ORIGINAL ARTICLE

Polypharmacy and medication errors on admission to palliative care

Tomasz Grądalski

St. Lazarus Hospice, Kraków, Poland

KEY WORDS

medication errors, palliative care, polypharmacy, referral

EDITORIAL

by Krajnik et al, see p. 654

ABSTRACT

INTRODUCTION Many patients at the end of their life are treated with multiple medications while some of the drugs may no longer be beneficial and should be reduced.

OBJECTIVES The aim of the study was to assess polypharmacy, overprescribing, and the incidence of presumable pharmacological errors at referral to palliative care.

PATIENTS AND METHODS Current treatment in consecutive patients was analyzed based on the clinical judgment of a palliative care specialist on the first appointment. The number of drugs/tablets with pharmacotherapy inappropriateness was counted, analyzed, and a new therapy was proposed.

RESULTS A total of 337 patients were admitted. The median number of drugs/tablets used at referral was 7/9 per day. In patients with short life prognosis, the corresponding numbers were higher (8/10). Polypharmacy was found in 265 patients (78.6%) and at least 1 drug inappropriateness occurred in 238 patients (70.6%). The most frequent error type was lack of necessary concomitant drug. Patients who were bed-bound (Palliative Performance Scale ≤40 points), with the shortest life expectancy (Gold Standards Framework, D), who died within 2 weeks or were discharged from the hospital and admitted to hospice had more often 1 or more potentially inappropriate medication. The risk of inappropriateness increased with the number of drugs/tablets prescribed by 13.3%/7.4% per drug/tablet. The median number of drugs/tablets decreased on palliative consultation by 1.0/2.0 ($P = 0.01$/$P < 0.001$, respectively). Subgroups with a higher number of errors had a larger drug reduction.

CONCLUSIONS Polypharmacy and increased risk of drug inappropriateness particularly affect elderly patients referred by hospitals, with poor prognosis, low performance, admitted to in-patient hospice. Therapy reduction may diminish the risk of therapeutic inappropriateness but requires further education within nonspecialist palliative care.

INTRODUCTION In palliative care (PC), it is of paramount importance to continuously ensure the best possible quality of life. In a recent European survey of patients with advanced cancer on opioids, it has been found they were given a mean of 7.8 drugs and more than 1 in 4 patients used 10 or more drugs.[1] Every medical intervention in PC, including pharmacotherapy, needs to be assessed according to achievable benefits and possible harms in the light of the expected prognosis. When drugs are no longer beneficial, and especially when they become potentially harmful, it is ethically justified to reduce or stop them. In the last months of life the majority of preventive drugs can be deprescribed, especially as patients may need additional symptom relieving medications.[2] This process is, however, difficult because of many barriers, such as the fear of confronting the patient with his or her poor prognosis or concerns over clinical complications.[3] Some 20% of drugs in common use in the treatment of elderly patients may be inappropriate, and that ratio increases beyond 30% in aged care facilities.[4] In the group of nursing home residents with advanced dementia, more than 1 in 2 patients are administered at least 1 drug whose beneficiary effect is challengeable. Approximately half of hospitalized patients or nursing home residents receive at least 1 unnecessary drug. However, current data from the first palliative appointment in Poland is still lacking. The aim of this study was to assess polypharmacy, overprescribing,

Correspondence to:
Tomasz Grądalski, MD, PhD, St. Lazarus Hospice, ul. Fatimska 17, 31-831 Kraków, Poland, phone: +48 12 641 46 59, email: tomgr@mp.pl
Received: August 29, 2019.
Revision accepted: September 6, 2019.
Published online: September 10, 2019.
Pol Arch Intern Med. 2019; 129 (10): 659-666
doi:10.20452/pamw.14969

WHAT'S NEW?

Polypharmacy is found in more than three-quarters of patients referred to palliative care. Two-thirds have at least 1 inappropriate medication prescribed, more frequently affecting those with more serious illness and correlating with the number of drugs/tablets received. The most common type of error is unnecessary treatment (eg, proton pump inhibitors and lipid-lowering drugs), the deficiency of necessary concomitant medication (eg, absence of laxatives in spite of regular opioid use), and insufficient clinical/metabolic monitoring. Clinicians regardless of discipline should have basic knowledge of symptom management and systematically assess patients' pharmacotherapy. At the end of life, only a few essential drugs are usually needed to maintain quality care. The physicians who are inexperienced in medication management in terminally ill patients should turn to a palliative care specialist for consultation. Reducing drug/tablet intake in these patients may be considered to diminish the risk of therapeutic inappropriateness.

TABLE 1 Routinely used checklist of potentially inappropriate medications in hospice care

Medication	Consideration for limited benefit
Cholesterol-lowering drugs (statins)	Time-to-benefit usually exceeds life expectancy
Aspirin	For primary prevention
Hypotonic drugs	If normotensive
Heparins	For primary prevention
Vitamin K antagonists	For non-high thromboembolic risk excluding prosthetic heart valve
Nitrates for stable angina	Ineffective in improving quality of life
Proton pump inhibitors in prevention	Time-to-benefit usually exceeds life expectancy
Osteoporosis medications	Excluding for hypercalcemia in bone metastasis
Oral hypoglycemic agents	In type 2 diabetes to reduce mild hyperglycemia
Vitamins/minerals/complementary drugs	No evidence of effectiveness

and the incidence of presumable pharmacological errors in patients at referral to palliative care.

