Medication optimisation in older adults with cancer

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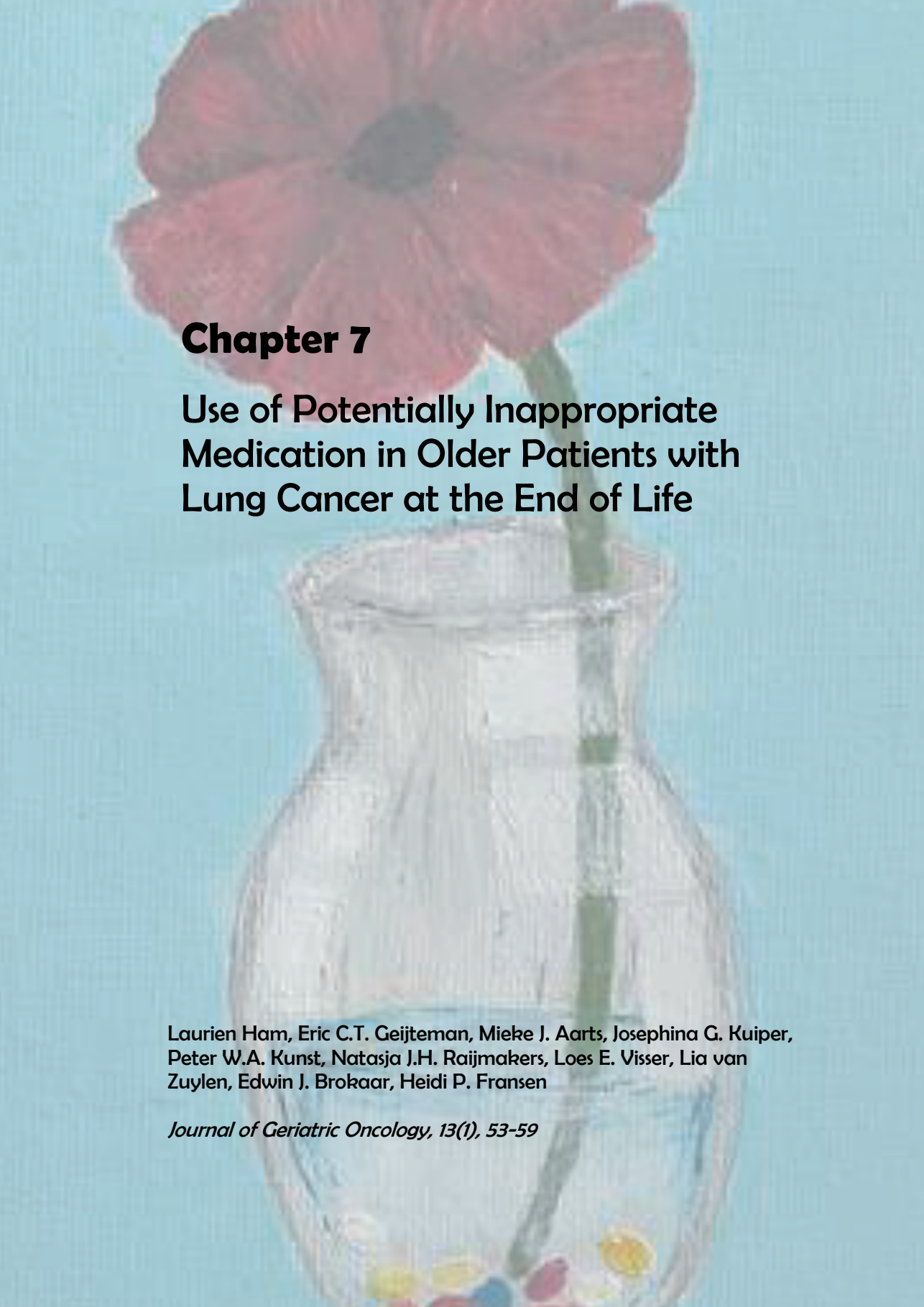

Chapter 7

Use of Potentially Inappropriate Medication in Older Patients with Lung Cancer at the End of Life

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Abstract

Objectives

Medications at the end of life should be used for symptom control. Medications which potential adverse effects outweigh their expected benefits are called 'potentially inappropriate medications' (PIMs). PIMs are related with adverse drug events and reduced quality of life. In this study, we investigated to what extent PIMs are dispensed to older patients with lung cancer in the last month of life.

