylaxis, symptom management, antibiotics), and time with respect to date of consult and date of death. Table 2 provides examples of common medications under each of the four medication

Table 1 Characteristics of patients.

No. of Patients	60
Average Age (yrs)	72.5
Gender M/F	59/1

Table 2 Classification of medications.

Medication Category	Examples*
Chronic medications	Anti-hypertensives, HMG-CoA Reductase inhibitors (statins), hypoglycemic agents, aspirin
Disease prevention/ prophylactic medications	Subcutaneous heparin, proton pump inhibitors, sliding scale insulin, topical ointments and creams to limit skin breakdown
Symptom specific medications	Analgesics, anxiolytics, constipation regimens, fluid/electrolytes
Antibiotics/antifungals	Short term oral and intravenous antibiotic or antifungal therapies such as vancomycin, piperacillin/tazobactam, fluconazole and cephalixin

*Not an exhaustive list.

classifications/indications employed in this study.

Data points as described above were collected and entered in a Microsoft Excel spreadsheet by the study investigators. Investigators subsequently utilized descriptive statistics to summarize and compare data for discussion.

3. Results

Two hundred and twenty three patients died on the palliative care units between the designated study dates. One-hundred and sixty patients were excluded for reasons including initial inpatient palliative care consult outside study time period, patients who received outpatient palliative care consults, patients discharged from hospital to either home or alternative

inpatient hospice, and those who died prior to transfer to either VA's inpatient end-of-life care unit. Eighty-seven patients met study criteria. Of the sixty patients randomly selected for inclusion, fifty-nine were male with an average age of 72.5 years. Terminal diagnoses varied greatly including, but not limited to, lung cancer, dementia, congestive heart failure, chronic kidney disease, and pneumonia.

The mean number of total analgesics per patient increased from 1.90 prior to consult to 3.17 on the last day of life. Specifically, opioid analgesics increased from 0.95 per patient prior to consult to 1.87 at death. Non-opioid analgesics increased from 0.95 per patient prior to consult to 1.30 at death. Table 3 describes the number of patients receiving opioids by specific routes

Table 3 Number of patients receiving different opioids and route of administration at T_{prior} , T_{+1} , and T_{death} .

	PO IR	PO SA	IV push	SQ push	TTS	PCA/CADD	Total
T_{prior}							
Codeine	1	-	-	-	-	-	1
Fentanyl	0	-	2	0	6	0	8
Hydrocodone	1	0	-	-	-	0	1
Hydromorphone	0	0	3	0	-	1	4
Methadone	0	0	0	0	-	0	0
Morphine	5	2	14	0	-	0	21
Oxycodone	21	1	0	0	-	0	22
Total	28	3	19	0	6	1	57*
T_{+1}							
Codeine	0	-	-	-	-	-	0
Fentanyl	0	-	1	0	9	1	11
Hydrocodone	3	0	-	-	-	0	3
Hydromorphone	2	0	15	11	-	4	32
Methadone	0	1	0	1	-	0	2
Morphine	2	3	23	7	-	2	37
Oxycodone	16	0	0	0	-	0	16
Total	24	3	39	19	9	7	101*
T_{death}							
Codeine	1	-	-	-	-	-	1
Fentanyl	0	-	1	0	15	1	17
Hydrocodone	1	0	-	-	-	-	1
Hydromorphone	5	0	15	20	-	2	42
Methadone	0	0	0	5	-	0	5
Morphine	2	1	21	6	-	6	36
Oxycodone	12	0	0	0	-	0	12
Total	21	1	37	31	15	9	114*

*Study patients could receive more than one opioid analgesic, therefore total opioids prescribed for each study time period could exceed 60 (number of total patients).

Abbreviations: PO, oral; IR, immediate release; SA, sustained action; IV, intravenous; SQ, subcutaneous; TTS, transdermal; PCA, patient controlled analgesia; CADD, continuous ambulatory delivery device.

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Table 4 Number of chronic medications by class at T_{prior} , T_{+1} , and T_{death}

Medication Class	T_{prior}	T_{+1}	T_{death}
Anti-hypertensives	47	34	12
Antiplatelet (Aspirin)	37	11	1
Respiratory (COPD/asthma)	36	25	10
Psychotropics (Antidepressants, anxiolytics)	31	16	5
Vitamin Supplements	29	8	0
Acid Reducers (PPIs, H2RAs)	20	13	8
Alpha Blockers (BPH)	13	8	1
HMG CoA Reductase Inhibitors	10	3	0
Thyroid Modulators	13	9	8
Intraocular Pressure Reducers	8	6	3
Hypoglycemics	8	8	7
Miscellaneous (frequency < 3)	57	50	19
Total	309	191	74
Average per patient	5.15	3.18	1.23