PATIENTS AND METHODS The following principles of prescribing in end-of-life patients according to the current literature[1,5-9] were applied to the routine clinical practice, starting in June 2016: 1) the aim is to have 1 prescribing physician for 1 patient; 2) the definition of treatment goals is of principal importance; 3) life-extending drugs within last weeks of life are seldom appropriate; 4) in the case of drugs for primary prevention, the time-to-benefit ratio is usually too long; 5) drugs indicated for tertiary prevention require periodic reevaluation; 6) prescribing more than 5 drugs in 1 patient should be avoided; 7) change of 1 drug at 1 time with close monitoring should be preferred; and 8) fewer tablets and doses per day (long acting/drug combination) should be chosen. The checklist comprising potential inappropriateness of pharmacotherapy in the PC setting was also implemented in the hospice (TABLE 1).[5]

In the current cross-sectional study, we enrolled all consecutive patients admitted to the palliative outpatient clinic (700 consultations per year) and free-standing, acute (median time of care of 7 days and inpatient mortality rate of 74%), 42-bed hospice between August 1, 2016 and December 31, 2017. The medications consumed in the last 24 hours (including prescription, over-the-counter, and herbal products) were analyzed on the first hospice appointment by 6 palliative medicine specialists with respect to the following subgroup categories: age (0–59, 60–75, and >75 years), prognosis (according to the Gold Standards Framework [GSF][10]: A–B, C–D), length of care (died within 0–7, 8–14, 15–30, 31–90, >90 days or discharged), and functional capacity (according to the Palliative Performance Scale [PPS]: 0–40, 50–100). The participating consultants in palliative care were asked to mention, based solely on clinical judgment, all inconsistencies between the patients' clinical condition, the goals of care, symptoms profile, and the list of drugs taken. Drugs were defined as unnecessary or inappropriate if: a) the time needed to obtain a clinically meaningful benefit was longer than the remaining survival time, b) the therapeutic target did not align with the preferences expressed by the patient regarding the goals of care, or c) the harm caused by the treatment outweighed the expected benefit, especially if the risks arose before the benefit.[11] The checklist of potentially inappropriate medications (TABLE 1) and the commonly known drug–drug interactions[1] were also taken into account. During the same appointment, the routinely performed process of therapy adjustment was initiated. The numbers of drugs/tablets used prior to admission were then counted and compared with those prescribed during the first PC consultation.

Ethics Institutional review board approval for this study was obtained and patients provided written informed consent to participate in the study. The study was performed in accordance with the Declaration of Helsinki. All patient data were handled and processed in accordance with the recommendations of Good Clinical Practice.

Statistical analysis Normality of data distribution was analyzed with the Shapiro–Wilk test. The Wilcoxon signed-rank test was used to compare ordinal data (number of drugs and tablets) before and after the intervention. In number of drugs/tablets comparisons between the subgroups of patients, the Mann–Whitney test or the Kruskal–Wallis analysis of variance with the Dunn post hoc test were performed. The Spearman rank correlation analysis was used to assess the relationship between number of errors and quantitative characteristics of patients (PPS, age, number of drugs/tablets). Number of patients with errors was compared between subgroups with the χ^2 test or the Fisher exact test.

TABLE 2 Diagnosis distribution of 337 admitted patients

Primary diagnosis		Value
Cancer	Total	323 (95.8)
	Digestive system	116 (34.4)
	Respiratory	81 (24.0)
	Female reproductive system	43 (12.8)
	Urinary tract	17 (5.0)
	Central nervous system	16 (4.7)
	Male reproductive system	12 (3.6)
	Skin	11 (3.3)
	Other	27 (8.0)
Nonmalignant diseases		14 (4.2)

Data are presented as number (percentage).

variables). Odds ratios (ORs) were reported along with 95% confidence intervals (CIs). Significance was set at *P* value of less than 0.05. All calculations were done with the R Project for Statistical Computing.[12]

RESULTS Patients' primary diagnoses are presented in TABLE 2. Out of the 337 referred patients (323 with advanced cancer)—at the mean (SD) age of 74.2 (11.7) years—192 (57%) were admitted to the inpatient hospice, and 145 (43%), to the palliative care outpatient clinic. Death occurred in 290 of the admitted patients (86.0%). Their median length of care reached 21.5 days (interquartile range [IQR], 5.5–83.3). Three-quarters of them had prognosis counted in weeks rather than months (GSF, stage C–D), and nearly half were bed-bound (PPS ≤40 points; mean [SD] PPS within the group, 51.8 [22.4] points).