Methods

We selected patients with lung cancer, aged 65+, diagnosed between 2009 and 2014, and who died before April 1st 2015 from the population-based Netherlands Cancer Registry (NCR). The NCR is linked to the PHARMO Database Network, that includes medications dispensed by community pharmacies in the Netherlands. The eight PIM groups were based on the OncPal Deprescribing Guideline: aspirin, dyslipidaemia medications, antihypertensives, osteoporosis medications, peptic ulcer prophylaxis, oral hypoglycaemics, vitamins and minerals.

Results

Data of 7864 patients with lung cancer were analyzed. Median age was 74 year (IQR=70–79) and 67% was male. 45% of all patients received at least one PIM in their last month of life. Taking into account all dispensed medications, patients receiving PIMs received more different medications compared to those receiving no PIMs, respectively 10 (SD = 5) vs. 3 (SD = 4) different medications ($P < 0.001$).

Conclusion

Almost half of the older patients with lung cancer in the Netherlands received PIMs in their last month of life. Since PIMuse is associatedwith reduced quality of life, it is important that health care professionals continue to critically assess which medication can be discontinued at the end of life.

Introduction

Medication at the end of life should be used for symptom control, such as pain relief [1]. However, patients with cancer frequently use multiple types of medications in the last phase of life that may cause potential harm and are considered not beneficial [2]. Most of those unnecessary medications are used for primary or secondary prevention [3,4]. Medications which potential adverse effects outweigh their expected benefits are called 'potentially inappropriate medications' (PIMs). PIM use is related to adverse drug events and reduced quality of life [5–7]. Next, the use of PIMs is associated with a higher risk of unplanned hospitalizations [8,9]. Patients with polypharmacy (concurrent use of multiple medications) have an increased risk of receiving PIMs [10–14]. Polypharmacy is a known problem in older patients with advanced cancer, and the prevalence of polypharmacy in older adults is increasing [4,15–17].

Especially in the last phase of life, medications may be potentially inappropriate as goals of care change. Furthermore, these may have a time until benefit which exceeds the limited life expectancy of patients [3]. Many PIMs are continued until the last phase of life, for example statins and antihypertensive medications [18–22]. Several small retrospective chart review studies investigated medication use in the last phase of life, highlighting that patients with a limited life expectancy continue to use prescribed inappropriate medications until the very end of life [23–27]. For better understanding of medication use in the last phase of life, large-scale unselected studies are needed. Recently, a Swedish nationwide study was conducted to explore medication use during the last year of life and showed that preventive medication were commonly used by older adults with cancer (e.g. 60% of the population used antihypertensives) [19].

In the last decade, there is a growing realization that adjusting patients' medication should be considered during the last phase of life [28]. Several deprescribing guidelines for PIMs are published, like the Beers Criteria, START/STOPP criteria, and the STOPPFrail, all focusing on older patients [29–32]. The STOPPFrail is developed for frailer older adults with a limited life expectancy [32]. There also is a guideline specifically developed for oncological patients in the last phase of life, the OncPal deprescribing guideline [33]. TheOncPal deprescribing guideline was developed as a tool to improve the rationalization of medications in patients with cancer in the palliative phase, with the aim to reduce adverse drug effects, pill burden and medication-associated costs.

It is unknown to what extent PIMs are prescribed to patients with lung cancer in the last phase of life. Therefore, aim of this study is to investigate on population level to what extent older patients with lung cancer received PIMs in the last month of life. Furthermore, trends in PIMs prescribing and the characteristics of these patients will be identified. The population of this study consists of older patients with lung cancer, knowing that this population has a high multimorbidity and a poor prognosis [34]. Since the majority of the patients with lung cancer are diagnosed with stage III or IV, it is especially important for this population that health care professionals critically assess which medication can be discontinued in the last phase of life [35].

