JAMDA xxx (2016) 1–5

JAMDA

journal homepage: www.jamda.com

Original Study

Changes in Prescribed Drugs Between Admission and the End of Life in Patients Admitted to Palliative Care Facilities

Ronald T.C.M. van Nordennen MD [a,*], Jan C.M. Lavrijsen MD, PhD [b], Malou J.A.B. Heesterbeek MD [c], Hans Bor BSc [b], Kris C.P. Vissers MD, PhD, FIPP [d], Raymond T.C.M. Koopmans MD, PhD [b,e]

[a] *Groenhuysen Organisation, Roosendaal, The Netherlands*
[b] *Radboud University Medical Centre, Nijmegen, The Netherlands*
[c] *Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands*
[d] *Radboudumc Expertise Centre for Pain and Palliative Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands*
[e] *Joachim en Anna, Centre for Specialized Geriatric Care Nijmegen, The Netherlands*

Keywords:
End-of-life care
medication use
comorbid disease

A B S T R A C T

Background: The aim of prescribing medication in palliative end-of-life care should be symptom control. Data are lacking regarding the prescription of medication at the end of life.
Aim: To investigate the prescription of medication in patients at the end of life in palliative care facilities.
Design, setting, and participants: An observational multicenter study in 7 inpatient palliative care facilities. Participants were adults with an estimated life expectancy of less than 3 months. The study was conducted from February 1, 2012, to January 1, 2013.
Results: A total of 155 patients were enrolled. On average, patients were prescribed 6.1 drugs at the moment of admission and 4.6 drugs on the day of death. The prescription of analgesics, psycholeptics, and drugs for functional gastrointestinal disorders increased from admission until death. In general, these are drug classes prescribed for symptom control. All other drug classes decreased between admission and the day of death, including different drug classes for the treatment of comorbid disease, such as anticoagulants, beta-blocking agents, drugs used in diabetes, and lipid-modifying agents.
Conclusions and relevance: A reduction in the total amount of medication is seen between admission and death in the palliative care facilities. Although there is an increase in prescribed symptom-specific medication and a reduction in medication prescribed for comorbid disease, there are still patients dying with medication not used for symptom control. This increases pill burden and indicates that physicians need to develop guidelines and educational programs for decreasing medication for comorbidities at the end of life.

Patients with life-limiting diseases, such as cancer, terminal heart failure, or terminal chronic obstructive pulmonary disease (COPD), are sometimes admitted to palliative care facilities at the end of their lives. Often, these patients also have several comorbidities. The prevalence of comorbidities in unselected community-dwelling patients with cancer is reported to be 63% in patients older than 75 years and is the highest for patients with lung cancer.[1] The most frequent comorbidities are cardiovascular diseases, hypertension, and diabetes mellitus, with prevalence rates of 10% to 30%, 11% to 25%, and 5% to 25%, respectively, depending on the type of tumor.[1]

Consequently, patients in need of palliative care are prescribed several drugs.[2] In general, 2 types of drugs are prescribed: symptom-specific medication (SSM), such as analgesics for the treatment of pain, and medications for specific comorbidities, such as lipid-modifying agents in cases of hypercholesterolemia.[3] The latter are often prescribed for chronic use to prevent disease. Polypharmacy, defined as the simultaneous use of more than 5 different medications, is highly prevalent in patients receiving palliative care, resulting in many problems, such as unwanted drug-drug interactions, adverse effects, noncompliance because of pill burden, and increased costs.[4,5] The indication, purpose, appropriateness, and usefulness of several of these drugs can be questioned for patients on a palliative trajectory,

The authors declare no conflicts of interest.

* Address correspondence to Ronald T.C.M. van Nordennen, MD, Groenhuysen Organisation, PO 1596, Roosendaal 4700 BN, The Netherlands.
E-mail address: ronald.vannordennen@radboudumc.nl (R.T.C.M. van Nordennen).