TABLE 3 Characteristics of admitted 337 patient and the numbers of drugs/tablets received

Patients characteristics		Total, n (%)	Drugs before, median (IQR)	Drugs change, median (IQR)	*P* value[a]	Tablets before, median (IQR)	Tablets change, median (IQR)	*P* value[a]
Total referred		337 (100)	7.0 (5.0)	–1.0 (3.0)	0.01	9.0 (8.0)	–2.0 (6.0)	<0.001
Age, y	≤75	175 (51.9)	8.0 (5.0)	–1.0 (3.0)	0.01	10.0 (9.0)	–1.0 (6.0)	0.01
	>75	162 (48.1)	7.0 (5.0)	–1.0 (3.0)	<0.001	9.0 (8.5)	–2.0 (5.8)	<0.001
	P value[b]	–	0.01	0.15	–	0.01	0.01	–
PPS	50–100	181 (53.7)	7.0 (5.0)	–1.0 (2.0)	0.07	9.0 (7.0)	0.0 (4.0)	0.06
	0–40	156 (46.3)	7.0 (5.0)	–2.0 (4.0)	<0.001	11.0 (10.3)	–4.0 (6.0)	<0.001
	P value[b]	–	0.85	0.02	–	0.02	<0.001	–
GSF	A–B	82 (24.3)	6.5 (4.0)	0.0 (2.0)	0.09	8.0 (7.0)	–1.0 (3.0)	0.06
	C–D	255 (75.7)	8.0 (5.0)	–1.0 (3.0)	<0.02	10.0 (9.0)	–2.0 (6.0)	0.01
	P value[b]	–	0.01	0.01	–	0.02	<0.001	–
Referring institution	General practitioner	96 (28.5)	7.0 (4.3)	–0.5 (3.0)	0.01	9.0 (9.3)	–1.0 (5.0)	0.02
	Hospital	147 (43.6)	8.0 (4.5)	–2.0 (4.0)	<0.001	11. 0 (10.0)	–4.0 (6.0)	<0.001
	Nonpalliative clinic	96 (28.4)	7.0 (6.0)	0.0 (2.0)	0.04	8.0 (6.3)	0.0 (3.0)	0.01
	P value[c]	–	0.45	0.02	–	0.83	<0.00	–
Admitted to	Hospice	192 (57.0)	7.0 (5.0)	–2.0 (4.0)	<0.001	11.0 (10.0)	–4.0 (6.0)	<0.001
	Palliative clinic	145 (43.0)	7.0 (5.0)	0.0 (2.0)	0.04	8.0 (6.8)	0.0 (3.0)	0.04
	P value[b]	–	0.94	<0.001	–	0.02	<0.001	–
Days to death	1–14	123 (36.5)	8.0 (5.0)	–2.0 (4.0)	<0.001	11.0 (10.0)	–4.0 (6.0)	<0.001
	15–30	39 (11.6)	8.0 (6.0)	–1.0 (3.0)	0.03	11.0 (8.0)	–2.0 (7.0)	0.01
	31–90	61 (18.1)	7.0 (5.0)	–1.0 (2.0)	0.01	10.0 (9.0)	–1.0 (4.0)	0.01
	>90	67 (19.8)	7.0 (6.0)	0.0 (1.0)	0.04	8.0 (6.0)	–1.0 (3.0)	0.03
	Discharged	47 (13.9)	7.0 (4.0)	–1.0 (3.0)	0.08	8.0 (6.5)	0.0 (3.5)	0.07
	P value[c]	–	0.36	<0.001	–	0.03	<0.001	–

a Wilcoxon signed-rank test

b Mann–Whitney test

c Kruskal–Wallis test

Abbreviations: GSF, Gold Standards Framework; IQR, interquartile range; PPS, Palliative Performance Scale

Univariate logistic regression was performed to assess the relationship between errors in treatment in a given patient (dependent variable) and his/her quantitative characteristics (independent

The median number of drugs used at referral to PC was 7.0 (and 9.0 tablets) per day (TABLE 3). In the subgroup with shorter prognosis, these numbers were even higher (8.0 and 10.0, respectively). Surprisingly, only 6 patients had subcutaneous route of drug administration. Polypharmacy (≥5 medications) was found in 265 cases (78.6%) with the maximum of 22 medications (a total of 44 tablets) in 1 patient. The median number of drugs on PC appointment decreased by 1.0 (IQR, 3.0; $P = 0.01$). In 188 cases (55.8%) the number of drugs decreased, in 43 (12.7%), increased, and in 106 (31.5%), did not change. The median number of tablets also decreased by 2.0 (IQR, 6.0; $P < 0.001$). In 210 of all consultations (62.3%), a reduction in the number of tablets was recommended, in 62 patients (18.4%) the proposed number of tablets increased, and in 65 (19.3%) it remained the same. Subgroup analysis revealed that bed-bound patients (PPS ≤40 points), those referred by hospitals, admitted to the hospice, with shorter prognosis had a higher reduction of drugs and tablets at the first PC consultation. In aged patients (>75 years) more pronounced reduction of tablets was seen.