Methods

Study Design and Data

In this population-based observational study, we retrospectively linked data of the Netherlands Cancer Registry (NCR) and the PHARMO Database Network. The NCR is a

population-based registry, covering the total Dutch population, containing data on cancer diagnosis and treatment, maintained by the Netherlands Comprehensive Cancer Organisation (IKNL). Information on patient and tumor characteristics, diagnosis and treatment is extracted from the medical records by trained datamanagers. The PHARMO Database Network is a population-based network of electronic healthcare databases and combines anonymous data from different primary and secondary healthcare settings in the Netherlands. For this study, data from the Out-Patient Pharmacy Database was used which comprises general practitioner or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, and prescriber specialty. Drug dispensing's are coded according to the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) Classification System [36]. Outpatient pharmacy data cover a catchment area representing 4.2 million residents (~25% of the Dutch population). As the NCR and the PHARMO Database Network contains de-identified data from existing databases without any direct enrollment of subjects, ethical approval or informed consent is not necessary according to the Dutch law regarding human medical scientific research (Wet medisch-wetenschappelijk onderzoek met mensen (WMO)),which is enforced by the Central Committee on Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek (CCMO)). The privacy committees of the NCR and the PHARMO Institute approved the conduct of this study.

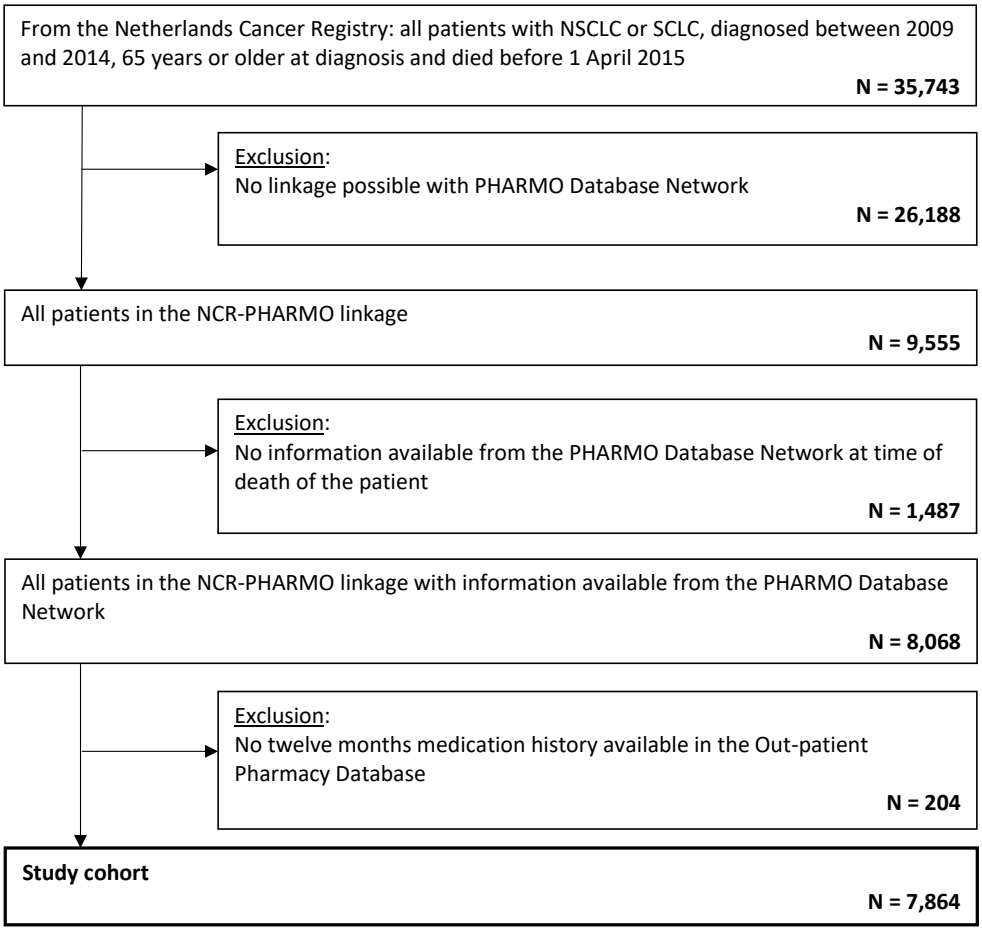
Study Population

All patients with non-small cell lung carcinoma and small cell lung carcinoma, aged 65 years or older at diagnosis, diagnosed between 2009 and 2014, and who died before April 1st 2015 were selected from the NCR – PHARMO Out-patient Pharmacy cohort (Fig. 1).

PIM Groups

To identify potentially inappropriate medications, eight PIM groups were formed based on the 'OncPal Deprescribing guideline' [33]. This guideline was chosen since it is the only validated deprescribing guideline available for palliative cancer patients. TheOncPal provides an overview of medication classes which can be discontinued during the palliative phase of patients with cancer. The OncPal Deprescribing guideline demonstrated its validity in 61 patients with a life expectancy of shorter than six months, correctly assessing 94% of medications with an overall Kappa value of 0.83, in comparison to an expert panel [33]. For this study,minor adjustments of the OncPal Deprescribing guideline were made, i.e. themedication class 'Complementary – alternative medicines' was not included, because in the Netherlands these medications are not delivered by the pharmacy. Therefore, no information about this medication class was available. In addition, the PIM groups in this study were categorized based on medication group. The eight potentially inappropriate medication groups included in this study are: aspirin, dyslipidaemia medications, antihypertensives, osteoporosis medications, peptic ulcer prophylaxis, oral hypoglycaemics, vitamins, and minerals (Table 1).