http://dx.doi.org/10.1016/j.jamda.2016.01.015
1525-8610/

particularly in the final period preceding death. Recently, it was shown that several factors should be weighed to make treatment decisions regarding the appropriateness of the medications, such as remaining life expectancy, goals of care, treatment targets, time until benefit, number needed to treat/harm, and adverse drug reactions.[6] Medication that does not benefit the patient in the short term should be avoided because the primary aim of medications at the end of life should be symptom control and not the prevention of disease.[6] However, specific guidelines or recommendations regarding the prescription of medication at the end of life are lacking.[7] Furthermore, more attention for the discontinuation of unnecessary medication in terminally ill patients is warranted.[8,9] The beneficial effect of several drugs, such as statins, antihypertensive agents, anticoagulants, and antihyperglycemic agents are highly questioned in patients with a short life expectancy. However, specific research studying the appropriateness and usefulness of different drugs at the end of life is scarce.[10] A recent study found that discontinuing statin therapy at the end of life was safe and even improved quality of life.[11] However, existing research mainly focuses on geriatric patients, who only partly overlap with patients in need of palliative care. One study about the use of statins in patients with end-stage dementia in nursing homes found that it was difficult for physicians to make a decision about stopping these medications, even if they knew the agents can cause muscle pain and do not contribute to the quality of life.[12,13] Among nursing home residents with advanced dementia, 53.9% received at least 1 medication with questionable benefit.[13]

Examples of patients using inappropriate drugs in palliative care indicate to physicians that adapted drug management may improve quality of life and reduce unnecessary pharmacotherapy.[14] The knowledge and education physicians have in the field of appropriate prescription at the end of life might play a role in the awareness of this specific topic. In the Netherlands, specialized elderly care physicians (ECP) are trained in a 3-year specialist training program, including palliative care issues and issues of polypharmacy and medication use in frail elderly at the end of life.[15] In this typical Dutch context in which ECPs are the primary responsible physicians in most hospices and palliative care units of nursing homes, we expect to observe a shift in focus in these settings toward drugs for relieving burdensome symptoms and a reduction in medication for comorbidities because these agents are less appropriate.

In this study, we aimed to observe specific changes in prescribed drugs in patients admitted to a palliative care facility between the day of admission and the day of death.

Methods

We conducted an observational multicenter cohort study with follow-up until death that investigated drug use in 7 “inpatient palliative care facilities” in the middle and southern part of the Netherlands: 6 hospices (1 free-standing hospice and 5 hospices that are part of a long-term care organization) and 1 palliative care unit in a nursing home, with a total capacity of 66 beds. Patients can be admitted to these facilities when their estimated life expectancy is less than 3 months. The inclusion period was between February 1, 2012, and September 1, 2012, with follow-up until January 1, 2013.

A regional medical ethics committee rendered the study not subject to ethical research legislation because in accordance with the criteria of the Dutch Medical Research Involving Human Subjects Act, no medical scientific research was involved. All participating patients or their representatives, ensured of their anonymity, gave their verbal informed consent.

All newly admitted patients in the given period were included in the study. Inclusion criteria were being older than 18 years and being able and willing to provide verbal informed consent. Patients unable to consent or without a legal representative present were excluded. Data were collected by the attending ECP. The first author instructed the physicians before the start of the study. The authors had no relationship to the prescribers. Data collection consisted of patient characteristics: gender, age, residency before admission, current medical diagnoses including all comorbidities if present, and type of malignancy and main diagnosis for admission to the palliative care facility. Diagnoses were coded using ICD-10 classification.[16] Main diagnosis was defined as the disease that, according to the ECP, is expected to be responsible for the estimated reduction in life expectancy and was therefore the primary reason for admission. The current medical diagnoses refer to comorbidities. The ECP collected medication lists of hospitals or general practitioners at admission. The electronic medical prescriptions of all oral, rectal, and parenteral drugs were photocopied or printed during the stay in the palliative care facility until death. For the classification of all drugs, the “Anatomic-therapeutic-chemical classification of drugs” was used.[17] Dose, frequency, and pro re nata use (prn) were registered; prn medication was defined as medication not regularly prescribed with a daily dose but available in time of need (eg, pain, shortness of breath).

Medians, means, and frequencies were calculated to describe the patient characteristics and drug use. Both the use of individual drugs and the use of drugs from different drug classes were reported at admission and on the day of death. We also reported the changes in drugs from different drug classes between admission and death. SPSS 20.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL)was used for analysis.

