Drugs Aging (2014) 31:501–512
DOI 10.1007/s40266-014-0182-4

REVIEW ARTICLE

Decision Making About Change of Medication for Comorbid Disease at the End of Life: An Integrative Review

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Published online: 14 May 2014

Abstract The main goal of palliative care is to improve quality of life by treating symptoms in patients with life-threatening illnesses. Most patients suffer from more than five severe comorbidities in the last 6 months of life. However, for patients receiving palliative care, interventions to prevent possible long-term complications of these comorbidities are no longer the primary aim of care. This paper aimed to review the literature regarding decision making about medication for comorbid disease at the end of life, defined as a life expectancy <3 months, and to formulate preliminary recommendations based on the existing literature. An integrative review approach was used. We searched the MEDLINE, EMBASE, and CINAHL databases. Papers were included if they had been published in the English language between 1 January 1995 and 31 December 2013, with an abstract. Additional studies were identified by searching bibliographies. Factors to consider when systematically reviewing medications are the goals of care, remaining life expectancy, treatment targets, time until benefit, number needed to treat, number needed to harm, and adverse drug reactions. Existing research focuses particularly on the use of certain drug classes during end-of-life care, including statins, antihypertensive agents, anticoagulants, antihyperglycaemic agents and antibiotics. Based on the results of this review, we made preliminary recommendations for these medication groups. Medication that does not benefit the patient in any way should be avoided. The aim of medication at the end of life should be symptom control. There is a need for prospective trials to give further insight into the decision-making process of medication management at the end of life.

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1 Introduction

Healthcare providers working with patients receiving palliative care are often faced with questions about the appropriateness of the continuation of drugs with preventative or curative purposes at the end of life. For a specific patient receiving palliative care, particularly when death is expected within 3 months, agents that may have been used for years should be reconsidered and re-evaluated for appropriateness [1]. The main goal of palliative care is to improve quality of life by treating symptoms in patients suffering from life-threatening illnesses [2]. Once life expectancy is <3 months, the term 'end-of-life care' or 'terminal care' is used [3, 4]. Underlying 'palliative index diseases' in these patients include advanced cancer, end-stage organ failure or neurodegenerative diseases. In addition, these patients can also suffer from comorbidities such as hypercholesterolaemia or diabetes. Most patients have more than five severe comorbidities in the last 6 months of their life [5]. However, for patients receiving palliative care, interventions to prevent possible long-term complications of these comorbidities are no longer the

primary aim [6]. For a patient in a palliative care setting, the main goal of pharmacologic therapy is no longer life prolongation or treating or curing diseases. Instead, the focus of palliative care is to relieve suffering in the terminal and dying patient, often through the treatment of symptoms that cause discomfort, such as pain, nausea, dyspnoea, cognitive disturbances, anxiety and depression [1, 2]. The number of symptom-specific medications (SSMs) can differ depending on the number of symptoms present and the related underlying diseases. SSMs are prescribed in addition to the medications already prescribed for comorbidities, which are typically used for several years or even decades [7–10].

Hospice patients take an average of five to six medications each [11]. Approximately 20 % of patients referred to a palliative care facility take more than eight different medications, mostly to treat and stabilize these comorbidities and to prevent long-term complications of comorbid diseases [8, 12, 13]. In end-of-life care, the number of SSMs increases and the number of medications intended to treat comorbid diseases decreases [7, 14]. However, there is scant knowledge and few existing guidelines regarding the systematic management of specific drugs intended to treat comorbid disease at the end of life [15]. Therefore, questions remain regarding whether to prolong, change, or lower a specific dose of medication or whether to stop medication for comorbid disease. The optimal timing for stopping of a specific drug is also unknown.

The aim of this paper was to review the literature regarding decision making about medication for comorbid disease at the end of life in order to formulate preliminary recommendations based on the existing literature. We searched for key elements of decision making during this process to determine the use of these elements in individual patient care with regards to different medication groups. The results of this review may guide further prospective studies in this field.