Figure 1. Flowchart: patient selection



Polypharmacy

We used the definition of cumulative polypharmacy of Fincke et al. to measure polypharmacy: the sum of all the different medication that were dispensed within a given time window [37]. Five or more different medications dispensed in the last month was defined as polypharmacy, excessive polypharmacy was defined as 15 or more different medications [38,39]. To determine polypharmacy, the total number of medications per patient were taken into account.

Outcomes

The primary outcome of this study is the use of PIMs in the last month of life. This was calculated as the number of patients who received at least one PIM dispensed by the outpatient pharmacy in the last month of life as proportion of all included patients. Medications which were dispensed before the cancer diagnosis were not included as PIMs, since the limited life expectancy was probably not yet known at the date of dispensation.

Statistical Analysis

Patient characteristics were presented as mean (standard deviation (SD)) or median (interquartile range (IQR)) for continuous variables and percentages for categorical variables. Descriptive statistics were used to describe the percentage of patients with at least one PIM per PIM group, by age, sex, days between diagnosis and death, tumor type, stage, and comorbidities. Comorbidities were only registered for 33% of the patients in the study population, percentages of prevalence of comorbidities were only calculated within this subgroup. Total number of medications per patient was expressed as mean (SD). Statistical differences were tested with Pearson's $\chi 2$ for categorical variables and Mann-Whitney U test for continuous variables. Statistical significance was set at $P < 0.05$. The research period was divided into three equal parts based on date of diagnosis (01-jan-2009–31-dec-2010, 01-jan-2011–31-dec-2012, and 01-jan-2013–31-dec-2014) to calculate change over time. Total number of medications per patient was expressed as mean (SD). Since there is some debate about the inappropriateness of diuretics and peptic ulcer prophylaxis and we do not have information about indications for medication use, a sensitivity analysis was performed to investigate their influence on the results. For this sensitivity analysis, PIM group 5 (peptic ulcer prophylaxis) was omitted completely, and diuretics were omitted from PIM group 3 (antihypertensive medications). Descriptive analysis was used to describe the percentage of patients with at least one PIM per PIM group in the sensitivity analysis. All statistical analyses were performed with Stata 16 (StataCorp LLC, College Station, Texas) statistical software.