Results

Demographics of the Study Population

In total, 177 patients were admitted during the inclusion period, of whom 22 were excluded because they were discharged or were still alive at the end of the study. At the end of the follow-up period, 155 patients had died (study population), with a median stay of 13 days (range 0–235) and mean stay of 26.4 days until death (SD 36.9). The study population consisted of 87 (56.1%) men. The mean age at admission was 75 years (SD 11.6). The youngest patient was 31, and the oldest was 95. Most were admitted from nonacademic hospitals or from home. Cancer was the most frequent main diagnosis (81.3%), with the most prevalent types being cancer of the digestive or respiratory tracts. The most frequent comorbid diseases were heart failure, COPD, hypertension, and diabetes mellitus (Table 1).

Drugs Prescribed at Admission and on the Day of Death

On average, patients were prescribed 6.1 (± SD 3.7; range 0–19) drugs at admission. Three patients had no drugs prescribed. The most prescribed drug classes were analgesics (63.2%), drugs for acid-related disorders (51.6%), psycholeptics (39.4%), and laxatives (38.7%). Lipid-modifying agents were used by 8.4% and drugs for diabetes by 12.9% of patients. On admission, beta-blocking agents were used by 25.8% of patients and anticoagulants by 33.5% (Table 2). The most frequently prescribed drugs on admission were paracetamol (38.7%), fentanyl (31.0%), and macrogol (23.2%). Drugs for acid-related disorders were mostly omeprazole (20.0%) and pantoprazole (18.7%). Psycholeptics were mostly temazepam (15.5%), haloperidol (11.0%), and oxazepam (9.0) (Table 3).

On average, patients were prescribed 4.6 (± 3.6; range 0–19) drugs on the day of their death. The most prescribed drug classes were analgesics (77.4%), psycholeptics (61.9%), drugs for acid-related disorders (27.1%), and laxatives (27.1%). Lipid-modifying agents were used by 2.6% and drugs for diabetes by 6.5% of patients. On the day of death, beta-blocking agents were used by 9.0% of patients and anticoagulants by 14.8% (Table 2). The most frequently prescribed drugs on the day of

Table 1
Characteristics of the Study Population

Study Population, n = 155	n (%)
Gender	
Male	87 (56.1)
Female	68 (43.9)
Age, y	
Mean age	75
Residence before admission	
Nonacademic hospital	87 (56.1)
Home	54 (34.8)
Nursing home	5 (3.2)
Residential home	4 (2.6)
Academic hospital	3 (1.9)
Other	2 (1.3)
Main diagnosis	
Cancer	126 (81.3)
Heart failure	12 (7.7)
COPD	4 (2.6)
Cerebrovascular disease	2 (1.3)
Parkinson disease	1 (0.6)
Other	10 (6.5)
Current diagnoses/comorbidities (multiple diseases possible)	
Cancer	132 (85.2)
Heart failure	25 (16.1)
COPD	19 (12.3)
Hypertension	16 (10.3)
Diabetes mellitus	15 (9.7)
Dementia	8 (5.2)
Cerebrovascular disease	8 (5.2)
Dyslipidemia	2 (1.3)
Parkinson disease	1 (0.6)

death were morphine (53.5%), midazolam (31.0%), and fentanyl (28.4%). Drugs for acid-related disorders were mostly omeprazole (10.3%) and pantoprazole (9.7%). The most used laxative was macrogol (12.3%) (Table 3).

In the most frequently prescribed drug classes, changes in prescribed drugs between admission and the end of life were found. For every drug class there are 4 different ways for changes in prescribed drugs to take place:

1. The patient had never been prescribed a drug from this drug class.
2. The patient had been prescribed a drug from this drug class at admission and at death.
3. The patient had been prescribed a drug from this drug class at admission, but not at death.
4. The patient had been prescribed a drug from this drug class at death, but not at admission.

The prescription of 3 drug classes increased between admission and death: analgesics, psycholeptics, and drugs for functional gastrointestinal disorders, such as antiemetics. In general, drugs from these classes are prescribed for symptom control. The prescription of all other drug classes decreased between admission and the day of death, including different drug classes for the treatment of comorbid disease, such as anticoagulants, beta-blocking agents, and drugs used in diabetes (Table 5).

Discussion

To our knowledge, this is the first study on the use of drugs in terminally ill patients, with a life expectancy of less than 3 months, admitted to palliative care facilities. We found that the mean number of drugs used decreased from 6.1 drugs at admission to 4.6 on the day of death. We also found, consistent with our hypothesis, a general tendency to stop drugs for comorbidities, such as statins, drugs for acid-related disorders, anticoagulants, beta-blocking agents, and drugs prescribed for diabetes, when death approached. We found an increase in SSMs, such as analgesics, psycholeptics, and drugs for functional gastrointestinal disorders. This shows that polypharmacy is more appropriate at the end of life and that the aim of palliative care, namely a focus on symptom control, is achieved.