At least 1 instance of drug inappropriateness could be found in 238 of the patients (70%) (TABLE 4). The most frequent type observed was concomitant drug deficiency (the lack of medications which are usually necessary when other therapy is implemented, eg, absence of laxatives in the cases of regular administration of strong opioids), the second most numerous group comprised inadequate drug monitoring (eg, antihypertensives, steroids, diuretics, or antidiabetics). Less commonly detected were possible drug–drug interactions, duplications, or antagonisms.

Patients who were bed-bound (PPS ≤40 points), with the shortest life expectancy (GSF, D), who died within 2 weeks, were discharged from hospital and admitted to the hospice had more often 1 or more potentially inappropriate medication (TABLE 5). The sum of noticed errors correlated with patients' lower performance status ($\rho = 0.23$; $P < 0.001$), the number of taken drugs ($\rho = 0.25$; $P < 0.001$) or tablets ($\rho = 0.24$; $P < 0.001$). With every 1-point decrease in PPS, the error risk increased by 2.1% (OR, 0.979; 95% CI, 0.969–0.99; $P < 0.001$). This risk increased by 13.3% with each drug (OR, 1.133; 95% CI, 1.057–1.215; $P < 0.001$) and by 7.4% with each tablet increase (OR, 1.079; 95% CI, 1.036–1.123; $P < 0.001$).

DISCUSSION To the best of my knowledge, this is the first cross-sectional study analyzing pharmacotherapy in the Polish PC population. Polypharmacy was found in more than three-quarters of patients, which was comparable with the Portuguese population of the tertiary oncologic center consulted in PC,[13] Belgian primary care patients,[3] or Japanese elderly cancer patients on strong opioids, and was associated with an increased number of comorbidities.[14] In Singapore, on palliative admission the mean number of medications varied between 5.6 (cancer patients) and 7.1 (in noncancer patients).[15] The current study confirmed the clinical relevance of drug inappropriateness in patients admitted to PC: more than two-thirds of patients on the first appointment had at least 1 inappropriate medication, which more frequently affected those more seriously ill (weaker and with poorer prognosis) and correlated with the number of drugs prescribed or tablets received.

The most common type of error was unnecessary and, in consequence, futile treatment, taking into account the limited life expectancy and longer time lag to benefit from these drugs. Nearly half of the patients had at least 1 such medication, which is consistent with the majority of previous studies.[1] The insufficient indication for prescribed drugs was also the leading inappropriateness observed in the literature, covering 23% of drugs.[13] Proton pump inhibitors and lipid-lowering drugs used in prevention were the most common examples, which might increase the risk of pneumonia, *Clostridium difficile* infection, or appetite loss due to the former[16] or muscle pain / weakness, diabetes risk due to the later.[17] The classification of many drugs as futile therapy, however, is often problematic, because disease-specific evidence--based guidelines for patients with advanced--stage disease, multimorbidities, and life expectancy shorter than 1 year are lacking. In these cases, American Geriatrics Society experts advise treatment deescalation, introducing symptom management and PC.[18]

Besides commonly observed polytherapy, the deficiency of necessary concomitant medication has currently been observed in nearly one--third of patients. The leading example has been the absence of laxatives in spite of regular opioid administration. The majority of patients who receive opioids have not been informed of the risk of the opioid-induced bowel disorder.[19] Half of constipated patients experience moderate to severe symptoms, but only seldom (12%) are they prescribed laxatives.[20] Opioids affect gut motility and secretion through multiple mechanisms, and laxatives should be prescribed unless there is a definite contraindication. PC consultants also noticed the common absence of rescue analgesics in the cases of an around-the-clock opioid regimen or the lack of coanalgesics in neuropathic pain (in 10.4% and 11% of patients, respectively), while these should be prescribed routinely, not only by PC specialists but also by any practitioner.[21-23]

Many drugs used in PC need clinical / metabolic monitoring, which has been insufficient in 25% of the current cases. This supervision refers to home blood pressure monitoring when hypertensives have been prescribed,[24] as gradual dosing reduction needs to be considered even in normotensive patients with poor prognosis.[6] Serum glucose monitoring is important not only when taking antidiabetics,[25] but also when steroids[26] or antipsychotics / antidepressants are prescribed.[27]

TABLE 4 Types and frequency of potential pharmacotherapy inappropriateness within the analyzed group of 337 patients referred to palliative care