2 Literature Search and Selection Methodology

2.1 Search Strategy

An integrative review approach was used [16, 17]. This method includes both empirical and theoretical publications. It uses diverse data sources, enhancing an holistic understanding of the topic of interest by presenting the state of the science and by contributing to theory development. The MEDLINE, EMBASE, and CINAHL databases were searched using the Medical Subject Headings (MeSH) and keywords ‘palliative care’ OR ‘end of life’ OR ‘terminal care’ OR ‘hospice care’ and ‘comorbid disease’ OR ‘comorbidity’ OR ‘comorbidities’ and ‘medication’ OR ‘medicines’ OR ‘pills’ OR ‘drugs’ and ‘prescribing’ OR ‘decision-making’ OR ‘managing’ OR ‘prolonging’ OR ‘stopping’ OR ‘continuing’ OR ‘mutation’. We searched articles about ‘palliative care’ in combination with the following medication groups: ‘statins’, ‘anticoagulants’, ‘antihyperglycaemic agents’, ‘antihypertensive agents’, ‘anti-bacterial agents’.

2.2 Study Selection

Papers that were published in the English language between 1 January 1995 and 31 December 2013, with an abstract, were included. In addition, papers were included if they described elements regarding the decision making about change of medication for comorbid disease at the end of life. Original research papers, systematic reviews, expert-opinion papers, and case studies were considered to identify elements of decision making. Additional studies were identified by searching bibliographies.

2.3 Preliminary Recommendations

The papers identified by the literature search were critically analysed to allow construction of preliminary recommendations (see Sect. 3).

3 Findings

3.1 Selected Papers

In total, 563 papers were related to end-of-life care, medication, prescribing and comorbid disease. Papers related to palliative care were searched in combination with different specific medication groups. This yielded a total of 129 papers related to the use of statins, 153 papers related to the use of anticoagulants, 129 papers related to the use of antihyperglycaemic agents, 255 papers related to the use of antihypertensive agents, and 771 papers related to the use of antibacterial agents. Duplicates were removed, which gave a total of 1,920 papers. After reviewing the abstracts from these 1,920 papers, the full text of 123 of these papers was examined. Of these papers, 57 met the inclusion criteria. Manually searching the bibliographies of the selected articles identified an additional 10 papers, giving a total of 67 papers that were included in the final review. The search strategy and process is outlined in Fig. 1.

Table 1 gives an overview of the 67 articles used in the review. The studies have been categorized in groups. The general studies provide key elements about decision making regarding change of medication for comorbid disease at the end of life. The available medication evaluation models mainly used in geriatrics are presented together. The

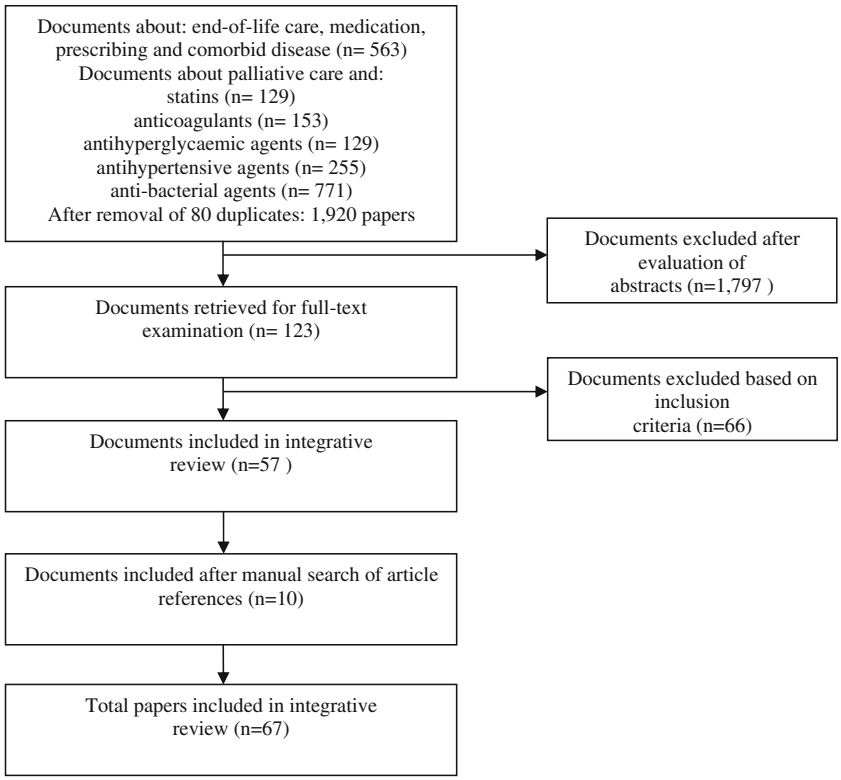

Fig. 1 Flowchart of studies from search to inclusion

remaining studies are categorized according to the five most salient preventative medication groups, namely statins, antihypertensive agents, antihyperglycaemic agents, anticoagulants and antibiotics.