Table 2
Most Frequently Prescribed Drug Classes at Admission and at Death

Drug Class	Patients Prescribed Drug Class at Admission, n = 155 (%)	Drug Class	Patients Prescribed Drug Class at Death, n = 155 (%)
Analgesics	98 (63.2)	Analgesics	120 (77.4)
Drugs for acid-related disorders	80 (51.6)	Psycholeptics*	96 (61.9)
Psycholeptics*	61 (39.4)	Drugs for acid-related disorders	42 (27.1)
Laxatives	60 (38.7)	Laxatives	42 (27.1)
Anticoagulants	52 (33.5)	Drugs for functional gastrointestinal disorders†	37 (23.9)
Beta-blocking agents	40 (25.8)	Corticosteroids	26 (16.8)
Corticosteroids	40 (25.8)	Anticoagulants	23 (14.8)
Diuretics	28 (18.1)	Anti-asthmatics	15 (9.7)
Anti-asthmatics	28 (18.1)	Beta-blocking agents	14 (9.0)
Psychoanaleptics‡	27 (17.4)	Psychoanaleptics‡	14 (9.0)
Agents on renin angiotensin system	24 (15.5)	Diuretics	13 (8.4)
Drugs used in diabetes	20 (12.9)	Ophthalmologicals	13 (8.4)
Drugs for functional gastrointestinal disorders†	19 (12.3)	Drugs used in diabetes	10 (6.5)
Antiepileptics	18 (11.6)	Antibacterial agents	10 (6.5)
Cardiac therapy	17 (11.0)	Other nervous system drugs	9 (5.8)
Ophthalmologicals	17 (11.0)	Cardiac therapy	8 (5.2)
Calcium antagonists	14 (7.9)	Antiepileptics	8 (5.2)
Vitamins	13 (8.4)	Urologics	7 (4.5)
Lipid-modifying agents	13 (8.4)	Lipid-modifying agents	4 (2.6)

*Psycholeptics consist of antipsychotics, anxiolytics, hypnotics, and sedatives.
†Drugs for functional gastrointestinal disorders consist of anticholinergics, antispasmodics, and propulsives.
‡The psychoanaleptic group comprises antidepressants, psychostimulants, antidementia drugs, and combinations with psycholeptics.

Table 3
Most Frequently Prescribed Drugs at Admission and at Death

Drugs	Patients Prescribed Drug at Admission, n = 155 (%)	Drugs	Patients Prescribed Drug at Death, n = 155 (%)
Paracetamol	60 (38.7)	Morphine	83 (53.5)
Fentanyl	48 (31.0)	Midazolam	48 (31.0)
Macrogol	36 (23.2)	Fentanyl	44 (28.4)
Omeprazole	31 (20.0)	Haloperidol	42 (27.1)
Pantoprazole	29 (18.7)	Paracetamol	33 (21.3)
Dexamethasone	29 (18.7)	Metoclopramide	31 (20.0)
Oxycodone	27 (17.4)	Dexamethasone	22 (14.2)
Temazepam	24 (15.5)	Macrogol	19 (12.3)
Metoprolol	22 (14.2)	Lactulose	18 (11.6)
Acetylsalicylic acid	20 (12.9)	Omeprazole	16 (10.3)
Furosemide	19 (12.3)	Pantoprazole	15 (9.7)
Esomeprazole	17 (11.0)	Oxazepam	14 (9.0)
Lactulose	17 (11.0)	Oxycodone	10 (6.5)
Haloperidol	17 (11.0)	Esomeprazole	9 (5.8)
Metoclopramide	15 (9.7)	Acetylsalicylic acid	9 (5.8)
Bisoprolol	14 (9.0)	Levomepromazine	9 (5.8)
Oxazepam	14 (9.0)	Temazepam	9 (5.8)

Prn medication was primarily prescribed for symptom control. At admission, morphine (23.9%), oxycodone (20.0%), and paracetamol (14.2%) were the most frequently prescribed drug as needed. After morphine (69.0%), midazolam (50.3%) and haloperidol (23,2%) were prescribed most often on the day of death (Table 4).