Inappropriateness type/drug		Patients, n (%)
All types of potential inappropriateness		238 (70.6)
Unnecessary treatment in expected prognosis <3 months	Total	142 (42.1)
	Proton pump inhibitors used in prevention	73 (21.0)
	Lipid-lowering drugs (statins)	32 (9.5)
	Heparins in primary prevention	28 (8.3)
	Dietary supplements (including iron for mild anemia)	28 (8.3)
	Dexamethasone >10 d when no improvement or megestrol	18 (5.3)
	Antibiotics for asymptomatic bacteriuria	10 (3.0)
	Oral anticoagulants	4 (1.2)
	Total parenteral nutrition	2 (0.6)
	Nitrates for stable angina	2 (0.6)
	Oral antidiabetics in type 2 diabetes to reduce mild hyperglycemia	2 (0.6)
	Others (bisphosphonates/anticholinesterase drugs/insulin in type 2 diabetes)	3 (0.9)
Concomitant drug deficiency	Total	106 (31.5)
	No laxative when opioid administered	81 (24.0)
	No coanalgetics in neuropathic component of pain	37 (11.0)
	No "rescue" drug when regular opioid administered	35 (10.4)
	No probiotic when antibiotic prescribed	2 (0.6)
Lack of drug monitoring	Total	87 (25.8)
	Antihypertensives if normotensive/no control	36 (10.7)
	Steroids without glycemia monitoring	34 (10.1)
	Diuretics if oral fluid intake <1 l/no intake control	20 (5.9)
	Antidiabetic without glycemia monitoring	7 (2.1)
	Oral anticoagulant with no prothrombin time monitoring/heparins when PT >2	7 (2.1)
	Parenteral fluids if anasarca	5 (1.5))
	Lactulose if oral fluid intake <1 l/no intake control/colic pain	4 (1.2)
	Megestrol if diagnosed thrombosis	2 (0.6)
	Inhaled drugs for dyspnea in uncooperative patients	1 (0.3)
Possible drug–drug interactions (reason for appropriateness)	Total	41 (12.2)
	Step III + step II opioids (sedation)	13 (3.9)
	NSAIDs + corticosteroids/anticoagulants/SSRI (↑ gastrointestinal bleeding)	11 (3.3)
	Tramadol + neuroleptic/antidepressant (↓ seizure threshold)	8 (2.4)
	Paracetamol + antiepileptic (Stevens–Johnson syndrome/toxic epidermal necrolysis)	8 (2.4)
	Metoclopramide + antipsychotics/SSRIs/SNRIs (extrapyramidal/serotonin syndrome)	2 (0.6)
	Oral anticoagulant + NSAID/antiplatelet/PPI/fluconazole/metronidazole (↑ bleeding risk)	2 (0.6)
Duplicates	Total	16 (4.7)
	NSAIDs	7 (2.1)
	Steroids	3 (0.9)
	Neuroleptics	3 (0.9)
	SSRIs	1 (0.3)
	Loperamide + atropine	1 (0.3)
Antagonisms	Total	5 (1.5)
	Metoclopramide + hyoscine	3 (0.9)
	Mucolytics + hyoscine	3 (0.9)
Renal impairment (GFR <30 ml/min/1.72 m^2)	Total	5 (1.5)
	Oral antidiabetics (excluding gliquidone)	3 (0.9)
	Morphine/oxycodone	2 (0.6)
Other inappropriateness	Total	28 (8.3)
	Dosing errors (eg, crumbing sustained release tablets)	15 (4.5)
	Absence of drug for severe symptom (pain/seizures/depression/delirium/thrombosis)	7 (2.1)
	Incorrect route of administration (eg, tablets in vomiting patient)	5 (1.5)
	Prescriptive cascade (bladder catheter for hygiene → infection → antibiotic → *C. difficile*)	3 (0.9)
	No indication for specific drug (eg, H2 blocker after gastrectomy)	3 (0.9)

↑ increase, ↓ decrease

Abbreviations: GFR, glomelural filtration rate; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; PT, prothrombin time; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

TABLE 5 Subgroup analysis of patients with drug errors (n = 337)

Subgroup		Patients with errors	*P* value
Men		116 (23.5)	0.55
Women		122 (68.9)	
Age, y	<60	27 (75.0)	0.31
	60–75	103 (74.1)	
	>75	108 (66.7)	
PPS	50–100	113 (62.4)	0.001
	0–40	125 (80.1)	
GSF	A	4 (36.6)	0.001[a]
	B	43 (60.6)	
	C	156 (72.2)	
	D	35 (89.7)	
	A–B	47 (57.3)	0.004
	C–D	191 (74.9)	
Referring institution	General practitioner	63 (65.6)	<0.001
	Hospital	114 (77.5)	
	Nonpalliative clinic	61 (63.5)	
Admitted to	Hospice	150 (78.1)	0.001
	Palliative clinic	88 (60.7)	
Days to death	1–7	60 (75.0)	<0.001
	8–14	32 (86.5)	
	15–30	30 (76.9)	
	31–90	46 (75.4)	
	>90	45 (67.2)	
	≤30	122 (78.2)	<0.001
	>30	91 (71.1)	
Discharged		25 (47.2)	–

Data are presented as number (percentage). *P* values refer to the χ^2 test.

a *P* values refer to the Fisher exact test.

Abbreviations: see TABLE 3

Close monitoring of hydration and fluid balance (eg, via simple body weight or diuresis) is necessary when administering diuretics,[28] parenteral fluids, or osmotic laxatives.[29] In the cases of obvious adverse effects of drugs, the causative drugs should be stopped (eg, megestrol when symptoms of deep vein thrombosis occur). The systematic monitoring of biochemical renal profile is also important, since renal impairment is common in PC patients.[30] Estimated glomerular filtration rate reflecting the kidney function may guide drug choice and dosing.[31] In the current study, 1.5% of the analyzed patients received inappropriate oral antidiabetic agents or opioids in spite of documented renal impairment.