3.2 Evaluation Models

There are different evaluation models available in the literature, mainly used in geriatrics, to support the decision-making process, such as the Beers criteria, the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP), the Medication Appropriateness Index (MAI) or the Good Palliative-Geriatric Practice algorithm [27, 29–34].

3.3 Factors for Decision Making

The literature provides different factors to consider when prescribing medication at the end of life (Table 2).

3.4 Medication Groups

The review articles found mainly focus on the use of certain drug classes in end-of-life care: statins, antihypertensive agents, anticoagulants, antihyperglycaemic agents and antibiotics. Apart from antibiotics, all of these agents are used for primary or secondary prevention, i.e. there is no disease at all, or if a disease is present, there are no symptoms.

3.4.1 Statins

The use of statins for the primary prevention of coronary heart disease has been studied in a population of patients with a relatively long life expectancy of more than 5 years [79]. Retrospective studies in palliative care settings found that approximately 1 in 4 patients use inappropriate medication (medications with no benefit in the last 3 months of life), of which more than half were statins (56 %) [14, 22, 36]. The adverse effects of statins, especially at the end of life, are not uncommon [40, 41]. Statins can cause acute renal failure, severe myopathy and liver dysfunction [39]. Statins may also interact with other drugs, increasing the risk for rhabdomyolysis when used with agents such as ketoconazole, verapamil and erythromycin, and increasing the anticoagulation effect when used with warfarin [37].

3.4.2 Antihypertensives

Literature about the use of antihypertensives at the end of life is scarce. Patients can experience low blood pressure at the end of life, even without using antihypertensive agents, due to cachexia and/or organ failure [1, 7, 24]. However, rebound hypertension and tachycardia can lead to serious problems when antihypertensive agents are withdrawn suddenly, especially when more than one antihypertensive agent is used [15].

Table 1 Integrative review of literature

Subject	Recommendations	Author	P/O/R	References
General	Consider remaining life expectancy, time until benefit, goals of care and treatment targets	Holmes	R	[11]
		Holmes et al.	O	[18]
	Review the original therapeutic goals	Currow et al.	P	[7]
	Consider number needed to treat and number needed to harm	Currow and Abernethy	O	[19]
	Consider psychological effect of stopping drugs and differences in drug metabolism (pharmacokinetics/pharmacodynamics) and number needed to treat	Stevenson et al.	R	[15]
	Optimal prescribing near end-of-life remains unexplored, more research needed	Cruz-Jentoft et al.	R	[20]
	Medication reconciliation should be performed routinely in advanced-cancer patients	Fede et al.	P	[13]
	Consider goals of care assessment	Fins et al.	P	[21]
	Consider polypharmacy at the end of life	McLean et al.	P	[22]
	Consider remaining life expectancy, goals of treatment, time-to-benefit, difficulties in administration, dangers of withdrawing treatment abruptly	O'Mahony and O'Connor	O	[23]
	Much of the literature is directed towards opinion rather than evidence, guiding clinical practice	Parsons et al.	R	[24]
	Always consider potential drug interactions	Riechelmann et al.	P	[25]
	Consider metabolic changes due to cachexia	Stevenson et al.	O	[26]
Evaluation models	Consider Beers criteria	Fick et al.	P	[27]
	Aim for discontinuing medication rationally	Bain et al.	O	[28]
	Consider STOPP prescription tool	Gallagher and O'Mahony	P	[29]
	Consider MAI prescription tool	Spinewine et al.	O	[30]
	Consider Beers, STOPP and MAI criteria prescription tools	Tjia et al.	R	[31]
	Consider lack of indication, lack of effectiveness, and therapeutic duplication	Suhrie et al.	P	[32]
	Consider Good Palliative-Geriatric practice algorithm	Garfinkel et al.	P	[33, 34]
	Aim for individualized medication regimens	Brandt and Stefanacci	O	[35]
Statins	Most frequently used, unnecessary medication	Riechelmann et al.	P	[14]
	Reduce therapeutic burden by stopping statins	Silveira et al.	P	[36]
	Discontinuation of statins towards end of life may be reasonable	Vollrath et al.	R	[37]
	Re-evaluate statins for primary prevention	Bayliss et al.	P	[38]
	Consider adverse effects: myopathy and renal failure	Hippisley-Cox and Coupland	P	[39]
	Consider severe drug interactions and adverse effects	Bottorff	R	[40]
	Consider removing medication that may add to patients suffering	Davis	O	[41]
Antihypertensives	Medication has little short-term benefit	Parsons et al.	R	[24]
	Cachexia: consider withdrawing antihypertensives	Currow et al.	P	[7]