Abbreviations: COPD, chronic obstructive pulmonary disease; PPIs, proton pump inhibitors; H2RAs, histamine 2 receptor antagonists; BPH, benign prostatic hypertrophy.

of administration throughout the focused study time points. Oral oxycodone immediate release was the most commonly prescribed opioid analgesic prior to palliative care consult. Overall, oral opioid analgesics represented 54% of all prescribed opioids prior to consult. There were no subcutaneous analgesic medications prescribed prior to consult and intravenous nurse push administration (predominantly morphine) represented one third of the prescribed opioid analgesics prior to consult. At death, oral opioids represented only 19% of all prescribed opioids. Further, opioid analgesics administered as intravenous or subcutaneous nurse push combined for nearly 60% of all prescribed opioids (32% and 27%, respectively) at time of death. Patients prescribed PCA (patient controlled analgesia) including that via CADD (continuous ambulatory delivery device) were reported separately from nurse intravenous and subcutaneous administration. The remaining 21% of opioids active at time of death were administered via PCA/CADD (8%) or topical transdermal systems (fentanyl patch, 13%).

Medications prescribed for chronic disease states decreased from 5.15 per patient prior to consult to 1.23 at death. Table 4 describes the number of chronic medications prescribed throughout the focused study time points, specified by medication class. Prior to

consultation, anti-hypertensive medications were the most commonly prescribed class of chronic medications followed by aspirin and COPD/asthma medications. The most common chronic medications continued until death included anti-hypertensive and COPD/asthma medications.

The frequency of intravenous fluid and electrolyte replacement was recorded with initial data collection. Study results here focus on analgesic and chronic disease-state regimens; however, authors would like to report that ten patients had active orders for intravenous fluids prior to palliative care consult; four had active orders the day after the palliative care consult, but no patient died with active orders for intravenous or subcutaneous hydration. Similarly, twenty patients had active electrolyte replacement orders prior to consult, eight received such orders the day after the palliative care consult, but no patient died with active orders for electrolyte replacement on either end-of-life care unit.

4. Discussion

The process of “trimming” or deprescribing non-essential medications in end-of-life care is not a commonplace practice and may be viewed as a patient-specific art. Moreover, targeted guidelines on

medication use to treat chronic and acute disease states in the terminally ill are not widely available and current data suggests potentially inappropriate medicines are continued in terminally ill patients [7-9]. However, since study completion, a deprescribing guideline for a targeted population was proposed by Lindsay et al in a 2015 study evaluating discontinuation of medications in palliative cancer patients [10]. Patterns of deprescribing identified in this retrospective study are consistent with recommendations outlined in Lindsay et al's OncPal Deprescribing Guideline.

Investigators anticipated the decline in chronic medications as death approached as both palliative care teams make an effort to discontinue non-essential medications. This was demonstrated as investigators found no active orders for HMG-CoA reductase inhibitors (statins) or vitamin supplements (multivitamin, cyanocobalamin, folic acid, iron) at T_{death} (day of death). Many chronic medications continued until death are also utilized to treat symptoms. Examples include conditions such as dyspepsia, hypothyroidism, depression, and anxiety. Proton pump inhibitors and H2 receptor antagonists should be considered for discontinuation in all patients without symptomatic gastritis or reflux, but are likely to be continued if patients have active symptom management concerns related to these disease states. Also, it is reasonable to discontinue low-dose aspirin when used for secondary prevention, unless the patient is wedded to its use. While the percentage of anti-hypertensives at death may seem high at first glance (16.2%), this is equivalent to 12 total anti-hypertensive medications among the 60 patients at death. Further, included in this data set are the anti-hypertensive classes of beta blockers and calcium channel blockers which may have been maintained on the profile as they were slowly tapered to limit rebound tachycardia.

The number of analgesics medications increased. Fifty-five of the 60 patients died with active orders for opioids for pain or dyspnea. The overall increase in

analgesic medications as death neared highlights a focus on symptom management and comfort care. Also, the use of analgesics to target symptom management other than pain, may further explain the increase observed. For example, opioid analgesic medications are thought to help relieve dyspnea, or a patient's feeling of breathlessness. It is a misconception that opiate/opioid medications should be avoided in patients with difficulty breathing secondary to terminal conditions like COPD, pulmonary fibrosis, CHF, and lung cancer. In fact, the preferred treatment for the relief of refractory dyspnea is a systemic (oral or parenteral), low dose opioid (level 1 evidence) [11-12]. The proposed mechanism for opioids in treating dyspnea seems to be related to central reduction in ventilator demand leading to altered perception of the breathlessness. In other words, opioids may reduce the regulatory drive caused by increase in CO_2 levels [13]. The patient subsequently feels less air hunger, even if breathing is not improved.