Various types of drug–drug interactions have recently been described.[1] In the present study, this reason for potential inappropriateness occurred less often than other types of errors (16.6% of patients) and encompassed pharmacodynamic interactions, or the use of drug antagonists / duplicates. While interactions on the level of receptors / mediators/enzymes can cause clinically dangerous toxicities, prescribed antagonists / duplicates can additionally be described as treatment futility.

Over 8% of the currently analyzed patients have shown other types of treatment malpractices, less obvious to classify, and therefore seldom published. The evident excessively high opioid dosage, the crumbing of sustained release tablets in the case of swallowing difficulties, the prescription of oral drugs to persistently vomiting patients, or ranitidine in spite of formerly performed total gastrectomy are typical examples of this subtype of malpractices. The management of drug prescriptions in patients with dysphagia was apparently suboptimal, if not iatrogenic. Within French geriatric population, 12.7% of the drug form modifications could have been harmful.[32] Professionals need to reevaluate their practices to reduce this risk. Better education of patients and caregivers is urgently needed to improve treatment adherence.[33]

Clinicians, regardless of specialty, should have rudimentary knowledge of symptom management and be skilled in the domains of utmost importance in their training. In the present study, over 2% of patients received no pharmacological symptomatic management despite the occurrence of severe symptoms (eg, pain, dyspnea, or seizures), which was particularly arresting. Although inadequate pain management can affect over 30% of cancer patients,[34-35] the complete current absence of such therapy in some persons could be daunting. In contrast, screening for opioid misuse in seriously ill outpatients could also be inadequate.[36] According to what has recently been evidenced, a training in symptom management for physicians from different clinical backgrounds is likely to contribute significantly to their approach and expertise,[37] so additional teaching is strongly advised. Specialist PC consultation supported by a team pharmacist can be instrumental in reducing inadequate dosage, converting one, or indicating untreated chronic moderate symptoms.[38]

The risk of drug errors increases with the number of medications / tablets, but also when multiorgan (hepato-renal) failure progresses or when drugs of narrow therapeutic index, which are often used in PC, are administered.[39] On the first PC consultation in this study, a clinically significant reduction in the number of medications and tablets has been observed. Similar results were obtained in Portugal, where more than one-quarter of the drugs (28.2%) was suspended (mainly due to the absence of indication for the drug) by a PC physician on the first appointment; however, no significant difference was noted between the number of drugs taken before and after this consultation.[13] The curbing of the number of drugs (deprescribing) appears to be a simple method of diminishing the risk of pharmacotherapy errors. In this study, PC consultants pointed out the need for drug reductions, especially in less fit individuals with a shorter prognosis. There are various arguments for it in the elderly patients, such as the possible risk of continuing

the therapy, questions about ongoing indication or benefits, prevalence of its overuse, or the availability of other treatment options—but also stopping the drug poses challenges when there is lack of evident deprescribing guidelines.[40] In the majority of geriatric patients, some drugs can be limited with the consequence of survival improvement and lowering of hospital admissions.[7] Similarly, in long-term care, gradual, individualized deprescribing of some regular drugs, with active involvement of patients' family members and a multidisciplinary team, is feasible. Most of preventive medications can be discontinued in advanced chronic obstructive lung disease, eg, 90% of the physicians would discontinue a cholesterol inhibitor when life expectancy is 3 months or less.[41] The majority of people with dementia experience no withdrawal symptoms when reducing antipsychotics, which should be personalized and monitored.[42] However, in the PC population in particular, this is not an effortless process, as the need of additional symptomatic pharmacotherapy usually increases as the disease proceeds. Patients with advanced cancer should be carefully followed in order to have their pharmacotherapy systematically evaluated.[1] Deprescribing consists in systematically reducing or discontinuing medications with the aim to minimize polypharmacy and improve patient outcomes.[4] Reducing the number of potentially inappropriate medications may result not only in a reduction of reported symptoms in the elderly but also in lowering healthcare expenditures.[43] The majority of patients taking many (≥10) drugs thought they took a large number of medications (would be comfortable taking fewer of them), and they would be willing to stop at least 1 if their doctor told them they could.[44] A Delphi survey among 135 palliative care clinicians in 9 countries suggested that only a few essential drugs are needed for quality care at the end of life (opioid, neuroleptic, anxiolytic, and/or antimuscarinic).[45] However, a high burden of unnecessary drugs is still found on the last day of life.[11] That is exactly why a management review by the primary treating clinician (eg, general practitioner when the patient stays at home) should be a substantial part of the care at the end of life. The physicians who are inexperienced in pharmacological management of terminally ill patients should turn to a palliative care specialist for consultation.[46] Quellet et al[47] recently proposed an iterative 3-step approach to medication decision making in older adults that could be adapted also to the PC. It posits: a) information gathering (patients' health priorities, disease trajectory, prognosis, and current treatment burden, b) balancing current/future possible harms with achievable benefits, and c) serial coordinated "therapeutical trials." It is helpful to ascertain SMART (specific, measurable, actionable, realistic, and time-limited) goals to evaluate the pharmacotherapy.[48]

Several study limitations are to be noted. It has been a single-institution trial reflecting palliative medicine physicians' therapeutic judgment according to the routine clinical practice, and carried out without a formal follow-up, hence the inability to assess the effectiveness of treatment modifications performed. Subcutaneous drugs routinely given instead of tablets within the last days of life have not been analyzed, and neither has intermittent pharmacotherapy (eg, periodical chemotherapy) been assessed.