Table 1 continued

Subject	Recommendations	Author	P/O/R	References
Antihyperglycaemic agents	International recommendations for DM type 2 have no scientific justification at the end of life	Vandenhaute	R	[42]
	Stop treatment and monitoring of DM type 2 in the terminal phase of life	Ford-Dunn et al.	P	[43]
	Address individual patient needs	Angelo et al.	O	[44]
	Aim is to avoid symptoms relating to hypoglycaemia or hyperglycaemia	King et al.	R	[45]
	Make a shift from tight control of blood sugar towards comfort and enhancing quality of life	Tice	O	[46]
Anticoagulants	Study based guidelines are scarce, research needed	Holmes et al.	P	[47]
	No increase of symptomatic VTE in end-of-life care, and thromboprophylaxis can be discontinued in most patients with a life expectancy of less than 6 months	Legault et al.	P	[48]
	Consider an increased risk of adverse drug reactions at end of life	Spiess	R	[49]
	Thromboprophylaxis in patients with advanced malignancy does not increase 1-year survival	Kakkar et al.	P	[50]
	Prophylaxis as prevention of symptoms that may never arise anyway is not the aim of palliative care	Chambers	O	[51]
	Primary thromboprophylaxis is inappropriate in the dying patient	Gillon et al.	P	[52]
	Consider risks and benefits of anticoagulant therapy	Soto-Cárdenas et al.	P	[53]
	LMWH is more effective in secondary prevention of VTE than warfarin	Johnson et al.	P	[54, 55]
	Consider thromboprophylaxis according to risks and benefits	Kierner et al.	P	[6]
	There is a need to balance the various diagnostic and therapeutic options	Kirkova and Fainsinger	O	[56]
	Involve the patient in the decision-making process whether to prescribe LMWH	McLean et al.	P	[57]
	Consider LMWH as first-line choice treatment in cancer-related VTE	Noble	R	[58]
	Symptomatic burden of VTE needs to be investigated	Noble et al.	P	[59]
	Long-term LMWH appears effective in treatment of VTE in the palliative care population	Noble et al.	P	[60]
	LMWH has a positive impact on overall quality of life	Noble	P	[61]
	Take into account needs and wishes of patients	Noble	R	[58]
	Explain risks and benefits of LMWH therapy at the end of life	Tran	R	[62]
	Consider mobility score at admission	Weber et al.	P	[63]

Table 1 continued

Subject	Recommendations	Author	P/O/R	References
Antibiotics	Clear definition of treatment goals needed at the end of life. Consider undesirable prolongation of the dying process	Stiel et al.	P	[64]
	Antibiotics are appropriate for symptoms such as dysuria (urinary tract infection) and dysphagia (oral Candida)	Enck	R	[65]
	Symptomatic improvement often not achieved with antibiotics in end-of-life-care patients	Oh et al.	P	[66]
	Consider the efficacy and futility of antibiotic treatment before prescribing	Lam et al.	P	[67]
	Consider assessment for potential benefits and treatment burdens	Chun et al.	P	[68]
	Consider antibiotics for symptom control in urinary tract infections. Antibiotics in end-of-life care do not influence survival	White et al	P	[69]
	Clear treatment goals are needed	Abduh Al-Shaqi et al.	P	[70]
	Consider decrease of fever-related discomfort because of antibiotic use	Chen et al.	P	[71]
	Consider antibiotics for dysuria	Mirhosseini et al.	P	[72]
	Further prospective studies needed because of high antibiotic use at the end of life	Oneschuk et al.	P	[73]
	Use an individualized approach	Nagy-Agren and Haley	R	[74]
	Consider antibiotics for symptom control	Pereira et al.	P	[75]
	Appropriate management of infection enhances symptom control at the end of life	Vitetta et al.	P	[76]
	Consider risks and burdens of antimicrobials at the end of life	Thompson et al.	P	[77]