Table 4
Most Frequently Prescribed 'As Needed' Drugs (n = 155)

	No. of Patients (%)
At Admission	
Morphine	37 (23.9)
Oxycodone	31 (20.0)
Paracetamol	22 (14.2)
Metoclopramide	16 (10.3)
Oxazepam	11 (7.1)
At death	
Morphine	107 (69.0)
Midazolam	78 (50.3)
Haloperidol	36 (23.2)
Metoclopramide	35 (22.6)
Butylscopolamine	23 (14.8)

Lipid-modifying agents were still used by 8.4% of our patients at admission, compared with 56.0% of patients reviewed in an earlier study.[18] That study retrospectively reviewed the charts of ambulatory patients with advanced cancer and found statins to be the most frequently prescribed futile medication.[18] Statin use could be due to the difference in the functional and clinical status of the ambulatory patients and patients admitted to an inpatient palliative care facility. Moreover, the physicians in our study who treated the patients before admission in the palliative care facility might have discontinued statins already. The ECP discontinued statins in 9 of 13 patients during admission in the palliative care facility. This number could have been 0 because when using the START/STOPP (Screening Tool to Alert doctors to Right Treatment/Screening Tool of Older Person's Prescriptions) criteria, statins are to be discontinued if the overall prognosis is expected to be 5 years or less.[19] For statins, time-to-benefit is long, with a recommended use of 3 to 6 years to benefit from risk reduction.[20]

In our study, 25.8% of patients were still using a beta-blocking agent at admission and 9.0% at the day of death. Although a reduction was seen, the percentages were high when the aim of treatment is symptom control. Antihypertensives are examples of secondary preventive drugs.[21] Many patients at the end of life experience low blood pressure even without antihypertensives, caused by progressive cachexia and the palliative index disease.[3,4] However, rebound hypertension and tachycardia can lead to serious problems when antihypertensives are withdrawn at once, especially when more than 1 antihypertensive is used.[21] A gradual decrease in antihypertensive use can be achieved over days or weeks, constantly checking with the patient if there is an increase in symptoms associated with rebound hypertension and tachycardia. Strict blood pressure control at the end of life does not provide extra quality of life and is therefore not needed.[22,23]

Table 5
Changes in Most Frequently Prescribed Drug Classes Between Admission and Death (n = 155)

Drug Classes	Patients Prescribed This Drug Class at Admission and Death	Patients Prescribed This Drug Class at Admission, Not at Death	Patients Prescribed This Drug Class at Death, Not at Admission
Analgesics	87 (56.1)	11 (7.1)	33 (21.3)
Psycholeptics	51 (32.9)	10 (6.5)	45 (29.0)
Drugs for acid-related disorders	37 (23.9)	43 (27.8)	5 (3.2)
Laxatives	32 (20.6)	28 (18.1)	10 (6.5)
Drugs for functional gastrointestinal disorders	12 (7.7)	7 (4.5)	25 (16.1)
Corticosteroids	18 (11.6)	22 (14.2)	8 (5.2)
Anticoagulants	21 (13.5)	31 (20.0)	2 (1.3)
Anti-asthmatics	14 (9.0)	14 (9.0)	1 (0.6)
Beta-blocking agents	14 (9.0)	26 (16.8)	0 (0)
Psychoanaleptics	9 (5.8)	18 (11.6)	5 (3.2)
Diuretics	12 (7.7)	16 (10.3)	1 (0.6)
Ophthalmologicals	9 (5.8)	8 (5.2)	4 (2.6)
Drugs used in diabetes	9 (5.8)	11 (7.1)	1 (0.6)
Antibacterial agents	5 (3.2)	6 (3.9)	5 (3.2)

We found that drugs for diabetes mellitus were discontinued in 11 of 20 patients who were admitted with these types of drugs. The rest died still using drugs for diabetes. The management of diabetes in palliative terminal care is mainly based on experience rather than scientific evidence. An algorithm based on the prognosis of the patient on how to approach the management of diabetes was created earlier.[24] It proposes stopping oral hypoglycemic drugs in patients who have an estimated life expectancy of only weeks to days. Frequent monitoring of glucose levels (eg, 4 times a day) is no longer necessary at the end of life and can often be reduced to once daily. Insulin can often be reduced in the last weeks of life because of a decrease in glucose intake. For patients prescribed insulin, with days to live, the insulin can often be stopped, which must be explained to family and caregivers. Additional attention should be given to, for example, hydration of the mouth, to avoid the feeling of thirst.