Conclusions The majority of patients admitted to PC are treated with multiple medications, which increases the risk of drug inappropriateness. This phenomenon affects in particular those referred by hospitals, older patients with a poor prognosis and poor condition, and those admitted to inpatient hospices. A significant drug/tablet intake reduction in these patients may be considered to diminish the risk of therapeutic inappropriateness. There is also an urgent need of therapeutic education within nonspecialist palliative care.

ARTICLE INFORMATION

ACKNOWLEDGMENTS This study was supported by Towarzystwo Przyjaciół Chorych Hospicjum im. św. Łazarza in Kraków. The author would like to thank all St. Lazarus Hospice PC consultants for collecting data and their advice on the study design.

CONTRIBUTION STATEMENT The author is fully responsible for all parts of the study.

CONFLICT OF INTEREST None declared.

HOW TO CITE Grądalski T. Polypharmacy and medication errors on admission to palliative care. Pol Arch Intern Med. 2019; 129: 659-666. doi:10.20452/pamw.14969

REFERENCES

1 Kotlińska-Lemieszek A, Paulsen O, Kaasa S, Klepstad P. Polypharmacy in patients with advanced cancer and pain: a European cross-sectional study of 2282 patients. J Pain Symptom Manage. 2014; 48: 1145-1159.

2 Paque K, Elseviers M, Vander Stichele R, et al. Changes in medication use in a cohort of patients with advanced cancer: the international multicentre prospective European Palliative Care Cancer Symptom study. Palliat Med. 2018; 32: 775-785.

3 Pype P, Mertens F, Helewaut F, et al. Potentially inappropriate medication in primary care at the end of life: a mixed-method study. Acta Clin Belg. 2018; 73: 213-219.

4 Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015; 175: 827-834.

5 Lindsay J, Dooley M, Martin J, et al. The development and evaluation of an oncological palliative care deprescribing guideline: the "OncPal deprescribing guideline". Support Care Cancer. 2015; 23: 71-78.

6 Pasierski T. Modification of cardiovascular pharmacotherapy in palliative care patients with cancer: a narrative review. Pol Arch Intern Med. 2017; 127: 687-693.

7 Garfinkel D, Zur-Gil S, Ben-Israel J. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. Isr Med Assoc J. 2007; 9: 430-434.

8 O'Mahony D, O'Connor MN. Pharmacotherapy at the end-of-life. Age Ageing. 2011; 40: 419-422.

9 Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992; 45: 1045-1051.

10 Gold Standards Framework. http://www.goldstandardsframework.org.uk/. Accessed April 15, 2019.

11 Roux B, Morin L, Papon A, Laroche ML. Prescription and deprescription of medications for older adults receiving palliative care during the last 3 months of life: a single-center retrospective cohort study. Eur Geriatr Med. 2019; 10: 463-471.

12 R Core Team. *R*: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing. https://www.R-project.org/. Accessed April 15, 2019.

13 Domingues D, Carneiro R, Costa I, et al. Therapeutic futility in cancer patients at the time of palliative care transition: an analysis with a modified version of the Medication Appropriateness Index. Palliat Med. 2015; 29: 643-651.

14 Morio K, Maeda I, Yokota I, et al. Risk factors for polypharmacy in elderly patients with cancer pain. Am J Hosp Palliat Care. 2019; 36: 598-602.

15 Wenedy A, Lim YQ, Lin Ronggui CK, et al. A study of medication use of cancer and non-cancer patients in home hospice care in Singapore: a retrospective study from 2011 to 2015. J Palliat Med. 2019 May 8. [Epub ahead of print].

16 Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf. 2017; 9: 273-297.

17 Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2019; 39: e38-e81.

18 Boyd C, Smith CD, Masoudi FA, et al. Decision making for older adults with multiple chronic conditions: executive summary for the American geriatrics society guiding principles on the care of older adults with multimorbidity. J Am Geriatr Soc. 2019; 67: 665-673.

19 Pottegård A, Knudsen TB, van Heesch K, et al. Information on risk of constipation for Danish users of opioids, and their laxative use. Int J Clin Pharm. 2014; 36: 291-294.

20 Christense HN, Olsson U, From J, Breivik H. Opioid-induced constipation, use of laxatives, and health-related quality of life. Scand J Pain. 2016; 11: 104-110.

21 Quill TE, Abernethy AP. Generalist plus specialist palliative care – creating a more sustainable model. N Engl J Med. 2013; 368: 1173-1175.

22 Mu A, Weinberg E, Moulin DE, Clarke H. Pharmacologic management of chronic neuropathic pain: review of the Canadian Pain Society consensus statement. Can Fam Physician. 2017; 63: 844-852.