Table 1 PIM groups, based on OncPal [33]

Medication class according to OncPal	Medication group according to OncPal	Included as PIM group	ATC-code
Blood and blood-forming organs	Aspirin	PIM group 1	B01AC06 & B01AC30
Cardiovascular system	Dyslipidaemia medications	PIM group 2	C10AA[a], C10B[a], C10AB[a] & C10AX09
	Antihypertensives	PIM group 3	C09A[a], C09B[a], C09CA[a], C09DA[a], C09DX[a], C07[a], C08[a] & C03[a]
Musculo-skeletal system	Osteoporosis medications	PIM group 4	M05BA[a], M05BBa, G03XC01, M05BX03 & M05BX04
Alimentary tract and metabolism	Peptic ulcer prophylaxis	PIM group 5	A02BC[a] & A02BA[a]
Oral Hypoglycaemics	Oral hypoglycaemics	PIM group 6	A10BA02, A10BB[a], A10BG[a], A10BH[a], A10BJ[a] & A10BF01[a]
Vitamins	Osteoporosis medications	PIM group 7	A11[a]
Minerals	Peptic ulcer prophylaxis	PIM group 8	A12[a]
Complementary – alternative medicines	-	No	-

Abbreviations: PIM, potentially inappropriate medication; ATC, anatomical therapeutic chemical.

[a] All ATC-codes starting with this code.

Results

Patient Characteristics

In total, 7864 older patients with lung cancer were included in the study cohort. Median age of the patients at diagnosis was 74 years (IQR = 70–79). 67% of the patients were male. Most of the patients (71%) had a non-small cell lung carcinoma and most were diagnosed with distant metastases (stage IV) (54%). The most common reported comorbidity in our study population was cardiovascular disease (52%). The median time between cancer diagnosis and death was 147 days (IQR=47–350; Table 2). Patients received on average six (SD=6) different medications, 55% of the patients was exposed to polypharmacy in their last month of life. Nine percent of patients were exposed to excessive polypharmacy (Table 3).

Table 2 Characteristics of the 7864 patients with lung cancer included in this study

Characteristics		**Receiving PIMs in the last month before death**		
	Total (N=7864)	**Yes (N=3514)**	**No (N=4350)**	**p-value**
Age, median (IQR)	74 (9)	75 (10)	74 (10)	**0.01**
Male, N (%)	5303 (67)	2425 (69)	2878 (66)	**0.01**
Days between diagnosis and death, median (IQR)	147 (303)	163 (292)	132 (311)	**0.00**
Tumortype, N (%)				0.16
Non-small cell lung carcinoma	5581 (71)	2513 (72)	3068 (71)	
Small cell lung carcinoma	1269 (16)	537 (15)	732 (17)	
Other and unspecified lung carcinoma	1014 (13)	464 (13)	550 (13)	
Stage, N (%)				0.48
I	611 (8)	290 (8)	321 (7)	
II	448 (6)	206 (6)	242 (6)	
III	1878 (24)	851 (24)	1027 (24)	
IV	4283 (54)	1884 (54)	2399 (55)	
Unknown	644 (8)	283 (8)	361 (8)	
Number of medications per patient, mean (SD)	6 (6)	10 (5)	3 (4)	**0.00**
Comorbidities, N (%)	N=2610	N=1231	N=1379	
Cardiovascular diseases	1362 (52)	697 (57)	665 (48)	**0.00**
Diabetes	468 (18)	255 (21)	213 (15)	**0.00**
Kidney disease	86 (3)	41 (3)	45 (3)	0.92
Pulmonary disease	830 (32)	417 (34)	413 (30)	**0.03**

Abbreviations: PIM, potentially inappropriate medication.