P primary data, *O* opinion, *R* review, *STOPP* Screening Tool of Older Persons' potentially inappropriate Prescriptions, *MAI* Medication Appropriateness Index, *DM* diabetes mellitus, *LMWH* low-molecular-weight heparin, *VTE* venous thromboembolism

Table 2 Factors to consider for decision making about change of medication for comorbid disease at the end of life

Factor to consider	Elements	References
1. Goals of care	Patient's wishes	[11, 18, 21]
2. Remaining life expectancy	Progression in time	[11, 18, 23]
3. Treatment targets	Therapeutic aim, symptom treatment	[11, 18, 7, 23]
4. Time until benefit	Benefits and burdens	[11, 18, 23]
5. Number needed to treat	Increase near end of life	[15]
6. Number needed to harm	Increase near end of life	[7, 19]
7. Adverse drug reactions	Pharmacodynamic changes and pharmacokinetic changes	[25, 28, 78]

3.4.3 Anticoagulants

Literature regarding anticoagulants focuses on thromboprophylaxis, for which evidence-based guidelines for palliative care patients at the end-of-life are scarce [47, 56, 58, 59]. Only 7 % of specialist palliative care units in Great Britain have thromboprophylaxis guidelines [59]. Recent research shows that thromboprophylaxis can be discontinued in most patients in end-of- life care without a significant increase in the incidence of symptomatic deep vein thrombosis (DVT) [48]. The annual risk of recurrent venous thromboembolism after discontinuation is 2–10 % [49]. The number needed to treat to prevent one symptomatic DVT is 190, and treatment will possibly cause 3.5 additional bleeding complications [51]. Low-molecular-weight heparin (LMWH) administration does not improve 1-year survival in patients with advanced malignancy in the final 3 months of life [50]. When the prognosis is for longer survival times, these medications can yield a small benefit, reducing episodes of DVT and possibly reducing silent, fatal pulmonary embolic disease. As a treatment for a DVT, LMWH administration is preferred by patients and physicians compared with warfarin treatment, which requires titration based on international normalized ratio (INR) [54, 55, 57, 61]. The use of LMWH can give patients a feeling of safety and reassurance [80].

3.4.4 Antihyperglycaemic Agents

The use of diabetes guidelines in end-of-life patients has no scientific justification and can conflict with the quality-of-life goals for these patients [42, 44]. Moreover, patients experience discomfort from injections and blood glucose checks. An approach that is more consistent with palliative care is to keep the insulin dose as low as possible and to only check blood glucose levels when the patient experiences symptoms of hyperglycaemia, such as thirst [42, 43]. Thus, the standard treatment and monitoring of type 2 diabetes according to guidelines can be discontinued in patients receiving end-of-life care [43, 46].

In type 1 diabetes, hypoglycaemia and severe hyperglycaemia should be avoided because of symptoms that cause discomfort [45]. The use of once-daily, long-acting insulin can prevent symptomatic hyperglycaemia and requires minimal monitoring [43].

3.4.5 Antimicrobials

In the last few years, there has been greater focus on the use of antimicrobials (antibiotics and antifungals) in end-of-life care as patients with advanced disease are highly susceptible to infections due to suppressed immunity. Research shows that antimicrobials are prescribed frequently at the end of life [64–66, 70, 71, 73, 77]. There are no generally accepted guidelines on antibiotic use in this patient population. The infections most commonly observed in hospice patients are, in order of occurrence, respiratory tract infections, urinary tract infections, gastrointestinal infections, wound infections and bloodstream infections [64, 67–69]. Antibiotics are most commonly initiated for respiratory and urinary tract infections [64, 74–76]. Urinary tract infections can cause serious symptoms, such as dysuria, and can be treated with oral or even parenteral antibiotics consistent with a palliative treatment plan [64, 65, 67, 69, 72, 76, 81]. In contrast, for respiratory tract infections, opioids are preferable to antibiotics for the treatment of dyspnoea and pain because opioids provide greater and more expedient symptom control in patients at the end of life [65, 66].