Anticoagulants were discontinued in 31 of 52 patients before death. In 2 patients, anticoagulants were started in the palliative care facility. This is remarkable because antithrombotic agents can be harmful in patients with lowered nutritional intake because of changed volumes of distribution.[25] In an earlier qualitative study, the factors doctors take into consideration in their decision-making of whether or not to prescribe anticoagulants to patients with advanced cancer at the end of life were investigated.[26] Potential risks, benefits, and the views of the patients and their families and/or caregivers should be regarded. Having cancer and/or being bedridden are known risk factors for deep venous thrombosis, but in view of dying in the short term, a decision considering all advantages and disadvantages should be made including the patient's prognosis, a perceived lack of immediate benefit and the discomfort of the injection, and whether or not death by thrombosis was considered a good way to die.

The aims of pharmacological intervention for comorbid disease can be primary, secondary, or tertiary prevention. This is important in the decision-making process of whether or not to continue or discontinue the intervention. When the aim is primary or secondary prevention of disease, the medication can quite easily be discontinued with little risk. Tertiary prevention minimizes the effect of a disease that is causing symptoms (eg, medication to prevent inflammatory arthritis). This can give comfort to the patient, which lies within the aim of palliative care.[21]

Some medication can be prescribed for symptom control and/or comorbid disease. Its prescription depends on the goal of treatment. For example, diuretics are prescribed for comorbid disease when the aim is the treatment of hypertension or heart failure. If diuretics are prescribed in a patient with progressive dyspnea caused by pulmonary edema, the goal of treatment with diuretics is symptom control, even if opioids are given concomitantly. Corticosteroids are prescribed in patients with COPD as medication for comorbid disease to prevent or treat dyspnea but are also prescribed for symptom control in patients with brain tumors. These different goals of treatment should be weighed when prescribing medication at the end of life.

Because of the prospective design of our study, few data are missing on the variables we set out to study. Because pharmaceutical lists of hospitals or general practitioners and electronic medical prescriptions were photocopied or printed, they were as complete as possible. Although we studied patients in specific end-of-life care facilities, there also is a large group of patients in long-term care facilities who receive end-of-life care. Here, a reduction in polypharmacy is

as much needed and therefore recommendations made in the discussion section apply to all patients receiving end-of-life care.

There are, however, several limitations to this study. The results describe the behavior of a limited number of ECPs. It might be possible that a few ECPs influence the results disproportionately starting or discontinuing some type of medication. However, it was our intention to describe the results as we found them in the 7 "inpatient palliative care facilities" of our study.

Patients who were functionally the worst and who could therefore not object or agree to participation were excluded. We have no data about how many potential patients were not consentable, because the hospice physicians left those patients out of the study, which may be a confounding factor. Patients were admitted for end-of-life care in the palliative care facilities. Medications might already have been pared down before admission (eg, cardiac and pulmonary drugs). This means that there might be less room for improvement.

Conclusions

Inappropriate drug use is a key issue in palliative care and especially in end-of-life care. To prevent the unnecessary prescription of drugs in the last phase of life, we need to carefully consider and reconsider whether each prescribed drug still has the therapeutic goal to improve or maintain the quality of life of the patient at hand. Clinicians should not wait until the patient facing the end of life is not able to swallow the prescribed medication anymore, but proactively review and adapt each medication for its intended treatment goal, particularly evaluating its benefit versus side effects and pill burden. In this way, less can be more. Generally, our study demonstrates a reduction of medication for comorbid diseases between admission and death in the palliative care facilities and a reduction in polypharmacy at the end of life. Current guidelines about the use of certain medications should describe not only when to start, but also when and how to stop. More research is needed to create specific guidelines for physicians on how to deal with medication at the end of life. Physicians are highly trained to start medications, but at the same time could be better trained in the discontinuation of medication, especially when death is expected soon, consequently contributing to better advance care planning and improved quality of life and dying for all vulnerable patients in the last days of their life.