Potentially Inappropriate Medications

In the last month before death, 45% of the patients had at least one PIM dispensed by the community pharmacy (Fig. 2). The most frequent dispensed PIMs were peptic ulcer prophylaxis, which were dispensed to 32% of the patients, and antihypertensives, which were dispensed to 28% of the patients.

Table 3 Polypharmacy among 7864 patients with lung cancer in their last month of life

Number of medications	All patients (N=7864)	Patients who received PIMs (N=3514)	Patients who did not receive PIMs (N=4350)
0 medications	2178 (28%)	0 (0%0	2178 (50%)
1-4 medications (no polypharmacy)	1375 (17%)	386 (11%)	989 (23%)
>5 medications (polypharmacy)	4311 (55%)	3128 (89%)	1183 (27%)
15 medications (excessive polypharmacy)	697 (9%)	657 (19%)	40 (1%)

Abbreviations: PIM, potentially inappropriate medication.

There were differences in patient characteristics between the group who received PIMs in the last month (n=3514) and the group who did not receive PIMs in the last month (n = 4350) (Table 2). In the group who received PIMs, 69% of the patients were male, while in the group who did not receive PIMs, 66% of the patients were male ($P < 0.05$). The median time between diagnosis and death was 163 days (IQR = 58–350) in the group receiving PIMs and 132 days (IQR = 38–349) in the group not receiving PIMs ($P < 0.001$). Patients receiving PIMs received more different medications compared to those receiving no PIMs, ten (SD = 5) vs. three (SD = 4) different medications, respectively ($P < 0.001$). 89% of the patients who received PIMs received five or more different medications in their last month of life, in contrast to 27% in patients who did not receive PIMs. In addition, the groups were similar with respect to tumor type and stage, 72% of the patients receiving PIMs and 71% of the patients that were not receiving PIMs had a non-small cell lung carcinoma(P=0.16), and 54% and 55% respectively, were diagnosed with stage four disease ($P = 0.48$).

When excluding peptic ulcer prophylaxis and diuretics from the PIMs in a sensitivity analysis, still nearly 30% of the patients in our study cohort received at least one PIM dispensed by the pharmacy in the last month of life. In that analysis, antihypertensives, which were dispensed to 20% of the patients, were the most dispended PIMs, and dyslipidemia medications the second most dispensed PIMs, dispensed to 9% of the patients (see Table 4).

Table 4 Sensitivity analysis of patients with lung cancer who received PIMs in the last month of life[a]

PIM groups	Last month (N=7864)
Overall PIM use	2234 (28%)
Aspirin	669 (9%)
Dyslipidaemia medications	682 (9%)
Antihypertensives	1592 (20%)
Osteoporosis medications	188 (2%)
Oral hypoglycaemics	463 (6%)
Vitamins	199 (3%)
Mineral	268 (3%)

Abbreviations: PIM, potentially inappropriate medication.

[a] PIM group 'peptic ulcer prophylaxis' was omitted in total and diuretics was omitted from PIM group 'antihypertensives'.