Use of such agents should be part of a total treatment plan that is made together with the patient and family members, in which goals of care are clear [69]. Clear explanation of the benefit-burden ratio is important as family members may believe that every infection should be treated with antibiotics [66]. The use of antibiotics in advanced cancer patients at the end of life does not increase survival [69]. This information is important for patients and caretakers. Infections in patients with advanced disease should only be treated with antibiotics if the aim of the treatment is symptom control and if there are

Table 3 Preliminary recommendations deduced from review

Preliminary recommendations/ consequences of continuation	Statins	Antihypertensives β-blockers, diuretics, ACE inhibitors, calcium antagonists	Anticoagulants Vitamin K antagonists	Antihyperglycaemic agents Biguanides, long-acting sulphonylurea, short-acting sulphonylurea, thiazolidinediones, DPP-IV inhibitors, insulin	Antimicrobials Antibiotics, anti-fungal agents
Continue or discontinue	Discontinue	Discontinue when used for hypertension	Discontinue when used for primary prevention of DVT	DM type 1: adjust to minimum dosage and once a day treatment. DM type 2: adjust to minimum dosage, without symptoms of hypoglycaemia or hyperglycaemia	Variable, aim should be symptom control
Gradual reduction necessary?	No	Yes. Rebound hypertension and tachycardia	No	Gradual reduction may or may not be necessary depending on the original dosage	No
Expected problems when medication is continued	Acute renal failure, severe myopathy and liver dysfunction. In case of myopathy and continued use, rhabdomyolysis can occur, followed by myoglobinaemia and damage to the kidneys and other organs	Many patients at the end of life experience low blood pressure even without antihypertensive agents due to cachexia and organ failure	Because of impaired nutritional intake, the use of anticoagulants can pose serious risks in patients receiving end-of-life care due to changes in drug therapy and drug–drug interactions.	Malnutrition at the end of life can cause serious hypoglycaemia when antihyperglycaemic agents are continued for DM type 2	Not found

DM diabetes mellitus, *DVT* deep vein thrombosis, *DPP* dipeptidyl peptidase, *ACE* angiotensin-converting enzyme

no better avenues available for control of symptoms. The use of antibiotics with only the intent to cure infection in patients at the end of life is contraindicated [64, 67].

Table 3 gives preliminary recommendations deduced from the literature in this review for five medication groups.

4 Discussion

In the absence of 'hard' evidence, the articles identified in this review can offer little more than suggestions about decision making in relation to changes of medication for comorbid disease at the end of life. Helpfully, the literature does provide different frameworks for enhancing medication safety in geriatric populations. In such populations, polypharmacy is a key issue. This is defined in terms of the number of medications taken, e.g. >5 medications [82–84]. However, we found this definition to be not useful in end-of-life care as patients use SSMs, which are counted in the total number of medications. A better definition of polypharmacy in this particular population would focus on the use of 'inappropriate medication'. To avoid inappropriate medication use in end-of-life-care patients, the same decision-making factors can be used as in geriatric care: goals of care, treatment targets, remaining life expectancy, time until benefit, number needed to treat, number needed to harm and adverse drug reactions (Table 2). Goals of care and treatment targets can be included in a treatment plan [85, 86] that provides an overview of goals of care and treatment targets by focusing on the different dimensions of care.

Goals of care are based on patient preferences [87]. This means that decision making about medication for comorbid disease at the end of life requires good communication between the healthcare provider and the patient and his/her relatives. This becomes more difficult when the patient is no longer able to communicate. Particularly in this setting, relatives can provide information and can be helpful in determining the patient's wishes [35].