23 Mercadante S, Portenoy RK. Breakthrough cancer pain: twenty-five years of study. Pain. 2016; 157: 2657-2663.

24 Liyanage-Don N, Fung D, Phillips E, Kronish IM. Implementing home blood pressure monitoring into clinical practice. Curr Hypertens Rep. 2019; 21: 14.

25 Garg SK, Hirsh IB. Self-monitoring of blood glucose. Diabetes Technol Ther. 2017; 19: S3-S10.

26 Caplan A, Fett N, Rosenbach M, et al. Prevention and management of glucocorticoid-induced side effects: a comprehensive review: gastrointestinal and endocrinologic side effects. J Am Acad Dermatol. 2017; 76: 11-16.

27 Himmerich H, Minkwitz J, Kirkby KC. Weight gain and metabolic changes during treatment with antipsychotics and antidepressants. Endocr Metab Immune Disord Drug Targets. 2015; 15: 252-260.

28 Bartoli E, Rossi L, Sola D, et al. Use, misuse and abuse of diuretics. Eur J Intern Med. 2017; 39: 9-17.

29 Emmanuel A. Mattace-Raso F, Neri MC, et al. Constipation in older people: a consensus statement. Int J Clin Pract. 2017; 71.

30 Deskur-Smielecka E. Kotlinska-Lemieszek A, Niemir ZI, Wieczorkowska-Tobis K. Prevalence of renal impairment in palliative care inpatients: a retrospective analysis. J Palliat Med. 2015; 18: 614-617.

31 Masman AD, Tibboel D, Baar FP, et al. Prevalence and implications of abnormal laboratory results in patients in the terminal phase of life. J Palliat Med. 2016; 19: 822-829.

32 Fodil M, Nghiem D, Colas M, et al. Assessment of clinical practices for crushing medication in geriatric units. J Nutr Health Aging. 2017; 21: 904-908.

33 Marengoni A, Monaco A, Costa E, et al. Strategies to improve medication adherence in older persons: consensus statement from the Senior Italia Federanziani Advisory Board. Drugs Aging. 2016; 33: 629-637.

34 Vuong S, Pulenzas N, DeAngelis C, et al. Inadequate pain management in cancer patients attending an outpatient palliative radiotherapy clinic. Support Care Cancer. 2016; 24: 887-892.

35 Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. a review of published literature. Ann Oncol. 2008; 19: 1985-1991.

36 Mitchell JL, Blackhall LJ, Barclay JS. Screening for opioid misuse in the nonhospitalized seriously ill patient. J Palliat Med. 2019; 22: 1115-1119.

37 Turrillas P, Teixeira MJ, Maddocks M. A systematic review of training in symptom management in palliative care within postgraduate medical curriculums. J Pain Symptom Manage. 2019; 57: 156-170.e4.

38 Geum MJ, Ahn JH, Kim JS, et al. Interprofessional collaboration between a multidisciplinary palliative care team and the team pharmacist on pain management. Am J Hosp Palliat Care. 2019; 36: 616-622.

39 Blix HS, Viktil KK, Moger TA, Reikvam A. Drugs with narrow therapeutic index as indicators in the risk management of hospitalised patients. Pharm Pract (Granada). 2010; 8: 50-55.

40 Farrell B, Tsang C, Raman-Wilms L, et al. What are priorities for deprescribing for elderly patients? Capturing the voice of practitioners: a modified Delphi process. PLoS One. 2015; 10: e0122246.

41 Geijteman ECT, Huisman BAA, Dees MK, et al. Medication discontinuation at the end of life: a questionnaire study on physicians' experiences and opinions. J Palliat Med. 2018; 21: 1166-1170.

42 Harrison SL, Cations M, Jessop T, et al. Approaches to deprescribing psychotropic medications for changed behaviours in long-term care residents living with dementia. Drugs Aging. 2019; 36: 125-136.

43 Whitman A, DeGregory K, Morris A, et al. Pharmacist-led medication assessment and deprescribing intervention for older adults with cancer and polypharmacy: a pilot study. Support Care Cancer. 2018; 26: 4105-4113.

44 Schiøtz ML, Frølich A, Jensen AK, et al. Polypharmacy and medication deprescribing: a survey among multimorbid older adults in Denmark. Pharmacol Res Perspect. 2018; 6: e00431.

45 Lindqvist O, Lundquist G, Dickman A, et al. Four essential drugs needed for quality care of the dying: a Delphi-study based international expert consensus opinion. J Palliat Med. 2013; 16: 38-43.

46 Huisman BAA, Geijteman ECT, Dees MK, et al. Better drug use in advanced disease: an international Delphi study. BMJ Support Palliat Care. 2018 Nov 15. [Epub ahead of print].

47 Quellet GM, Quellet JA, Tinetti ME. Principle of rational prescribing and deprescribing in older adults with multiple chronic conditions. Ther Adv Drug Saf. 2018, 9: 639-652.

48 Naik AD, Martin LA, Moye J, Karel MJ. Health values and treatment goals of older, multimorbid adults facing life-threatening illness. J Am Geriatr Soc. 2016; 64: 625-631.