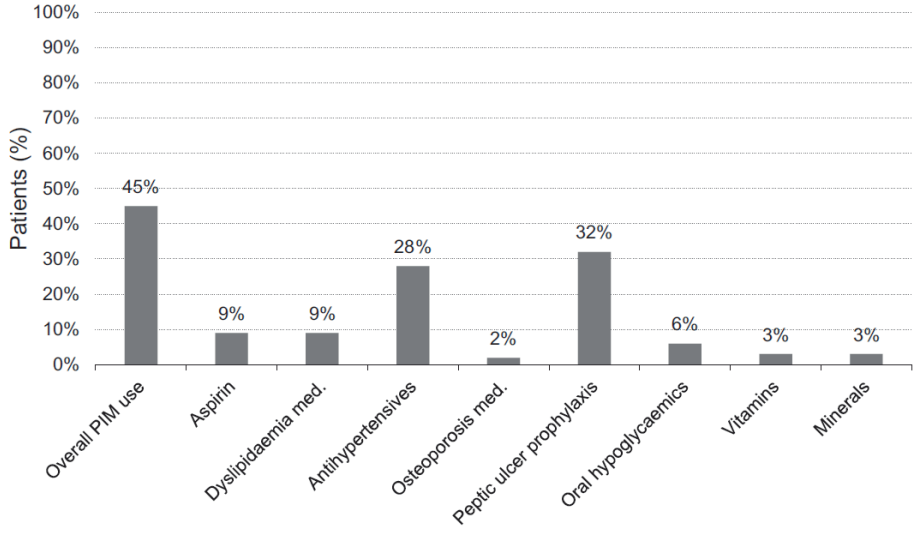


Fig. 2. Patients with lung cancer who received PIMs in the last month of life N = 7864.

Change in Dispended PIMs Over Time

We compared three time periods (2009–2010, 2011–2012, and 2013–2014) and found no significant changes in PIM use (P = 0.14). In the period 2009–2010, 44% of the patients received one or more PIMs, in 2011–2012 46% and in 2013–2014 44% of the patients received one or more PIMs (Table 5).

Table 5 Patients with lung cancer who received PIMs in the last month of life over three time periods

PIM-groups	Time period		
	01-01-2009 – 31-12-2010 (N=2830)	01-01-2011 – 31-12-2012 (N=2880)	01-01-2013 – 31-12-2014 (N=2145)
Overall PIM use	1241 (44%)	1329 (46%)	944 (44%)
Aspirin	212 (7%)	270 (9%)	187 (9%)
Dyslipidaemia medications	209 (7%)	270 (9%)	203 (9%)
Antihypertensives	770 (27%)	809 (28%)	590 (28%)
Osteoporosis medications	66 (2%)	78 (3%)	44 (2%)
Peptic ulcer prophylaxis	859 (30%)	976 (34%)	665 (31%)
Oral hypoglycaemics	157 (6%)	188 (7%)	118 (6%)
Vitamins	47 (2%)	75 (3%)	77 (4%)
Mineral	83 (3%)	102 (4%)	83 (4%)

Abbreviations: PIM, potentially inappropriate medication.

Discussion

Our study showed that almost half of the older patients with lung cancer received one or more potentially inappropriate medications in their last month of life. This high proportion of patients receiving PIMs in the last month of life is stable over time. In addition, over 50% of the patients with lung cancer experienced polypharmacy. Therefore, it is important that health-care professionals critically assess the medication use of patients in the last phase of life.

When we compare our results (45% of the patients received PIMs) to the results of other, smaller, retrospective studies in patients with a limited life expectancy, there is a variation in results. Two studies in the Netherlands found comparable percentages of patients with PIMs, while a study in Israel found higher percentages [18,21,27]. There is a variation in the results of larger cohort studies as well. A retrospective cohort study in Belgium showed that PIMs were not discontinued in 49% of the population [40],which is comparable to our results. However, a nationwide cohort study in deceased older adults with cancer in Sweden and a retrospective longitudinal study in Italy found considerably higher results. The investigators in Sweden showed that antihypertensives were prescribed in 60% of the population in the last month of life, antidiabetics in 15% and vitamins in 9%, compared to our results of 28%, 6%, and 3%, respectively [19]. The Italian investigators found that 61% of the patients received preventive medication at the last prescription before death [41]. The higher percentages found in the studies from Sweden and Israel compared to our study could be explained by the fact that they included all PIMs which were considered to be used within the last month, while our study only included medications with an actual dispensing date within the last month. The higher percentage found in the study from Italy could be explained by the fact that they used other criteria to define medications as potentially inappropriate. In addition, different systematic reviews regarding the use of preventive medications at the end of life confirmed the result of continuing PIMs until the very end of life [42–44]. Our study also highlights that patients with polypharmacy received PIMs more often than patients who received fewer medications, 90% and 25% respectively. This is in agreement with a retrospective cohort study in Texas, which demonstrated that the prevalence of PIM use was significantly higher in patients receiving polypharmacy (36%) compared to those not receiving polypharmacy (19%) [45]. There are different reasons why potentially inappropriate medications are continued in patients with a limited life expectancy. Possibly the most important reason is insufficient awareness [46]. Given the increased knowledge on benefits of early and specialized palliative care and the growing realization that adjusting patients' medication should be considered during the last phase of life [28,47–49], it was expected that there would be a decline over time in the number of patients receiving PIMs in the final month of life. However, in our comparison of three time periods (2009–2010, 2011–2012, 2013–2014) we did not found a decline in PIM use. However, our data was collected in 2009–2014. The percentage of PIM use in patients who receive palliative care may be lower nowadays, since health care professionals are more aware of the need for reducing inappropriate prescribing in patients with a limited life expectancy. Further research is necessary to confirm this expectation. Other reasons why PIMs are continued until the very end of life are low priority, and uncertainty about the consequences [46]. A Belgian study highlighted that 17% of the patients received chemotherapy in the last 30 days before death [50]. One would not expect to discontinue potentially inappropriate medications if chemotherapy is still continued. With the rapid development of novel anticancer agents in lung cancer it will be even more difficult to predict the end of life and anticipate on it. Until now, only one randomized controlled study into the