Treatment targets in end-of-life-care patients can vary. Some patients prefer only treatment of symptoms without life-prolonging measures, e.g. morphine for dyspnoea in patients with chronic obstructive pulmonary disease (COPD), the aim in such situations being to improve quality of life without treating the underlying disease. However, palliative care also considers patients' psychological distress, and patients may experience a feeling of abandonment following discontinuation of certain long-term medications [88]. Patients' wishes have not been studied in depth and there is a lack of evidence regarding how they address these advanced decisions.

Sometimes a patient's prognosis and therefore remaining life expectancy is not clear, which may pose an additional problem when focusing on the medication used. Both the prescribing doctor and the pharmacist should be aware of possible adverse drug reactions, necessitating good communication between these two professionals. The indications for medications must be reconsidered carefully as the disease progresses, and declines in functional status become manifest. It is also important to consider the side effects of medications, such as loss of appetite, and treatment-related burdens, such as pain with injections and difficulty swallowing medications. Concepts such as the number needed to treat and the number needed to harm can be useful in this decision-making process and can be discussed with the patient to explain how a particular medication provides more pill burdens than benefits. Medication use at the end of life should be minimized to prevent this 'pill burden' and should aim to control symptoms.

As proposed in the previous section, we can make a few preliminary recommendations for some medication groups at the end of life.

- Continuation of statins for primary prevention has no benefit [38]. A reduction in therapeutic burden by removing the need to swallow these pills can therefore be achieved by discontinuing statins at the end of life.
- Little literature exists about the use of antihypertensives at the end of life. Intake of food and fluids becomes less, patients experience cachexia and blood pressure decreases as a consequence [7]. However, long-term prevention of cardiac events and stroke is not needed anymore. When symptom relief is the main goal, strict blood pressure control has no place at the end of life.
- Anticoagulants at the end of life are mainly used to prevent DVT. LMWH administration for DVT is the preferred therapy in patients with a prognosis >3 months receiving palliative care [60, 63]. Because of impaired nutritional intake, the use of anticoagulants can pose serious risks in patients receiving end-of-life care due to changes in drug therapy and interactions [49]. The risks and benefits of LMWH administration need to be weighed up [53, 62]. Frequent monitoring is needed when administering warfarin or acenocoumarol; this is burdensome for the patient and should be avoided [49]. Initiating thromboprophylaxis at the end of life as a preventive measure is not appropriate [6, 52].
- Malnutrition at the end of life can cause serious hypoglycaemia when antihyperglycaemic agents are continued in patients with diabetes. Often, type 2 diabetes medication can be stopped and insulin therapy in type 1 diabetes can be reduced as long as symptoms do not occur. Symptom management of diabetes means

glucose checks are required only when the patient experiences discomfort.

- Physicians must weigh the benefit-burden ratio of antibiotics at the end of life. Infections need to be treated only when the patient experiences discomfort, such as dysuria caused by a urinary tract infection. The aim of antibiotics in palliative care should be symptom control.

Because of the absence of good evidence, further discussion is needed and future research should include prospective trials to obtain more insight into decision making about change of medication for comorbid disease at the end of life.

Our findings are reported in the context of several limitations. First, our recommendations are preliminary only—strong recommendations cannot be made in the absence of data from prospective trials. Second, we did not employ a systematic review approach. We included studies with a methodologically weaker design and opinion-based articles. Third, while a combined search with specific MeSH headings and keywords was used, not all keywords in this field of research are clear and some might have been missed.

5 Conclusions

All medication used for comorbid diseases at the end of life should be critically evaluated. Medication that does not benefit the patient in any way and is not given for the purpose of symptom control should be stopped. Several factors, also used in geriatric medication evaluation models, can be used to evaluate the medication: goals of care, remaining life expectancy, treatment targets, time until benefit, number needed to treat, number needed to harm, pill burden and adverse drug reactions. For any patient receiving end-of-life care, an individual approach should be taken when evaluating medications, and the patient's wishes should be part of a treatment plan. There is a need for prospective trials in this field to give further insight into decision making about change of medication for comorbid disease at the end of life. Good treatment consists not only of knowing when to begin but also of knowing how and when to stop.

Acknowledgments No sources of funding were used to assist in the preparation of this review. Ronald T.C.M. van Nordennen, Jan Lavrijsen, Kris Vissers and Raymond Koopmans have no potential conflicts of interest that are directly relevant to the content of this review.

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