A further explanation of the increase in opioid medication prescribing before (T_{prior}) as compared to after palliative care consult (T_{+1} , T_{death}) may be related to palliative care specialty teams being more comfortable prescribing a range of opioid analgesics. Specifically, no patients were receiving methadone therapy prior to the palliative care consult; five of sixty patients died on an end-of-life care unit with active orders for methadone. Methadone is a versatile opioid analgesic secondary to multiple mechanisms of action beyond that at the opioid receptor (NMDA receptor antagonist, 5HT/NE reuptake inhibitor, for example). Complicated pharmacokinetics result in much fear around its use and only those familiar with methadone and the care needed with titrations should be utilizing this medication. Further, the number of patient receiving therapy with the fentanyl patch nearly doubled from the time prior to consult (T_{prior}) to time of death (T_{death}). Palliative care team members may be more experienced with both titration and general use of fentanyl patches in cachectic and opioid naïve patients.

Particular barriers exist for professionals working outside specialty pain, palliative or hospice care and include concerns about giving high doses and having insufficient training in opioid use; working partnerships between specialist and palliative care teams are important for increasing generalist confidence in prescribing [14].

The decline in the oral route of medication administration across the study time period highlights the importance of having an early plan with alternative routes of medication administration in place on patients' active orders; many patients may develop difficulties with swallowing associated with terminal illness and the dying process. Further, the oral route of medications has a slower onset to effect as compared to intravenous and subcutaneous routes and is therefore not preferred when comfort care needs dictate rapid medication action. The subcutaneous administration route for comfort care medications is not well known outside of the palliative care/hospice specialties. This route has not been fully studied and many of the medications commonly employed are used off-label [15]. Study authors have had great success with the use of haloperidol, morphine, hydromorphone, methadone, lorazepam, dexamethasone and ondansetron via the subcutaneous route. There is no known difference in efficacy when comparing intravenous to subcutaneous administration. The intravenous route was a common form of administration for patients in this study who already had IV access (whether peripheral line versus more permanent line including a PICC (peripherally inserted central catheter)). However, it is not routine practice to replace lost or sluggish intravenous lines at the two end-of-life care units in this study as the subcutaneous route has proven very effective, simple, and minimally invasive.

There is inconsistent data regarding the benefit/burden ratio of artificial nutrition at the end-of-life. Study investigators have observed worse outcomes in patients where artificial hydration is continued in the last hours to days of life. Specifically,

reduced oral intake is recognized as a normal phenomenon in the dying process [16]. The dying patient's body may not accept artificial hydration, leading to fluid overload and third spacing. Open communication with patients and families is paramount and medical providers must consider individual values and preferences.

5. Limitations

Medication changes were evaluated using the active medication list for patients at "snap shots" in time (T_{prior} , T_{+1} , T_{death}). Medications may have been held by nursing staff or declined by the patient, especially as death approached; however, all active medications, regardless of nurse holds, were included in this analysis to better capture prescribing patterns. Further, palliative care consult team recommendations are implemented when there is agreement between the palliative care team, primary care team (prior to patient being transferred to palliative care unit) and the veteran or veteran's family. In addition, the classification of medications warrants discussion. The same investigator classified all medications based on diagnoses listed in the "problems" feature within the electronic medical record as well as outpatient medication history. Single-investigator classifications were utilized to reduce risk of inconsistencies. Lastly, limited generalizability must be acknowledged due to population being predominantly elderly and male. Average age among 60 patients was 72.5 years old with only 1 female veteran. Investigators anticipated an over-representation of elderly, male lung-cancer patients. However, terminal diagnoses widely ranged and researchers hope to investigate medication prescribing trends in specific terminal diagnoses in the future. The small study sample size can also be viewed as a limitation.

6. Conclusion

As Currow et al [4] have pointed out, results indicating a decline in the number of chronic

medications and an increase in analgesics in a palliative care population as death nears may seem intuitive; however, literature guiding clinicians on appropriate prescribing in patients with limited life expectancy is scarce. Investigators aimed to describe medication prescribing patterns in terminally ill patients, specifically analgesic and chronic disease- regimens, at two VA end-of-life care units, including changes in routes of medication administration. Study results suggest an increase in the range of analgesics in the dying patient, with a shift away from oral formulations. The overall increase in analgesics as death neared reflects a focus on symptom management and comfort care in this special population. Certainly, trimming of non-essential medications is a patient-specific art. While uniform guidelines are not used at the two end-of-life care units involved in this study, continued efforts are made to reduce pill burden in the dying patient by removing medications that are not directly related to comfort-care. As van der Cammen et al [9] concluded, there is a need to develop consensus criteria to assess appropriate versus inappropriate medication use for individuals at the end of life [7].

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