consequences of deprescribing medications in patients with a limited life expectancy has been published. This study evaluated the safety of discontinuing statins for patients with an estimated life expectancy ranging from one month to one year [51]. The results demonstrated that statins can be safely stopped and discontinuation of statins in this patient group was even associated with improved quality of life.

To the best of our knowledge, this is the first population-based study in the Netherlands that examined to what extent PIMs are dispatched to older patients with lung cancer in their last month of life. Another strength of this study is that we used the OncPal Deprescribing guideline to identify PIM groups. This guideline was specifically developed for patients with cancer in the palliative phase [33]. However, this study also has some limitations. A general limitation of working with data of medication dispensed by the pharmacy is that it is unknown whether a patient has actually taken the medications dispensed by the pharmacy. Medications dispensed by the pharmacy is a proxy of medication use. A second limitation is that in practice, patients are marked as palliative at a certain point following their diagnosis and from that point PIM use should be addressed. As we did not know when or whether the patient's treatment was labelled as palliative in their medical records, we looked at medication use in the last month of life. Another limitation is that there could be an underestimation of PIMs. There are several reasons for this potential underestimation. First of all, it is possible that a patient received medications from other sources than the public pharmacy, for example vitamin and mineral supplements can also be obtained as over-the-counter drugs in the Netherlands. Second, in our study, dispensing date was used to define medication use in the last month of life. It is possible that medications were already dispensed before the last month of life and were continued during the last month of life. These medications were not counted as PIMs, because it is unsure whether patients actually still use these medications. Third, medication dispensed by in-patient pharmacies (i.e. during hospitalization) was not taken into account in this study as this information was only known for a small group of patients in our study population.

Another limitation of using standard dispensing data is that the indications for medication prescription are unknown. Medications can be preventive in one situation, while given for symptom relief in another situation. Therefore, a sensitivity analysis was performed, in which diuretics and peptic ulcer prophylaxis were omitted as PIMs. The sensitivity analysis showed lower percentages of patients receiving one or more PIMs, as the largest PIM group (peptic ulcer prophylaxis) was omitted. Still almost 30% of the patients received one or more PIMs. The NCR – PHARMO Out-patient Pharmacy cohort covers a catchment area representing ~25% of the Dutch population. Our study cohort is representative for the total cohort and for the total population of patients with lung cancer in the Netherlands [52,53]. Our study focused on older patients with lung cancer, but it is expected that comparable results will be found in cancer types with a similar course of disease [19].

Conclusion

Almost half of the older patients with lung cancer in the Netherlands received potentially inappropriate medications in their last month of life and polypharmacy also often occurred. Since there is a known relationship between PIM use, quality of life, and adverse drug events, it is important that health care professionals continue to critically assess which medications can be discontinued in the last phase of life.

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