References

1. Coebergh JW, Janssen-Heijnen ML, Post PN, Razenberg PP. Serious co-morbidity among unselected cancer patients newly diagnosed in the southeastern part of The Netherlands in 1993–1996. J Clin Epidemiol 1999;52:1131–1136.
2. Riechelmann RP, Krzyzanowska MK, O'Carroll A, Zimmermann C. Symptom and medication profiles among cancer patients attending a palliative care clinic. Support Care Cancer 2007;15:1407–1412.
3. Currow DC, Stevenson JP, Abernethy AP, et al. Prescribing in palliative care as death approaches. J Am Geriatr Soc 2007;55:590–595.
4. Koh NY, Koo WH. Polypharmacy in palliative care: Can it be reduced? Singapore Med J 2002;43:279–283.
5. Bushardt RL, Massey EB, Simpson TW, et al. Polypharmacy: Misleading, but manageable. Clin Interv Aging 2008;3:383–389.
6. van Nordennen RT, Lavrijsen JC, Vissers KC, Koopmans RT. Decision making about change of medication for comorbid disease at the end of life: An integrative review. Drugs Aging 2014;31:501–512.
7. McLean S, Sheehy-Skeffington B, O'Leary N, O'Gorman A. Pharmacological management of co-morbid conditions at the end of life: Is less more? Ir J Med Sci 2012;182:107–112.
8. Holmes HM, Todd A. Evidence-based deprescribing of statins in patients with advanced illness. JAMA Intern Med 2015;175:701–702.
9. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: The process of deprescribing. JAMA Intern Med 2015;175:827–834.
10. Graham J. End-of-life medications draw more attention, greater scrutiny. JAMA 2015;313:231–233.
11. Kutner JS, Blatchford PJ, Taylor DH, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: A randomized clinical trial. JAMA Intern Med 2015;175:691–700.
12. Tjia J, Cutrona SL, Peterson D, et al. Statin discontinuation in nursing home residents with advanced dementia. J Am Geriatr Soc 2014;62:2095–2101.
13. Tjia J, Briesacher BA, Peterson D, et al. Use of medications of questionable benefit in advanced dementia. JAMA Intern Med 2014;174:1763–1771.
14. Geijteman EC, van Gelder T, van Zuylen L. Sense and nonsense of treatment of comorbid diseases in terminally ill patients. JAMA Intern Med 2015;175:346.
15. Koopmans RT, Lavrijsen JC, Hoek JF, et al. Dutch elderly care physician: A new generation of nursing home physician specialists. J Am Geriatr Soc 2010;58:1807–1809.
16. Manchikanti L, Falco FJ, Hirsch JA. Necessity and implications of ICD-10: Facts and fallacies. Pain Physician 2011;14:E405–E425.
17. Skrbo A, Zulic I, Hadzic S, Gaon ID Anatomic-therapeutic-chemical classification of drugs. Med Arh 1999;53:57–60. Croatian.
18. Riechelmann RP, Krzyzanowska MK, Zimmermann C. Futile medication use in terminally ill cancer patients. Support Care Cancer 2009;17:745–748.
19. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther 2008;46:72–83.
20. Amarenco P, Labreuche J, Lavallee P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: Systematic review and up-to-date meta-analysis. Stroke 2004;35:2902–2909.
21. Stevenson J, Abernethy AP, Miller C, Currow DC. Managing comorbidities in patients at the end of life. BMJ 2004;329:909–912.
22. Parsons C, Hughes CM, Passmore AP, Lapane KL. Withholding, discontinuing and withdrawing medications in dementia patients at the end of life: A neglected problem in the disadvantaged dying? Drugs Aging 2010;27:435–449.
23. Holmes HM, Sachs GA, Shega JW, et al. Integrating palliative medicine into the care of persons with advanced dementia: Identifying appropriate medication use. J Am Geriatr Soc 2008;56:1306–1311.
24. King EJ, Haboubi H, Evans D, et al. The management of diabetes in terminal illness related to cancer. QJM 2012;105:3–9.
25. Lyman GH. Venous thromboembolism in the patient with cancer: Focus on burden of disease and benefits of thromboprophylaxis. Cancer 2011;117:1334–1349.
26. Sheard L, Prout H, Dowding D, et al. The ethical decisions UK doctors make regarding advanced cancer patients at the end of life—the perceived (in) appropriateness of anticoagulation for venous thromboembolism: A qualitative study. BMC Med Ethics 2012;13:22.